Study Report

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DARWIN EU® - Drug utilisation study of intramuscular depot olanzapine

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LIST OF ABBREVIATIONS

Acronyms/terms	Description
AP	Antipsychotic
CI	Confidence interval
CIPH	Croatian Institute of Public Health
CDM	Common Data Model
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DDD	Defined Daily Dose
DK-DHR	Danish Data Health Registries
DKMA	Danish Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EU/EEA	European Union and European Economic Area
EUPAS	EU Post-Authorisation Studies Register
HI-SPEED	Health Impact - Swedish Population Evidence Enabling Data-linkage
IM	Intramuscular
IQR	Interquartile Range
IQVIA DA Germany	IQVIA Disease Analyzer Germany
N/A	Not Applicable
NAJS	Croatian National Public Health Information System
OMOP	Observational Medical Outcomes Partnership
PYs	Person-years
SD	Standard Deviation
SMPA-GU	Swedish Medical Products Agency - Gothenburg University
SU	Semmelweis University
SUCD	Semmelweis University Clinical Data
WHO	World Health Organization

1. ABSTRACT

Rationale

A prolonged shortage of intramuscular (IM) depot olanzapine across the European Union and European Economic Area (EU/EEA) since 2024 may have affected treatment use and led to discontinuation or switching to alternative antipsychotic (AP) treatments. Given the limited Real-World Evidence on these treatment patterns, this study aimed to characterise IM depot olanzapine use, discontinuation, and subsequent AP treatment.

Objectives

The aim of this study was to characterise IM depot olanzapine use and treatment patterns during 2018–2025 by (1) estimating the incidence of use, (2) describing initial and maintenance doses, (3) estimating the prevalence of discontinuation, and (4) describing subsequent switching to other AP treatments.

Methods

A cohort study was conducted using routinely collected healthcare data from five DARWIN EU® Data Sources in Croatia (Croatian National Public Health Information System (NAJS)), Denmark (Danish Data Health Registries (DK-DHR)), Germany (IQVIA Disease Analyzer Germany (IQVIA DA Germany)), Hungary (Semmelweis University Clinical Data (SUCD)), and Sweden (Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED)), comprising registry and electronic health record data from primary and/or secondary care settings mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). NAJS, DK-DHR, IQVIA DA Germany, and SUCD contributed to all objectives, while HI-SPEED only contributed to objectives 2–4. The study period covered 2018–2025, with HI-SPEED contributing from 2019 onwards. IM depot olanzapine use was identified from prescription or dispensation records, with sequential records concatenated into treatment eras using a 42-day gap. New use was defined as no IM depot olanzapine exposure during the prior 365 days, while discontinuation was defined as the end of a new-user treatment era with at least 42 days of subsequent observation. Incidence of new use was estimated per 100,000 person-years (PYs), and the prevalence of discontinuation was estimated as the proportion of new users who discontinued treatment during the respective periods; both were estimated monthly and, because of low counts, additionally quarterly, annually, and over the entire study period. Initial dose was assessed at treatment initiation, and maintenance dose was characterised at day 60 and day 120. AP treatment initiated within 60 days after IM depot olanzapine discontinuation was characterised by ingredient, formulation (oral/injectable non-depot/depot), and class (typical/atypical AP).

Results

Across the included data sources, between 59 (IQVIA DA Germany) and 1,534 (HI-SPEED) IM depot olanzapine users were identified. Low counts precluded interpretation of monthly incidence trends in DK-DHR, IQVIA DA Germany, and SUCD. In NAJS, monthly incidence of new IM depot olanzapine use ranged in 2019 between 4.64–9.61 per 100,000 PYs, and subsequently declined to 2.35–4.39 per 100,000 PYs in 2023, with no new users identified from September 2024 to July 2025. The 300 mg preparation was the most common initial dose in DK-DHR, IQVIA DA Germany, SUCD, and HI-SPEED, whereas the 405 mg preparation dominated in NAJS. Among those who remained on treatment, most individuals continued with their initial preparation at day 120; however, 32.26–67.59% of new use records starting with the 300 mg preparation and 31.33–56.25% of those starting with the 405 mg preparation had no IM depot olanzapine record at day 120. Monthly prevalence of discontinuation increased from July 2024 onwards in NAJS, and from 2025 in DK-DHR and HI-SPEED. Low counts precluded interpretation of trends in IQVIA DA Germany and SUCD. Most records of discontinuation were not followed by initiation of AP treatment other than IM depot olanzapine within 60 days (74.53–89.62%). An additional analysis was conducted to characterise overall AP use at the ingredient level, including treatment initiated within 60 days after IM depot olanzapine discontinuation, or initiated before discontinuation and continued afterwards. The proportions of records

without overall AP use decrease to 30.27–60.00%. Olanzapine (other than IM depot preparation) was the most commonly observed AP ingredient (25.00–49.57%).

Discussion

Observed IM depot olanzapine use was uncommon, with reduced initiation and increased discontinuation observed during 2024–2025 in three data sources. These changes in the trends coincided with the period of IM depot olanzapine shortage. However, the study is descriptive and was not designed to formally assess the impact of the shortage. A substantial proportion of records had no observed IM depot olanzapine use by day 120 after initiation. Among individuals who remained on treatment, most continued at their initial dose. Following discontinuation, initiation of AP treatment was uncommon. However, overall AP use was more frequent when treatment with another AP initiated before IM depot olanzapine discontinuation and continued thereafter was also considered, with olanzapine being the most commonly observed ingredient. Differences in drug exposure duration data quality and the granularity of drug records across data sources should be considered while interpreting the results in discontinuation and the subsequent treatment patterns.

Overall, the findings indicate changes in the temporal trends of IM depot olanzapine use and discontinuation coinciding with the shortage period.

2. RATIONALE AND BACKGROUND

Since 2024, there has been a critical and prolonged shortage of intramuscular (IM) 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, it was subsequently extended to mid-2026, as a result of manufacturing and supply-chain issues. This shortage affected all European Union and European Economic Area (EU/EEA) countries where Zypadhera is marketed.

The IM depot olanzapine is used for the maintenance treatment of schizophrenia in individuals stabilised on an initial course of oral olanzapine. The initial dose and maintenance dose of IM depot olanzapine are 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 olanzapine pamoate salt at the injection site, resulting in sustained olanzapine exposure that may persist for up to 6–8 months after injection.[2]

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

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

IM = intramuscular.

In the context of the ongoing shortage, individuals previously treated with IM depot olanzapine may need to discontinue treatment and switch to another antipsychotic (AP) medication. Treatment switching options could be either alternative long-acting IM AP or oral AP. The product information of IM depot olanzapine recommends close clinical supervision and monitoring, particularly during the first two months after discontinuation, when switching to another AP is considered appropriate.[2] However, there is a lack of Real-World Evidence specifically addressing switching patterns following discontinuation of IM depot olanzapine preparation.

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

3. OBJECTIVES

The aim of this study was to estimate the monthly incidence of IM depot olanzapine use and describe the switching patterns after discontinuation during the study period of 2018–2025.

The specific objectives of this study were:

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

4. RESEARCH METHOD

The detailed Study Protocol is available at EUPAS1000000980.

Study Design

The cohort study comprised drug utilisation studies at the population level to estimate incidence rates of IM depot olanzapine use among the general population (objective 1) and to estimate the prevalence of IM depot olanzapine discontinuation among individuals prescribed with IM depot olanzapine (objective 3); drug utilisation studies at the patient level described the initial and maintenance doses of IM depot olanzapine among the new users of IM depot olanzapine (objective 2), as well as treatment switching patterns among those who discontinued IM depot olanzapine (objective 4).

Follow-up

The study period was 01/01/2018–31/12/2025. The study population inclusion period was from 01/01/2018 up until 6 months before the end of the study period within each data source. For objective 1, follow-up started on the latest of either 01/01/2018, the date when at least 365 days of individuals' prior history was available, or 365 days after the end of IM depot olanzapine drug use (i.e. washout period). Follow-up ended on the earliest of loss to follow-up, death, end of the observation period (the latest available data), the study end date 31/12/2025, or the start of IM depot olanzapine. For objectives 2 and 3, follow-up started on the start date of the new IM depot olanzapine treatment era and ended on the earliest of loss to follow-up, death, end of the observation period, or the study end date. For objective 4, follow-up started on the end date of the IM depot olanzapine treatment era and ended on the earliest of loss to follow-up, death, end of the observation period, or the study end date; individuals were required to have at least 42 days of follow-up after discontinuation.

Population

For all objectives, individuals were required to have at least 365 days of prior history before the index date, with the study population inclusion period extending from 01/01/2018 to 6 months before the end of the study period within each data source. Individuals with missing age or sex information were excluded. For Objectives 2 and 3, new users of IM depot olanzapine were identified based on the start of a treatment era, with no IM depot olanzapine treatment era within the prior 365 days. For Objective 4, records of IM depot olanzapine discontinuation were identified based on the end of a new-user treatment era between 01/01/2018 and 31/12/2025 (or the latest available date), with at least 42 days of subsequent observation required after the end of the treatment era.

Definition of the Exposure and Main Study Variables

For all objectives, use of IM depot olanzapine was identified by prescription or dispensation records of IM depot olanzapine. Treatment episodes of sequential prescriptions (i.e. drug era) that had 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) were generated. A 42-day treatment gap was 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 for the same individual were permitted. New use of IM depot olanzapine was defined as no exposure to the IM depot olanzapine within 365 days prior to the start date of the treatment era (i.e. washout period).

For objectives 3 and 4, discontinuation of IM depot olanzapine was defined as the end of the new user treatment era, provided that the individual remained observable in the data source for at least 42 days after the end of the treatment era. To ensure no prescription/dispensation of IM depot olanzapine was recorded in the immediate time after the end of treatment, at least 42 days of available follow-up time/future observation were required for the definition of "discontinuation". The date of discontinuation was defined as the end date of the treatment era, without adding the 42-day observation period.

For objective 2, the maintenance dose of IM depot olanzapine use was assessed separately within each initial dose cohort (150/210 mg, 300 mg, and 405 mg). The maintenance dose was assessed on day 60 and day 120 after the start date of a new treatment era by characterising the new treatment era into these dose cohorts.

For objective 4, the outcomes were the initiation of oral olanzapine, injectable non-depot olanzapine, oral AP other than olanzapine, injectable non-depot AP other than olanzapine, and depot AP other than olanzapine within 1 to 60 days after discontinuation [1, 60]. AP use was described by formulation (oral, injectable non-depot, and depot), class (typical and atypical), and ingredient.

Statistical Analysis

Incidence rates of IM depot olanzapine (objective 1) were calculated as the number of new users of IM depot olanzapine after 365 days of no use per 100,000 person-years (PYs) of the population at risk of getting exposed for each calendar month. The incidence rate of IM depot olanzapine was also calculated for each quarter, each year, and over the entire study period, due to the low counts of users. Multiple records of new use were allowed, with individuals' contributions to time-at-risk paused during a defined washout period of 365 days. Incidence rates were given together with 95% exact Poisson confidence intervals (CI). Incidence was only estimated for those intervals where the data source captured the complete interval.

Prevalence of IM depot olanzapine discontinuation (objective 3) summarised the total number of individuals who discontinued IM depot olanzapine divided by the new user population during each calendar month, each quarter, each year, and over the entire study period. Therefore, period prevalence gave the proportion of individuals who discontinued the drug at any time during a specified interval. Binomial exact 95% CI were calculated. Prevalence was only estimated for those intervals where the data source captured the complete interval.

Dose cohorts of 150/210 mg, 300 mg, and 405 mg were created, based on the information available from the standardised drug codes (i.e. Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) drug concepts). The initial dose (objective 2) was characterised by the dose cohort on the index date [0, 0], which was the start date of the treatment era. Individuals appearing in more than one dose cohort on the index date were excluded. The initial dose was summarised as the number of new use records (N, %) in each dose cohort on the index date among the new users. The maintenance dose (objective 2) was characterised by the dose cohort on day 60 and day 120 after the start date of the new treatment era within each initial dose cohort. The "multiple" group was assigned if the new user appeared in more than one dose cohort on the same assessment date. Individuals who were out of observation or not classified into any dose cohort were categorised as "out of observation" or "no record", respectively. Within each initial dose cohort (150/210 mg, 300 mg, and 405 mg), maintenance dose was summarised on the assessment date as the number of new use records (N, %) in each category (150/210 mg, 300 mg, 405 mg, "multiple", "out of observation", or "no record").

Treatment switching identification (objective 4) was conducted to identify the most commonly prescribed/dispensed AP ingredients, by formulation (oral, injectable non-depot, and depot) and by class (typical and atypical), within the pre-specified time window of one day to 60 days after discontinuation of IM depot olanzapine [1, 60]. The primary analysis focused on AP treatment initiated within 60 days following IM depot olanzapine discontinuation. Analysis was conducted with full sets of all AP ingredients in each included data source to obtain the number of records (N, %) with AP treatment initiated during this period for each ingredient-formulation combination. Drug records of oral AP were concatenated into the same drug era using a 90-day treatment gap, and drug records of injectable AP were concatenated by a 42-day treatment gap. Findings of the three most commonly prescribed AP ingredients across all data sources, by class and by formulation, are reported in the main results.

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

Incidence of IM depot olanzapine use (objective 1) and prevalence of IM depot olanzapine discontinuation (objective 3) were estimated based on OMOP CDM mapped data using the R package *IncidencePrevalence*, developed by DARWIN EU®.[3] The initial dose and maintenance dose of IM depot olanzapine use (objective 2) were described using the R package *PatientProfiles*,[4] and switching patterns after discontinuation of IM depot olanzapine (objective 4) were described using the R package *CohortCharacteristics*,[5] both R packages having been developed by DARWIN EU®.

Sensitivity analyses were conducted for objectives 3 and 4. For objective 3, the study population was restricted to individuals with a treatment duration of less than two years to estimate the prevalence of discontinuation in a population excluding longer-term users and to assess the potential influence of longer-term treatment on discontinuation estimates. For objective 4, the assessment window for treatment switching after discontinuation was extended from days [1, 60] to days [-7, 60] relative to the end of the IM depot olanzapine treatment era.

Data Sources

This study used routinely collected healthcare data from five data sources within the DARWIN EU® Network, covering five EU member states: Croatian National Public Health Information System (NAJS) from Croatia, Danish Data Health Registries (DK-DHR) from Denmark, IQVIA Disease Analyzer Germany (IQVIA DA Germany) from Germany, Semmelweis University Clinical Data (SUCD) from Hungary, and Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED) from Sweden. These data sources comprise national or regional registries and electronic health records from primary and/or secondary care settings and were *a priori* mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM), enabling the application of a common analytical approach across data sources. Based on a preliminary feasibility assessment, the expected number of person-counts for IM depot olanzapine in the included data sources ranged from 1,200 (IQVIA DA Germany) to 4,000 (NAJS). NAJS, DK-DHR, IQVIA DA Germany, and SUCD contributed to all study objectives. HI-SPEED only contributed to objectives 2–4 but not objective 1, as records on inpatient administrations of IM depot olanzapine were not available in the data source, which could have resulted in underestimation of incidence. In addition, the study period in HI-SPEED began in January 2019, due to drug data only being available from 2018 onwards, as to provide sufficient prior drug history for new-user identification. Data availability and governance requirements across all participating data sources were considered compatible with the planned study period and study timelines.

Deviations from the Protocol

Several supplementary analyses were added during study implementation. For objectives 1 and 3, low counts were observed across data sources during the cohort diagnostic process after applying the study period restriction. Therefore, in addition to the prespecified analysis of the monthly incidence of IM depot olanzapine use (objective 1) and the monthly prevalence of IM depot olanzapine discontinuation (objective 3) in the study protocol, supplementary analyses were conducted at the quarterly and annual level and over the entire study period. For objective 4, the identification of AP treatment after IM depot olanzapine discontinuation relied on the granularity and completeness of drug records available within each data source. To reduce the potential for treatment records with insufficient granularity to be incorrectly interpreted as indicating no treatment after discontinuation, an additional sensitivity analysis was conducted at the ingredient level, irrespective of formulation, compared with the ingredient-formulation level used in the primary analysis. An additional analysis was conducted to characterise overall AP use within 60 days following IM depot olanzapine discontinuation, including AP treatment initiated during this period or initiated before discontinuation and continued into the assessment window. Overall AP use was assessed at both the ingredient-formulation level and at ingredient level.

5. RESULTS

The full set of results for this study is available through an interactive web-application Shiny app at EUPAS1000000980.

5.1. Participants

Across the full data source populations and before any inclusion criteria were applied, the study identified 2,553 IM depot olanzapine users in NAJS, 1,013 in DK-DHR, 131 in IQVIA DA Germany, 391 in SUCD, and 2,210 in HI-SPEED. After fulfilling the requirement of at least 365 days of prior observation before the first prescription/dispensation of IM depot olanzapine, applying the 365-day washout period of no IM depot olanzapine use, and restricting to the study period, 1,279 records from 1,167 individuals in NAJS, 369 records from 351 individuals in DK-DHR, 61 records from 59 individuals in IQVIA DA Germany, 163 records from 149 individuals in SUCD, and 1,602 records from 1,534 individuals in HI-SPEED were identified (**Table 2**).

Table 2. Number of individuals and records included in each objective.

Analysis	Requirement	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
Number of IM depot olanzapine users in the entire data source population	N/A	Number records	4,232	1,480	284	672	4,423
		Number individuals	2,553	1,013	131	391	2,210
Objective 1	At least 365 days of prior observation, 365-day washout period, restricted to the study period	Number records	1,279	369	61	163	1,602[a]
		Number individuals	1,167	351	59	149	1,534[a]
Objective 2	In addition to objective 1: No multiple dose preparation of IM depot olanzapine on the index date	Number records	1,273	364	60	163	1,592
		Number individuals	1,165	346	58	149	1,525
Objectives 3 and 4	In addition to objective 1: Discontinuation of IM depot olanzapine, defined by the end of the treatment era, provided that the individual remained observable in the data source for at least 42 days after the end of the treatment era	Number records	1,272	347	50	140	1,532
		Number individuals	1,160	330	49	128	1,466

DK-DHR = Danish Data Health Registries; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; IM = intramuscular; IQVIA DA Germany = IQVIA Disease Analyzer Germany; N/A = not applicable; NAJS = Croatian National Public Health Information System; SUCD = Semmelweis University Clinical Data.
[a] HI-SPEED did not contribute to objective 1 (analysis on incidence of IM depot olanzapine use). The number of records and individuals are presented to provide context on the overall numbers of IM depot olanzapine use identified during the study period.

5.2. Main results

Objective 1. Incidence of intramuscular depot olanzapine use

In the monthly incidence analysis (**Figure 1**), most results from IQVIA DA Germany and SUCD, and more than half of the results from DK-DHR, were either zero or suppressed because fewer than five new IM depot olanzapine users were identified.

Among the months with non-suppressed results in NAJS, the monthly incidence of IM depot olanzapine use ranged from 1.75 (95% CI 0.64–3.82) to 9.61 (95% CI 6.58–13.57) per 100,000 PYs. The highest monthly incidence in NAJS was observed in 2019, ranging from 4.64 (95% CI 2.65–7.54) to 9.61 (95% CI 6.58–13.57) per 100,000 PYs, followed by a decrease to 2.35 (95% CI 1.01–4.62)–4.39 (95% CI 2.46–7.24) per 100,000 PYs in 2023. No new users were identified in NAJS from September 2024 to July 2025. A small number of new users were subsequently observed from August 2025 onwards, with results suppressed because there were fewer than five new users per month.

To further assess temporal trends in the incidence of IM depot olanzapine use in DK-DHR, IQVIA DA Germany, and SUCD, incidence was additionally estimated quarterly and annually (**Figures 2–3**).

In DK-DHR, the quarterly incidence of IM depot olanzapine use remained relatively stable (**Figure 2**), from 0.79 (95% CI 0.39–1.40) to 1.27 (95% CI 0.75–2.00) per 100,000 PYs in 2018 to 0.69 (95% CI 0.33–1.27) to 0.90 (95% CI 0.48–1.54) per 100,000 PYs in 2024.

In SUCD, the annual number ranged from 3.72 (95% CI 2.39–5.54) to 4.58 (95% CI 3.04–6.61) per 100,000 PYs during 2019–2021 and decreased to 3.42 (95% CI 2.03–5.41) to 3.79 (95% CI 2.21–6.06) per 100,000 PYs during 2022–2025 (**Figure 3**). In IQVIA DA Germany, the total number of new IM depot olanzapine users was too low to allow for meaningful interpretation of temporal trends.

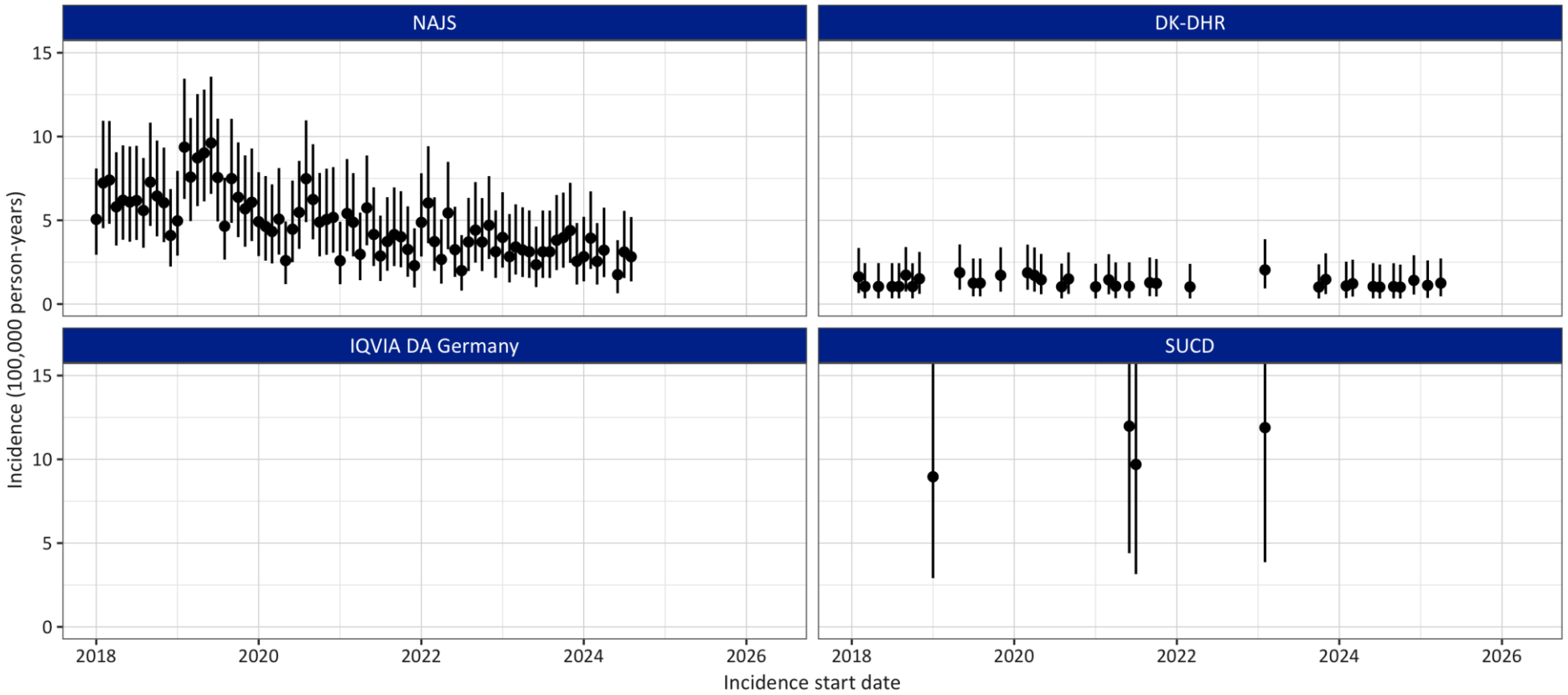


Figure 1. Monthly incidence of intramuscular depot olanzapine.

Low counts were suppressed. Suppressed and zero counts were not shown in the figure. No results were displayed for IQVIA DA Germany, as all counts were either suppressed or zero. Vertical bars represented 95% confidence intervals. 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.

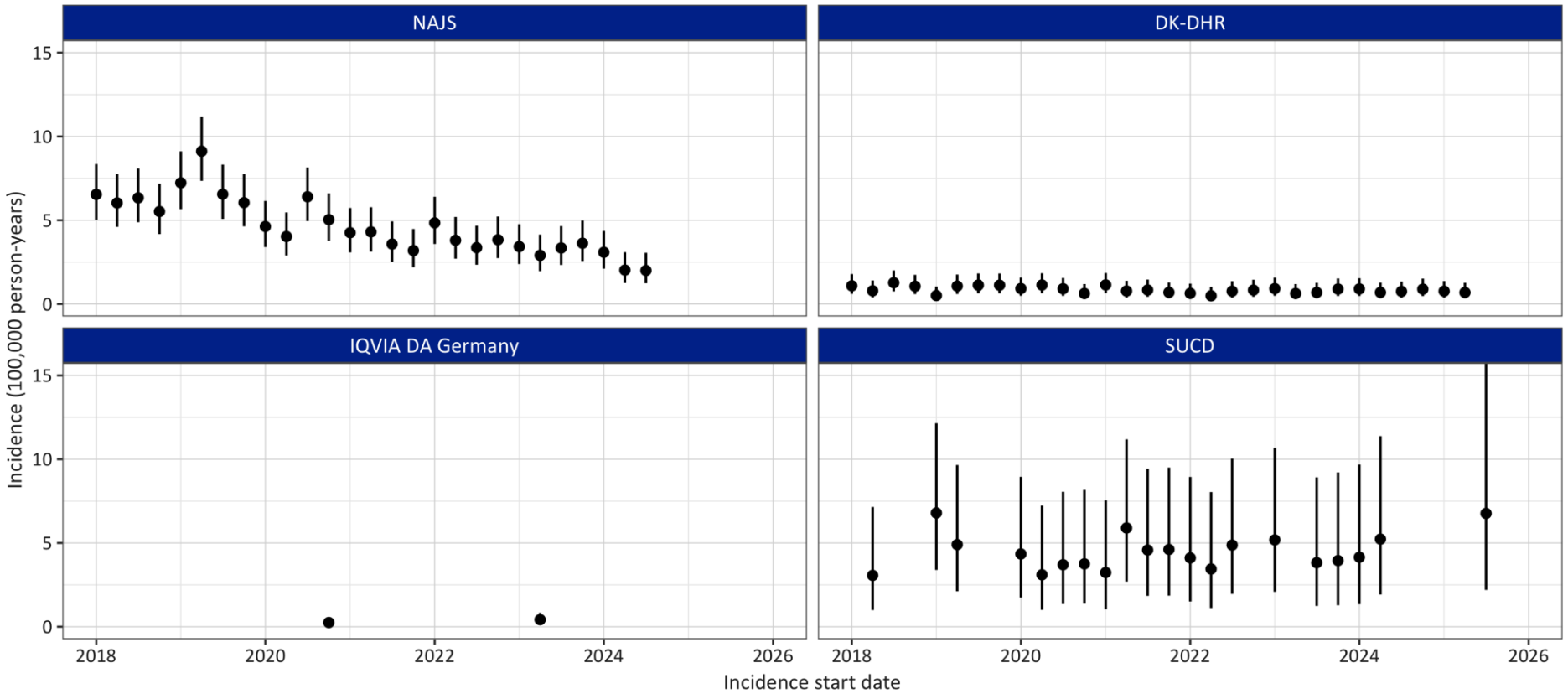


Figure 2. Quarterly incidence of intramuscular depot olanzapine.

Low counts were suppressed. Suppressed and zero counts were not shown in the figure. Vertical bars represented 95% confidence intervals. 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.

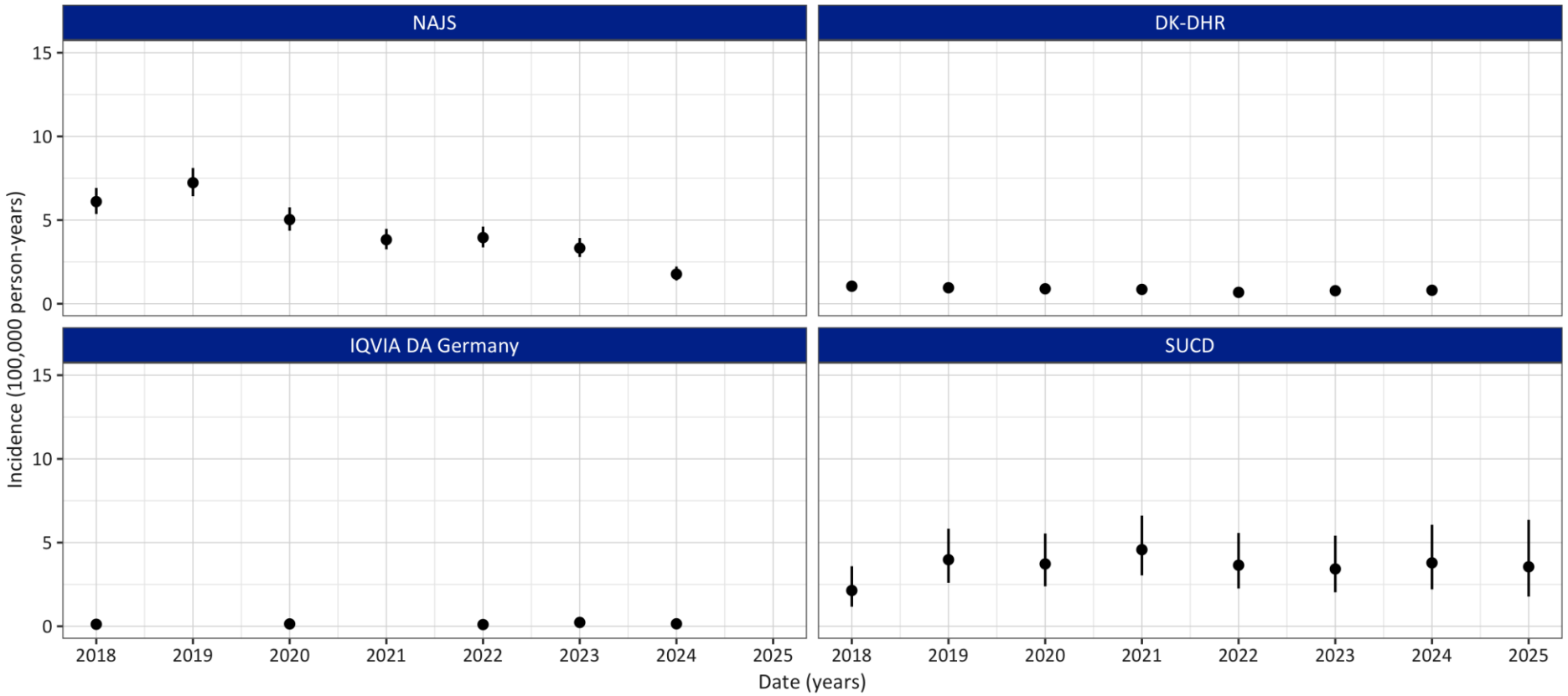


Figure 3. Annual incidence of intramuscular depot olanzapine.

Low counts were suppressed. Suppressed and zero counts were not shown in the figure. Vertical bars represented 95% confidence intervals. 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.

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

A total of 1,273 (NAJS), 364 (DK-DHR), 60 (IQVIA DA Germany), 163 (SUCD), and 1,592 (HI-SPEED) records of new IM depot olanzapine use without multiple doses on the index date were identified (**Table 3**). Among these records, median age ranged from 37 years (interquartile range (IQR) 29–50) in HI-SPEED to 45 years (IQR 32–56) in IQVIA DA Germany. Most records were among individuals aged 18–64 years, ranging from 87.64% in DK-DHR to 96.67% in IQVIA DA Germany. No new users under 18 years were identified in NAJS, DK-DHR, IQVIA DA Germany, or SUCD, and fewer than five in HI-SPEED. Across all data sources, there were more records from males than females, with the proportions of males ranging from 54.52% in NAJS to 67.40% in HI-SPEED. Most of the records started with the 300 mg preparation in DK-DHR (56.87%), IQVIA DA Germany (51.67%), SUCD (66.26%), and HI-SPEED (50.94%). In NAJS, 51.22% of records started with the 405 mg preparation. The 150/210 mg preparation was least frequently recorded in all data sources, ranging from 3.07% (SUCD) to 21.67% (IQVIA DA Germany).

Table 3. Initial dose of intramuscular depot olanzapine.

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
Number records	–	N	1,273	364	60	163	1,592
Number individuals	–	N	1,165	346	58	149	1,525
Age	–	Median [IQR]	40 [29–51]	44 [32–56]	45 [32–56]	41 [32–50]	37 [29–50]
		Mean (SD)	41 (14)	45 (15)	45 (14)	42 (13)	40 (14)
Age group	0 to 17	N (%)	0	0	0	0	<5
	18 to 64	N (%)	1,205 (94.66%)	319 (87.64%)	58 (96.67%)	152 (93.25%)	1,490 (93.59%)
	65 or above	N (%)	68 (5.34%)	45 (12.36%)	<5	11 (6.75%)	98 (6.16%)
Sex	Female	N (%)	579 (45.48%)	140 (38.46%)	24 (40.00%)	73 (44.79%)	519 (32.60%)
	Male	N (%)	694 (54.52%)	224 (61.54%)	36 (60.00%)	90 (55.21%)	1,073 (67.40%)
Initial dose	150/210mg	N (%)	92 (7.23%)	31 (8.52%)	13 (21.67%)	5 (3.07%)	248 (15.58%)
	300mg	N (%)	529 (41.56%)	207 (56.87%)	31 (51.67%)	108 (66.26%)	811 (50.94%)
	405mg	N (%)	652 (51.22%)	126 (34.62%)	16 (26.67%)	50 (30.67%)	533 (33.48%)

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

Maintenance dose was assessed at day 60 and day 120 within each initial dose cohort (**Table 4, Figures 4–8**). There were 5 (SUCD) to 248 (HI-SPEED) records starting with the 150/210 mg preparation (**Table 4**). Median age ranged from 31 years (IQR 24–50) in SUCD to 60 years (IQR 38–70) in DK-DHR. Due to the low counts observed in SUCD, no meaningful interpretation of results can be made. At day 60, proportions still receiving the 150/210 mg preparation ranged from 29.03% (DK-DHR) to 61.54% (IQVIA DA Germany), while the proportions with no recorded use ranged from 32.66% (HI-SPEED) to 51.61% (DK-DHR). At day 120, the proportions with the 150/210 mg preparation ranged from 22.58% (DK-DHR) to 46.15% (IQVIA DA

Germany), while the proportions with no recorded use ranged from 38.46% (IQVIA DA Germany) to 60.87% (NAJS).

There were 31 (IQVIA DA Germany) to 811 (HI-SPEED) records starting with the 300 mg preparation (**Table 4**). Median age ranged from 36 years (IQR 29–49) in HI-SPEED to 45 years (IQR 32–58) in IQVIA DA Germany. At day 60, the 300 mg preparation was the most commonly recorded dose in NAJS, DK-DHR, IQVIA DA Germany, and HI-SPEED, with the proportions ranging from 51.61% (IQVIA DA Germany) to 65.47% (HI-SPEED). In SUCD, 26.85% still received a 300 mg preparation, 57.41% had no recorded IM depot olanzapine use, and 11.11% were no longer under observation. At day 120, the proportion recorded with the 300 mg preparation decreased across data sources, ranging from 19.44% (SUCD) to 48.39% (IQVIA DA Germany); the proportion with no recorded use ranged from 32.26% (IQVIA DA Germany) to 67.59% (SUCD).

There were 16 (IQVIA DA Germany) to 652 (NAJS) records starting with the 405 mg preparation (**Table 4**). Median age ranged from 37 years (IQR 30–49) in HI-SPEED to 44 years (IQR 33–55) in DK-DHR. At day 60, the proportions with the 405 mg preparation ranged from 32.00% (SUCD) to 76.17% (HI-SPEED), while the proportions with no recorded use ranged from 19.32% (HI-SPEED) to 56.00% (SUCD). At day 120, the proportions with the 405 mg preparation decreased across all data sources, ranging from 26.00% (SUCD) to 60.79% (HI-SPEED), while the proportions with no recorded use ranged from 31.33% (HI-SPEED) to 56.25% (IQVIA DA Germany).

Regardless of the initiating dose preparation (150/210 mg, 300 mg, 405 mg), most records either remained on the same dose preparation or had no recorded IM depot olanzapine use at days 60 and 120. This pattern was consistent across all data sources (**Figures 4–8**).

Table 4. Maintenance dose of intramuscular depot olanzapine.

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
Initial dose: 150/210mg							
Number records	–	N	92	31	13	5	248
Number individuals	–	N	87	31	13	5	245
Age	–	Median [IQR]	47 [31–58]	60 [38–70]	52 [32–55]	31 [24–50]	41 [31–59]
		Mean (SD)	46 (17)	55 (17)	48 (13)	42 (25)	45 (17)
Age group	0 to 17	N (%)	0	0	0	0	<5
	18 to 64	N (%)	77 (83.70%)	20 (64.52%)	13 (100.00%)	<5	200 (80.65%)
	65 or above	N (%)	15 (16.30%)	11 (35.48%)	–	<5	46 (18.55%)
Sex	Female	N (%)	59 (64.13%)	12 (38.71%)	7 (53.85%)	<5	110 (44.35%)
	Male	N (%)	33 (35.87%)	19 (61.29%)	6 (46.15%)	<5	138 (55.65%)
Time: 60 days	150/210mg	N (%)	30 (32.61%)	9 (29.03%)	8 (61.54%)	0	125 (50.40%)
	300mg	N (%)	7 (7.61%)	<5	<5	0	20 (8.06%)
	405mg	N (%)	6 (6.52%)	<5	<5	0	7 (2.82%)
	Multiple	N (%)	<5	0	0	0	13 (5.24%)

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
	No records	N (%)	47 (51.09%)	16 (51.61%)	<5	<5	81 (32.66%)
	Not in observation	N (%)	<5	<5	0	<5	<5
Time: 120 days	150/210mg	N (%)	24 (26.09%)	7 (22.58%)	6 (46.15%)	0	83 (33.47%)
	300mg	N (%)	<5	<5	<5	0	26 (10.48%)
	405mg	N (%)	7 (7.61%)	<5	0	0	10 (4.03%)
	Multiple	N (%)	0	0	0	0	9 (3.63%)
	No records	N (%)	56 (60.87%)	17 (54.84%)	5 (38.46%)	<5	115 (46.37%)
	Not in observation	N (%)	<5	<5	<5	<5	5 (2.02%)
Initial dose: 300mg							
Number records	–	N	529	207	31	108	811
Number individuals	–	N	501	200	29	103	793
Age	–	Median [IQR]	40 [29–50]	43 [31–55]	45 [32–58]	42 [32–51]	36 [29–49]
		Mean (SD)	41 (14)	44 (15)	45 (15)	42 (13)	40 (14)
Age group	0 to 17	N (%)	0	0	0	0	<5
	18 to 64	N (%)	499 (94.33%)	183 (88.41%)	29 (93.55%)	100 (92.59%)	771 (95.07%)
	65 or above	N (%)	30 (5.67%)	24 (11.59%)	<5	8 (7.41%)	38 (4.69%)
Sex	Female	N (%)	262 (49.53%)	89 (43.00%)	11 (35.48%)	53 (49.07%)	251 (30.95%)
	Male	N (%)	267 (50.47%)	118 (57.00%)	20 (64.52%)	55 (50.93%)	560 (69.05%)
Time: 60 days	150/210mg	N (%)	<5	<5	0	<5	8 (0.99%)
	300mg	N (%)	275 (51.98%)	124 (59.90%)	16 (51.61%)	29 (26.85%)	531 (65.47%)
	405mg	N (%)	46 (8.70%)	<5	<5	<5	42 (5.18%)
	Multiple	N (%)	15 (2.84%)	0	<5	<5	35 (4.32%)
	No records	N (%)	189 (35.73%)	78 (37.68%)	9 (29.03%)	62 (57.41%)	193 (23.80%)
	Not in observation	N (%)	0	0	<5	12 (11.11%)	<5
Time: 120 days	150/210mg	N (%)	5 (0.95%)	<5	0	0	12 (1.48%)
	300mg	N (%)	213 (40.26%)	80 (38.65%)	15 (48.39%)	21 (19.44%)	385 (47.47%)
	405mg	N (%)	73 (13.80%)	8 (3.86%)	<5	<5	69 (8.51%)
	Multiple	N (%)	<5	<5	<5	0	27 (3.33%)

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
	No records	N (%)	234 (44.23%)	108 (52.17%)	10 (32.26%)	73 (67.59%)	314 (38.72%)
	Not in observation	N (%)	<5	<5	<5	12 (11.11%)	<5
Initial dose: 405mg							
Number records	–	N	652	126	16	50	533
Number individuals	–	N	610	122	16	48	523
Age	–	Median [IQR]	38 [29–50]	44 [33–55]	38 [31–52]	40 [32–46]	37 [30–49]
		Mean (SD)	40 (13)	45 (14)	42 (13)	40 (12)	39 (12)
Age group	0 to 17	N (%)	0	0	0	0	0
	18 to 64	N (%)	629 (96.47%)	116 (92.06%)	16 (100.00%)	48 (96.00%)	519 (97.37%)
	65 or above	N (%)	23 (3.53%)	10 (7.94%)	–	<5	14 (2.63%)
Sex	Female	N (%)	258 (39.57%)	39 (30.95%)	6 (37.50%)	19 (38.00%)	158 (29.64%)
	Male	N (%)	394 (60.43%)	87 (69.05%)	10 (62.50%)	31 (62.00%)	375 (70.36%)
Time: 60 days	150/210mg	N (%)	<5	0	0	0	<5
	300mg	N (%)	20 (3.07%)	<5	<5	<5	8 (1.50%)
	405mg	N (%)	422 (64.72%)	84 (66.67%)	10 (62.50%)	16 (32.00%)	406 (76.17%)
	Multiple	N (%)	5 (0.77%)	0	0	<5	13 (2.44%)
	No records	N (%)	203 (31.13%)	38 (30.16%)	<5	28 (56.00%)	103 (19.32%)
	Not in observation	N (%)	0	<5	<5	<5	<5
Time: 120 days	150/210mg	N (%)	5 (0.77%)	<5	0	0	<5
	300mg	N (%)	30 (4.60%)	<5	0	<5	22 (4.13%)
	405mg	N (%)	350 (53.68%)	69 (54.76%)	6 (37.50%)	13 (26.00%)	324 (60.79%)
	Multiple	N (%)	<5	0	0	0	10 (1.88%)
	No records	N (%)	264 (40.49%)	49 (38.89%)	9 (56.25%)	28 (56.00%)	167 (31.33%)
	Not in observation	N (%)	<5	5 (3.97%)	<5	5 (10.00%)	6 (1.13%)

"No record" was defined as no IM depot olanzapine use was recorded in any dose cohort (150/210 mg, 300 mg, or 405 mg) on the assessment date (60 or 120 days), while the individual remained under observation in the data source. DK-DHR = Danish Data Health Registries; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; IM = intramuscular; IQR = interquartile range; IQVIA DA Germany = IQVIA Disease Analyzer Germany; NAJS = Croatian National Public Health Information System; SD = standard deviation; SUCD = Semmelweis University Clinical Data.

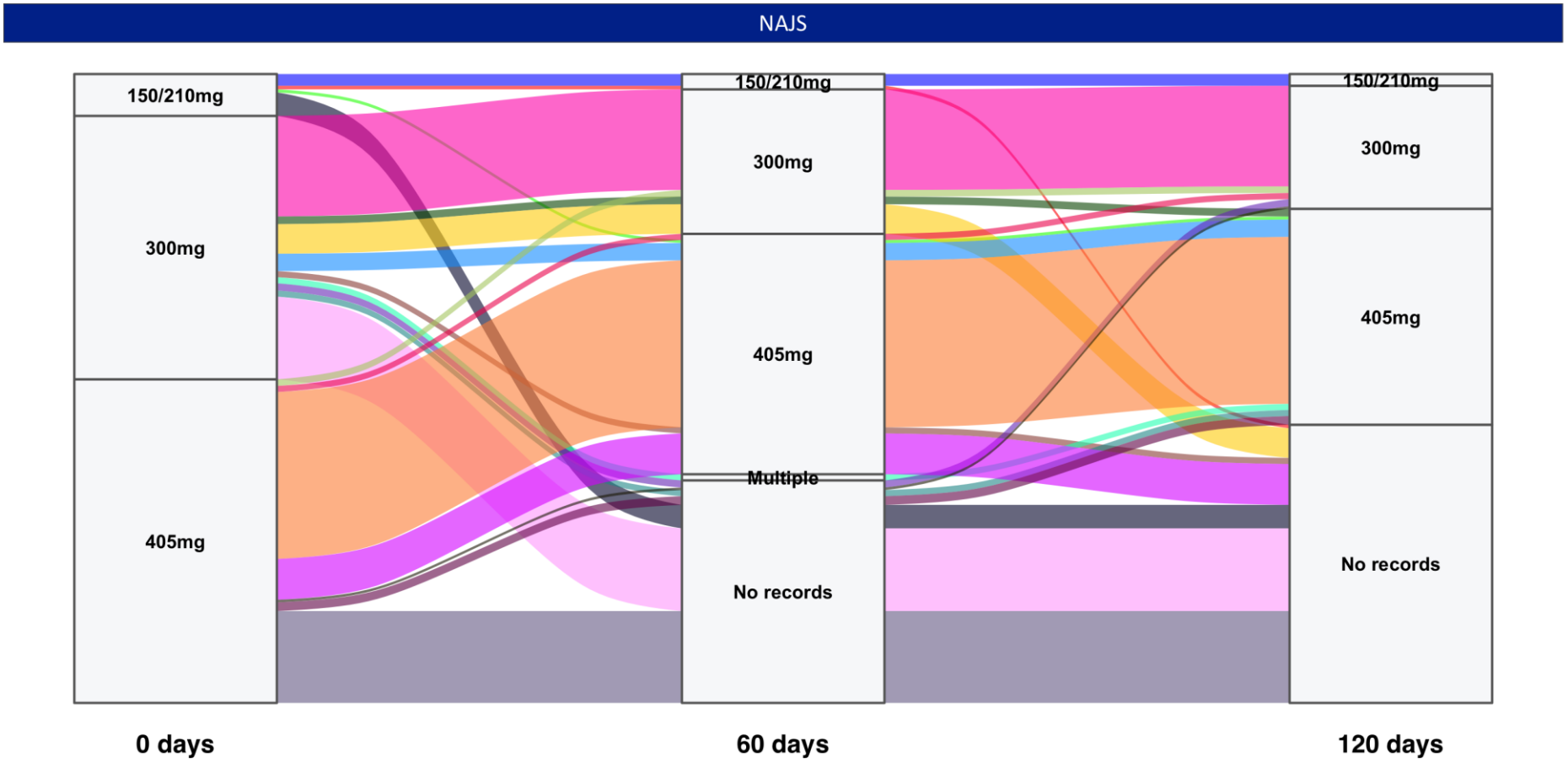


Figure 4. Sankey plot on maintenance dose of intramuscular depot olanzapine in NAJS.

"No record" was defined as no IM depot olanzapine use was recorded in any dose cohort (150/210 mg, 300 mg, or 405 mg) on the assessment date (60 or 120 days), while the individual remained under observation in the data source. IM = intramuscular; NAJS = Croatian National Public Health Information System.

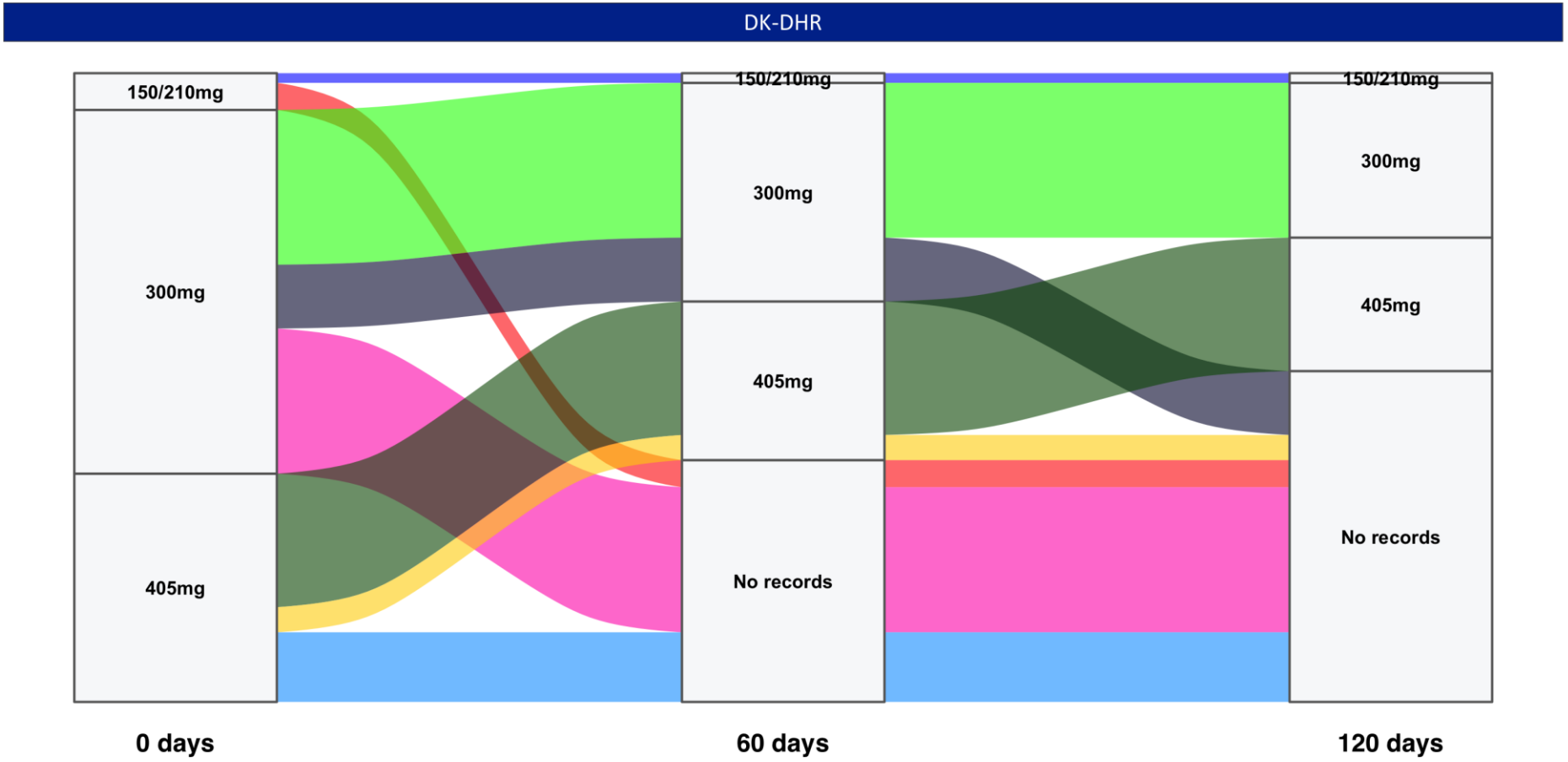


Figure 5. Sankey plot on maintenance dose of intramuscular depot olanzapine in DK-DHR.

"No record" was defined as no IM depot olanzapine use was recorded in any dose cohort (150/210 mg, 300 mg, or 405 mg) on the assessment date (60 or 120 days), while the individual remained under observation in the data source. IM = intramuscular; DK-DHR = Danish Data Health Registries.

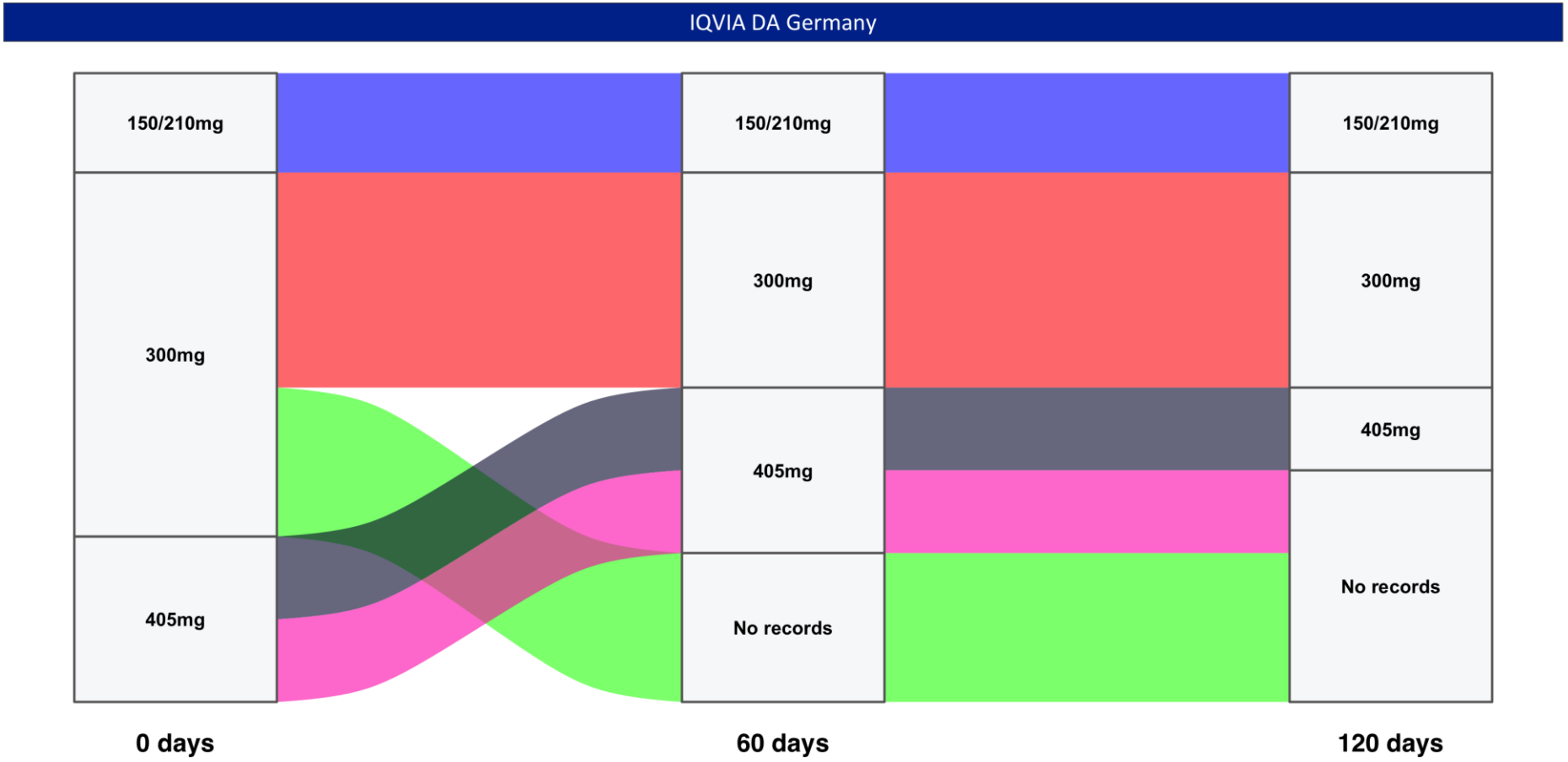


Figure 6. Sankey plot on maintenance dose of intramuscular depot olanzapine in IQVIA DA Germany.

"No record" was defined as no IM depot olanzapine use was recorded in any dose cohort (150/210 mg, 300 mg, or 405 mg) on the assessment date (60 or 120 days), while the individual remained under observation in the data source. IM = intramuscular; IQVIA DA Germany = IQVIA Disease Analyzer Germany.

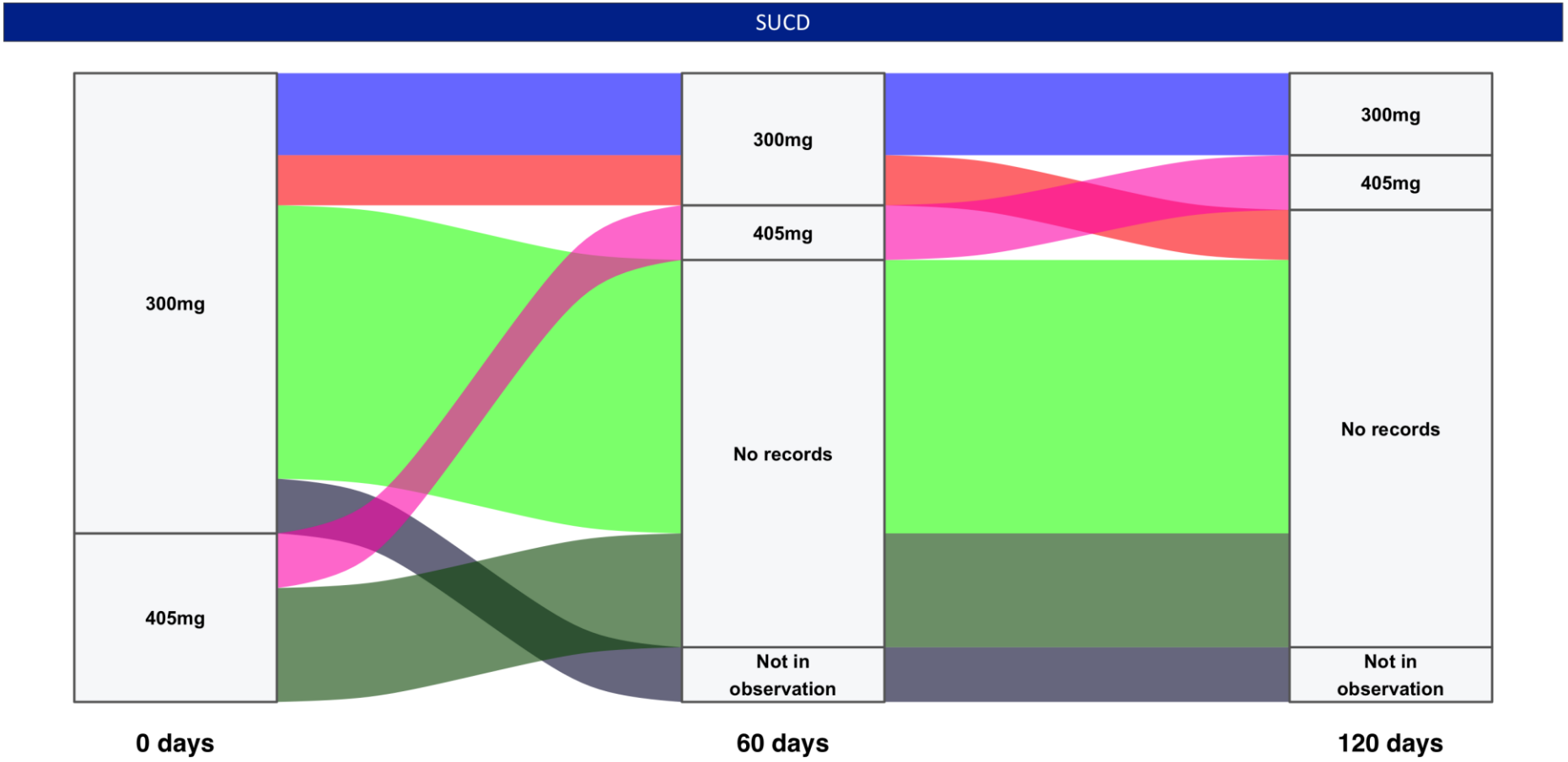


Figure 7. Sankey plot on maintenance dose of intramuscular depot olanzapine in SUCD.

"No record" was defined as no IM depot olanzapine use was recorded in any dose cohort (150/210 mg, 300 mg, or 405 mg) on the assessment date (60 or 120 days), while the individual remained under observation in the data source. IM = intramuscular; SUCD = Semmelweis University Clinical Data.

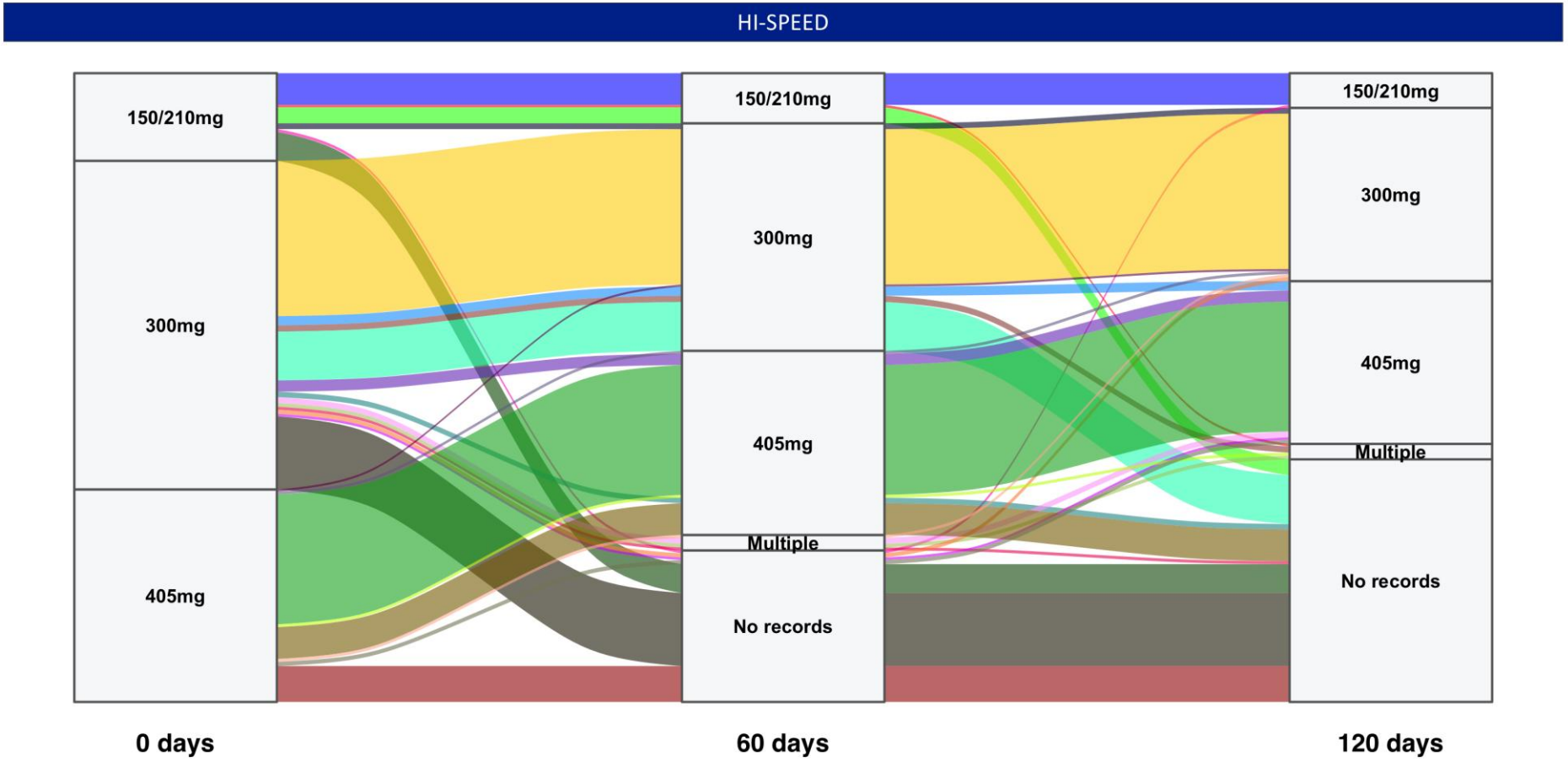


Figure 8. Sankey plot on maintenance dose of intramuscular depot olanzapine in HI-SPEED.

"No record" was defined as no IM depot olanzapine use was recorded in any dose cohort (150/210 mg, 300 mg, or 405 mg) on the assessment date (60 or 120 days), while the individual remained under observation in the data source. IM = intramuscular; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage.

Objective 3. Monthly prevalence of intramuscular depot olanzapine discontinuation

In this objective, the prevalence of IM depot olanzapine discontinuation was estimated as a proportion of IM depot olanzapine users who discontinued treatment with at least 42 days of subsequent observation. No clear trend in the monthly prevalence of discontinuation (**Figure 9**) was observed in IQVIA DA Germany or SUCD because of low counts and suppressed results.

In NAJS, monthly prevalence of discontinuation remained stable, ranging from 4.97% (95% CI 2.54–9.50) to 17.97% (95% CI 12.28–25.52) during 2018–2019, and mostly below 10% from 2020 to July 2024. The monthly prevalence of discontinuation then increased from 6.67% (95% CI 4.08–10.71) to 13.64% (95% CI 9.72–18.80) in July–August 2024, and from 81.58% (95% CI 75.46–86.45) to 91.43% (95% CI 77.62–97.04) in September–October 2024. There were few or no IM depot olanzapine users from November 2024 onwards.

In DK-DHR, excluding months with suppressed results, monthly discontinuation ranged from 8.07% (95% CI 3.49–17.53) to 20.83% (95% CI 11.73–34.26) from the start of the study period to March 2025 and subsequently ranged from 30.44% (95% CI 15.60–50.87) to 35.29% (95% CI 17.31–58.70) between April and July 2025.

In HI-SPEED, the monthly prevalence of discontinuation increased from January 2025 onwards. Monthly discontinuation ranged from 3.94% (95% CI 2.15–7.09) to 13.84% (95% CI 9.92–18.97) during 2019–2024, increased from 4.26% (95% CI 2.40–7.47) in January 2025 to 29.69% (95% CI 23.68–36.50) in April 2025, and remained at 26.62% (95% CI 19.97–34.52) to 33.01% (95% CI 24.68–42.56) for May–July 2025.

Given the low counts observed in the monthly analysis, discontinuation was additionally estimated quarterly and annually (**Figures 10–11**). Annual discontinuation remained broadly similar over time in IQVIA DA Germany and SUCD (**Figure 11**).

An additional sensitivity analysis, restricting the denominator to individuals who had received IM depot olanzapine for a maximum of two years, was conducted to assess whether the observed temporal trend in discontinuation could be influenced by differences in treatment duration, given that the probability of discontinuation may vary according to how long an individual has received treatment. The results were similar to those of the main analysis and are available through the Shiny app at EUPAS1000000980.

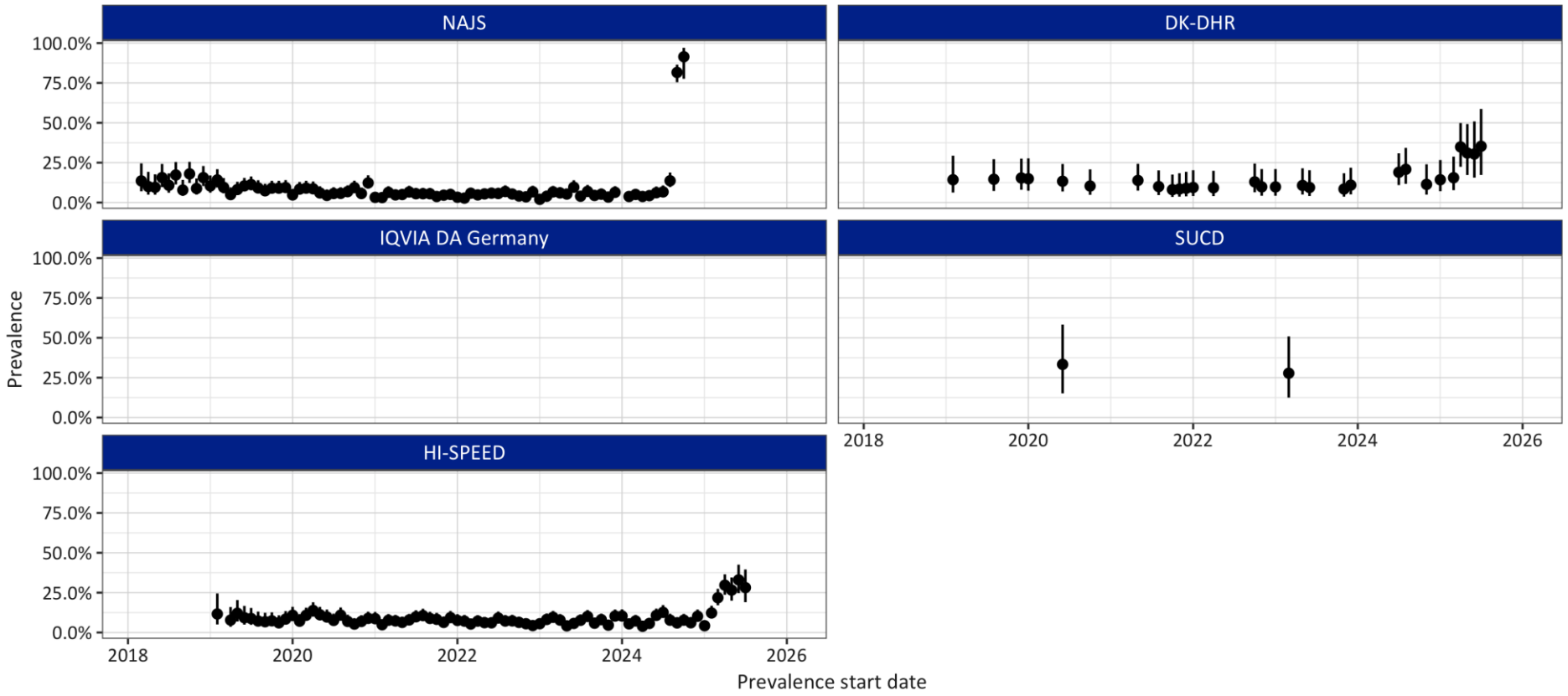


Figure 9. Monthly prevalence of intramuscular depot olanzapine discontinuation.

Low counts were suppressed. Suppressed and zero counts were not shown in the figure. No results were displayed for IQVIA DA Germany, as all counts were either suppressed or zero. Vertical bars represented 95% confidence intervals. 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.

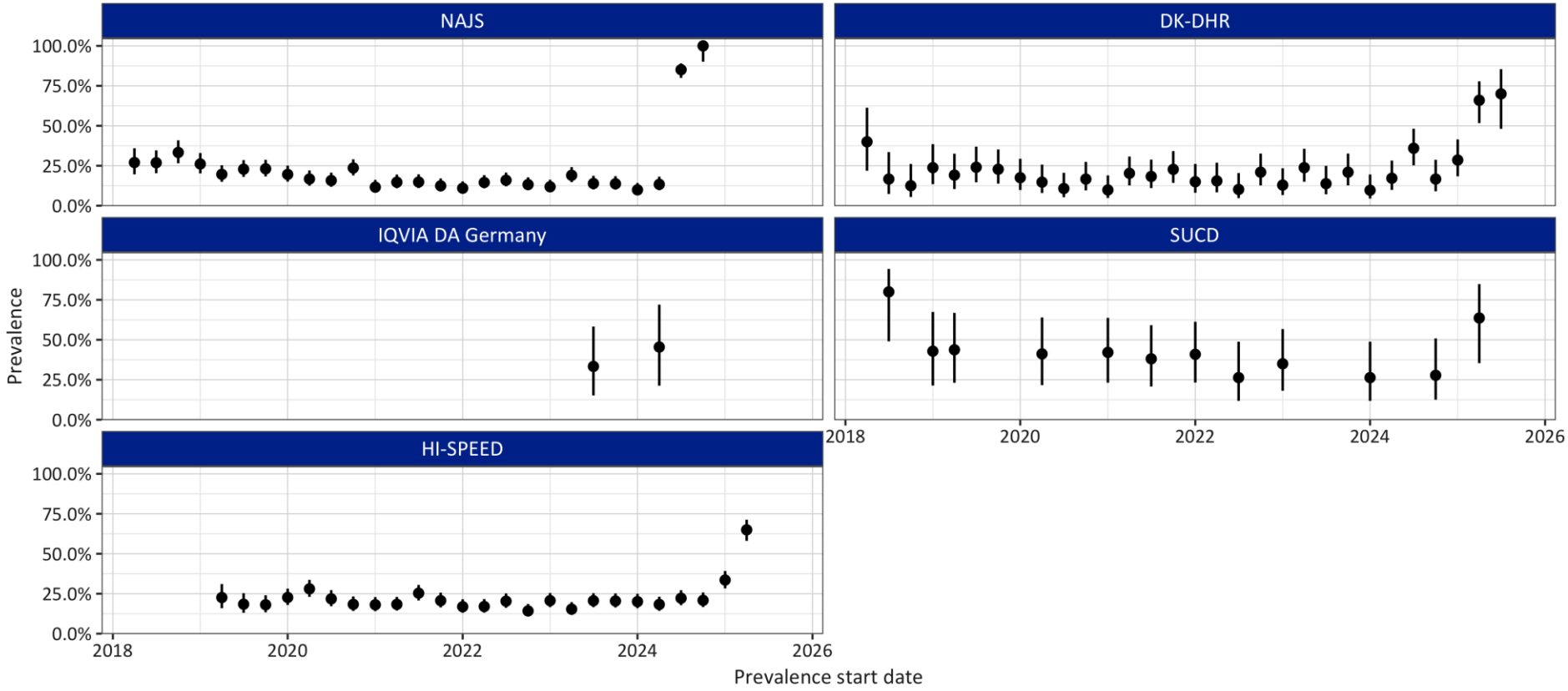


Figure 10. Quarterly prevalence of intramuscular depot olanzapine discontinuation.

Low counts were suppressed. Suppressed and zero counts were not shown in the figure. Vertical bars represented 95% confidence intervals. 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.

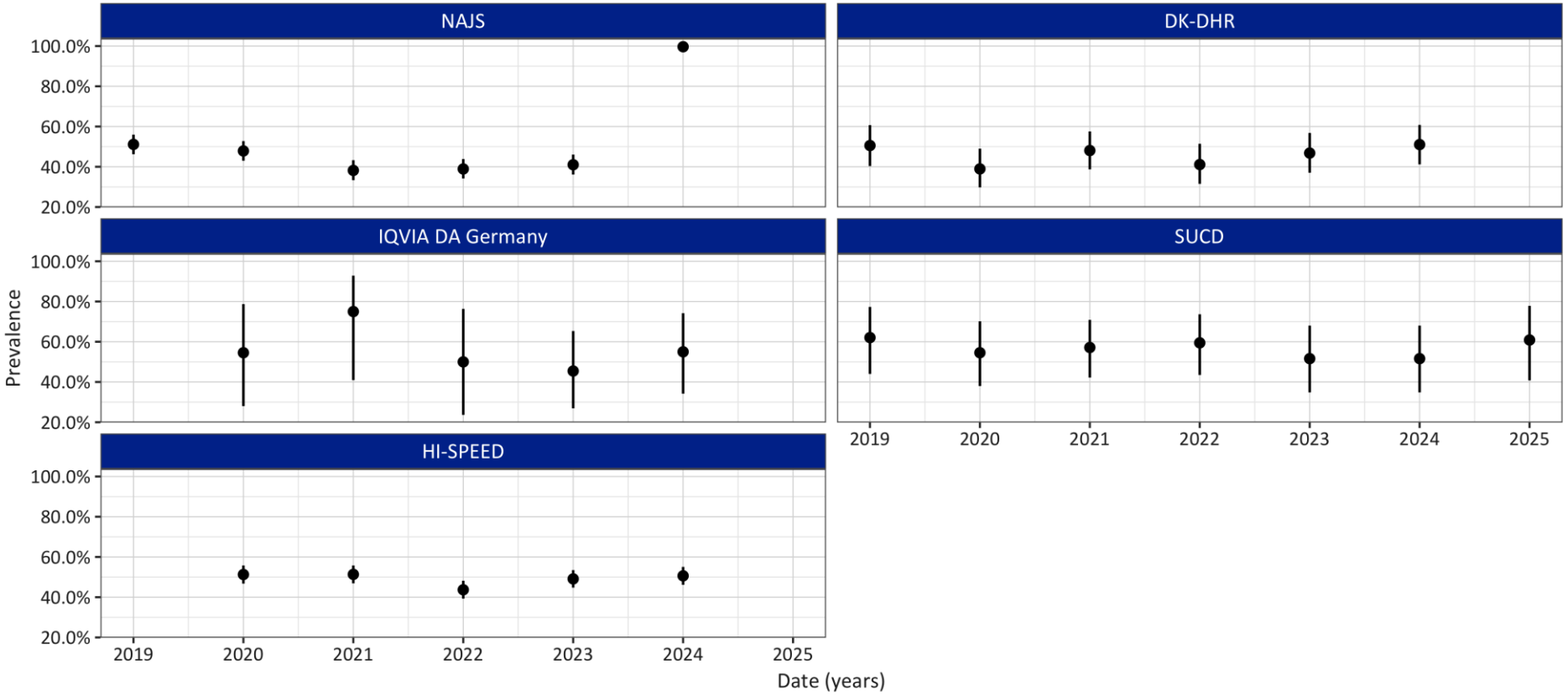


Figure 11. Annual prevalence of intramuscular depot olanzapine discontinuation.

Low counts were suppressed. Suppressed and zero counts were not shown in the figure. Vertical bars represented 95% confidence intervals. 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.

Objective 4. Switching patterns after discontinuation of intramuscular depot olanzapine

A total of 1,272 records of IM depot olanzapine discontinuation were identified in NAJS, 347 in DK-DHR, 50 in IQVIA DA Germany, 140 in SUCD, and 1,532 in HI-SPEED (**Table 5**). Among these records, median age ranged from 38 years (IQR 30–51) in HI-SPEED to 46 years (IQR 32–55) in IQVIA DA Germany. Most records of IM depot olanzapine discontinuation were among individuals aged 18–64 years, ranging from 87.61% in DK-DHR to 96.00% in IQVIA DA Germany. Across all data sources, there were more records of discontinuation from males than females, with the proportions of males ranging from 54.56% in NAJS to 66.97% in HI-SPEED.

Most records had no initiation of other type of AP treatment within 60 days after IM depot olanzapine discontinuation in the current study, ranging from 74.53% in NAJS to 89.62% in HI-SPEED.

Due to low counts in IQVIA DA Germany and SUCD, no meaningful interpretation of AP switching patterns after IM depot olanzapine discontinuation could be made for these data sources. Therefore, results on AP switching patterns for the main analysis, stratified analysis by age group, and stratified analysis by sex in IQVIA DA Germany and SUCD were not reported.

Within 60 days after IM depot olanzapine discontinuation, oral olanzapine was initiated in 3.13% (HI-SPEED) to 9.59% (NAJS) of records. Oral AP other than olanzapine were initiated in 0.98% (HI-SPEED) to 6.05% (DK-DHR) of records. No injectable non-depot olanzapine use was recorded. Initiation of injectable non-depot AP use other than olanzapine was only observed in NAJS (2.20%), whereas initiation of depot AP other than olanzapine ranged from 2.88% (DK-DHR) to 6.27% (HI-SPEED).

Among oral AP other than olanzapine, promazine, fluphenazine, and haloperidol were, in descending order, the most commonly identified typical AP, with non-suppressed results only available in NAJS (2.28% for promazine, 2.04% for fluphenazine, 1.81% for haloperidol). The most commonly identified atypical AP included quetiapine (0.39% in HI-SPEED to 2.31% in DK-DHR), aripiprazole (3.38% in NAJS), and clozapine (3.30% in NAJS). Among injectable non-depot AP other than olanzapine, only haloperidol (1.81%) and promazine (1.18%) were identified, both in NAJS. Among depot AP other than olanzapine, the most commonly identified typical AP included zuclopenthixol (1.44% in DK-DHR, 0.46% in HI-SPEED), fluphenazine (0.86% in NAJS), and perphenazine (0.59% in HI-SPEED), while the most commonly identified atypical AP included aripiprazole (2.12% in NAJS, 2.61% in HI-SPEED), paliperidone (1.65% in NAJS, 1.76% in HI-SPEED), and risperidone (0.72% in HI-SPEED).

Table 5. Switching patterns after intramuscular depot olanzapine discontinuation.

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
Number records	–	N	1,272	347	50	140	1,532
Number individuals	–	N	1,160	330	49	128	1,466
Age at the record of IM depot olanzapine discontinuation	_	Median [IQR]	40 [30–52]	44 [33–57]	46 [32–55]	41 [31–50]	38 [30–51]
		Mean (SD)	42 (14)	45 (15)	44 (14)	42 (13)	41 (14)
Age group at the record of IM depot olanzapine discontinuation	0 to 17	N (%)	0	0	0	0	<5
	18 to 64	N (%)	1,196 (94.03%)	304 (87.61%)	48 (96.00%)	129 (92.14%)	1,423 (92.89%)
	65 or above	N (%)	76 (5.97%)	43 (12.39%)	<5	11 (7.86%)	106 (6.92%)

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
Sex	Female	N (%)	578 (45.44%)	133 (38.33%)	18 (36.00%)	60 (42.86%)	506 (33.03%)
	Male	N (%)	694 (54.56%)	214 (61.67%)	32 (64.00%)	80 (57.14%)	1,026 (66.97%)
Initiated AP during the 60 days following IM depot olanzapine discontinuation	No AP initiated	N (%)	948 (74.53%)	287 (82.71%)	43 (86.00%)	125 (89.29%)	1,373 (89.62%)
	Oral olanzapine	N (%)	122 (9.59%)	22 (6.34%)	<5	<5	48 (3.13%)
	Injectable non-depot olanzapine	N (%)	0	0	0	0	0
	Oral AP other than olanzapine	N (%)	59 (4.64%)	21 (6.05%)	<5	5 (3.57%)	15 (0.98%)
	Injectable non-depot AP other than olanzapine	N (%)	28 (2.20%)	0	0	0	0
	Depot AP other than olanzapine	N (%)	61 (4.80%)	10 (2.88%)	<5	<5	96 (6.27%)
	Oral typical AP: fluphenazine	N (%)	26 (2.04%)	0	0	0	0
	Oral typical AP: haloperidol	N (%)	23 (1.81%)	<5	0	0	<5
	Oral typical AP: promazine	N (%)	29 (2.28%)	0	0	0	0
	Oral atypical AP: aripiprazole	N (%)	43 (3.38%)	<5	<5	<5	0
	Oral atypical AP: clozapine	N (%)	42 (3.30%)	<5	<5	0	0
	Oral atypical AP: quetiapine	N (%)	29 (2.28%)	8 (2.31%)	0	<5	6 (0.39%)
	Injectable non-depot typical AP: haloperidol	N (%)	23 (1.81%)	0	0	0	0
	Injectable non-depot typical AP: promazine	N (%)	15 (1.18%)	0	0	0	0
	Depot typical AP: fluphenazine	N (%)	11 (0.86%)	0	0	0	0
	Depot typical AP: perphenazine	N (%)	0	0	0	0	9 (0.59%)
	Depot typical AP: zuclopenthixol	N (%)	0	5 (1.44%)	0	0	7 (0.46%)
	Depot atypical AP: aripiprazole	N (%)	27 (2.12%)	<5	0	<5	40 (2.61%)
	Depot atypical AP: paliperidone	N (%)	21 (1.65%)	<5	0	<5	27 (1.76%)

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
	Depot atypical AP: risperidone	N (%)	<5	<5	<5	0	11 (0.72%)

AP = antipsychotic; DK-DHR = Danish Data Health Registries; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; IM = intramuscular; IQR = interquartile range; IQVIA DA Germany = IQVIA Disease Analyzer Germany; NAJS = Croatian National Public Health Information System; SD = standard deviation; SUCD = Semmelweis University Clinical Data.

No records of IM depot olanzapine discontinuation among individuals aged 0–17 years were identified in NAJS and DK-DHR, with only less than five records being identified in HI-SPEED. Due to the low counts observed, switching patterns in aged 0–17 years group was not reported.

The stratified analysis by age group (**Table 6**) showed similar proportions of records with no AP initiated during the 60 days after IM depot olanzapine discontinuation among those aged 18–64 years (74.67% in NAJS to 89.74% in HI-SPEED) and ≥65 years (72.37% in NAJS to 90.91% in SUCD). Further interpretation of switching patterns among those aged ≥65 years was limited by low counts.

The stratified analysis by sex (**Table 7**) showed similar proportions with no AP initiated following discontinuation of IM depot olanzapine among males and females in NAJS (73.63% versus 75.61%) and HI-SPEED (89.86% versus 89.13%), while the proportion was higher among males than females in DK-DHR (85.51% versus 78.20%).

In addition to the primary analysis of switching patterns during days 1–60 after IM depot olanzapine discontinuation, a sensitivity analysis was conducted using an extended assessment window from 7 days before to 60 days after discontinuation, with results available through the Shiny app at EUPAS1000000980. The proportion with no initiation of AP treatment decreased from 74.53% in the primary analysis to 66.12% in the sensitivity analysis in NAJS, 82.71% to 78.67% in DK-DHR, 86.00% to 82.00% in IQVIA DA Germany, 89.29% to 86.43% in SUCD, and 89.62% to 87.79% in HI-SPEED. Initiation of oral olanzapine increased from 9.59% to 14.54% in NAJS, 6.34% to 8.36% in DK-DHR, and 3.13% to 3.66% in HI-SPEED. Initiation of oral AP other than olanzapine increased from 4.64% to 7.86% in NAJS and from 6.05% to 7.49% in DK-DHR, while initiation of other IM depot AP other than olanzapine increased from 4.80% to 6.53% in NAJS, 2.88% to 3.46% in DK-DHR, and 6.27% to 7.70% in HI-SPEED. The distribution of individual typical and atypical AP by formulation was generally similar between the two assessment windows, with low counts limiting further interpretation.

Table 6. Switching patterns after intramuscular depot olanzapine discontinuation, stratified by age group.

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
Age group: 18 to 64							
Number records	–	N	1,196	304	48	129	1,423
Number individuals	–	N	1,089	290	47	119	1,360
Age at the record of IM depot olanzapine discontinuation	–	Median [IQR]	39 [29–50]	41 [31–51]	44 [32–55]	40 [29–49]	37 [30–48]
		Mean (SD)	40 (12)	41 (12)	44 (14)	39 (11)	39 (12)
Sex	Female	N (%)	531 (44.40%)	112 (36.84%)	18 (37.50%)	53 (41.09%)	451 (31.69%)

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
	Male	N (%)	665 (55.60%)	192 (63.16%)	30 (62.50%)	76 (58.91%)	972 (68.31%)
Initiated AP during the 60 days following IM depot olanzapine discontinuation	No AP initiated	N (%)	893 (74.67%)	251 (82.57%)	42 (87.50%)	115 (89.15%)	1,277 (89.74%)
	Oral olanzapine	N (%)	115 (9.62%)	19 (6.25%)	<5	<5	46 (3.23%)
	Injectable non-depot olanzapine	N (%)	0	0	0	0	0
	Oral AP other than olanzapine	N (%)	55 (4.60%)	19 (6.25%)	<5	5 (3.88%)	14 (0.98%)
	Injectable non-depot AP other than olanzapine	N (%)	27 (2.26%)	0	0	0	0
	Depot AP other than olanzapine	N (%)	58 (4.85%)	8 (2.63%)	<5	<5	86 (6.04%)
	Oral typical AP: fluphenazine	N (%)	23 (1.92%)	0	0	0	0
	Oral typical AP: haloperidol	N (%)	23 (1.92%)	<5	0	0	<5
	Oral typical AP: promazine	N (%)	25 (2.09%)	0	0	0	0
	Oral atypical AP: aripiprazole	N (%)	41 (3.43%)	<5	0	<5	0
	Oral atypical AP: clozapine	N (%)	40 (3.34%)	<5	<5	0	0
	Oral atypical AP: quetiapine	N (%)	28 (2.34%)	8 (2.63%)	0	<5	6 (0.42%)
	Injectable non-depot typical AP: haloperidol	N (%)	22 (1.84%)	0	0	0	0
	Injectable non-depot typical AP: promazine	N (%)	14 (1.17%)	0	0	0	0
	Depot typical AP: fluphenazine	N (%)	10 (0.84%)	0	0	0	0
	Depot typical AP: perphenazine	N (%)	0	0	0	0	7 (0.49%)
	Depot typical AP: zuclopenthixol	N (%)	0	<5	0	0	7 (0.49%)
	Depot atypical AP: aripiprazole	N (%)	25 (2.09%)	<5	0	<5	37 (2.60%)
	Depot atypical AP: paliperidone	N (%)	21 (1.76%)	<5	0	0	25 (1.76%)
	Depot atypical AP: risperidone	N (%)	<5	0	<5	0	9 (0.63%)
Age group: 65 or above							

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
Number records	–	N	76	43	<5	11	106
Number individuals	–	N	73	40	<5	9	106
Age at the record of IM depot olanzapine discontinuation	_	Median [IQR]	70 [67–72]	69 [67–74]	<5	68 [67–69]	69 [66–73]
		Mean (SD)	70 (5)	71 (5)	<5	68 (2)	70 (5)
Sex	Female	N (%)	47 (61.84%)	21 (48.84%)	0	7 (63.64%)	54 (50.94%)
	Male	N (%)	29 (38.16%)	22 (51.16%)	<5	<5	52 (49.06%)
Initiated AP during the 60 days following IM depot olanzapine discontinuation	No AP initiated	N (%)	55 (72.37%)	36 (83.72%)	<5	10 (90.91%)	94 (88.68%)
	Oral olanzapine	N (%)	7 (9.21%)	<5	0	0	<5
	Injectable non-depot olanzapine	N (%)	0	0	0	0	0
	Oral AP other than olanzapine	N (%)	<5	<5	<5	0	0
	Injectable non-depot AP other than olanzapine	N (%)	<5	0	0	0	0
	Depot AP other than olanzapine	N (%)	<5	<5	0	<5	10 (9.43%)
	Oral typical AP: fluphenazine	N (%)	<5	0	0	0	0
	Oral typical AP: haloperidol	N (%)	0	0	0	0	0
	Oral typical AP: promazine	N (%)	<5	0	0	0	0
	Oral atypical AP: aripiprazole	N (%)	<5	0	<5	0	0
	Oral atypical AP: clozapine	N (%)	<5	0	0	0	0
	Oral atypical AP: quetiapine	N (%)	<5	0	0	0	0
	Injectable non-depot typical AP: haloperidol	N (%)	<5	0	0	0	0
	Injectable non-depot typical AP: promazine	N (%)	<5	0	0	0	0
	Depot typical AP: fluphenazine	N (%)	<5	0	0	0	0
	Depot typical AP: perphenazine	N (%)	0	0	0	0	<5
	Depot typical AP: zuclopenthixol	N (%)	0	<5	0	0	0

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
	Depot atypical AP: aripiprazole	N (%)	<5	0	0	0	<5
	Depot atypical AP: paliperidone	N (%)	0	0	0	<5	<5
	Depot atypical AP: risperidone	N (%)	0	<5	0	0	<5

AP = antipsychotic; DK-DHR = Danish Data Health Registries; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; IM = intramuscular; IQR = interquartile range; IQVIA DA Germany = IQVIA Disease Analyzer Germany; NAJS = Croatian National Public Health Information System; SD = standard deviation; SUCD = Semmelweis University Clinical Data.

Table 7. Switching patterns after intramuscular depot olanzapine discontinuation, stratified by sex.

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
Sex: Female							
Number records	–	N	578	133	18	60	506
Number individuals	–	N	529	127	18	55	491
Age at the record of IM depot olanzapine discontinuation	–	Median [IQR]	45 [34–56]	49 [33–61]	47 [35–55]	48 [40–56]	44 [34–57]
		Mean (SD)	45 (14)	48 (16)	45 (13)	48 (13)	45 (15)
Age group at the record of IM depot olanzapine discontinuation	0 to 17	N (%)	0	0	0	0	<5
	18 to 64	N (%)	531 (91.87%)	112 (84.21%)	18 (100.00%)	53 (88.33%)	451 (89.13%)
	65 or above	N (%)	47 (8.13%)	21 (15.79%)	0	7 (11.67%)	54 (10.67%)
Initiated AP during the 60 days following IM depot olanzapine discontinuation	No AP initiated	N (%)	437 (75.61%)	104 (78.20%)	17 (94.44%)	53 (88.33%)	451 (89.13%)
	Oral olanzapine	N (%)	55 (9.52%)	10 (7.52%)	0	<5	17 (3.36%)
	Injectable non-depot olanzapine	N (%)	0	0	0	0	0
	Oral AP other than olanzapine	N (%)	32 (5.54%)	10 (7.52%)	0	<5	7 (1.38%)
	Injectable non-depot AP other than olanzapine	N (%)	14 (2.42%)	0	0	0	0
	Depot AP other than olanzapine	N (%)	23 (3.98%)	6 (4.51%)	0	<5	34 (6.72%)
	Oral typical AP: fluphenazine	N (%)	15 (2.60%)	0	0	0	0
	Oral typical AP: haloperidol	N (%)	14 (2.42%)	0	0	0	<5

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
	Oral typical AP: promazine	N (%)	12 (2.08%)	0	0	0	0
	Oral atypical AP: aripiprazole	N (%)	20 (3.46%)	<5	0	<5	0
	Oral atypical AP: clozapine	N (%)	20 (3.46%)	<5	0	0	0
	Oral atypical AP: quetiapine	N (%)	15 (2.60%)	<5	0	<5	<5
	Injectable non-depot typical AP: haloperidol	N (%)	10 (1.73%)	0	0	0	0
	Injectable non-depot typical AP: promazine	N (%)	9 (1.56%)	0	0	0	0
	Depot typical AP: fluphenazine	N (%)	<5	0	0	0	0
	Depot typical AP: perphenazine	N (%)	0	0	0	0	5 (0.99%)
	Depot typical AP: zuclopenthixol	N (%)	0	<5	0	0	<5
	Depot atypical AP: aripiprazole	N (%)	15 (2.60%)	<5	0	<5	11 (2.17%)
	Depot atypical AP: paliperidone	N (%)	<5	0	0	0	13 (2.57%)
	Depot atypical AP: risperidone	N (%)	0	0	0	0	<5
Sex: Male							
Number records	–	N	694	214	32	80	1,026
Number individuals	–	N	631	203	31	73	975
Age at the record of IM depot olanzapine discontinuation	–	Median [IQR]	37 [28–47]	41 [33–52]	42 [32–58]	37 [26–45]	36 [29–47]
		Mean (SD)	39 (13)	43 (14)	44 (15)	37 (12)	39 (13)
Age group at the record of IM depot olanzapine discontinuation	0 to 17	N (%)	0	0	0	0	<5
	18 to 64	N (%)	665 (95.82%)	192 (89.72%)	30 (93.75%)	76 (95.00%)	972 (94.74%)
	65 or above	N (%)	29 (4.18%)	22 (10.28%)	<5	<5	52 (5.07%)
Initiated AP during the 60 days following IM depot olanzapine discontinuation	No AP initiated	N (%)	511 (73.63%)	183 (85.51%)	26 (81.25%)	72 (90.00%)	922 (89.86%)
	Oral olanzapine	N (%)	67 (9.65%)	12 (5.61%)	<5	<5	31 (3.02%)
	Injectable non-depot olanzapine	N (%)	0	0	0	0	0

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
	Oral AP other than olanzapine	N (%)	27 (3.89%)	11 (5.14%)	<5	<5	8 (0.78%)
	Injectable non-depot AP other than olanzapine	N (%)	14 (2.02%)	0	0	0	0
	Depot AP other than olanzapine	N (%)	38 (5.48%)	<5	<5	<5	62 (6.04%)
	Oral typical AP: fluphenazine	N (%)	11 (1.59%)	0	0	0	0
	Oral typical AP: haloperidol	N (%)	9 (1.30%)	<5	0	0	<5
	Oral typical AP: promazine	N (%)	17 (2.45%)	0	0	0	0
	Oral atypical AP: aripiprazole	N (%)	23 (3.31%)	<5	<5	<5	0
	Oral atypical AP: clozapine	N (%)	22 (3.17%)	<5	<5	0	0
	Oral atypical AP: quetiapine	N (%)	14 (2.02%)	5 (2.34%)	0	<5	5 (0.49%)
	Injectable non-depot typical AP: haloperidol	N (%)	13 (1.87%)	0	0	0	0
	Injectable non-depot typical AP: promazine	N (%)	6 (0.86%)	0	0	0	0
	Depot typical AP: fluphenazine	N (%)	7 (1.01%)	0	0	0	0
	Depot typical AP: perphenazine	N (%)	0	0	0	0	<5
	Depot typical AP: zuclopenthixol	N (%)	0	<5	0	0	<5
	Depot atypical AP: aripiprazole	N (%)	12 (1.73%)	<5	0	0	29 (2.83%)
	Depot atypical AP: paliperidone	N (%)	17 (2.45%)	<5	0	<5	14 (1.36%)
	Depot atypical AP: risperidone	N (%)	<5	<5	<5	0	9 (0.88%)

AP = antipsychotic; DK-DHR = Danish Data Health Registries; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; IM = intramuscular; IQR = interquartile range; IQVIA DA Germany = IQVIA Disease Analyzer Germany; NAJS = Croatian National Public Health Information System; SD = standard deviation; SUCD = Semmelweis University Clinical Data.

During the diagnostics stage of the study, it was observed that a certain proportion of AP drug records were only recorded at ingredient level, without information on dose or formulation being available. An additional analysis was therefore conducted at the ingredient level, irrespective of formulation (**Table 8**). Compared with the analysis at ingredient-formulation level, the proportion with no initiation of AP treatment

decreased from 89.62% to 80.48% in HI-SPEED, remained unchanged at 86.0% in IQVIA DA Germany, and increased from 74.53% to 76.42% in NAJS, 82.71% to 84.44% in DK-DHR, and 89.29% to 90.71% in SUCD.

Olanzapine was identified in 6.92% (DK-DHR) to 9.53% (HI-SPEED) of records. The most commonly identified typical AP were haloperidol (1.11–2.04%), promazine (2.44% in NAJS), and fluphenazine (2.04% in NAJS). The most commonly identified atypical AP other than olanzapine were aripiprazole (3.00–3.62%), quetiapine (1.17–2.31%), and risperidone (1.50–2.99%).

Table 8. Switching patterns after intramuscular depot olanzapine discontinuation at ingredient level.

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
Number records	–	N	1,272	347	50	140	1,532
Number individuals	–	N	1,160	330	49	128	1,466
Age at the record of IM depot olanzapine discontinuation	–	Median [IQR]	40 [30–52]	44 [33–57]	46 [32–55]	41 [31–50]	38 [30–51]
		Mean (SD)	42 (14)	45 (15)	44 (14)	42 (13)	41 (14)
Age group at the record of IM depot olanzapine discontinuation	0 to 17	N (%)	0	0	0	0	<5
	18 to 64	N (%)	1,196 (94.03%)	304 (87.61%)	48 (96.00%)	129 (92.14%)	1,423 (92.89%)
	65 or above	N (%)	76 (5.97%)	43 (12.39%)	<5	11 (7.86%)	106 (6.92%)
Sex	Female	N (%)	578 (45.44%)	133 (38.33%)	18 (36.00%)	60 (42.86%)	506 (33.03%)
	Male	N (%)	694 (54.56%)	214 (61.67%)	32 (64.00%)	80 (57.14%)	1,026 (66.97%)
Initiated AP during the 60 days following IM depot olanzapine discontinuation	No AP initiated	N (%)	972 (76.42%)	293 (84.44%)	43 (86.00%)	127 (90.71%)	1,233 (80.48%)
	Olanzapine (excluding depot)	N (%)	121 (9.51%)	24 (6.92%)	<5	<5	146 (9.53%)
	Typical AP: fluphenazine	N (%)	26 (2.04%)	0	0	0	0
	Typical AP: haloperidol	N (%)	26 (2.04%)	<5	0	0	17 (1.11%)
	Typical AP: promazine	N (%)	31 (2.44%)	0	0	0	0
	Atypical AP: aripiprazole	N (%)	46 (3.62%)	<5	<5	<5	46 (3.00%)
	Atypical AP: quetiapine	N (%)	29 (2.28%)	8 (2.31%)	0	<5	18 (1.17%)
	Atypical AP: risperidone	N (%)	38 (2.99%)	<5	<5	<5	23 (1.50%)

AP = antipsychotic; DK-DHR = Danish Data Health Registries; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; IM = intramuscular; IQR = interquartile range; IQVIA DA Germany = IQVIA Disease Analyzer Germany; NAJS = Croatian National Public Health Information System; SD = standard deviation; SUCD = Semmelweis University Clinical Data.

During the diagnostics stage of the study, it was also observed that there was strong assumption made around duration, especially in DK-DHR and IQVIA DA Germany, where duration was calculated based on the World Health Organization (WHO) defined daily dose (DDD), where DDD for olanzapine is 10 mg. Furthermore, in NAJS, there was a default assumption of 30 days for all prescription records during the source data mapping process. With these assumptions, a relaxed assessment window from [1, 60] days to [-7, 60] days around observed discontinuation might not be adequate to observe initiation of AP. To further assess the potential impact, overall AP use within 60 days after observed IM depot olanzapine discontinuation was additionally summarised, including both (1) AP treatment initiated within the period, and (2) AP treatment initiated before IM depot olanzapine discontinuation and continued afterwards. Analyses were conducted at the ingredient-formulation level (**Table 9**) and ingredient level (**Table 10**). Substantial differences were observed between primary analysis (AP treatment initiated within 60 days after IM depot olanzapine discontinuation) and sensitivity analysis (overall AP use after discontinuation).

When overall AP use, including those initiated within 60 days after IM depot olanzapine discontinuation and those initiated before discontinuation but continuing into the assessment window, was considered at the ingredient-formulation level (**Table 9**), substantially more AP use was observed after IM depot olanzapine discontinuation. The proportions of records with no AP use within 60 days following IM depot olanzapine discontinuation ranged from 30.19% in NAJS to 67.82% in HI-SPEED when taking into consideration AP use initiated before discontinuation that continued into the assessment window, compared with 74.53–89.62% when only AP initiated within 60 days after discontinuation was considered. Specifically, these proportions decreased from 74.53% in primary analysis to 30.19% in sensitivity analysis in NAJS, 82.71% to 40.63% in DK-DHR, 86.00% to 40.00% in IQVIA DA Germany, 89.29% to 60.00% in SUCD, and 89.62% to 67.82% in HI-SPEED. Oral olanzapine use ranged from 7.70% in HI-SPEED to 41.12% in NAJS, while use of oral AP other than olanzapine ranged from 4.90% in HI-SPEED to 52.75% in NAJS. Depot AP other than olanzapine also increased, from 4.80% in primary analysis to 9.75% in sensitivity analysis in NAJS, 2.88% to 14.70% in DK-DHR, and 6.27% to 22.78% in HI-SPEED. Among oral AP other than olanzapine, the most commonly observed typical AP were haloperidol (0.39–9.43%), promazine (17.22% in NAJS), and fluphenazine (8.96% in NAJS), while the most commonly observed atypical AP were aripiprazole (0.52–13.76%), risperidone (2.59–12.00%), and quetiapine (2.68–10.66%). Injectable non-depot AP other than olanzapine were only observed in NAJS, including haloperidol (2.36%) and promazine (1.49%). Among depot AP other than olanzapine, the most commonly observed typical AP were zuclopenthixol (2.74–5.48%), perphenazine (2.02–3.26%), and haloperidol (0.39–2.22%), while the most commonly observed atypical AP were aripiprazole (2.88–8.62%), paliperidone (3.17–4.40%), and risperidone (2.42% in HI-SPEED).

Overall AP use after IM depot olanzapine discontinuation was also examined at the ingredient level, irrespective of formulation (**Table 10**). Compared with the ingredient-formulation analysis, the proportions with no AP use decreased from 40.63% to 34.87% in DK-DHR, 40.00% to 36.00% in IQVIA DA Germany, and 67.82% to 34.99% in HI-SPEED, remained similar in NAJS (30.19% versus 30.27%), and was unchanged in SUCD (60.00%). Olanzapine (excluding IM depot olanzapine) was the most commonly observed AP, ranging from 25.00% in SUCD to 49.57% in DK-DHR. The most commonly observed typical AP were haloperidol (4.03–10.61%), promazine (17.61% in NAJS), and zuclopenthixol (5.48–6.92%). The most commonly observed atypical AP other than olanzapine were aripiprazole (6.63–14.70%), risperidone (3.46–14.00%), and quetiapine (6.46–10.66%).

Table 9. Overall antipsychotic use after intramuscular depot olanzapine discontinuation.

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
Number records	–	N	1,272	347	50	140	1,532
Number individuals	–	N	1,160	330	49	128	1,466
Overall AP during the 60 days following IM depot olanzapine discontinuation	No AP use	N (%)	384 (30.19%)	141 (40.63%)	20 (40.00%)	84 (60.00%)	1,039 (67.82%)
	Oral olanzapine	N (%)	523 (41.12%)	141 (40.63%)	17 (34.00%)	35 (25.00%)	118 (7.70%)
	Injectable non-depot olanzapine	N (%)	0	0	0	0	0
	Oral AP other than olanzapine	N (%)	671 (52.75%)	99 (28.53%)	18 (36.00%)	30 (21.43%)	75 (4.90%)
	Injectable non-depot AP other than olanzapine	N (%)	35 (2.75%)	0	0	0	0
	Depot AP other than olanzapine	N (%)	124 (9.75%)	51 (14.70%)	6 (12.00%)	6 (4.29%)	349 (22.78%)
	Oral typical AP: fluphenazine	N (%)	114 (8.96%)	0	0	0	0
	Oral typical AP: haloperidol	N (%)	120 (9.43%)	12 (3.46%)	<5	9 (6.43%)	6 (0.39%)
	Oral typical AP: promazine	N (%)	219 (17.22%)	0	0	0	0
	Oral atypical AP: aripiprazole	N (%)	175 (13.76%)	15 (4.32%)	<5	10 (7.14%)	8 (0.52%)
	Oral atypical AP: quetiapine	N (%)	106 (8.33%)	37 (10.66%)	<5	<5	41 (2.68%)
	Oral atypical AP: risperidone	N (%)	123 (9.67%)	9 (2.59%)	6 (12.00%)	<5	<5
	Injectable non-depot typical AP: haloperidol	N (%)	30 (2.36%)	0	0	0	0
	Injectable non-depot typical AP: promazine	N (%)	19 (1.49%)	0	0	0	0
	Depot typical AP: haloperidol	N (%)	5 (0.39%)	<5	0	0	34 (2.22%)
	Depot typical AP: perphenazine	N (%)	0	7 (2.02%)	0	0	50 (3.26%)
	Depot typical AP: zuclopenthixol	N (%)	0	19 (5.48%)	0	0	42 (2.74%)
	Depot atypical AP: aripiprazole	N (%)	49 (3.85%)	10 (2.88%)	<5	<5	132 (8.62%)
	Depot atypical AP: paliperidone	N (%)	56 (4.40%)	11 (3.17%)	<5	<5	63 (4.11%)

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
	Depot atypical AP: risperidone	N (%)	<5	<5	<5	0	37 (2.42%)

AP = antipsychotic; DK-DHR = Danish Data Health Registries; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; IM = intramuscular; IQR = interquartile range; IQVIA DA Germany = IQVIA Disease Analyzer Germany; NAJS = Croatian National Public Health Information System; SD = standard deviation; SUCD = Semmelweis University Clinical Data.

Table 10. Overall antipsychotic use after intramuscular depot olanzapine discontinuation, at ingredient level.

Variable name	Variable level	Estimate name	Data source				
			NAJS	DK-DHR	IQVIA DA Germany	SUCD	HI-SPEED
Number records	–	N	1,272	347	50	140	1,532
Number individuals	–	N	1,160	330	49	128	1,466
Overall AP during the 60 days following IM depot olanzapine discontinuation	No AP use	N (%)	385 (30.27%)	121 (34.87%)	18 (36.00%)	84 (60.00%)	536 (34.99%)
	Olanzapine (excluding depot)	N (%)	523 (41.12%)	172 (49.57%)	18 (36.00%)	35 (25.00%)	514 (33.55%)
	Typical AP: haloperidol	N (%)	135 (10.61%)	14 (4.03%)	<5	9 (6.43%)	89 (5.81%)
	Typical AP: promazine	N (%)	224 (17.61%)	0	0	0	0
	Typical AP: zuclopenthixol	N (%)	0	24 (6.92%)	<5	<5	84 (5.48%)
	Atypical AP: aripiprazole	N (%)	187 (14.70%)	23 (6.63%)	<5	10 (7.14%)	213 (13.90%)
	Atypical AP: quetiapine	N (%)	106 (8.33%)	37 (10.66%)	<5	<5	99 (6.46%)
	Atypical AP: risperidone	N (%)	124 (9.75%)	12 (3.46%)	7 (14.00%)	<5	71 (4.63%)

AP = antipsychotic; DK-DHR = Danish Data Health Registries; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; IM = intramuscular; IQR = interquartile range; IQVIA DA Germany = IQVIA Disease Analyzer Germany; NAJS = Croatian National Public Health Information System; SD = standard deviation; SUCD = Semmelweis University Clinical Data.

6. DISCUSSION

6.1. Strengths and limitations of the research methods

A key strength of this study was the use of five routinely collected healthcare data sources from different European countries, enabling the characterisation of IM depot olanzapine use and discontinuation across diverse healthcare settings over an extended study period. The study examined multiple aspects of the treatment pathway, including temporal trends in initiation and discontinuation, initial and maintenance dose patterns, and AP treatment following IM depot olanzapine discontinuation. These analyses provided a more comprehensive understanding of treatment patterns while allowing for the potential influence of assumptions regarding drug exposure duration and differences in drug-record granularity across data sources to be explored.

There were fewer identified IM depot olanzapine users compared with the feasibility assessment. This was mainly due to the restriction of the study period in the current study, whereas no study period restriction was applied in the feasibility assessment that instead relied upon data contained in each of the full data sources. In addition, the feasibility assessment summarised the number of IM depot olanzapine users and records by adding up all record- and person-counts and did not account for individuals switching between different preparations.

In addition, IM depot olanzapine is administered by healthcare professionals, and treatment provided in hospital-based outpatient settings may not be fully captured in data sources relying primarily on prescription or dispensing records. This could have contributed to the low numbers observed in some data sources, despite the availability of treatment records being considered during the feasibility assessment. Differences in healthcare-setting coverage across data sources may also have influenced the identification of AP treatment following IM depot olanzapine discontinuation. In hospital-based data sources, AP treatment initiated following IM depot olanzapine discontinuation in these settings may not have been identified.

The low number of discontinuation events presented challenges in estimating the monthly prevalence of treatment discontinuation. To provide more interpretable estimates, the prevalence of discontinuation was additionally evaluated on a quarterly and yearly basis.

The assessment of treatment switching after discontinuation, particularly when specifying the formulation (oral/injectable non-depot/depot), was restricted by the granularity of the available data. To address this limitation and provide a broader understanding of treatment options after IM depot olanzapine discontinuation, switching was additionally evaluated at the ingredient level without considering the formulation. This aimed to improve the detection of AP treatment following IM depot olanzapine discontinuation.

The current analysis also relied heavily on drug exposure duration, which may be derived based on assumptions that differ across data sources. Drug exposure duration in DK-DHR and IQVIA DA Germany was estimated using the WHO DDD, while in NAJS it is recorded as 30 days by default during the source data mapping process. When inspecting the diagnostic results prior to actual study analysis, comparison of the exposure duration with the number of days between the start dates of two consecutive drug records indicated that exposure durations were longer than the observed intervals between consecutive records. For higher dose preparations, use of the DDD to derive exposure duration may have resulted in an artificially prolonged exposure period relative to the expected administration interval. While this may shift the estimated timing of discontinuation without necessarily affecting overall discontinuation prevalence, it could lead to an underestimation of AP treatment initiation following discontinuation, as treatment initiated after the actual discontinuation date but before the calculated end of exposure may not be identified as treatment initiated after discontinuation. To assess the impact of this limitation without altering the exposure information provided by the individual data sources, overall AP use after IM depot

olanzapine discontinuation, including both (1) AP treatment initiated after discontinuation, and (2) AP treatment continued from before discontinuation, was additionally examined as part of the analyses for objective 4. However, it should be noted that continued AP use may also reflect genuine concomitant treatment rather than solely assumptions regarding exposure duration.

Last but not least, the study was descriptive and was not designed to formally assess the impact of the shortage.

6.2. Interpretation

This study was motivated by the need to understand whether changes in IM depot olanzapine use, including an increase in treatment discontinuation, were observed following the drug shortage and to characterise AP treatment following treatment discontinuation. Overall, IM depot olanzapine was not commonly observed across the included data sources. Among individuals who continued treatment after initiation, most remained on the same preparation, while a substantial proportion had no IM depot olanzapine use observed by day 120. Towards the end of the study period, reduced initiation and increased discontinuation of IM depot olanzapine were observed, with increases in discontinuation particularly evident during 2024–2025 in NAJS, DK-DHR, and HI-SPEED. These temporal trend changes coincided with the period of the IM depot olanzapine shortage. However, it should be noted that this study was intended to be descriptive, providing context on temporal changes during the shortage period, rather than to formally assess the impact of the drug shortage. Within 60 days following IM depot olanzapine discontinuation, olanzapine (other than IM depot formulation) was the most commonly observed AP initiated.

Findings on the initial and maintenance dose should be interpreted in the context of the recommended dosing regimen for IM depot olanzapine. According to the product information, dosing and subsequent dose adjustment depend on the corresponding oral olanzapine dose (**Table 1**). Therefore, changes in the dose preparation would also be expected according to the recommended dosing scheme. However, the current study observed that staying on the same dose preparation was common among individuals who continued treatment. A high proportion of individuals had no observed IM depot olanzapine use by day 120. This finding was broadly consistent with a previous meta-analysis, which found that dropout due to inefficacy was more frequent among individuals receiving long-acting injectable olanzapine than among those receiving oral olanzapine (relative risk 1.52, 95% CI 1.12–2.07), based on pooled results from two randomised trials including 1,445 patients.[6] Findings from another multicentre observational study in Italy also indicated a high level of olanzapine discontinuation, with olanzapine having the highest 12-month discontinuation rate among the long-acting injectable AP assessed following the first prescription (62.5%, 95% CI 35.4–84.8%), compared with an overall discontinuation rate of 39.3% (95% CI 25.3–43.5%).[7] However, the reasons for the absence of subsequent IM depot olanzapine records were not investigated in the current study, and therefore, findings from the current study cannot be interpreted as treatment discontinuation due to inefficacy. To account for the possibility that the absence of treatment records resulted from individuals being out of observation in the data source, individuals with no subsequent record of IM depot olanzapine use were distinguished from those who were no longer under observation.

Identification of treatment following discontinuation was a major objective of the current study. Most individuals did not initiate a AP treatment after the observed discontinuation of IM depot olanzapine in the primary analysis. However, additional analyses considering overall AP use indicated that AP use after discontinuation was more common than that suggested by analyses restricted to treatment initiated within 60 days after IM depot olanzapine discontinuation. Oral AP were commonly observed following IM depot olanzapine discontinuation, with oral olanzapine being the most commonly observed AP and use of other AP ingredients remaining relatively uncommon. The frequent observation of oral olanzapine following discontinuation is clinically plausible, given that individuals receiving IM depot olanzapine have previously demonstrated tolerability and response to oral olanzapine. Indeed, IM depot olanzapine is indicated for

maintenance treatment in adults with schizophrenia who have been sufficiently stabilised with oral olanzapine before initiation.[2]

The ingredient level sensitivity analysis was intended to increase the detection of AP treatment following discontinuation by removing restrictions related to formulation (oral/injectable non-depot/depot). Unexpectedly, however, the number of individuals classified as not having initiated AP treatment within 60 days from discontinuation of IM depot olanzapine increased in NAJS, DK-DHR, and SUCD. One possible explanation could be due to the concatenation of individual drug exposure records into drug eras. The start of a subsequent exposure record after IM depot olanzapine discontinuation may be incorporated into an existing drug era and therefore be treated as continued use rather than treatment initiated within 60 days after discontinuation.

The analysis of overall AP use at the ingredient level, including both (1) treatment initiated within 60 days after IM depot olanzapine discontinuation, and (2) initiated before discontinuation and continued afterwards, was expected to improve detection of AP use and consequently decrease the proportion classified as having no AP use after discontinuation. However, in NAJS, a minimal increase of one individual classified as having no AP use was observed. This may be related to differences in the drug era concatenation definition. The number of days for gap era definition was changed from 42 days for injectable and IM depot formulations and 90 days for oral formulations in the primary analysis to 90 days at the ingredient level, regardless of formulation. As a result, two discrete injectable or IM depot exposure records separated by more than 42 days, but fewer than 90 days, could be concatenated into a single drug era in the sensitivity analysis. This could have altered whether an individual was treated within the assessment window of 1 day to 60 days after IM depot olanzapine discontinuation.

This study demonstrated the challenges of identifying discontinuation and subsequent AP switching patterns using routinely collected drug exposure records. Even in nationwide data sources with adequate numbers of IM depot olanzapine users, identification of treatment discontinuation and switching may have been affected by assumptions regarding drug exposure duration and the granularity of drug information available within each data source. These issues were particularly relevant for long-acting injectable treatments, for which prescription or dispensation records may not necessarily correspond directly to the duration of pharmacological exposure. The current study therefore not only provides information on temporal trend of IM depot olanzapine use and subsequent AP treatment following discontinuation, but also highlights methodological considerations for using routinely collected drug exposure records to investigate discontinuation and subsequent treatment management.

6.3. Generalisability

The results estimated from this study 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 five data sources from Croatia, Denmark, Germany, Hungary, and Sweden limits generalisability to the countries and settings covered by the respective data sources.

7. CONCLUSION

Observed IM depot olanzapine use was uncommon, with reduced initiation and increased discontinuation observed during 2024–2025. These changes in the trends coincided with the period of IM depot olanzapine shortage. A substantial proportion of records had no observed IM depot olanzapine use by day 120. Among individuals who remained on depot olanzapine treatment, most continued with their initial dose. Following discontinuation, initiation of AP treatment was uncommon, whereas overall AP use was more frequent when continued use was also considered, with olanzapine being the most commonly observed ingredient. Differences in drug exposure duration and the granularity of drug records across data sources should be considered while interpreting the results in discontinuation and the subsequent treatment patterns.

Overall, the findings indicate changes in the temporal trends of IM depot olanzapine use and discontinuation coinciding with the shortage period.

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9. ANNEXES

ANNEX I. Description of the Study Team

Study team role	Names	Organisation
Principal Investigator	Amy Lam	University of Oxford
Data Scientist	Nuria Mercade Besora Edward Burn	University of Oxford
Epidemiologist	Amy Lam Annika Jödicke	University of Oxford
Clinical Domain Expert	Anna Saura Lazaro	University of Oxford
Study Manager	Natasha Yefimenko Nosova	University of Oxford
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 (CIPH)
Danish Data Health Registries (DK-DHR)	Elvira Bräuner Susanne Bruun	Danish Medicines Agency (DKMA)
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 (SU)
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 (SMPA-GU)

*Data Partners do not have an investigator role. The role of the Data Partners is to execute analytical code and review and approve outputs using their expert knowledge about their respective data sources.

ANNEX II. Report Amendments

None.