Study Protocol

P4-C1-026

DARWIN EU® - Drug utilisation study of intramuscular depot olanzapine

18/05/2026

Version 5.0

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Public

CONTENTS

Study title	DARWIN EU® - Drug utilisation study of intramuscular depot olanzapine
Protocol version	V5.0
Date	18/05/2026
EUPAS number	EUPAS1000000980
Active Substance	Olanzapine (ATC code: N05AH03)
Medicinal Product	Intramuscular depot olanzapine (Zypadhera)
Research question and objectives	This study aims to address the following research questions: 1. What is the monthly incidence of intramuscular depot olanzapine use since 2018? 2. What is the switching pattern observed after intramuscular depot olanzapine discontinuation, and has this pattern changed since 2024? The specific study objectives are: 1. To estimate monthly incidence of intramuscular depot olanzapine use 2. To estimate the initial dose and maintenance dose of intramuscular depot olanzapine use 3. To estimate monthly prevalence of intramuscular depot olanzapine discontinuation 4. To describe treatment switching patterns among those who discontinued intramuscular depot olanzapine
Countries of study	Croatia, Denmark, Germany, Hungary, Sweden
Authors	Amy Lam (a.lam@darwin-eu.org)

LIST OF ABBREVIATIONS

Acronyms/terms	Description
ATC	Anatomical Therapeutic Chemical
CC	Coordination centre
CDM	Common Data Model
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
DOI	Declaration of Interests
DQD	Data Quality Dashboard
DRE	Digital Research Environment
DTZ	Data Transfer Zone
ED	Emergency Department
EHR	Electronic Health Records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUPAS	EU Post-Authorisation Studies Register
GDPR	General Data Protection Regulation
GP	General Practitioner
HI-SPEED	Health Impact - Swedish Population Evidence Enabling Data-linkage
ICD	International Classification of Diseases
IP	Inpatient
IQVIA DA Germany	IQVIA Disease Analyzer Germany
IRB	Institutional Review Board
N/A	Not Applicable
NAJS	Croatian National Public Health Information System
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
RxNorm	Medical prescription normalised
SNOMED	Systemised Nomenclature of Medicine
SUCD	Semmelweis University Clinical Data
WHO	World Health Organisation

1. TITLE

DARWIN EU® - Drug utilisation study of intramuscular depot olanzapine

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
Principal Investigator	Amy Lam	DARWIN EU® CC
Data Scientist	Nuria Mercade Besora Edward Burn	DARWIN EU® CC
Epidemiologist	Amy Lam Annika Jödicke	DARWIN EU® CC
Clinical Domain Expert	Anna Saura Lazaro	DARWIN EU® CC
Study Manager	Natasha Yefimenko Nosova	DARWIN EU® CC
Data source	**Names**	**Data Partner Organisation***
Croatian National Public Health Information System (NAJS)	Anamaria Jurcevic Jakov Vukovic Marko Cavlina Karlo Pintarić Antea Jezidžić Ivan Pristas	Croatian Institute of Public Health
Danish Data Health Registries (DK-DHR)	Elvira Bräuner Susanne Bruun	Danish Medicines Agency
IQVIA Disease Analyzer Germany (IQVIA DA Germany)	Dina Vojinovic Ellen Gerritsen Akram Mendez Gargi Jadhav	IQVIA
Semmelweis University Clinical Data (SUCD)	Zsolt István Bagyura Loretta Zsuzsa Kiss Tibor Héja Dániel Stankovics Orsolya Székely	Semmelweis University
Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED)	Huiqi Li Fredrik Nyberg Rickard Ljung Mats Talbäck Marcel Ballin	Swedish Medical Products Agency - Gothenburg University

*Data partners do not have an investigator role. Data partners execute code at their data source, review, and approve their results.

3. ABSTRACT

Title

DARWIN EU® - Drug utilisation study of intramuscular depot olanzapine

Rationale and background

Since 2024, there has been a critical and prolonged shortage of intramuscular depot olanzapine preparation (brand name: Zypadhera®), with the shortage affecting all marketed strengths in the European Union (210 mg, 300 mg, and 405 mg). Intramuscular depot olanzapine is indicated for the maintenance treatment of schizophrenia in patients stabilised on oral olanzapine, and its prolonged-release formulation results in sustained exposure that may persist for up to 6–8 months after injection. In the context of the ongoing shortage, patients previously treated with intramuscular depot olanzapine may need to discontinue treatment and switch to another antipsychotic medication. Treatment switching options could be either alternative long-acting intramuscular antipsychotics or oral antipsychotics. However, there is a lack of real-world evidence specifically addressing switching patterns following discontinuation of intramuscular depot olanzapine preparation. Understanding the prescribing trend and switching patterns during this prolonged shortage period is essential to inform clinical decision-making, healthcare planning, and future regulatory guidance.

Research question and objectives

Research questions

This study aims to address the following research questions:

1. What is the monthly incidence of intramuscular depot olanzapine use since 2018?
2. What is the switching pattern observed after intramuscular depot olanzapine discontinuation, and has this pattern changed since 2024?

Objectives

The aim of this study is to assess the monthly incidence of intramuscular depot olanzapine use and evaluate the switching patterns after discontinuation during the study period of 2018–2025.

The specific objectives of this study are:

1. To estimate monthly incidence of intramuscular depot olanzapine use since 2018
2. To estimate the initial dose and maintenance dose of intramuscular depot olanzapine use
3. To estimate monthly prevalence of intramuscular depot olanzapine discontinuation
4. To describe treatment switching pattern among those who discontinued intramuscular depot olanzapine

Methods

Study design

The study will comprise of a drug utilisation study: at population level to assess incidence rate of intramuscular depot olanzapine use among general population (objective 1) and to assess prevalence of intramuscular depot olanzapine discontinuation among individuals prescribed with intramuscular depot olanzapine (objective 3); and at patient level to assess initial and maintenance doses of intramuscular depot olanzapine among the intramuscular depot olanzapine new users (objective 2) and to assess treatment switching patterns among those who discontinued intramuscular depot olanzapine (objective 4).

Population

The study population will include all individuals who meet the eligibility criteria at study entry and are present in the data source during the study period (from 01/01/2018 to 6 months before the study period ends within each data source) with at least 365 days of data source history prior to index date

Eligibility criteria for specific objectives are:

- Start of intramuscular depot olanzapine treatment era between 01/01/2018 to 6 months before study period ends within each data source, without the presence of another intramuscular depot olanzapine treatment era within the prior 365 days (objective 2, 3)
- Discontinuation of intramuscular depot olanzapine (objective 4)

Objective 1: Monthly incidence of intramuscular depot olanzapine

Variables

Outcome: incidence of intramuscular depot olanzapine use

Statistical analysis

Monthly incidence rates per 100,000 person-months of intramuscular depot olanzapine will be estimated in the general population. Incidence rates will be reported together with 95% exact Poisson confidence intervals. The statistical analyses will be performed based on Observational Medical Outcomes Partnership common data model (OMOP CDM) mapped data using the R package *IncidencePrevalence*.

Objective 2: Estimation of initial and cumulative dose of intramuscular depot olanzapine

Variables

Exposure: new use of intramuscular depot olanzapine

Outcome: initial dose and maintenance dose of intramuscular depot olanzapine use

Statistical analysis

Drug utilisation analyses will be conducted among the intramuscular depot olanzapine new users with a washout of 365 days. Dose cohorts of 150/210mg, 300mg, and 405mg will be created based on the concepts. Initial dose will be assessed on the start date of a new treatment era by characterising new users into these dose cohorts. Maintenance dose will be assessed on Day 60 and Day 120 after the start date of new treatment era. Initial dose will be summarised as number of individuals (N, %) in each dose cohort on the index date among the new users. Maintenance dose will be summarised as number of individuals (N, %) in each dose cohort, “multiple”, “out of observation”, or “no record” group on the assessment date within each initial dose cohort (150/210mg, 300mg, and 405mg). The statistical analyses will be performed using the R package *PatientProfiles.*

Objective 3: Monthly prevalence of intramuscular depot olanzapine discontinuation

Variables

Exposure: new use of intramuscular depot olanzapine

Outcome: discontinuation of intramuscular depot olanzapine

Statistical analysis

Discontinuation will be defined as the end of a new continuous treatment era of intramuscular depot olanzapine with no additional prescription in the next 42 days. To ensure no prescription of intramuscular depot olanzapine is recorded in the immediate time after the end of treatment, at least

42 days of available follow-up time/future observation will be required for the definition of "discontinuation".

Monthly period prevalence of intramuscular depot olanzapine discontinuation will be estimated in the general population. The statistical analyses will be performed using the R package *IncidencePrevalence*.

Objective 4: Switching pattern after intramuscular depot olanzapine discontinuation

Variables

Exposure: discontinuation of intramuscular depot olanzapine

Outcome: oral olanzapine, injectable non-depot olanzapine, oral antipsychotics (typical or atypical), injectable non-depot antipsychotics (typical or atypical), depot antipsychotics (typical or atypical)

Statistical analysis

Discontinuation will be defined as end of a new continuous treatment era of intramuscular depot olanzapine with at least 42 days of future observation period. Index date will be the date of discontinuation, i.e., the estimated end date of the depot olanzapine treatment era. Prescription or pre-defined medicines of interest, i.e., other intramuscular antipsychotics, oral olanzapine, or other oral antipsychotics, in the assessment window of 60 days after discontinuation will be reported.

Analysis will be conducted in two stages: initial analysis will be conducted to identify the three most commonly prescribed antipsychotic ingredients, by class (typical and atypical) and by each route of administration (oral, injectable non-depot, and depot), after discontinuation of intramuscular depot olanzapine. Subsequent characterisation on switching pattern will be conducted on these identified antipsychotic ingredients, by class (typical and atypical) and by route (oral, injectable non-depot, and depot). Analyses will be conducted overall and stratified by age group and by sex. The statistical analyses will be performed using the R package *CohortCharacteristics*.

For all analyses, a minimum cell count of 5 will be used when reporting results, with any smaller count reported as "<5" and zero counts as "0".

Data sources

1. Croatia: Croatian National Public Health Information System (NAJS)
2. Denmark: Danish Data Health Registries (DK-DHR)
3. Germany: IQVIA Disease Analyzer Germany (IQVIA DA Germany)
4. Hungary: Semmelweis University Clinical Data (SUCD)
5. Sweden: Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED)

Study size

No sample size has been calculated, as this is an exploratory study which will not test a specific hypothesis. Based on a preliminary feasibility assessment, the expected number of persons counts for intramuscular depot olanzapine preparation in the data sources included in this study range from 1,200 (IQVIA DA Germany) to 4,000 (NAJS).

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study milestones and deliverables	Planned dates*
Final Study Protocol	April 2026
Creation of Analytical code	May–June 2026
Execution of Analytical Code on the data	June–August 2026
Draft Study Report	September 2026
Final Study Report	To be confirmed by EMA

*Planned dates are dependent on obtaining approvals from the internal review boards of the data sources.

6. RATIONALE AND BACKGROUND

Since 2024, there has been a critical and prolonged shortage of intramuscular depot olanzapine preparation (brand name: Zypadhera), with the shortage affecting all marketed strengths in the European Union (210 mg, 300 mg, and 405 mg).[1] The shortage was initially expected to last until October 2025. However, the shortage has subsequently been extended to mid-2026 as a result of manufacturing and supply-chain problems. This shortage affects all European Union and European Economic Area (EU/EEA) countries where Zypadhera is marketed.

Intramuscular depot olanzapine is used for the maintenance treatment of schizophrenia in patients stabilised on an initial course of oral olanzapine. The initial dose and maintenance dose of intramuscular depot olanzapine is determined by the oral olanzapine daily dose, with the following recommended dose scheme (**Table 1**). The prolonged-release formulation is characterised by slow dissolution of the olanzapine pamoate salt at the injection site, resulting in sustained olanzapine exposure that may persist for up to 6–8 months after final injection.[2]

Table 1. Recommended dose scheme between oral olanzapine and intramuscular depot olanzapine injection.

Target oral olanzapine dose	Recommended starting dose of intramuscular depot olanzapine injection	Maintenance dose after 2 months of intramuscular depot olanzapine treatment
10mg/day	210mg every 2 weeks, or 405mg every 4 weeks	150mg every 2 weeks, or 300mg every 4 weeks
15mg/day	300mg every 2 weeks	210mg every 2 weeks, or 405mg every 4 weeks
20mg/day	300mg every 2 weeks	300mg every 2 weeks

In the context of the ongoing shortage, patients previously treated with intramuscular depot olanzapine may need to discontinue treatment and switch to another antipsychotic medication. Treatment switching options could be either alternative long-acting intramuscular antipsychotics or oral antipsychotics. The product information of intramuscular depot olanzapine recommends close clinical supervision and monitoring, particularly during the first two months after discontinuation, when switching to another antipsychotic is considered medically appropriate.[2] However, there is a lack of real-world evidence

specifically addressing switching patterns following discontinuation of intramuscular depot olanzapine preparation.

Understanding the prescribing trend and switching patterns during this prolonged shortage is essential to inform clinical decision-making, healthcare planning, and future regulatory guidance.

7. RESEARCH QUESTION AND OBJECTIVES

Research questions

This study aims to address the following research questions:

1. What is the monthly incidence of intramuscular depot olanzapine use since 2018?
2. What is the switching pattern after intramuscular depot olanzapine discontinuation, and has this pattern changed since 2024?

Research objectives

The aim of this study is to assess the monthly incidence of intramuscular depot olanzapine use and evaluate the switching patterns after discontinuation during the study period of 2018–2025.

The specific objectives of this study are:

1. To estimate monthly incidence of intramuscular depot olanzapine use since 2018
2. To estimate the initial dose and maintenance dose of intramuscular depot olanzapine use
3. To estimate monthly prevalence of intramuscular depot olanzapine discontinuation since 2018
4. To describe treatment switching patterns to other antipsychotics among those who discontinued intramuscular depot olanzapine

8. RESEARCH METHODS

8.1. Study design

A cohort study will be conducted using health data from 5 data sources from 5 EU member states. The study will comprise of drug utilisation study at population level to assess incidence rate of intramuscular depot olanzapine use among general population (objective 1) and to assess prevalence of intramuscular depot olanzapine discontinuation among individuals prescribed with intramuscular depot olanzapine (objective 3); and at patient level to assess initial and maintenance doses of intramuscular depot olanzapine among the intramuscular depot olanzapine new users (objective 2) and to assess treatment switching patterns among those who discontinued intramuscular depot olanzapine (objective 4). The study design for each objective has been illustrated in **Figures 1–4**.

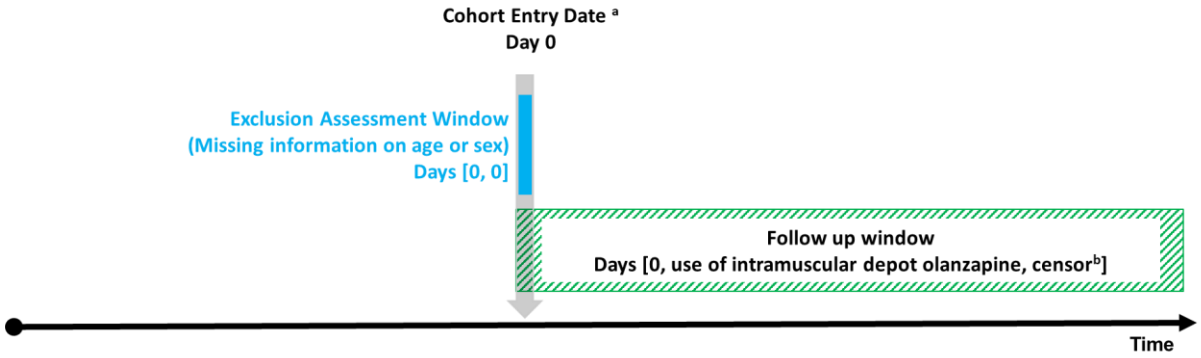

Figure 1. Study design for estimating monthly incidence of intramuscular depot olanzapine (objective 1).

a. Cohort inclusion period will be from 01/01/2018 to 6 months before the end of study period within each data source. Cohort entry date for the denominator cohort will be the latest of: (1) 01/01/2018, (2) the date when at least 365 days of prior history of individuals is available, or (3) 365 days after the end of intramuscular depot olanzapine (i.e., washout period). As there are multiple cohort entry criteria, the order of criteria application will be as follows: (1) washout period of 365 days, (2) 365 days prior history, (3) cohort inclusion period of 01/01/2018–6 months before end of study period within each data source.
b. Individuals will be censored at death, end of observation period, or end of study period (31/12/2025).

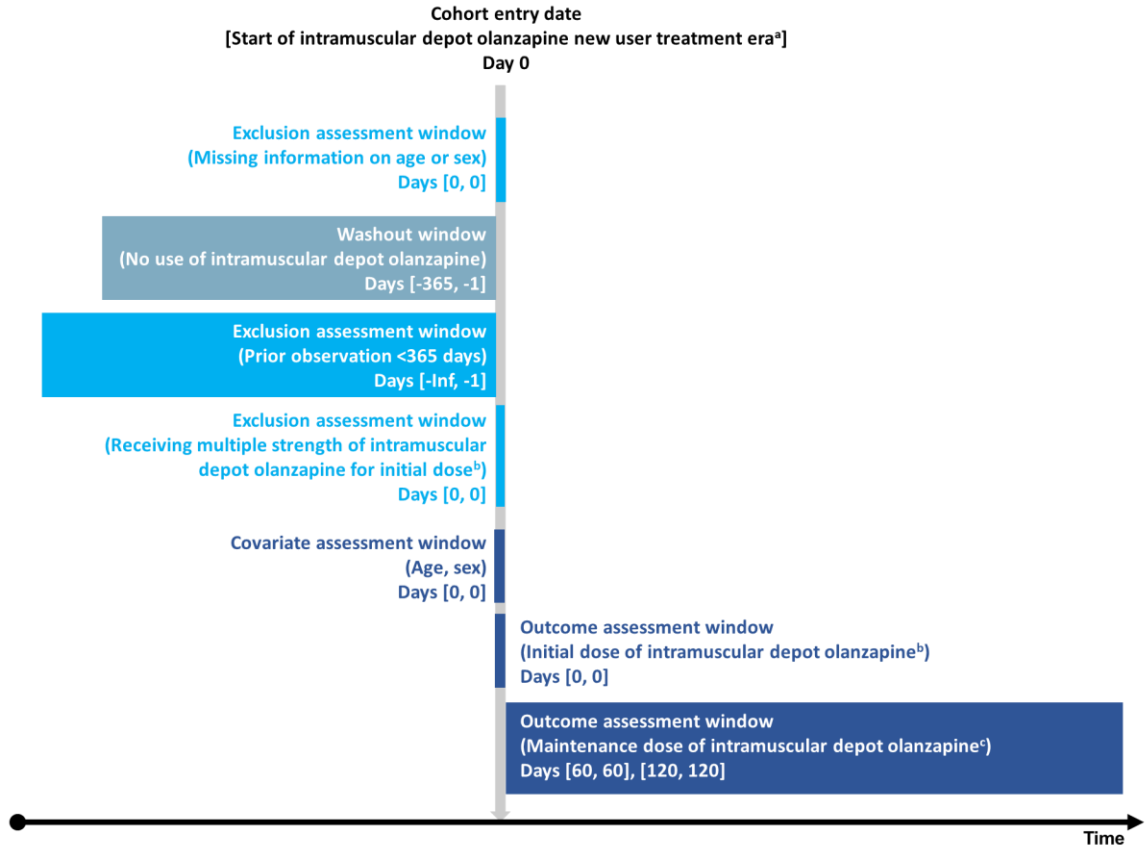

Figure 2. Study design for estimating the initial dose and maintenance dose of intramuscular depot olanzapine (objective 2).

a. Treatment episodes of sequential prescriptions (i.e., drug era) that have a maximum of 42 days between the end date of one prescription and the start date of the next prescription (i.e., definition of gap), will be generated. A 42-day treatment gap will be used to allow flexibility around the recommended 2- or 4-week dosing intervals and to account for delays in real-world administration. Only new user cohort with 365-day washout period will be included.
b. Dose cohort of 150/210mg, 300mg, and 405mg will be created based on concepts. If individuals appear in more than one dose cohort during the initial dose assessment, they will be categorised in the group “multiple”. Individuals in the “multiple” group for the initial dose will be excluded.
c. Dose cohort of 150/210mg, 300mg, and 405mg will be created based on concepts. Maintenance dose will be assessed in the initial dose cohort of 150/210mg, 300mg, and 405mg, respectively. If individuals appear in more than one dose cohort during the maintenance dose assessment, they will be categorised in the group “multiple”. For individuals who do not appear in any of the dose cohort or who are out of observation on the assessment date, they will be categorised in the group “no record” and “not in observation”, respectively.

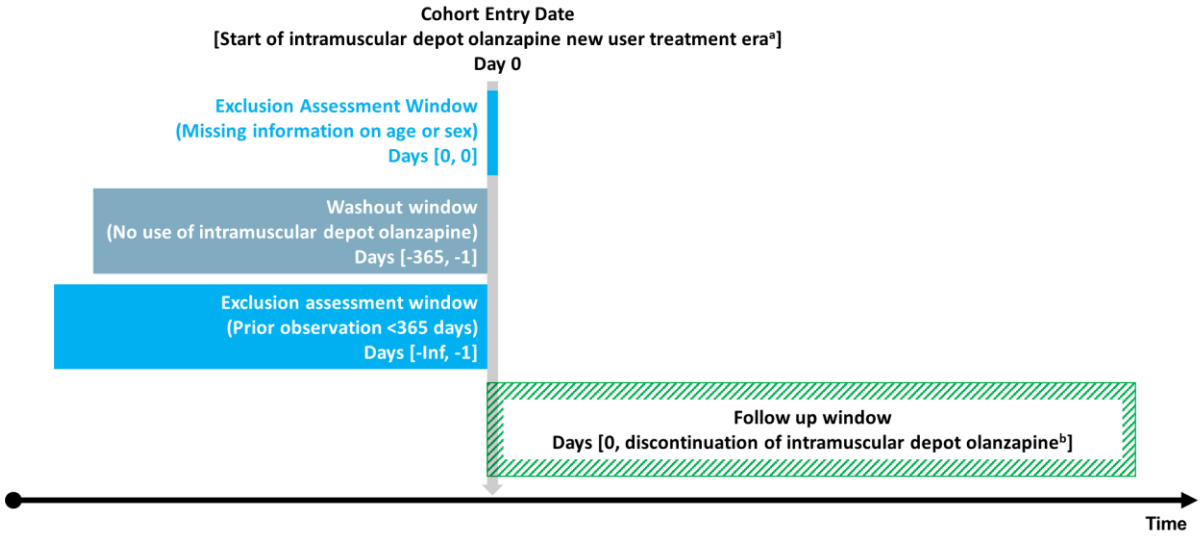

Figure 3. Study design for estimating monthly prevalence of intramuscular depot olanzapine discontinuation. (objective 3).

a. Treatment episodes of sequential prescriptions (i.e., drug era) that have a maximum of 42 days between the end date of one prescription and the start date of the next prescription (i.e., definition of gap), will be generated. Only new user cohort with 365-day washout period will be included.
b. Discontinuation of intramuscular depot olanzapine will be defined as end of new user treatment era with at least 42 days of future observation period.

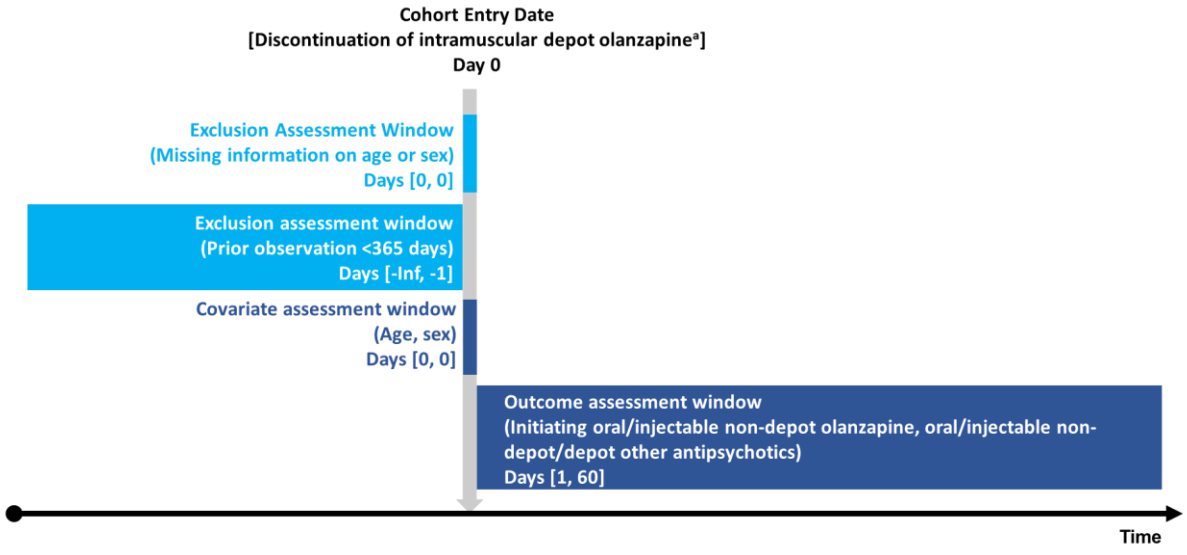

Figure 4. Study design for describing treatment switching pattern among those who discontinued intramuscular depot olanzapine (objective 4).

a. Discontinuation of intramuscular depot olanzapine will be defined as end of new user treatment era with at least 42 days of future observation period.

8.2. Follow-up

Objective 1: Monthly incidence of intramuscular depot olanzapine use

The study population for incidence will comprise the general population. Study population inclusion period will be from 01/01/2018 to 6 months before the end of study period within each data source.

Follow-up will start on the latest of: (1) 01/01/2018, (2) the date when at least 365 days of prior history of individuals is available, or (3) 365 days after the end of intramuscular depot olanzapine drug use (i.e., washout period).

Follow-up will end on the earliest of: loss to follow-up, death, end of observation period (the latest available data), study end date 31/12/2025, or start of intramuscular depot olanzapine.

An example of entry and exit into the denominator population is shown in **Figure 5**. In this example, ID 1 already has sufficient prior history before the study start date, and the observation period ends after the study end date, so this individual will contribute during the complete study period. ID 2 enters the study only when they have sufficient prior history. ID 3 leaves when exiting the data source (the end of the observation period). ID 4 has an outcome of interest for certain duration. After being washed out for 365 days, this individual will contribute again until the end of study period. ID 5 has an outcome of interest before fulfilling the sufficient prior history requirement. This individual will not start contributing to time-at-risk until being washed out for 365 days.

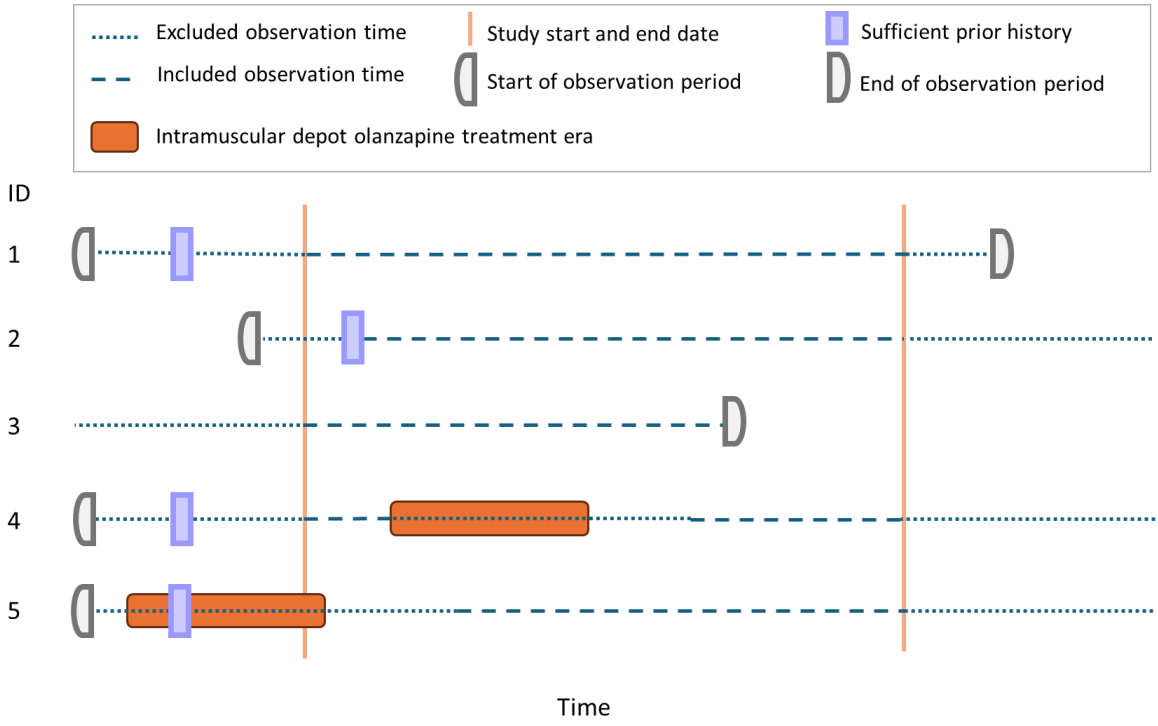

Figure 5. Included observation time for the denominator population (objective 1).

Objective 2: Initial dose and maintenance dose of intramuscular depot olanzapine use

The study population will comprise intramuscular depot olanzapine new users, with at least 365 days of washout period related to prior intramuscular depot olanzapine treatments and at least 365 days of prior history. Study population inclusion period will be from 01/01/2018 to 6 months before the end of study period within each data source.

Follow-up will start on the start date of the new intramuscular depot olanzapine treatment era.

Follow-up will end on the earliest of: loss to follow-up, death, end of observation period (the latest available data), or study end date 31/12/2025.

Maintenance dose will be assessed on the day 60 and day 120 after the start of new intramuscular depot olanzapine treatment era.

Objective 3: Monthly prevalence of intramuscular depot olanzapine discontinuation

The study population for prevalence estimation will comprise intramuscular depot olanzapine new users, with at least 365 days washout period related to prior intramuscular depot olanzapine treatments and at least 365 days of prior history. Study population inclusion period will be from 01/01/2018 to 6 months before the end of study period within each data source.

Follow-up will start on the start date of the new intramuscular depot olanzapine treatment era.

Follow-up will end on the earliest of: loss to follow-up, death, end of observation period (the latest available data), study end date 31/12/2025.

Objective 4: Report switching patterns for intramuscular depot olanzapine

The study population will comprise of intramuscular depot olanzapine new users who discontinued the treatment, of which discontinuation will be defined as end of new user treatment era. For this analysis, at least 60 days of follow-up time/future observation time after the end of the continuous treatment era is required.

Follow-up will start on the end date of the drug era of intramuscular depot olanzapine.

Follow-up will end on the earliest of: loss to follow-up, death, end of observation period (the latest available data), or study end date 31/12/2025.

Assessment window for switching pattern will be from one day to 60 days after intramuscular depot olanzapine discontinuation.

8.3. Study population with inclusion and exclusion criteria

All Objectives

Inclusion criteria

- Present between 01/01/2018 to 6 months before study period ends within each data source
- Minimum 365 days of available history before index date

Exclusion criteria

- Missing information on age or sex

Objective 2 and 3: Initial dose and maintenance dose of intramuscular depot olanzapine use, and monthly prevalence of intramuscular depot olanzapine discontinuation

Inclusion criteria

- Start of intramuscular depot olanzapine treatment era between 01/01/2018 to 6 months before study period ends within each data source

Exclusion criteria

- Presence of another intramuscular depot olanzapine treatment era within the prior 365 days

Objective 4: Report switching patterns for intramuscular depot olanzapine

Inclusion criteria

- End of intramuscular depot olanzapine new user treatment era between 01/01/2018 and 31/12/2025 (or the latest available date), of which the new user treatment era starts between 01/01/2018 to 6 months before study period ends within each data source
- With at least 42 days individual's future observation period after the end of treatment era

Exclusion criteria

- Presence of another intramuscular depot olanzapine treatment era within the 365 days prior to the start of treatment era under assessment

8.4. Study setting and data sources

This study will be conducted using routinely collected data from 5 data sources in the DARWIN EU® network of data partners from 5 EU member states. All data were *a priori* mapped to the Observational Medical Outcomes Partnership common data model (OMOP CDM).

Table 2. Data sources.

Country	Name of Data source	Health Care setting	Type of Data	Number of active individuals	Calendar period covered by each data source	Contributing to
Croatia	NAJS	Primary care (GP), secondary care (inpatient, outpatient)	Registries	4.3 million	01/2018–06/2025	All objectives
Denmark	DK-DHR	Secondary care (inpatient, outpatient)	Registries	5.98 million	01/2018–10/2024	All objectives
Germany	IQVIA DA Germany	Primary care (GP, specialists)	EHR	4.72 million	01/2018–06/2025	All objectives
Hungary	SUCD	Secondary care (inpatient, outpatient)	EHR	227 thousand	01/2018–03/2025	All objectives
Sweden	HI-SPEED	Primary care (GP), secondary care (inpatient, outpatient)	Registries	10.6 million	01/2019–08/2025	Objectives 2–4

DK-DHR = Danish Data Health Registries; EHR = Electronic Health Record; GP = General Practitioner; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; IQVIA DA Germany = IQVIA Disease Analyzer Germany; NAJS = Croatian National Public Health Information System; SUCD = Semmelweis University Clinical Data.

NAJS, DK-DHR, IQVIA DA Germany, and SUCD will contribute to all objectives, while HI-SPEED will only contribute to objectives 2–4. Due to the incomplete capture of intramuscular depot olanzapine records in HI-SPEED, there will be an underestimation of drug use, and therefore, interpretation of incidence of

intramuscular olanzapine depot injection will be affected. For this reason, HI-SPEED will only participate in the study for the objectives 2–4, for which the study population will be the intramuscular depot olanzapine users.

NAJS, DK-DHR, IQVIA DA Germany, and SUCD will contribute to the study with the study period starting from 01/2018 on, while HI-SPEED will contribute to the study starting from 01/2019 on. Despite the drug records being available since 2018 in HI-SPEED, the study period will start from 01/2019 on in HI-SPEED to allow adequate history of drug records to construct the new user cohort for the analysis.

Data sources selection

These data sources fulfil the criteria required in terms of data quality, completeness, timeliness, and representativeness for the drug utilisation study while covering different regions of Europe (**Annex I and II**).

8.5. Study period

The study period is from 01/01/2018 to 31/12/2025.

8.6. Variables

8.6.1. Exposure

Objective 1: Monthly incidence of intramuscular depot olanzapine use

No exposure will be defined for objective 1, as the population-level drug utilisation analyses will be conducted in the general population.

Objective 2 and 3*:* Initial dose and maintenance dose of intramuscular depot olanzapine use, and monthly prevalence of intramuscular depot olanzapine discontinuation

The exposure for objectives 2 and 3 will be the new use of intramuscular depot olanzapine.

Use of intramuscular depot olanzapine will be identified by prescription or dispensation records of intramuscular depot olanzapine. Treatment episodes of sequential prescriptions (i.e., drug era) that have a maximum of 42 days between the end date of one prescription and the start date of the next prescription (i.e., definition of gap), will be generated. Index date will be defined as first date of the drug era record. A 42-day treatment gap will be used to allow flexibility around the recommended 2- or 4-week dosing intervals and to account for delays in real-world administration. Multiple drug era records of the same individual will be allowed. New use of intramuscular depot olanzapine will be defined as no exposure to the intramuscular depot olanzapine within 365 days prior to index date (i.e., washout period).

Objective 4: Switching patterns after discontinuation of intramuscular depot olanzapine

The study population for objective 4 will be intramuscular depot olanzapine users who discontinued the drug. Discontinuation of intramuscular depot olanzapine will be defined as end of new user treatment era with at least 42 days of future observation period. To ensure no prescription of intramuscular depot olanzapine was recorded in the immediate time after the end of treatment, at least 42 days of available follow-up time/future observation will be required for the definition of “discontinuation”.

The preliminary concept sets used for the identification of exposures are described in **Annex IV**. These codes will be refined during the study execution following the DARWIN EU® phenotyping standard processes, which involve the review of code lists by pharmacists after their execution in the participating data sources.

8.6.2. Outcome

Objective 1. Monthly incidence of intramuscular depot olanzapine use

The outcome for this objective will be the new use of intramuscular depot olanzapine.

Use of intramuscular depot olanzapine will be identified by the prescription or dispensation records of intramuscular depot olanzapine. Treatment episodes of sequential prescriptions (i.e., drug era) that have a maximum of 42 days between the end date of one prescription and the start date of the next prescription (i.e., definition of gap), will be generated. Date of outcome will be defined as first date of the drug era record. New use of intramuscular depot olanzapine will be defined as no exposure to the intramuscular depot olanzapine within the prior 365 days (i.e., washout period).

Objective 2. Initial dose and maintenance dose of intramuscular depot olanzapine use

The outcomes for this objective will be the initial dose and maintenance dose of intramuscular depot olanzapine use.

Dose cohorts of 150/210mg, 300mg, and 405mg will be created based on the concepts. Initial dose of intramuscular depot olanzapine use will be assessed on the start date of a new treatment era by characterising new users into these dose cohorts. If a new user appears in more than one dose cohort on the index date, s/he will be excluded.

Maintenance dose of intramuscular depot olanzapine use will be assessed separately within each initial dose cohort (150/210mg, 300mg, and 405mg). Maintenance dose will be assessed on Day 60 and Day 120 after the start date of new treatment era by characterising the new users into these dose cohorts. If an individual appears in more than one dose cohort on the same assessment date, s/he will be categorised into the “multiple” group. Individuals who are out of observation or not classified into either any dose cohorts will be categorised as “out of observation” or “no record”, respectively.

Objective 3. Monthly prevalence of intramuscular depot olanzapine discontinuation

The outcome for this objective will be the discontinuation of intramuscular depot olanzapine.

Discontinuation of intramuscular depot olanzapine will be defined as end of new user treatment era with at least 42 days of future observation period. To ensure no prescription of intramuscular depot olanzapine was recorded in the immediate time after the end of treatment, at least 42 days of available follow-up time/future observation will be required for the definition of “discontinuation”.

Objective 4. Switching pattern after discontinuation of intramuscular depot olanzapine

The outcomes for this objective will be the use of oral olanzapine, injectable non-depot olanzapine, oral antipsychotics, injectable non-depot antipsychotics, and depot antipsychotics. Antipsychotics will be further classified into typical and atypical antipsychotics. For each outcome (oral/injectable non-depot/depot typical/atypical antipsychotics), the three most commonly prescribed ingredients will be identified and characterised.

Use of injectable non-depot/depot antipsychotics (with 42-day treatment gap concatenation), use of oral olanzapine (with 90-day treatment gap concatenation), and use of other oral antipsychotics (with 90-day treatment gap concatenation) will be identified by the prescription or dispensation records of respective drug of interest. The assessment window for switching pattern will be from one day to 60 days ([1, 60]) after intramuscular depot olanzapine discontinuation.

The preliminary concept sets used for the identification of outcomes are described in **Annex IV**.

8.6.3. Covariates

The covariates are assessed on index date as follows:

- Sex (objective 2, 4)
- Age (objective 2, 4)
- Age group (<18 years, 18–64 years, ≥65 years) (objective 2, 4)

8.7. Study size

No sample size has been calculated, as this is a drug utilisation study which will not test a specific hypothesis. In addition, we will use already collected available data to estimate incidence of intramuscular depot olanzapine. Thus, the sample size is driven by the availability of data for individuals with records of intramuscular depot olanzapine. Based on a preliminary feasibility assessment, the expected number of persons counts for intramuscular depot olanzapine in the data sources included in this study range from 1,200 (IQVIA DA Germany) to 4,000 (NAJS).

8.8. Analysis

8.8.1. Federated network analyses

All analyses will be conducted separately for each data source and will be carried out in a federated manner, allowing analyses to be run locally without sharing individuals' data.

Before sharing the study package, test runs of the analytics will be performed on a subset of the data sources, and quality control checks will be performed. After all the tests are passed (see **Annex III. Operational and reporting considerations**), the final package will be released in a version-controlled study repository for execution against all the participating data sources.

8.8.2. Data privacy protection

The data partners will locally execute the analytics against the OMOP CDM in R Studio and review and approve the default aggregated results. They will then be made available to the Principal Investigators and study team in secure online repository of DTZ (Data Transfer Zone). All results will be locked and timestamped for reproducibility and transparency. The study results of all data sources will be checked, after which they are made available to the team, and the Study Dissemination Phase can start. All analyses will be conducted separately for each data source, and will be carried out in a federated manner, allowing analyses to be run locally without sharing patient-level data. Cell counts <5 will be suppressed when reporting results to comply with the data source's privacy protection regulations.

8.8.3. Statistical model specification and assumptions of the analytical approach considered

R-packages

The monthly incidence of intramuscular depot olanzapine use (objective 1) and monthly prevalence of intramuscular depot olanzapine discontinuation (objective 3) will be calculated based on OMOP CDM mapped data using the R package *IncidencePrevalence*, developed by DARWIN EU®.[3] The initial dose and maintenance dose of intramuscular depot olanzapine use (objective 2) will be described using the R package *PatientProfiles*,[4] and switching pattern after discontinuation of intramuscular depot olanzapine (objective 4) will be described using the R package *CohortCharacteristics*.[5]

Drug era definition

Drug eras will be defined as follows: exposure starts at date of the first prescription after a washout of 365 days. For each prescription, the estimated duration of use is retrieved from the drug exposure table in the data source, using the start and end date of the exposure. Subsequent prescriptions will be combined into continuous exposed episodes (drug eras) using the following specifications:

Two drug eras will be merged into one continuous drug era if the distance in days between end of the first era and start of the second era is ≤42 days. The time between the two joined eras will be considered as exposed by the first era, as shown in **Figure 6**, first row.

Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"		NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

Figure 6. Illustration for gap era joint mode.

Discontinuation

Discontinuation will be defined as the end of new user treatment era with at least 42 days of future observation period. This aligns with the 42-day treatment gap used to construct drug eras and reduces the risk of immortal time bias among individuals without sufficient follow-up. An example is shown in **Figure 7**. ID 1 has end of new user treatment era on day 56 and with future observation period of at least 42 days. Therefore, there is an outcome of drug discontinuation. ID 2 also has end of new user treatment era on day 56, however the individual does not have sufficient future observation period of 42 days. The end of treatment era in ID 2 on day 56 will not be regarded as drug discontinuation.

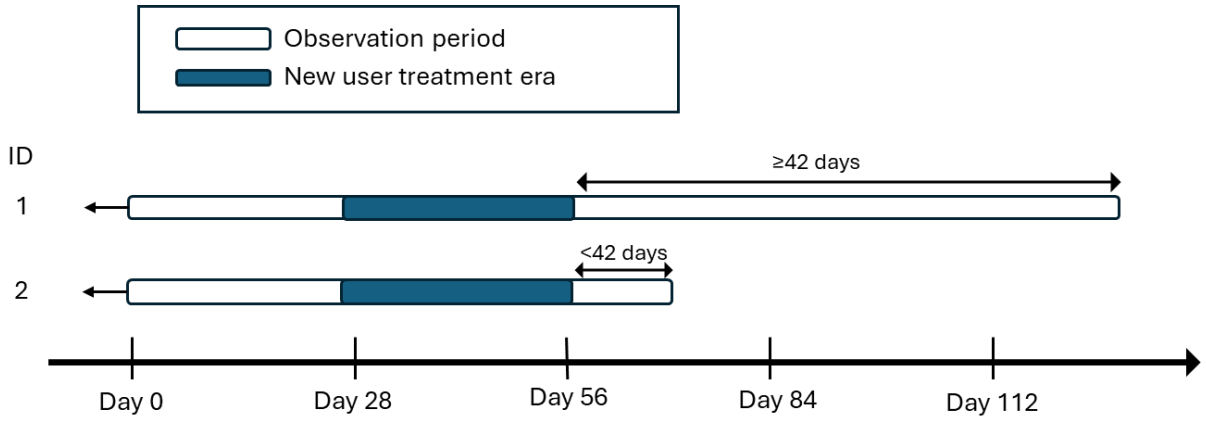

Figure 7. Definition of discontinuation.

Incidence calculation

Monthly incidence rates of the selected pre-specified medication of interest will be calculated as the number of new users of intramuscular depot olanzapine after 365 days of no use per 100,000 person-months of the population at risk of getting exposed during the period for each calendar month. Those study individuals who enter the denominator population will then contribute time-at-risk up to start of their new intramuscular depot olanzapine prescription during the study period. Multiple prescriptions are allowed, with individuals' time contributions paused during a defined outcome washout period of 365 days. Individuals without drug exposure will contribute time-at-risk, as described above. Time-at-risk of individuals who die will be censored at the time of death. Similarly, time-at-risk of individuals who are lost to follow-up will be censored at the time of loss to follow-up (i.e., last contact). Individuals with data until the end of the study period without experiencing exposure will be administratively censored at the end of

the study period. Incidence rates will be given together with 95% Poisson confidence intervals. Incidence will only be estimated for those intervals where the data source captures the complete interval.

Prevalence calculation for discontinuation

Prevalence will be calculated as monthly period prevalence which summarises the total number of individuals who discontinue using the drug of interest during a given month divided by the new user population during that month. Therefore, period prevalence gives the proportion of individuals that discontinue the drug at any time during a specified interval. Binomial exact 95% confidence intervals will be calculated. Prevalence will only be estimated for those intervals where the data source captures the complete interval.

Initial dose and maintenance dose estimation

Dose cohorts of 150/210mg, 300mg, and 405mg will be created based on the concepts. Initial dose will be characterised by the dose cohort on the index date [0, 0], which is the start date of treatment era. Individuals appearing in more than one dose cohort on the index date will be excluded. Initial dose will be summarised as number of persons (N, %) being in each dose cohort on the index date among the new users.

Maintenance dose will be characterised by the dose cohort on Day 60 and Day 120 after the start date of new treatment era within each initial dose cohort. “Multiple” group will be assigned if the new user appears in more than one dose cohort on the same assessment date. Individuals who are out of observation or not classified into either any dose cohorts will be categorised as “out of observation” or “no record”, respectively. Maintenance dose will be summarised as number of persons (N, %) being in each dose cohort, “multiple”, “out of observation”, or “no record” group on the assessment date within each initial dose cohort (150/210mg, 300mg, and 405mg).

Two-stage treatment switching identification

Analysis will be conducted in two stages:

Initial analysis will be conducted to identify the three most commonly prescribed antipsychotic ingredients, by class (typical and atypical) and by each route of administration (oral, injectable non-depot, and depot), within the pre-specified time window of one day to 60 days after discontinuation of intramuscular depot olanzapine [1, 60]. Analysis will be conducted with full sets of all antipsychotic ingredients in each included data sources to obtain number of persons (N, %) switching to each antipsychotic ingredient. Percentages will then be averaged across data sources, and these averaged percentages will be used to identify the three most commonly prescribed antipsychotic ingredients.

Subsequent characterisation on switching pattern will be conducted on these identified antipsychotic ingredients, by class (typical and atypical) and by route (oral, injectable non-depot, and depot). Switching patterns will be summarised as number of persons (N, %), starting within the pre-specified time window of one day to 60 days after discontinuation of intramuscular depot olanzapine [1, 60].

Oral drug of interest will be concatenated by 90-day of treatment gap, and injectable drug of interest will be concatenated by 42-day of treatment gap.

Findings of the three most commonly prescribed antipsychotic ingredients across all data sources, by class and by route, will be reported in the main results. Findings of the three most commonly prescribed antipsychotic ingredients within each data source, as identified from the initial analysis, will be given in the supplementary tables.

New user cohort

New users will be selected based on their incident prescriptions of the respective drug of interest after the start of the study. For each individual, at least 365 days of data visibility will be required prior to a

prescription. Individuals who initiate treatment are required to not have been exposed to the drug of interest for at least 365 days prior to the current prescription. If the start date of a prescription does not fulfil the exposure washout criteria of 365 days of no use, the whole exposure will be eliminated.

Methods to handle missing data

For the drug utilisation studies, we assume that the absence of a prescription record means that the individual does not receive the respective drug. For covariates, individuals with missing information on age or sex will be excluded, as illustrated in **Section 8.1** and **Section 8.3**.

Sensitivity analysis

Description of sensitivity analyses are presented by means of **Table 3**.

Table 3. Sensitivity analyses – rationale, strengths, and limitations.

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Objective 3. Prevalence of discontinuation	Study population will be further confined to those with treatment duration less than 2 years	To assess discontinuation within a more consistent population over time	This would allow assessment within a more consistent population over time, reducing variation due to differing treatment durations.	This would restrict the study population and could therefore be less representative of the overall intramuscular depot olanzapine user population.
Objective 4. Switching pattern after discontinuation	Assessment window will be changed from [1, 42] to [-7, 42]	To allow a grace period before the discontinuation of intramuscular depot olanzapine treatment era	Initiation of medication shortly before the end of intramuscular depot olanzapine treatment era will not be missed while describing switching patterns.	There may be risk of capturing concurrent medication use rather than switching after discontinuation.

8.8.4. Output

Output will include the following:

A PDF report, including an executive summary, and the following tables and figures.

- Figure 1. Monthly incidence of intramuscular depot olanzapine (objective 1).
- Figure 2. Sankey plot on maintenance dose of intramuscular depot olanzapine (objective 2).
- Figure 3. Monthly prevalence of intramuscular depot olanzapine discontinuation (objective 3).
- Table 1. Initial dose of intramuscular depot olanzapine (objective 2).
- Table 2. Maintenance dose of intramuscular depot olanzapine (objective 2).
- Table 3. Switching pattern after intramuscular depot olanzapine discontinuation, overall (objective 4).
- Table 4. Switching pattern after intramuscular depot olanzapine discontinuation, stratified by age group (objective 4).
- Table 5. Switching pattern after intramuscular depot olanzapine discontinuation, stratified by sex (objective 4).

Mock tables and figures are included in **Annex V**.

An interactive dashboard will be generated by incorporating all the results (tables and figures) included in the PDF report mentioned above.

8.9. Evidence synthesis

Results from analyses described in **Section 8.8** will be presented separately for each data source. No meta-analysis of results will be conducted.

9. STRENGTHS AND LIMITATIONS

The study will be informed by healthcare data collected in usual clinical care and so, data quality issues must be considered.

Intramuscular depot olanzapine is administered by healthcare professionals, and its recording may vary across data sources, either by individual administrations or by prescriptions. This heterogeneity may affect the consistency of drug exposure duration and dose information across data sources. Therefore, careful diagnostic procedures to inspect drug records within each data source using, *DrugExposureDiagnostics*[6], would be essential to ensure accurate and reliable results.

Based on the feasibility assessment, the person counts of intramuscular depot olanzapine use ranged from 1,200 to 4,000 across included data sources. While the person counts appear adequate, the planned monthly analyses of incidence and discontinuation may result in small cell counts <5, leading to reporting of the corresponding results as "<5" instead of the true value, and then limiting interpretability.

Dose cohort has been created based on the concept name and concept ID, with details given in **Annex IV Table S2**. According to the recommended dosing scheme (**Table 1**), dose cohorts of 150mg, 210mg, 300mg, and 405mg would be expected. However, during code list development, no concept corresponding to a 150mg preparation was identified. In practice, a dose of 150mg is administered using the 210mg preparation.[7] Therefore, instead of four separate dose cohorts, the analysis will include dose cohorts of 150/210mg, 300mg, and 405mg. This approach limits the ability to distinguish between 150mg and 210mg dosing, thus limiting the assessment of initial and maintenance dose.

Discontinuation of intramuscular depot olanzapine will be defined based on the end of the treatment era. However, towards the end of the study period within each data source, it may not be possible to distinguish true treatment discontinuation from insufficient follow-up time to observe the next administration. Furthermore, individuals may have died or exited the data source before receiving their next dose. To minimise misinterpretation and reduce potential immortal time bias, discontinuation will be defined as end of treatment era with sufficient future observation period. In the current study, we take reference to gap era duration of 42 days, based on the assumption that any prescription or dispensation within 42 days will be deemed as same treatment era.

Discontinuation of intramuscular depot olanzapine will be assessed in the population of intramuscular depot olanzapine users. However, the probability of discontinuation may differ among users with varying durations of treatment, and the composition of users may change over the study period. This may make the interpretation of discontinuation challenging. Therefore, we propose a sensitivity analysis restricted to intramuscular depot olanzapine users with a treatment duration of less than 2 years to allow for assessment within a more consistent population over time.

Detection of switching patterns depends on the accurate definition of drug exposure duration. Switching will be defined as initiation of oral olanzapine or other antipsychotics (injectable formulations, depot formulations, or oral formulations) following intramuscular depot olanzapine treatment discontinuation. If oral olanzapine or other antipsychotics are prescribed shortly before the end of the intramuscular depot olanzapine treatment era, such switching may not be captured, potentially leading to underestimation of switching patterns. To allow capturing of switching pattern shortly before the discontinuation of

intramuscular depot olanzapine, a sensitivity analysis will be conducted with the assessment window of 7 days before to 60 days after the end of intramuscular depot olanzapine treatment era to allow a grace period of 7 days before drug discontinuation.

Lastly, the results estimated from this study will only reflect the populations from the included data sources. Electronic health records have certain inherent limitations because they were collected for clinical purposes rather than primarily for research use. Consequently, using 5 data sources from Croatia, Denmark, Germany, Hungary, and Sweden limits generalisability to those countries.

10. REFERENCES

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2.Zypadhera: EPAR - Product Information [Internet]. 2026. Available from: https://www.ema.europa.eu/en/documents/product-information/zypadhera-epar-product-information_en.pdf.

3.Burn E, Raventos B, Catala M. IncidencePrevalence: Estimate Incidence and Prevalence using the OMOP Common Data Model 2025 [R package version 1.2.0. Available from: https://darwin-eu.github.io/IncidencePrevalence/.

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6.Inberg G, Burn E, Burkard T. DrugExposureDiagnostics: Diagnostics for OMOP Common Data Model Drug Records 2025 [R package version 1.1.4. Available from: https://darwin-eu.github.io/DrugExposureDiagnostics/.

7.ZYPREXA [Internet]. 2026. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/22173s050lbl.pdf.

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9.Burn E, Catala M, Chen X, Alcalde-Herraiz M, Prats-Uribe A. PhenotypeR: Assess Study Cohorts Using a Common Data Model 2025 [R package version 0.1.6. Available from: https://ohdsi.github.io/PhenotypeR/.

11. ANNEXES

ANNEX I. Description of data sources

Croatian National Public Health Information System (NAJS)

#	Section	Description
1	Data source identification and country	NAJS (Croatian National Public Health Information System) Croatia
2	Data partner information section	Croatian Institute of Public Health Department of Data Science and Analytics
3	Coverage and timespan	Data collection since: 1998 Extent: Nation-wide. Geographic coverage covers whole Croatia, with various levels of resolution for different registries. Current estimates for the population in Croatia will be available at: https://podaci.dzs.hr/hr/podaci/stanovnistvo/procjena-stanovnistva/ for each year. The total and active person count in the NAJS data is larger than the current population of Croatia. This explained by: a) the person table included deceased and all previously insured people and b) there is no information about insurance ending, c) healthcare is also used by people with dual citizenship from neighbouring countries It is known that a lot of people emigrated (300k-400k) and weren't included in the last population census but still are in the NAJS database. There is also an influx of immigrant workers that are insured and registered but weren't included in the census.
4	Healthcare setting / type of data	Primary care – General Practitioner, and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. Primary care – gps, and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. For both inpatient and outpatient setting diagnoses, medication, procedures, and measurements are captured. The year of availability of information depends on the setting • 2014-2025 for biochemical lab tests in primary care from EHR patients records (measurements with results) • 2015-2025 for primary care data from EHR patient records (conditions, procedures, and drug prescriptions) • 2015- 2024 for inpatient hospital data from EHR administrative records (conditions, procedures, measurements without results and drug administrations) • 2016-2025 for health risk assessment data entered by GPs (measurements with results - height, weight…) • 2016-2022 for secondary conciliatory care data from EHR administrative records (conditions, procedures, measurements without results and drug administrations) • 2016-2022 for emergency care data from EHR patient records (conditions) • 2017-2025 for hospital records from registry data (conditions and procedures) • 2020-2025 for vaccination data from EHR patient records
5	Data collection process	Inpatient hospital billing systems, and Other. Data is entered by clinicians at healthcare contact, then combined by CIPH into the NAJS database and integrated with registries for public health purposes.
6	General representativeness	The data is collected from the evidence of public health records collected for public health purposes, as the majority of health care in Croatia is public and under single health insurance provider. Personal details are collected to a better extent for insured individuals compared to uninsured patients, who are excluded in the ETL process.
7	Data content /source coding	Medication prescriptions are recorded with ATC codes with an additional 3 digit code denoting the package. Diagnoses with ICD10 codes (Australian modification). Procedures with local source codes. Lab results with local source codes.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Records from 2017 include insured patients with reliable IDs. Uninsured patients do not have reliable IDs. For example, if a patient changed her status from insured to uninsured, or vice versa,

#	Section	Description
		she could be counted several times, as could tracking records from before 2017 and after. By using the unique personal identifier for Croatian citizens, it can be checked and verified.
9	Quality control (data source specific)	There is a network of registry personnel (leaders, administrators, coders, sources) working on data coverage and other quality dimensions. An analytical team routinely checks for erroneous entries in hospital records, removing double entries, false dates, and overlapping stays. Entries without enough data or with obviously erroneous dates from primary care analysis are being excluded.
10	Linkage	The national death registry is updated yearly, with one year lag, but the fact of someone's death (just the date) is updated daily, without the cause of death or any other additional details. Primary care is updated weekly and hospital level care monthly. Specific registries are included in NAJS (e.g., diabetes registry), where inclusion criteria vary across these registries.
11	Vital status	NAJS is linked to the national death registry.
12	Limitations	Hospital data is available from 2017 onwards. This is often used as start of data collection, while laboratory and GP data is captured before that (since 2014 and 2015 respectively). Drug duration is often not available and set to 1 day for administration and 30 days for prescription. Hospital discharge summaries are currently not captured in NAJS. Hospital drug administration data is less reliable than prescription data from primary care, with some drugs (monoclonal antibodies / precision medicine drugs) that require additional approval not being recorded at all.
13	Main references	No main reference provided.
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111155 Website: https://www.hzjz.hr/nacionalni-javnozdravstveni-informacijski-sustav-najs/

Danish Data Health Registries (DK-DHR)

#	Section	Description
1	Data source identification and country	DK-DHR (Danish Data Health Registries) Denmark
2	Data partner information section	Danish Medicines Agency (DKMA) Data Analytics Centre (DAC)
3	Coverage and timespan	Data collection since: 1995 Extent: Nation-wide. The data is representative of the entire Danish population.
4	Healthcare setting / type of data	Community pharmacists, and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. The following data elements are collected: diagnosis (including rare diseases and pregnancy data), hospital admissions, discharge and ICU data, Cause of death, Drug prescriptions, dispensing, vaccination and contraception, Procedures (surgical and non-surgical hospital), and Sociodemographic information (sex and age only).
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Registries, and Other. All causes of deaths, all retrieved drug prescriptions, all records of vaccinations, all hospital inpatient and outpatients contacts including disease diagnoses and hospital surgical and non-surgical procedures, histologically confirmed incident cancers, laboratory test results for the entire Danish population from 1/1/1995 onwards.
6	General representativeness	The data is representative of the entire Danish population. Healthcare is free in Denmark, so we do not expect any bias in data collection based on socio-economic status.

#	Section	Description
7	Data content /source coding	Diagnoses and causes of death are collected using the ICD-10 vocabulary. ATC and RxNorm are used for Drugs. SNOMED codes are used for Procedures.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Patients have unique identifiers used to link datasets.
9	Quality control (data source specific)	The data we have received relating to nationwide Danish Health Data registries offer an opportunity for large-scale, population-based studies with several advantages 1) Their large size improves the precision of estimates and enables the study of rare exposures and outcomes with long-term latency, 2) Inclusion of nearly all individuals in the target population ensures that the data reflect routine clinical care and all clinical segments of the source population, 3) Data are collected independently of each research study, thus minimising certain types of bias, e.g., non-response, and the influence from attention to the research question on the diagnostic process. Before the source data is sent to us, the Danish Health Data Authority runs and does comprehensive checks of the registry table data validity of the variables, breaks in data, changes in variable coding, missingness, etc. We perform checks of missingness/completeness in relation to requested variables. In essence, we are receiving a dump of a mirror of the data that is controlled by the SDS. The documentation performed by SDS is available online, in Danish primarily https://www.esundhed.dk/Dokumentation (all variables), but also in English https://sundhedsdatastyrelsen.dk/da/english/health_data_and_registers/national_health_registers
10	Linkage	There is no linkage in this data source.
11	Vital status	The Cause of Death registry (DAR) is used, the cause of death is collected using ICD-10 codes.
12	Limitations	DK-DHR has the following limitations, which may be relevant confounders for certain complex Darwin EU studies: - We lack information on key socio-economic status (SES) factors, such as occupation, education, and income. These variables may be important for analysis in some studies. - We only have complete data on lifestyle factors (such as smoking status and weight) for pregnant women. - We have no information on patient contacts in primary care (visits to the GP). Consequently, the incidence of chronic diseases like Type 2 Diabetes (T2D) and asthma must be determined using drug prescriptions as a proxy. Stillborn children will not have any records in our CDM. This means that e.g., birth length of stillborns is not recorded.
13	Main references	Schmidt M, Schmidt SAJ,Adelborg K,Sundbøll J,Laugesen K,Ehrenstein V,Sørensen HT "The Danish health care system and epidemiological research: from health care contacts to database records." Clinical epidemiology (2019): 31372058
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111217 Website: https://sundhedsdatastyrelsen.dk/da/english/health_data_and_registers/healthdatadenmark

Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED)

#	Section	Description
1	Data source identification and country	HI-SPEED (Health Impact - Swedish Population Evidence Enabling Data-linkage) Sweden
2	Data partner information section	SMPA-GU, Läkemedelsverket, Box 26, 751 03 Uppsala, Sweden - Box 469, 405 30 Gothenburg, Sweden Pharmacoepidemiology and Analysis Department (FeA) - School of Public Health and Community Medicine, Institute of Medicine
3	Coverage and timespan	Data collection since: 2015 Extent: Nation-wide.

#	Section	Description
		The catchment area includes the whole of Sweden, covering the full population of approximately 11.7 million.
4	Healthcare setting / type of data	Primary care – General Practioner, and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. Primary care (GPs) is available only for the 2 largest regions (~40% of national population) The following data elements are collected: Socio-demographics, dispensed drug prescriptions, cause of death, diagnoses and procedures from secondary (specialist) care and inpatient visits or clinical events, as well as from primary care visits (40%pop only).
5	Data collection process	Registries. The data is acquired from the relevant Swedish national and regional registries, only once all legislative, GDPR and ethical approvals have been granted. Therefore only relevant data is passed on, which will then be entered and processed by the study team. The data are updated several times annually.
6	General representativeness	The coverage includes all patients of all sociodemographic characteristics. Therefore it should mirror the source population to a very good extent.
7	Data content /source coding	Medicines are coded with ATC and NPLID (National Product ID), ICD10-SE is used for diagnoses and the Swedish procedure coding system (KVA) is used for clinical procedures.
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. No.
9	Quality control (data source specific)	The source data are obtained from the relevant Swedish National and Regional Registers. The registers perform some regular quality controls on their data. After receiving the data, we perform additional checks and cleaning. We also run regular quality checks on the data we manage.
10	Linkage	Data on specialist care is acquired from the National Patient Register, mortality information is provided by the Cause-Of-Death Registry. Drug data is provided by the Patient Drug Register. And similarly for other registers. Data are linked very accurately using the national personal ID number, and pseudonymized before delivery to HI-SPEED. All data are updated 2-4 times per year.
11	Vital status	Data on death and underlying + contributing causes-of-death are extracted from the Cause-of-Death registry (i.e., based on death certificates).
12	Limitations	General limitations for the data type applicable. This is a research project where all studies require ethics approval. Data collection since: 2015 for most data, except prescribed drug register (from 2018), and some COVID-related data (tests, vaccination) from 2020 Primary care is only available for a subset.
13	Main references	Nyberg F, Franzén S,Lindh M,Vanfleteren L,Hammar N,Wettermark B,Sundström J,Santosa A,Björck S,Gisslén M "Swedish Covid-19 Investigation for Future Insights - A Population Epidemiology Approach Using Register Linkage (SCIFI-PEARL)." Clinical epidemiology (2021): 34354377
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/node/4463/ Website: https://www.gu.se/en/research/scifi-pearl

IQVIA Disease Analyzer Germany (IQVIA DA Germany)

#	Section	Description
1	Data source identification and country	IQVIA DA Germany (IQVIA Disease Analyzer Germany) Germany
2	Data partner information section	IQVIA
3	Coverage and timespan	Data collection since: 1989 Extent: Nation-wide. GP and specialists in Germany using specific patient management software.
4	Healthcare setting / type of data	Primary care – General Practitioner, and primary care specialists (e.g., paediatricians). Diagnoses, medication, and procedures from an ambulatory setting. Medications are recorded as prescriptions of marketed products.
5	Data collection process	Outpatient electronic health records. By clinicians at healthcare contact.
6	General representativeness	No specific details on general representativeness given.
7	Data content /source coding	Prescription is on product code level (German PZN), ICD10, NFC, Local lab coding.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. There can be patients registered under different ID numbers, because there is no linkage between different GPs.
9	Quality control (data source specific)	Data is quality checked on plausibility.
10	Linkage	No.
11	Vital status	Death information is derived from medical events.
12	Limitations	No database-specific limitations documented. General limitations for the data type applicable.
13	Main references	No main reference provided.
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/104282 Website: https://www.iqvia.com/

Semmelweis University Clinical Data (SUCD)

#	Section	Description
1	Data source identification and country	SUCD (Semmelweis University Clinical Data) Budapest, Hungary
2	Data partner information section	Semmelweis University -
3	Coverage and timespan	Data collection since: 2010 Extent: Regional. The general catchment area of SU is the central region of the country, Budapest city and Pest county, although patients can be referred from anywhere in Hungary. The total population of Budapest and Pest county is approximately 4,200,000 people. The total population of Hungary is around 9,500,000.

#	Section	Description
4	Healthcare setting / type of data	Secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care, and claims data, and other (specify). diagnostic data (laboratory tests, radiology, pathology)
5	Data collection process	Insurance/administrative claims, and Outpatient electronic health records, and Inpatient hospital electronic health records, and Inpatient hospital billing systems, and Registries. Data is extracted directly from the source database. From there, the data entry in the system is heavily controlled and validated on the user interface before being made available for further research.
6	General representativeness	SU captures information on patients who are covered by the public health insurance system. This covers all Hungarian citizens, and therefore the database should mirror the source population well. Although, besides Semmelweis University Clinics, there are multiple hospitals in the region, and data on visits in other hospitals in not represented in the database. Therefore, the patient population is not directly representative of the general population.
7	Data content /source coding	Regarding SU's source data, procedures and diagnoses are coded in SNOMED, measurements are coded in LOINC, and drugs are stored in RxNorm and ATC.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Patients have a unique identifier (SSN).
9	Quality control (data source specific)	The clinical database is the source database and therefore it has to be treated as a trusted database. Data entry in the systems is heavily controlled by validation on the user interface, and there are large number of rules that controls the data on the insurer's side that has to be corrected in the system by the users to be able to close the encounters. OMOP mapping is done in the framework by EHDEN recognized partners under quality check by the EHDEN society.
10	Linkage	No known linkages.
11	Vital status	Source for vital status unknown.
12	Limitations	Medication prescribed in secondary care is fully present in our database, but medication given in the hospital is rarely documented. General limitations for the data type applicable. General practitioner data is not present in our database; therefore, this part of the patient journey is not represented.
13	Main references	No main reference provided.
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1000000184 Website: https://www.semmelweis.hu

ANNEX II. Fitness for use assessment

Data source justification for inclusion and key characteristics

Croatian National Public Health Information System (NAJS)

NAJS will be included in this study because it is a national population-based health registries data source covering primary care and secondary care data that provides relevant information on the use of intramuscular depot olanzapine injection in the general population.

Based on a preliminary feasibility assessment, the expected number of person counts for intramuscular depot olanzapine injection in NAJS will be 4,000.

Moreover, data availability and follow-up in NAJS is sufficient, as data availability starts in 2014, and the date of most recent data extraction is 06/2025, which aligns with the study period. The median follow-up of the first observation period in NAJS is 10.5 years.

There are no study specific limitations present in NAJS.

Lastly, NAJS is applying for blanket approval with estimated approval time to be in 03/2026, which makes the execution of this study feasible within the current study timelines.

Danish Data Health Registries (DK-DHR)

DK-DHR will be included in this study because it is a national population-based health registries data source covering hospital and secondary care specialists' data that provides relevant information on the use of intramuscular depot olanzapine injection in the general population.

Based on a preliminary feasibility assessment, the expected number of person counts for intramuscular depot olanzapine injection in DK-DHR will be 1,500.

Moreover, data availability and follow-up in DK-DHR is sufficient, as data availability starts in 1995, and the date of most recent data extraction is 10/2024. The data source expects to provide data update with records from 2025 in 02/2026, which aligns with the study period. The median follow-up of the first observation period in DK-DHR is 21.7 years.

There are no study specific limitations present in DK-DHR.

Lastly, DK-DHR has blanket approval, which makes the execution of this study feasible within the current study timelines.

Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED)

HI-SPEED will be included in this study because it is a national population-based health registries data source covering primary care and secondary care data that provides relevant information on the use of intramuscular depot olanzapine injection in the general population.

Based on a preliminary feasibility assessment, the expected number of person counts for intramuscular depot olanzapine injection in HI-SPEED will be 3,200.

Moreover, data availability and follow-up in HI-SPEED is sufficient, as drug data availability starts in 2018, and the date of most recent data extraction is 08/2025, which aligns with the study period. The median follow-up of the first observation period in HI-SPEED is 10.7 years.

There are some study specific limitations present in HI-SPEED, namely: drug records will be given as dispensed drug prescriptions, and therefore, inpatient administration of intramuscular depot olanzapine will not be captured in the data source, leading to underestimation of intramuscular depot olanzapine use in HI-SPEED. To avoid misinterpretation of incidence of drug use in HI-SPEED, the data source will not

contribute to the objective 1 of the study. Drug data is only available since 2018 in HI-SPEED. To allow adequate drug data history in HI-SPEED, the study period will start from 01/2019 in the data source.

Lastly, IRB approval for HI-SPEED is estimated to take 5 weeks, which makes the execution of this study feasible within the current study timelines.

IQVIA Disease Analyzer Germany (IQVIA DA Germany)

IQVIA DA Germany will be included in this study because it is a national primary care (general practitioners and specialists) data source that provides relevant information on the use of intramuscular depot olanzapine injection in the general population.

Based on a preliminary feasibility assessment, the expected number of person counts for intramuscular depot olanzapine injection in IQVIA DA Germany will be 1,200.

Moreover, data availability and follow-up in IQVIA DA Germany is sufficient, as data availability starts in 1992, and the date of most recent data extraction is 06/2025, which aligns with the study period. The median follow-up of the first observation period in IQVIA DA Germany is 121 days.

There are some study specific limitations present in IQVIA DA Germany, namely: observation period of individuals is defined by visit, leading to decreasing denominator and thus increasing incidence rate towards the end of observation period. Extra care is needed to define observation period in this data source.

Lastly, IQVIA DA Germany does not require IRB approval, which makes the execution of this study feasible within the current study timelines.

Semmelweis University Clinical Data (SUCD)

SUCD will be included in this study because it is a regional hospital data source that provides relevant information on the use of intramuscular depot olanzapine injection in the general population.

Based on a preliminary feasibility assessment, the expected number of person counts for intramuscular depot olanzapine injection in SUCD will be 1,200.

Moreover, data availability and follow-up in SUCD is sufficient, as data availability starts in 2008, and the date of most recent data extraction is 03/2025, which aligns with the study period. The median follow-up of the first observation period in SUCD is 243 days.

There are some study specific limitations present in SUCD, namely: observation period of individuals defined by hospital visit, leading to decreasing denominator and thus increasing incidence rate towards the end of observation period. Extra care is needed to define observation period in this data source.

Lastly, IRB approval for SUCD is estimated to take 2 months, which makes the execution of this study feasible within the current study timelines.

Table S1. Fitness-for-use assessment of data sources.

Design elements	Operational definition	Data elements for valid capture	Criticality of the quality of the element, including justification where relevant	Suggested extensiveness assessment	Suggested assessment of other quality dimensions	Suggested substantiation by documentation
Study population	General population (objective 1)	N/A	N/A			
Treatment/ exposure	Intramuscular depot olanzapine (objectives 2–4)	Prescription or dispensation records of intramuscular depot olanzapine	High	Setting of data source should cover primary care specialist or hospital outpatient care to ensure adequate number of records of intramuscular depot olanzapine. Based on a preliminary feasibility assessment, the expected number of persons counts for intramuscular depot olanzapine preparation in the data sources included in this study range from 1,200 (IQVIA DA Germany) to 4,000 (NAJS).	N/A	N/A
Outcomes (if relevant)	Intramuscular depot olanzapine (objective 1)	Prescription or dispensation records of intramuscular depot olanzapine	High	Setting of data source should cover primary care specialist or hospital outpatient care to ensure adequate number of records of intramuscular depot olanzapine. Based on a preliminary feasibility assessment, the expected number of	N/A	N/A

Design elements	Operational definition	Data elements for valid capture	Criticality of the quality of the element, including justification where relevant	Suggested extensiveness assessment	Suggested assessment of other quality dimensions	Suggested substantiation by documentation
				persons counts for intramuscular depot olanzapine preparation in the data sources included in this study range from 1,200 (IQVIA DA Germany) to 4,000 (NAJS).		
	Initial dose and maintenance dose of intramuscular depot olanzapine (objective 2)	Prescription or dispensation records of intramuscular depot olanzapine	High	Dose information depends highly on the granularity of drug records in each data source. Further assessment should be deemed as part of this study objective.	N/A	N/A
	Intramuscular depot olanzapine discontinuation (objective 3)	Prescription or dispensation records of intramuscular depot olanzapine	High	Discontinuation of intramuscular depot olanzapine will be detected by end of treatment era. However, this would highly depend on how the drug records are in each data source, e.g., one injection with exposure duration of 1 day would yield different result of one injection with exposure duration of 14 days. Further assessment should be deemed as	N/A	N/A

Design elements	Operational definition	Data elements for valid capture	Criticality of the quality of the element, including justification where relevant	Suggested extensiveness assessment	Suggested assessment of other quality dimensions	Suggested substantiation by documentation
				part of this study objective.		
	Switching pattern after intramuscular depot olanzapine discontinuation (objective 4)	Prescription or dispensation records of oral olanzapine or other antipsychotics (oral or intramuscular)	High	Detection of switching pattern would be done after discontinuation of intramuscular depot olanzapine, which is as mentioned above. Further assessment should be deemed as part of this study objective.	N/A	N/A

IQVIA DA Germany = IQVIA Disease Analyzer Germany; N/A = not applicable; NAJS = Croatian National Public Health Information System.

EMA Data Quality Framework for EU medicines regulation: application to Real-World Data for more information (https://www.ema.europa.eu/system/files/documents/other/data-quality-framework-eu-medicines-regulation-application-real-world-data_en.pdf).

ANNEX III. Operational and reporting considerations

DATA MANAGEMENT

Data management

All data sources have previously mapped their data to the Observational Medical Outcomes Partnership (OMOP) common data model (CDM). This enables the use of standardised analytics and using DARWIN EU® tools across the network, since the structure of the data and the terminology system is harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org.

The analytic code for this study will be written in R and will use standardized analytics wherever possible. Each data partner will execute the study code against their data source containing patient-level data and then return the results (csv files), which will only contain aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

Data storage and protection

For this study, individuals from various EU member states will process personal data from individuals that is collected in national/regional electronic health record data sources. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All data sources used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results.

The output files are stored in the DARWIN EU® Digital Research Environment (DRE). These output files do not contain any data that allow identification of individuals included in the study. The DRE implements further security measures to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

QUALITY CONTROL

Data source quality control

When defining drug cohorts, non-systemic products will be excluded from the list of included codes summarised on the ingredient level.

When defining cohorts for conditions, a systematic search of possible codes for inclusion will be identified using the *CodelistGenerator* R package (https://github.com/darwin-eu/CodelistGenerator).[8] This package allows the user to define a search strategy and will use this to query the vocabulary tables of the OMOP CDM so as to find potentially relevant codes. In addition, the *PhenotypeR* (https://github.com/OHDSI/phenotypeR)[9] and *DrugExposureDiagnostics* (https://cran.r-project.org/web/packages/DrugExposureDiagnostics/index.html)[6] R packages will be run, if needed, to assess the use of different codes across the data sources contributing to the study and identify any codes potentially omitted in error. The *DrugExposureDiagnostics* package evaluates ingredient-specific attributes and patterns in drug exposure records.

The study code will be based on DARWIN EU® R packages: *IncidencePrevalence*[3] to estimate incidence and prevalence, *PatientProfiles*[4] to characterise the initial and maintenance dose cohort, and *CohortCharacteristics*[5] to characterise the switching pattern. These packages will include numerous

automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package will be made publicly available via GitHub.

PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A PDF report including an executive summary, and the specified tables and/or figures will be submitted to EMA by the DARWIN EU® CC upon completion of the study.

An interactive dashboard incorporating all the results (tables and figures) will be provided alongside the PDF report. The full set of underlying aggregated data used in the dashboard will also be made available, if requested.

ANNEX IV. List of concept definitions

Table S2. Preliminary list of concept ID for intramuscular depot olanzapine preparation.

Concept ID	Concept Name	Dose group	Counts in included data source
1971931	olanzapine 300 MG Injectable Solution [Zypadhera] by Medicopharm	dose_300	No
21023337	olanzapine 300 MG Injection [Zypadhera] Box of 1 by Lilly	dose_300	No
21043023	olanzapine 210 MG Injection Box of 1	dose_210	No
21072541	olanzapine 210 MG Injection [Zypadhera] Box of 1 by Lilly	dose_210	No
21082236	olanzapine 300 MG Injection Box of 1	dose_300	No
21101882	olanzapine 300 MG Injection [Zypadhera] by Lilly	dose_300	No
21121386	olanzapine 405 MG Injection [Zypadhera] Box of 1	dose_405	No
21121391	olanzapine 210 MG Injection [Zypadhera]	dose_210	No
21131150	olanzapine 405 MG Injection Box of 1	dose_405	No
21141122	olanzapine 210 MG Injection [Zypadhera] Box of 1	dose_210	No
21150948	olanzapine 210 MG Injection [Zypadhera] by Lilly	dose_210	No
21150949	olanzapine 300 MG Injection [Zypadhera] Box of 1	dose_300	No
21170653	olanzapine 405 MG Injection [Zypadhera]	dose_405	No
21170654	olanzapine 405 MG Injection [Zypadhera] by Lilly	dose_405	No
21170655	olanzapine 405 MG Injection [Zypadhera] Box of 1 by Lilly	dose_405	No
21170664	olanzapine 300 MG Injection [Zypadhera]	dose_300	No
35603051	olanzapine 405 MG Injection	dose_405	No
35603054	olanzapine 405 MG Injection [Zyprexa]	dose_405	No
35603056	olanzapine 300 MG Injection	dose_300	No
35603058	olanzapine 300 MG Injection [Zyprexa]	dose_300	No
35603132	olanzapine 210 MG Injection	dose_210	No
35603134	olanzapine 210 MG Injection [Zyprexa]	dose_210	No
35744074	olanzapine 300 MG Injectable Solution [Zypadhera] by Lilly	dose_300	No
35748305	olanzapine 405 MG Injectable Solution [Zypadhera] by Lilly	dose_405	No
35752437	olanzapine 405 MG Injectable Suspension [Zypadhera] by Lilly	dose_405	No
35769121	olanzapine 405 MG Injectable Solution [Zypadhera] Box of 1 by Lilly	dose_405	Yes
35773480	olanzapine 210 MG Injectable Solution [Zypadhera] by Lilly	dose_210	No
36036476	olanzapine 405 MG Injectable Solution [Zypadhera] by Aca Mueller	dose_405	No
36260125	olanzapine 100 MG/ML Injectable Solution [Zypadhera]	dose_300	No
36262693	olanzapine 70 MG/ML Injectable Solution [Zypadhera]	dose_210	No
36264739	olanzapine 135 MG/ML Injectable Solution	dose_405	No
36269830	olanzapine 70 MG/ML Injectable Solution	dose_210	No
36270369	olanzapine 135 MG/ML Injectable Solution [Zypadhera]	dose_405	No
36274919	olanzapine 100 MG/ML Injectable Solution	dose_300	No

Concept ID	Concept Name	Dose group	Counts in included data source
36278432	3 ML olanzapine 70 MG/ML Injectable Solution [Zypadhera]	dose_210	No
36278458	3 ML olanzapine 135 MG/ML Injectable Solution	dose_405	No
36278463	3 ML olanzapine 100 MG/ML Injectable Solution [Zypadhera]	dose_300	No
36278503	3 ML olanzapine 70 MG/ML Injectable Solution	dose_210	No
36278557	3 ML olanzapine 100 MG/ML Injectable Solution [Zypadhera] by Eli Lilly	dose_300	No
36278589	3 ML olanzapine 135 MG/ML Injectable Solution [Zypadhera]	dose_405	No
36278599	3 ML olanzapine 70 MG/ML Injectable Solution [Zypadhera] by Eli Lilly	dose_210	No
36278602	3 ML olanzapine 135 MG/ML Injectable Solution [Zypadhera] by Eli Lilly	dose_405	No
36278607	3 ML olanzapine 100 MG/ML Injectable Solution	dose_300	No
36781100	3 ML olanzapine 70 MG/ML Injectable Suspension [Zypadhera] Box of 1 by Eli Lilly	dose_210	No
36781101	3 ML olanzapine 100 MG/ML Injectable Suspension [Zypadhera] Box of 1 by Eli Lilly	dose_300	No
36781102	3 ML olanzapine 135 MG/ML Injectable Suspension [Zypadhera] Box of 1 by Eli Lilly	dose_405	No
37592333	olanzapine 405 MG Injectable Solution [Zypadhera] by Fd	dose_405	Yes
40748332	olanzapine 300 MG Injectable Suspension [Zypadhera] Box of 1 by Eli Lilly	dose_300	No
40748333	olanzapine 300 MG Injectable Suspension [Zypadhera] by Eli Lilly	dose_300	No
40748334	olanzapine 300 MG Injectable Solution [Zypadhera] Box of 1 by Eli Lilly	dose_300	No
40748335	olanzapine 300 MG Injectable Solution [Zypadhera] by Eli Lilly	dose_300	No
40748450	olanzapine 210 MG Injectable Suspension [Zypadhera] Box of 1 by Eli Lilly	dose_210	No
40748451	olanzapine 210 MG Injectable Suspension [Zypadhera] by Eli Lilly	dose_210	No
40748452	olanzapine 210 MG Injectable Solution [Zypadhera] Box of 1 by Eli Lilly	dose_210	No
40748453	olanzapine 210 MG Injectable Solution [Zypadhera] by Eli Lilly	dose_210	No
40748466	olanzapine 405 MG Injectable Suspension [Zypadhera] Box of 1 by Eli Lilly	dose_405	No
40748467	olanzapine 405 MG Injectable Suspension [Zypadhera] by Eli Lilly	dose_405	No
40748468	olanzapine 405 MG Injectable Solution [Zypadhera] Box of 1 by Eli Lilly	dose_405	No
40748469	olanzapine 405 MG Injectable Solution [Zypadhera] by Eli Lilly	dose_405	No
40853150	olanzapine 405 MG Injectable Solution [Zypadhera] Box of 1 by Eurim-Pharm	dose_405	No
40866064	olanzapine 300 MG Injectable Solution	dose_300	No
40866065	olanzapine 405 MG Injectable Suspension	dose_405	Yes
40873746	olanzapine 300 MG Injectable Solution [Zypadhera] Box of 1	dose_300	Yes

Concept ID	Concept Name	Dose group	Counts in included data source
40915310	olanzapine 300 MG Injectable Solution [Zypadhera] Box of 1 by Lilly	dose_300	Yes
40915327	olanzapine 210 MG Injectable Solution [Zypadhera] Box of 1 by Europharma	dose_210	No
40946655	olanzapine 300 MG Injectable Suspension [Zypadhera] Box of 1 by Eurim-Pharm	dose_300	No
40946667	olanzapine 405 MG Injectable Suspension [Zypadhera] Box of 1 by Abacus Medicine	dose_405	No
40967106	olanzapine 405 MG Injectable Solution [Zypadhera]	dose_405	No
40977665	olanzapine 300 MG Injectable Suspension [Zypadhera] Box of 1 by Kohlpharma	dose_300	No
40977678	olanzapine 210 MG Injectable Suspension [Zypadhera] Box of 1 by Beragena	dose_210	No
41009020	olanzapine 405 MG Injectable Suspension [Zypadhera] Box of 1 by Lilly	dose_405	No
41009021	olanzapine 405 MG Injectable Suspension [Zypadhera] Box of 1 by Cc	dose_405	No
41021755	olanzapine 405 MG Injectable Solution	dose_405	No
41029488	olanzapine 300 MG Injectable Solution [Zypadhera]	dose_300	Yes
41029507	olanzapine 405 MG Injectable Suspension [Zypadhera]	dose_405	Yes
41052997	olanzapine 300 MG Injectable Solution Box of 1	dose_300	Yes
41060645	olanzapine 405 MG Injectable Suspension [Zypadhera] Box of 1	dose_405	Yes
41071404	olanzapine 300 MG Injectable Solution [Zypadhera] Box of 1 by Gerke	dose_300	No
41084564	olanzapine 300 MG Injectable Suspension Box of 1	dose_300	No
41084566	olanzapine 405 MG Injectable Solution Box of 1	dose_405	Yes
41102812	olanzapine 300 MG Injectable Suspension [Zypadhera] Box of 1 by Lilly	dose_300	No
41102825	olanzapine 405 MG Injectable Solution [Zypadhera] Box of 1 by Kohlpharma	dose_405	No
41115818	olanzapine 300 MG Injectable Suspension	dose_300	Yes
41134191	olanzapine 405 MG Injectable Suspension [Zypadhera] Box of 1 by Veron	dose_405	No
41147337	olanzapine 210 MG Injectable Suspension	dose_210	Yes
41147338	olanzapine 210 MG Injectable Solution	dose_210	No
41147339	olanzapine 405 MG Injectable Suspension Box of 1	dose_405	No
41154912	olanzapine 210 MG Injectable Suspension [Zypadhera] Box of 1	dose_210	Yes
41178344	olanzapine 210 MG Injectable Suspension Box of 1	dose_210	No
41178345	olanzapine 210 MG Injectable Solution Box of 1	dose_210	Yes
41185965	olanzapine 210 MG Injectable Suspension [Zypadhera]	dose_210	No
41196861	olanzapine 210 MG Injectable Suspension [Zypadhera] Box of 1 by Lilly	dose_210	Yes

Concept ID	Concept Name	Dose group	Counts in included data source
41196862	olanzapine 210 MG Injectable Suspension [Zypadhera] Box of 1 by Gerke	dose_210	No
41196863	olanzapine 210 MG Injectable Suspension [Zypadhera] Box of 1 by Eurim-Pharm	dose_210	No
41227895	olanzapine 300 MG Injectable Suspension [Zypadhera] Box of 1 by Europharma	dose_300	No
41227896	olanzapine 300 MG Injectable Solution [Zypadhera] Box of 1 by Emra-Med	dose_300	No
41248303	olanzapine 300 MG Injectable Suspension [Zypadhera] Box of 1	dose_300	No
41248320	olanzapine 210 MG Injectable Solution [Zypadhera]	dose_210	No
41279106	olanzapine 210 MG Injectable Solution [Zypadhera] Box of 1	dose_210	No
41279107	olanzapine 405 MG Injectable Solution [Zypadhera] Box of 1	dose_405	No
41289828	olanzapine 210 MG Injectable Suspension [Zypadhera] Box of 1 by Cc	dose_210	No
41310383	olanzapine 300 MG Injectable Suspension [Zypadhera]	dose_300	No
41321142	olanzapine 210 MG Injectable Solution [Zypadhera] Box of 1 by Lilly	dose_210	No
41321143	olanzapine 405 MG Injectable Suspension [Zypadhera] Box of 1 by Gerke	dose_405	No
43039774	3 ML olanzapine 70 MG/ML Injectable Suspension [Zypadhera] by Eli Lilly	dose_210	No
43039775	3 ML olanzapine 135 MG/ML Injectable Suspension [Zypadhera] by Eli Lilly	dose_405	No
43039776	3 ML olanzapine 100 MG/ML Injectable Suspension [Zypadhera] by Eli Lilly	dose_300	No
43134152	olanzapine 100 MG/ML Injectable Suspension Box of 1	dose_300	No
43141630	3 ML olanzapine 135 MG/ML Injectable Suspension Box of 1	dose_405	No
43141631	3 ML olanzapine 70 MG/ML Injectable Suspension Box of 1	dose_210	No
43141632	3 ML olanzapine 70 MG/ML Injectable Suspension [Zypadhera] Box of 1	dose_210	No
43152739	3 ML olanzapine 100 MG/ML Injectable Suspension Box of 1	dose_300	No
43156260	olanzapine 135 MG/ML Injectable Suspension Box of 1	dose_405	No
43156261	olanzapine 135 MG/ML Injectable Suspension [Zypadhera] Box of 1	dose_405	No
43156267	olanzapine 100 MG/ML Injectable Suspension [Zypadhera] Box of 1	dose_300	No
43156268	olanzapine 70 MG/ML Injectable Suspension [Zypadhera]	dose_210	No
43163831	3 ML olanzapine 135 MG/ML Injectable Suspension [Zypadhera] Box of 1	dose_405	No
43163832	3 ML olanzapine 100 MG/ML Injectable Suspension	dose_300	No
43174828	3 ML olanzapine 135 MG/ML Injectable Suspension	dose_405	No
43174829	3 ML olanzapine 135 MG/ML Injectable Suspension [Zypadhera]	dose_405	No
43174830	3 ML olanzapine 100 MG/ML Injectable Suspension [Zypadhera] Box of 1	dose_300	No

Concept ID	Concept Name	Dose group	Counts in included data source
43178281	olanzapine 100 MG/ML Injectable Suspension [Zypadhera]	dose_300	No
43178282	olanzapine 70 MG/ML Injectable Suspension Box of 1	dose_210	No
43178283	olanzapine 70 MG/ML Injectable Suspension [Zypadhera] Box of 1	dose_210	No
43185702	3 ML olanzapine 70 MG/ML Injectable Suspension [Zypadhera]	dose_210	No
43189194	olanzapine 135 MG/ML Injectable Suspension	dose_405	No
43189195	olanzapine 135 MG/ML Injectable Suspension [Zypadhera]	dose_405	No
43196667	3 ML olanzapine 100 MG/ML Injectable Suspension [Zypadhera]	dose_300	No
43196668	3 ML olanzapine 100 MG/ML Injectable Suspension [Zypadhera] Box of 1 by Lilly	dose_300	No
43207599	3 ML olanzapine 70 MG/ML Injectable Suspension [Zypadhera] Box of 1 by Lilly	dose_210	No
43211028	olanzapine 100 MG/ML Injectable Suspension	dose_300	No
43211029	olanzapine 70 MG/ML Injectable Suspension	dose_210	No
43218602	3 ML olanzapine 135 MG/ML Injectable Suspension [Zypadhera] Box of 1 by Lilly	dose_405	No
43218603	3 ML olanzapine 70 MG/ML Injectable Suspension	dose_210	No
44159692	olanzapine 210 MG Injectable Solution [Zypadhera] Box of 1 by Eurim-Pharm	dose_210	No
44159693	olanzapine 210 MG Injectable Solution [Zypadhera] Box of 1 by Beragena	dose_210	Yes
44167240	olanzapine 300 MG Injectable Solution [Zypadhera] Box of 1 by Eurim-Pharm	dose_300	No
44167241	olanzapine 300 MG Injectable Suspension [Zypadhera] Box of 1 by Emra-Med	dose_300	No
44167242	olanzapine 210 MG Injectable Suspension [Zypadhera] Box of 1 by Kohlpharma	dose_210	No
44170977	olanzapine 405 MG Injectable Solution [Zypadhera] Box of 1 by Veron	dose_405	No
44174721	olanzapine 210 MG Injectable Solution [Zypadhera] Box of 1 by Gerke	dose_210	No
44174722	olanzapine 405 MG Injectable Suspension [Zypadhera] Box of 1 by Kohlpharma	dose_405	Yes
44178486	olanzapine 210 MG Injectable Solution [Zypadhera] Box of 1 by Kohlpharma	dose_210	No
44178487	olanzapine 405 MG Injectable Suspension [Zypadhera] Box of 1 by Abacus Medicine	dose_405	No
44178488	olanzapine 405 MG Injectable Solution [Zypadhera] Box of 1 by Abacus Medicine	dose_405	No
44178489	olanzapine 405 MG Injectable Solution [Zypadhera] Box of 1 by Cc	dose_405	No
44178490	olanzapine 405 MG Injectable Solution [Zypadhera] Box of 1 by Gerke	dose_405	No
44182193	olanzapine 300 MG Injectable Solution [Zypadhera] Box of 1 by Kohlpharma	dose_300	Yes
44182195	olanzapine 210 MG Injectable Solution [Zypadhera] Box of 1 by Cc	dose_210	No

Concept ID	Concept Name	Dose group	Counts in included data source
44185958	olanzapine 300 MG Injectable Suspension [Zypadhera] Box of 1 by Gerke	dose_300	No
44185959	olanzapine 300 MG Injectable Solution [Zypadhera] Box of 1 by Europharma	dose_300	No
44185960	olanzapine 210 MG Injectable Suspension [Zypadhera] Box of 1 by Europharma	dose_210	No
44185961	olanzapine 405 MG Injectable Suspension [Zypadhera] Box of 1 by Eurim-Pharm	dose_405	No

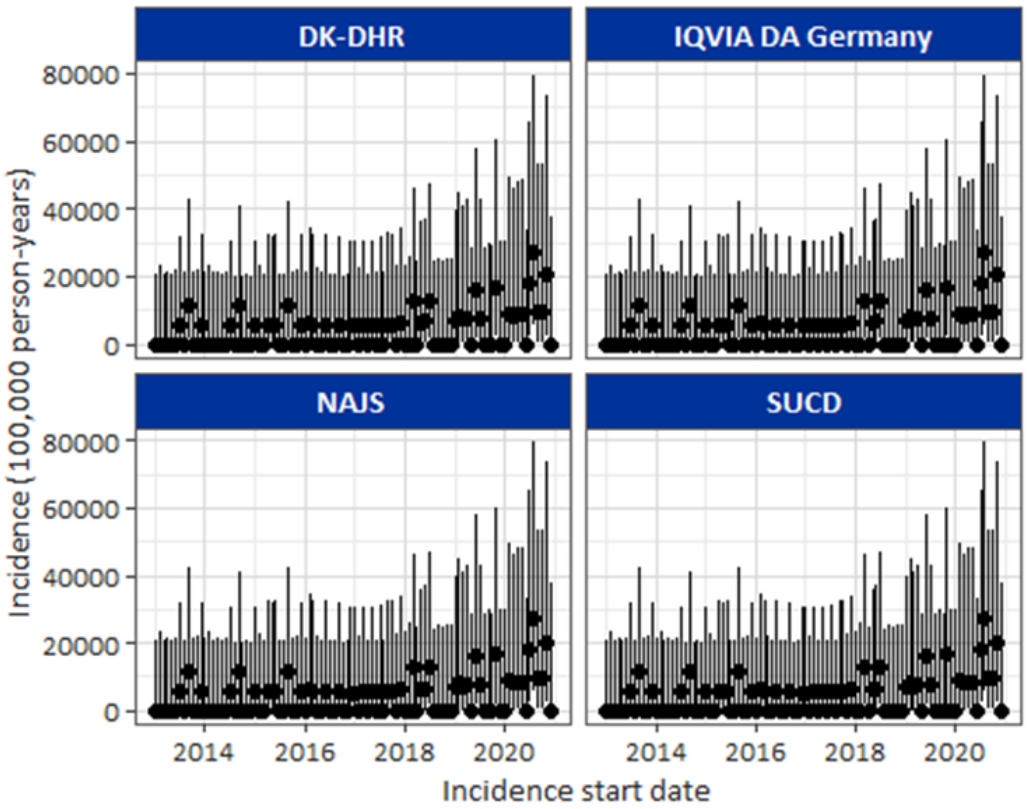
Table S3. Preliminary list of medicines definitions.

Substance Name	ATC code	Ingredient Concept ID	Concept name	Class	Include descendants	Counts in included data source
Olanzapine	N05AH03	785788	olanzapine	atypical	Yes	Yes
Antipsychotics[a]	N05A	19018226	acepromazine	typical	Yes	Yes
		19029555	acetophenazine	typical	Yes	Yes
		19057607	amisulpride	atypical	Yes	Yes
		757688	aripiprazole	atypical	Yes	Yes
		40164052	asenapine	atypical	Yes	Yes
		19016440	benperidol	typical	Yes	Yes
		46275300	brexpiprazole	atypical	Yes	Yes
		19039227	bromperidol	typical	Yes	Yes
		40798666	Butaperazine	typical	Yes	No
		35603277	cariprazine	atypical	Yes	Yes
		19122262	chlorproethazine	typical	Yes	No
		794852	chlorpromazine	typical	Yes	Yes
		19095002	chlorprothixene	typical	Yes	Yes
		19100363	clothiapine	atypical	Yes	No
		800878	clozapine	atypical	Yes	Yes
		19051234	cyamemazine	typical	Yes	No
		40798772	Dixyrazine	typical	Yes	Yes
		739323	droperidol	typical	Yes	Yes
		40798823	Fluanisone	typical	Yes	Yes
		19055982	flupenthixol	typical	Yes	Yes
		756018	fluphenazine	typical	Yes	Yes
		19056465	fluspirilene	typical	Yes	Yes
		766529	haloperidol	typical	Yes	Yes
		19017241	iloperidone	atypical	Yes	No
		43009023	levosulpiride	atypical	Yes	No
		792263	loxapine	typical	Yes	Yes
		37498659	lumateperone	atypical	Yes	No
		40230761	lurasidone	atypical	Yes	Yes
		703083	mesoridazine	typical	Yes	No
		19005147	methotrimeprazine	typical	Yes	Yes
		19072088	metylperon	atypical	Yes	Yes
		709699	molindone	typical	Yes	No
		40798964	Moperone	typical	Yes	No

Substance Name	ATC code	Ingredient Concept ID	Concept name	Class	Include descendants	Counts in included data source
		35198101	mosapramine hydrochloride	atypical	Yes	No
		19025922	oxypertine	typical	Yes	No
		703244	paliperidone	atypical	Yes	Yes
		19028044	penfluridol	typical	Yes	Yes
		19131663	perazine	typical	Yes	Yes
		19053565	periciazine	typical	Yes	Yes
		733008	perphenazine	typical	Yes	Yes
		42628962	pimavanserin	atypical	Yes	No
		745790	pimozide	typical	Yes	Yes
		19093225	pipamperone	typical	Yes	Yes
		19133992	pipothiazine	typical	Yes	Yes
		752061	prochlorperazine	typical	Yes	Yes
		19052903	promazine	typical	Yes	Yes
		19115044	prothipendyl	typical	Yes	Yes
		766814	quetiapine	atypical	Yes	Yes
		19035226	remoxipride	atypical	Yes	Yes
		735979	risperidone	atypical	Yes	Yes
		19050633	sertindole	atypical	Yes	Yes
		19136626	sulpiride	typical	Yes	Yes
		19100431	sultopride	atypical	Yes	No
		19041817	thiopropazate	typical	Yes	No
		19000305	thioproperazine	typical	Yes	No
		700299	thioridazine	typical	Yes	Yes
		700465	thiothixene	typical	Yes	Yes
		19008012	tiapride	atypical	Yes	Yes
		704984	trifluoperazine	typical	Yes	Yes
		19005101	trifluperidol	typical	Yes	Yes
		19005104	triflupromazine	typical	Yes	Yes
		19043327	veralipride	atypical	Yes	No
		712615	ziprasidone	atypical	Yes	Yes
		19102109	zotepine	atypical	Yes	Yes
		19010886	zuclopenthixol	typical	Yes	Yes

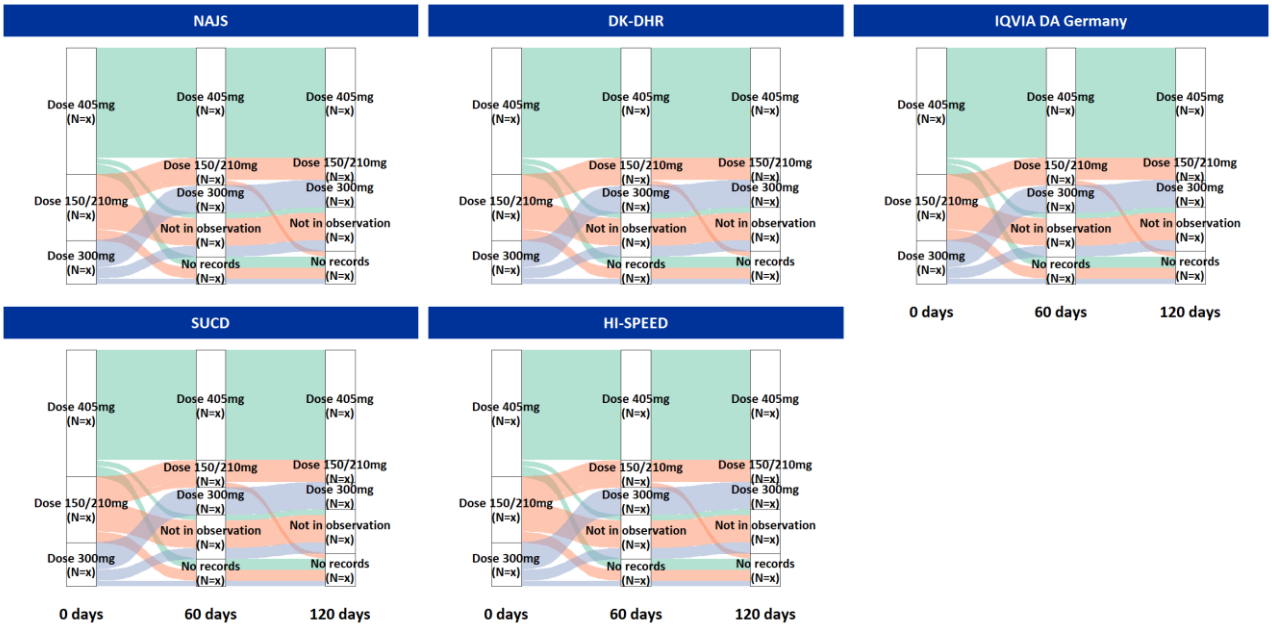
The list of antipsychotics ingredient is identified based on ATC code and does not include olanzapine and lithium.

ANNEX V. Mock tables and figures



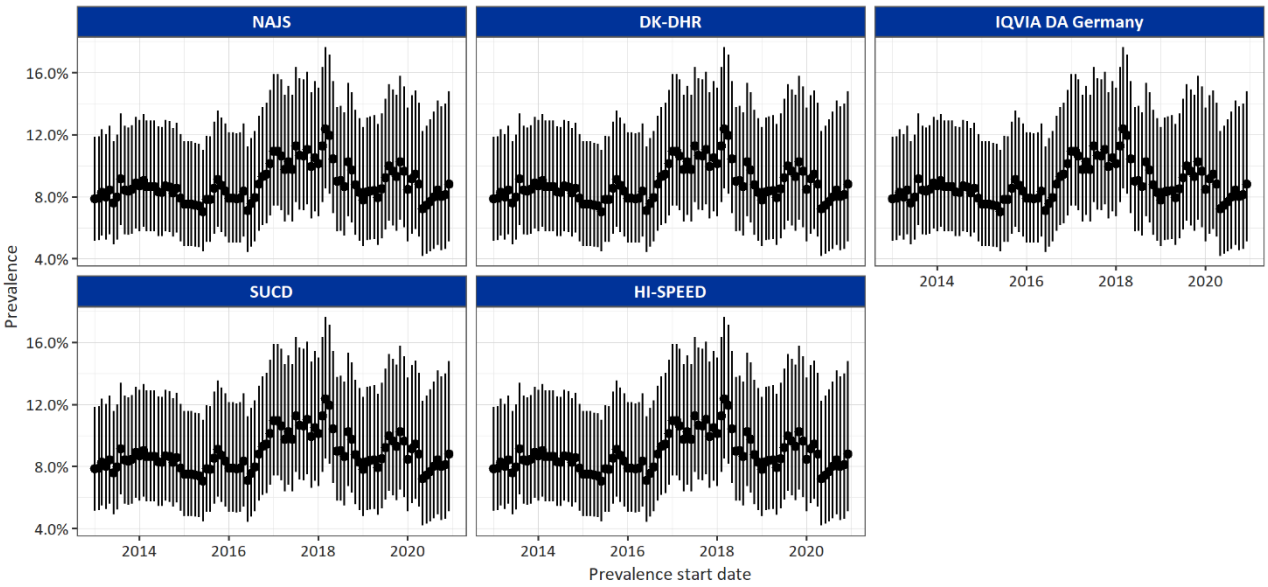
Mock Figure 1. Monthly incidence of intramuscular depot olanzapine (objective 1).

Remarks: Incidence in the mock figure is shown from 2013 to 2021 due to the constraint from mock data. Study period will be updated to 2018–2025 in the actual figure.
DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; NAJS = Croatian National Public Health Information System; SUCD = Semmelweis University Clinical Data.



Mock Figure 2. Sankey plot on maintenance dose of intramuscular depot olanzapine (objective 2).

DK-DHR = Danish Data Health Registries; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; IQVIA DA Germany = IQVIA Disease Analyzer Germany; NAJS = Croatian National Public Health Information System; SUCD = Semmelweis University Clinical Data.



Mock Figure 3. Monthly prevalence of intramuscular depot olanzapine discontinuation (objective 3).

Remarks: Prevalence in the mock figure is shown from 2013 to 2021 due to the constraint from mock data. Study period will be updated to 2018–2025 in the actual figure.
DK-DHR = Danish Data Health Registries; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; IQVIA DA Germany = IQVIA Disease Analyzer Germany; NAJS = Croatian National Public Health Information System; SUCD = Semmelweis University Clinical Data.

Mock Table 1. Initial dose of intramuscular depot olanzapine (objective 2).

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
Number records	–	N					
Number individuals	–	N					
Age	–	Median [Q25–Q75]					
		Mean (SD)					
Age group	0 to 17	N (%)					
	18 to 64	N (%)					
	65 or above	N (%)					
Sex	Female	N (%)					
	Male	N (%)					
Initial dose	Dose 150/210mg	N (%)					
	Dose 300mg	N (%)					
	Dose 405mg	N (%)					

DK-DHR = Danish Data Health Registries; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; IQVIA DA Germany = IQVIA Disease Analyzer Germany; NAJS = Croatian National Public Health Information System; SUCD = Semmelweis University Clinical Data.

Mock Table 2. Maintenance dose of intramuscular depot olanzapine (objective 2).

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
Initial dose: 150/210mg							
Number records	–	N					
Number individuals	–	N					
Age	–	Median [Q25–Q75]					
		Mean (SD)					
Age group	0 to 17	N (%)					
	18 to 64	N (%)					
	65 or above	N (%)					
Sex	Female	N (%)					
	Male	N (%)					
Time: 60 days	Dose 150/210mg	N (%)					
	Dose 300mg	N (%)					
	Dose 405mg	N (%)					
	Multiple	N (%)					
	No records	N (%)					
	Not in observation	N (%)					
Time: 120 days	Dose 150/210mg	N (%)					

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
	Dose 300mg	N (%)					
	Dose 405mg	N (%)					
	Multiple	N (%)					
	No records	N (%)					
	Not in observation	N (%)					
Initial dose: 300mg							
Number records	–	N					
Number individuals	–	N					
Age	–	Median [Q25–Q75]					
		Mean (SD)					
Age group	0 to 17	N (%)					
	18 to 64	N (%)					
	65 or above	N (%)					
Sex	Female	N (%)					
	Male	N (%)					
Time: 60 days	Dose 150/210mg	N (%)					
	Dose 300mg	N (%)					
	Dose 405mg	N (%)					
	Multiple	N (%)					
	No records	N (%)					
	Not in observation	N (%)					
Time: 120 days	Dose 150/210mg	N (%)					
	Dose 300mg	N (%)					
	Dose 405mg	N (%)					
	Multiple	N (%)					
	No records	N (%)					
	Not in observation	N (%)					
Initial dose: 405mg							
Number records	–	N					
Number individuals	–	N					
Age	–	Median [Q25–Q75]					
		Mean (SD)					
Age group	0 to 17	N (%)					
	18 to 64	N (%)					
	65 or above	N (%)					

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
Sex	Female	N (%)					
	Male	N (%)					
Time: 60 days	Dose 150/210mg	N (%)					
	Dose 300mg	N (%)					
	Dose 405mg	N (%)					
	Multiple	N (%)					
	No records	N (%)					
	Not in observation	N (%)					
Time: 120 days	Dose 150/210mg	N (%)					
	Dose 300mg	N (%)					
	Dose 405mg	N (%)					
	Multiple	N (%)					
	No records	N (%)					
	Not in observation	N (%)					

DK-DHR = Danish Data Health Registries; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; IQVIA DA Germany = IQVIA Disease Analyzer Germany; NAJS = Croatian National Public Health Information System; SUCD = Semmelweis University Clinical Data.

Mock Table 3. Switching pattern after intramuscular depot olanzapine discontinuation, overall (objective 4).

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
Number records	–	N					
Number individuals	–	N					
Age	–	Median [Q25–Q75]					
		Mean (SD)					
Age group	0 to 17	N (%)					
	18 to 64	N (%)					
	65 or above	N (%)					
Sex	Female	N (%)					
	Male	N (%)					
Switching pattern	No treatment	N (%)					
	Oral olanzapine	N (%)					
	Injectable non-depot olanzapine	N (%)					

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
	Oral AP	N (%)					
	Injectable non-depot AP	N (%)					
	Depot AP	N (%)					
	Oral typical AP 1	N (%)					
	Oral typical AP 2	N (%)					
	Oral typical AP 3	N (%)					
	Oral atypical AP 1	N (%)					
	Oral atypical AP 2	N (%)					
	Oral atypical AP 3	N (%)					
	Injectable non-depot typical AP 1	N (%)					
	Injectable non-depot typical AP 2	N (%)					
	Injectable non-depot typical AP 3	N (%)					
	Injectable non-depot atypical AP 1	N (%)					
	Injectable non-depot atypical AP 2	N (%)					
	Injectable non-depot atypical AP 3	N (%)					
	Depot typical AP 1	N (%)					
	Depot typical AP 2	N (%)					
	Depot typical AP 3	N (%)					
	Depot atypical AP 1	N (%)					
	Depot atypical AP 2	N (%)					

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
	Depot atypical AP 3	N (%)					

AP = antipsychotics; DK-DHR = Danish Data Health Registries; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; IQVIA DA Germany = IQVIA Disease Analyzer Germany; NAJS = Croatian National Public Health Information System; SUCD = Semmelweis University Clinical Data.

Mock Table 4. Switching pattern after intramuscular depot olanzapine discontinuation, stratified by age group (objective 4).

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
Age group: 0 to 17							
Number records	–	N					
Number individuals	–	N					
Age	–	Median [Q25–Q75]					
		Mean (SD)					
Sex	Female	N (%)					
	Male	N (%)					
Switching pattern	No treatment	N (%)					
	Oral olanzapine	N (%)					
	Injectable non-depot olanzapine	N (%)					
	Oral AP	N (%)					
	Injectable non-depot AP	N (%)					
	Depot AP	N (%)					
	Oral typical AP 1	N (%)					
	Oral typical AP 2	N (%)					
	Oral typical AP 3	N (%)					
	Oral atypical AP 1	N (%)					
	Oral atypical AP 2	N (%)					

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
	Oral atypical AP 3	N (%)					
	Injectable non-depot typical AP 1	N (%)					
	Injectable non-depot typical AP 2	N (%)					
	Injectable non-depot typical AP 3	N (%)					
	Injectable non-depot atypical AP 1	N (%)					
	Injectable non-depot atypical AP 2	N (%)					
	Injectable non-depot atypical AP 3	N (%)					
	Depot typical AP 1	N (%)					
	Depot typical AP 2	N (%)					
	Depot typical AP 3	N (%)					
	Depot atypical AP 1	N (%)					
	Depot atypical AP 2	N (%)					
	Depot atypical AP 3	N (%)					
Age group: 18 to 64							
Number records	–	N					
Number individuals	–	N					
Age	–	Median [Q25–Q75]					
		Mean (SD)					
Sex	Female	N (%)					
	Male	N (%)					
Switching pattern	No treatment	N (%)					

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
	Oral olanzapine	N (%)					
	Injectable non-depot olanzapine	N (%)					
	Oral AP	N (%)					
	Injectable non-depot AP	N (%)					
	Depot AP	N (%)					
	Oral typical AP 1	N (%)					
	Oral typical AP 2	N (%)					
	Oral typical AP 3	N (%)					
	Oral atypical AP 1	N (%)					
	Oral atypical AP 2	N (%)					
	Oral atypical AP 3	N (%)					
	Injectable non-depot typical AP 1	N (%)					
	Injectable non-depot typical AP 2	N (%)					
	Injectable non-depot typical AP 3	N (%)					
	Injectable non-depot atypical AP 1	N (%)					
	Injectable non-depot atypical AP 2	N (%)					
	Injectable non-depot atypical AP 3	N (%)					
	Depot typical AP 1	N (%)					
	Depot typical AP 2	N (%)					

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
	Depot typical AP 3	N (%)					
	Depot atypical AP 1	N (%)					
	Depot atypical AP 2	N (%)					
	Depot atypical AP 3	N (%)					
Age group: 65 or above							
Number records	–	N					
Number individuals	–	N					
Age	–	Median [Q25–Q75]					
		Mean (SD)					
Sex	Female	N (%)					
	Male	N (%)					
Switching pattern	No treatment	N (%)					
	Oral olanzapine	N (%)					
	Injectable non-depot olanzapine	N (%)					
	Oral AP	N (%)					
	Injectable non-depot AP	N (%)					
	Depot AP	N (%)					
	Oral typical AP 1	N (%)					
	Oral typical AP 2	N (%)					
	Oral typical AP 3	N (%)					
	Oral atypical AP 1	N (%)					
	Oral atypical AP 2	N (%)					
	Oral atypical AP 3	N (%)					

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
	Injectable non-depot typical AP 1	N (%)					
	Injectable non-depot typical AP 2	N (%)					
	Injectable non-depot typical AP 3	N (%)					
	Injectable non-depot atypical AP 1	N (%)					
	Injectable non-depot atypical AP 2	N (%)					
	Injectable non-depot atypical AP 3	N (%)					
	Depot typical AP 1	N (%)					
	Depot typical AP 2	N (%)					
	Depot typical AP 3	N (%)					
	Depot atypical AP 1	N (%)					
	Depot atypical AP 2	N (%)					
	Depot atypical AP 3	N (%)					

AP = antipsychotics; DK-DHR = Danish Data Health Registries; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; IQVIA DA Germany = IQVIA Disease Analyzer Germany; NAJS = Croatian National Public Health Information System; SUCD = Semmelweis University Clinical Data.

Mock Table 5. Switching pattern after intramuscular depot olanzapine discontinuation, stratified by sex (objective 4).

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
Sex: Female							
Number records	–	N					
Number individuals	–	N					

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
Age	–	Median [Q25–Q75]					
		Mean (SD)					
Age group	0 to 17	N (%)					
	18 to 64	N (%)					
	65 or above	N (%)					
Switching pattern	No treatment	N (%)					
	Oral olanzapine	N (%)					
	Injectable non-depot olanzapine	N (%)					
	Oral AP	N (%)					
	Injectable non-depot AP	N (%)					
	Depot AP	N (%)					
	Oral typical AP 1	N (%)					
	Oral typical AP 2	N (%)					
	Oral typical AP 3	N (%)					
	Oral atypical AP 1	N (%)					
	Oral atypical AP 2	N (%)					
	Oral atypical AP 3	N (%)					
	Injectable non-depot typical AP 1	N (%)					
	Injectable non-depot typical AP 2	N (%)					
	Injectable non-depot typical AP 3	N (%)					
	Injectable non-depot atypical AP 1	N (%)					
	Injectable non-depot atypical AP 2	N (%)					

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
	Injectable non-depot atypical AP 3	N (%)					
	Depot typical AP 1	N (%)					
	Depot typical AP 2	N (%)					
	Depot typical AP 3	N (%)					
	Depot atypical AP 1	N (%)					
	Depot atypical AP 2	N (%)					
	Depot atypical AP 3	N (%)					
Sex: Male							
Number records	–	N					
Number individuals	–	N					
Age	–	Median [Q25–Q75]					
		Mean (SD)					
Age group	0 to 17	N (%)					
	18 to 64	N (%)					
	65 or above	N (%)					
Switching pattern	No treatment	N (%)					
	Oral olanzapine	N (%)					
	Injectable non-depot olanzapine	N (%)					
	Oral AP	N (%)					
	Injectable non-depot AP	N (%)					
	Depot AP	N (%)					
	Oral typical AP 1	N (%)					
	Oral typical AP 2	N (%)					
	Oral typical AP 3	N (%)					
	Oral atypical AP 1	N (%)					

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
	Oral atypical AP 2	N (%)					
	Oral atypical AP 3	N (%)					
	Injectable non-depot typical AP 1	N (%)					
	Injectable non-depot typical AP 2	N (%)					
	Injectable non-depot typical AP 3	N (%)					
	Injectable non-depot atypical AP 1	N (%)					
	Injectable non-depot atypical AP 2	N (%)					
	Injectable non-depot atypical AP 3	N (%)					
	Depot typical AP 1	N (%)					
	Depot typical AP 2	N (%)					
	Depot typical AP 3	N (%)					
	Depot atypical AP 1	N (%)					
	Depot atypical AP 2	N (%)					
	Depot atypical AP 3	N (%)					

AP = antipsychotics; DK-DHR = Danish Data Health Registries; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; IQVIA DA Germany = IQVIA Disease Analyzer Germany; NAJS = Croatian National Public Health Information System; SUCD = Semmelweis University Clinical Data.

ANNEX VI. ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 4)

Study title: DARWIN EU® - Drug utilisation study of intramuscular depot olanzapine

EU PAS Register® number: EUPAS1000000980
Study reference number (if applicable): P4-C1-026

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☐	
1.1.4 Interim report(s)	☐	☐	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	6, 7
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)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

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 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary, or combined data collection?	☒	☐	☐	8.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.6, 8.8
3.4	Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	8.5
	4.2.2 Age and sex	☒	☐	☐	8.3
	4.2.3 Country of origin	☒	☐	☐	8.4
	4.2.4 Disease/indication	☐	☐	☒	
	4.2.5 Duration of follow-up	☐	☐	☒	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	8.3

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.6.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.4 Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	8.6.2
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.6.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.6.2
6.3 Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	Annex I, II
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	Annex I, II
9.1.3 Covariates and other characteristics?	☒	☐	☐	Annex I, II
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	Annex I, II
9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Annex I, II
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	Annex I, II
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Annex IV
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Annex IV
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.8
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	8.8
10.3 Are descriptive analyses included?	☒	☐	☐	8.8

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.4 Are stratified analyses included?	☒	☐	☐	8.8
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	8.8
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	Annex III
11.2 Are methods of quality assurance described?	☒	☐	☐	Annex III
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9
12.1.2 Information bias?	☒	☐	☐	9
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	Annex II

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	Annex II

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	Annex III

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	Annex III
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	Annex III

Comments:

Name of the main author of the protocol: Amy Lam

Date: 27/02/2026

Signature: A. Lam

ANNEX VII. Glossary

Additional definitions are available in the EMA Glossary of terms https://www.ema.europa.eu/en/about-us/glossaries.

Aggregated Data

Data collected and combined from multiple sources to generate summary information, typically anonymised.

Benefit-Risk Assessment

Evaluation of the positive therapeutic effects of a medicine compared to its risks (e.g., side effects).

Common Data Model (CDM)

A standardized data structure that enables data from multiple sources to be harmonized, making analysis consistent and reproducible. DARWIN EU® utilises the OMOP CDM maintained by the OHDSI community.

Complex Studies (C3)

Studies requiring the development or customisation of specific study designs, protocols, and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data. Examples include etiological studies measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome in a defined population considering sources of bias, potential confounding factors, and effect modifiers.

Coordination Centre (CC)

The central hub responsible for managing and overseeing the activities within DARWIN EU®. It is based at Erasmus University Medical Centre in Rotterdam, the Netherlands.

Data Access

The process of obtaining permission to use specific datasets for regulatory or scientific studies.

Data Quality Framework

A set of standards and procedures to ensure accuracy, completeness, timeliness, and consistency of data used in DARWIN EU®.

Data Source

A data source or repository of structured health-related data, such as electronic health records (EHRs), insurance claims, or registries.

DARWIN EU®

The European Medicines Agency's (EMA) federated network of real-world data sources designed to generate evidence to support regulatory decision-making.

EMA (European Medicines Agency)

The regulatory body responsible for the evaluation and supervision of medicinal products in the EU, overseeing DARWIN EU®.

Evidence Generation

The process of analysing real-world data to produce scientific information that can inform healthcare or regulatory decisions.

Federated Network

A data infrastructure where data remain at their original location but can be analysed in a harmonised way across multiple partners using a common model and tools.

GDPR (General Data Protection Regulation)

The EU regulation governing the protection of personal data and privacy, crucial to how DARWIN EU® handles health data.

Health Technology Assessment (HTA)

A systematic evaluation of properties and impacts of health technology, often using DARWIN EU® data to support assessments.

Metadata

Descriptive information about a data source (e.g., its content, quality, and structure), essential for identifying relevant data sources in DARWIN EU® studies.

Off-the-Shelf Studies (OTS)

Studies for which a standard protocol per study/analysis type and standardised analytics may be developed and applied or adapted, typically relating to a descriptive research question. This includes studies on disease epidemiology, for example, the estimation of the prevalence or incidence of health outcomes in defined time periods and population groups, or drug utilisation studies at the population or patient level.

OHDSI (Observational Health Data Sciences and Informatics)

An open-science collaborative community that develops tools and standards (including the OMOP CDM) to enable large-scale analytics of observational health data. OHDSI provides the technical and scientific foundation for DARWIN EU®'s analytical ecosystem.

Patient-Level Data

Data related to individuals, de-identified, used for longitudinal or detailed analyses.

OMOP (Observational Medical Outcomes Partnership)

A common data model (CDM) that standardises the structure and content of observational healthcare data, enabling systematic analysis across disparate datasets. DARWIN EU® uses the OMOP CDM to ensure interoperability and consistency in real-world evidence generation.

Real-World Data (RWD)

Data relating to individual health status or healthcare delivery that is collected from routine clinical practice rather than from randomised controlled trials.

Real-World Evidence (RWE)

Clinical evidence derived from the analysis of RWD, used to inform decisions by regulators, payers, or clinicians.

Regulatory Decision-Making

The process by which authorities like EMA assess data to authorise, monitor, or modify the use of medicines in the EU.

Routine Repeated Studies (RR)

Studies that are either Off-the-Shelf or Complex studies repeated on a regular basis, following the same protocol and study code, but with updated data and/or different data partners.

Study Protocol

A detailed plan describing how a specific real-world study will be conducted, including objectives, design, data sources, and analyses.

Very Complex Studies (C4)

Studies which cannot rely only on electronic health care data sources, or which would require complex methodological work, for example, due to the occurrence of events that cannot be defined by existing diagnosis codes, including events that do not yet have a diagnosis code, where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations. These studies might require the collection of data prospectively, or the inclusion of new (not previously onboarded) data sources.