Randomized clinical trial replication and second-stage study to evaluate the risk of serious infections in biological drug users with psoriatic arthritis and psoriasis using the Italian VALORE distributed database network

Introduction

The "Post-marketing evaluation of the benefit-risk profile of Originator and biosimilar biological drugs in the dermatological, rheumatological, gastroenterological and onco-hematological areas through the establishment of a single multi-regional network for the integrated analysis of data from health databases, active surveillance and clinical registries - VALORE project" is a post-marketing surveillance project aimed at evaluating safety, efficacy and drug utilization of biological drugs in Italy. This project was able to collect information on more than 300.000 biological drug users from 14 Italian region claims data, covering an overall population of about 50 million inhabitants. Several studies have already been published, but the reliability of this data source in the conduction of safety and efficacy studies has not yet been explored.

Index trial replication is a cutting-edge methodology in pharmacoepidemiology research that seeks to emulate the design and conditions of randomized controlled trials (RCTs) using observational data. It can enhance the credibility and reliability of observational study findings and allow the calibration of safety and effectiveness real-world outcomes on biological drugs.

The EXCEED trial (NCT02745080) was chosen as index trial to demonstrate the potential of the VALORE distributed database network in assessing efficacy and safety outcomes. The EXCEED trial is a randomized, double-blind, active-controlled, multicenter, parallel-group study evaluating secukinumab monotherapy and adalimumab monotherapy in patients with active psoriatic arthritis (PsA) who are naïve to biologic therapy and are intolerant or having inadequate response to conventional disease-modifying anti-rheumatic drugs (cDMARDs). More details about this clinical trial can be found in the article by McInnes et al.[1] The protocol of this study was published at the following link: https://cdn.clinicaltrials.gov/large-docs/80/NCT02745080/Prot_000.pdf.

Objective

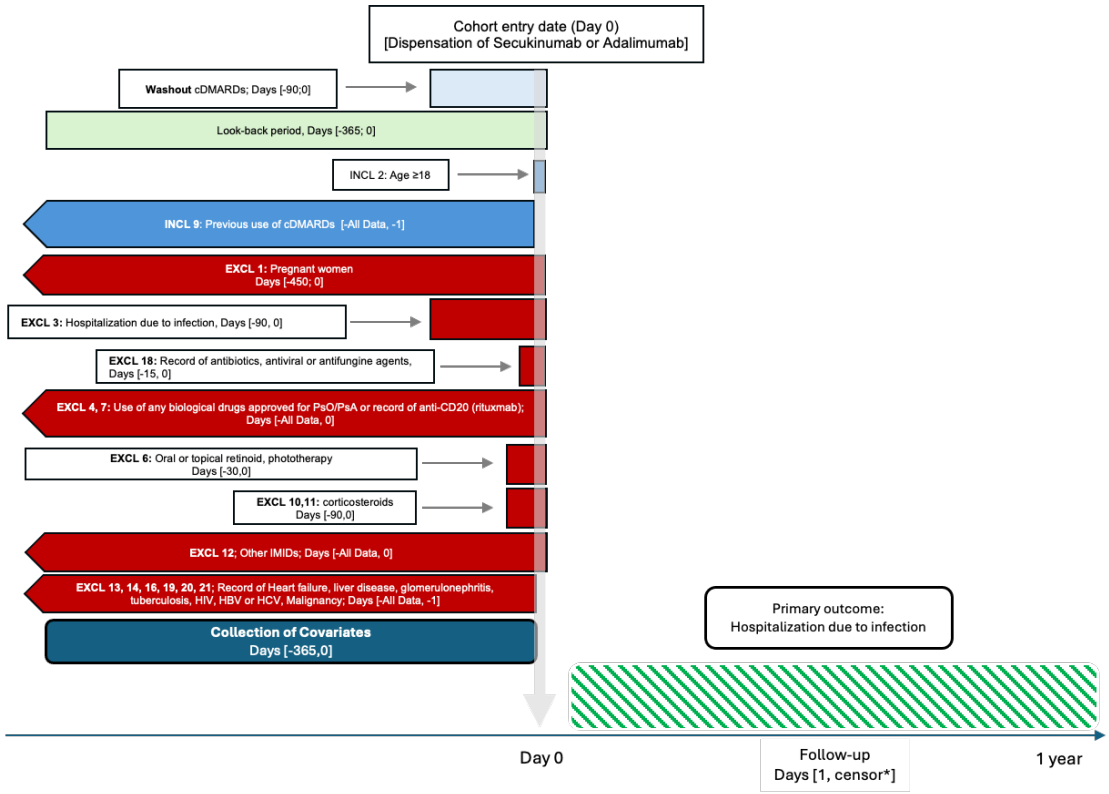
The aim of this study is to replicate the EXCEED trial assessing the safety in terms of serious infections (primary objective) and effectiveness (secondary objective) of secukinumab *vs* adalimumab in patients with psoriatic arthritis (PsA) and psoriasis (PsO) using data from the VALORE distributed database network.

1. Methods

1.1 Study design

This is an observational, propensity score-matched cohort study. **Fig 1** shows the design diagram.

Fig 1. Design diagram



*see "Study follow-up" section for censoring criteria; light blue box: washout period; green box: look-back period; green stripy box: follow-up period; blue: inclusion criteria; red: exclusion criteria; dark blue: covariates time-window. If the inclusion/exclusion box was too small to report the text, a blank box was reported using the -> symbol. More information about the single EXCL and INCL of the emulated trial and their definition is reported in Table A1 (i.e., INCL 3, EXCL 1…). Indication for use was retrieved through a validated META-algorithm.

1.2 Data source

This study used the claims databases from 14 Italian regions, which are part of the VALORE distributed database. The following regional claim data banks were considered: (1) inhabitant registry, including demographic information about the date of birth, sex, and date of registration in the regional healthcare system; (2) drug dispensing from pharmacy claims database; (3) hospital discharge records, including information on the date of hospital admission and discharge, principal diagnosis and up to five secondary diagnoses, and principal procedure and up to five secondary procedures; (4) exemptions from healthcare service co-payment database, collecting coded information about chronic diseases; and (5) outpatient diagnostic tests and specialist's visits database. Coverage of all these healthcare services is very high since Italy has a National Health Service offering universal care for all residents in each region. Drugs were coded using the Anatomical Therapeutic Chemical (ATC) classification system and the national drug code, while indication of use and causes of hospitalization were coded using the International Classification of Disease, 9th revision, Clinical Modification (ICD 9-CM). An R-based tool for distributed analyses developed by the Italian National Institute of Health (TheShinISS) was employed by each center

to locally elaborate claims data using a common data model, sharing only a fully anonymized dataset for central analysis, in compliance with EU General Data Protection Regulation regulations

1.3 Cohort selection

Subjects will be included according to the following steps:

- New users of secukinumab and adalimumab (defined as no previous use of adalimumab and secukinumab before the index date, i.e., the first dispensation) will be identified.
- At least 1 year of look-back (history in the database before the index date)
- The index date must be after December 31, 2014, and before January 1, 2022.
    - Rationale: The market authorization of secukinumab in Europe started on 01/2015, and the VALORE project collected data for each region at least until the end of 2022, allowing patients to be followed for at least one year after the index date (this was not true for Lazio region for which only data until 2020 were available).
- See other inclusion and exclusion criteria for cohort entry. Inclusion and exclusion criteria were adapted from the EXCEED trial as closely as possible. **Table A1 and Table A2** in the appendix show all the inclusion and exclusion criteria of the EXCEED trial with the respective emulation strategy and the flow chart of the study respectively.

1.4 Variables

1.4.1 Exposure-related variables

EXCEED trial	Replication	Approved posology for PsA and PsO (EMA)
Drug: Secukinumab Secukinumab 300 mg administered at Baseline, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks	**Drug: Secukinumab** The posology used in the EXCEED trial is the approved posology of secukinumab in patients with PsA and PsO	300 mg of secukinumab by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing
Drug: Adalimumab Adalimumab 40 mg administered at Baseline followed by dosing every 2 weeks	**Drug: Adalimumab** The posology used in the EXCEED trial is the approved posology of secukinumab in patients with PsA	PsA: 40 mg adalimumab administered every other week as a single dose via subcutaneous injection. As for PsO patients should have an initial loading dose of 80 mg

EMA: European Medicine Agency; PsA: Psoriatic arthritis; PsO: Psoriasis

As for adalimumab, patients will be characterized as originator or biosimilar users (index use)

1.4.2. Outcome variables

- Primary outcome

The occurrence of a serious infection during the follow-up will be considered as the primary outcome. In particular, the following serious infections requiring hospitalization will be included in the outcome definition: herpes simplex, herpes zoster, primary tuberculosis, pulmonary tuberculosis, extra-pulmonary tuberculosis, non-invasive candidiasis, invasive candidiasis, sepsis, endocarditis, viral hepatitis, pneumonia, non-invasive fungal infections, invasive fungal infections, infections of conjunctiva and other infections of the eye, COVID-19, osteomyelitis/infection of

joints, cystitis, infections of kidney, infections of skin and subcutaneous tissue, intestinal infectious diseases, other bacterial infection, nervous system infections, urinary tract infections, gynecological infections, infections of the upper respiratory tract (See **Table A3** of the Appendix). Time to onset will also be estimated as the number of days between the index date and the occurrence of serious infection disease.

- Secondary outcome

Discontinuation of the biological drug: If a subject has more than 60 days of treatment gap between the estimated end of exposure of the previous dispensing and the start of the next one (if any) or switches/swaps to another active ingredient, he/she will be defined as a discontinuer. *A defined daily dose* (DDD) will be used to define dispensation coverage of a single drug episode (secukinumab: 10 mg, adalimumab: 2.9 mg).
According to the summary of product characteristics, patients starting secukinumab with PsO/PsA should receive four doses in the first month after treatment initiation, while patients with PsO should initiate adalimumab with a loading dose of 80 mg; thus, stockpiling will not be considered to avoid overestimating the treatment coverage (DDD is calculated on the maintenance treatment regimen). Moreover, to avoid immortal time bias, the grace period will not be defined as a risk-free period, and gaps found within the grace period will be prospectively filled.[2]

1.4.3 Covariates

- Sex (0: male; 1: female)
- Age (years) at index date
- Calendar year of cohort entry
- Region
- Drugs used in the look-back period (y/n): At least one drug dispensing in all the look-back period for the following drugs: csDMARDs (methotrexate, leflunomide, cyclosporine and sulfasalazine). At least one drug dispensing in the year before index date: systemic corticosteroids, apremilast. Also, other non-immunosuppressant drugs will be searched: NSAIDs, antibiotics, antivirals, antifungal drugs, and acitretin.
    - Note: From the washout period and exclusion criteria, patients with a record of cDMARDs (3 months), corticosteroids (1 months) and antibiotics, antifungals and antivirals in the 15 days before the index date will be excluded
- Comorbidities (y/n):
    - diabetes mellitus (exemption from co-payment, hospital discharge record, drugs), any time prior index date
    - hypertension (exemption from co-payment, hospital discharge record, drugs), any time prior index date
    - chronic obstructive pulmonary disease (exemption from co-payment, hospital discharge record), any time prior index date
    - serious infections (hospital discharge record), in the year before index date
        - Note: From the exclusion criteria, patients with a record of infections in the 3 months before the index date will be excluded
- Specific record of PsO and PsA: to be searched in all the look-back period

1.5 Study follow-up

1.5.1. Primary outcome (hospitalization due to infections)

Both as-treated (AT), and intention-to-treat (ITT) analyses will be conducted with treatment defined as the index drug on the day of cohort entry.

For the AT analysis, the follow-up will start the day after initiation of secukinumab and adalimumab and will continue until the earliest date of the following events:

- Hospitalization due to serious infection (outcome)
- Date of drug discontinuation: If a subject has more than 60 days of treatment gap between the estimated end of exposure of the previous dispensing and the start of the next one (if any) or is switched/swapped to another biological active ingredient, he/she will be defined as a *discontinuer*. The date of drug discontinuation is the date of the end of coverage of the last dispensing.
- Record of JAK-i during follow-up.
    - Rationale: patients with JAK-i show similar risk of infection as those in treatment with biological drugs[3], and patients can move from a biological drug to JAK-i.
- End of availability of data/death
- 365 days after the index date
    - Rationale: The safety endpoint of the index trial was evaluated at 52 weeks after the start of the treatment

In case of the outcome occurrence, patients will be considered as events, otherwise as censored observations.

For the ITT analysis, patients will only leave the study in case of outcome occurrence, at the end of availability of data/death, or at one year after the index date.

1.5.2. Secondary outcome (discontinuation)

An AT analysis will be conducted: the follow-up will start the day after initiation of secukinumab and adalimumab and will continue at the earliest date of the following events:

- Discontinuation (outcome) – see section 1.5.1.
- End of follow-up/death
- 365 days after the index date

In case of the outcome occurrence, patients will be considered as events, otherwise as censored observations.

1.6 Confounding adjustment

<u>Propensity score (PS) fine stratification method</u>
Randomization cannot be replicated in healthcare claims data, but will be proxied through statistical balancing of measured covariates according to standard practice. The propensity score (PS) fine stratification approach[4] will be used to create pseudopopulations of secukinumab and

adalimumab users with balanced baseline characteristics. This approach is particularly suitable for very low exposure prevalences. Strata will be defined based on the PS distribution computed across the whole cohort (i.e. secukinumab and adalimumab users). Creating finer strata will provide greater confounding control without meaningful loss in precision. To this end, 50 strata will be considered. Observations from the nonoverlapping regions of the PS distributions were excluded (trimmed) from the analysis. To compute the PS, a multivariable logistic regression will be performed to predict the individual probability of having secukinumab or adalimumab dispensed based on the following covariates: age at index date (categorical variable with the following groups: ≤18, 19-44, 45-64, 65-79, ≥80 years), sex, calendar year, region, previous use of drugs (immunosuppressant as well as other classes), and comorbidities (see Section 1.4.3).
To assess the adequacy of covariates balance, the standardized difference[5] will be calculated for each covariate in the pseudo populations and will be compared to the one calculated in the original cohorts. Achieving a negligible difference (i.e. d< 10%) is recommended for prognostically important covariates[6]. To assess the reliability of the adopted PS-based fine stratification approach, a visual inspection of the histograms of the estimated PS distribution will be shown separately for secukinumab and adalimumab users in the pseudo populations. A complete overlap of the PS distributions will indicate the success of the method. For reference, the histograms of the estimated PS will also be shown in the original cohorts.

1.7 Statistical analysis

Descriptive analysis: characteristics of secukinumab and adalimumab incident users at the index date, stratified by drug classes, will be reported as absolute and relative frequencies (percentages). Moreover, the overall distribution of sex, age and other available covariates of patients reported in the index trial will be compared with those calculated in the selected cohort from the fully anonymized dataset.

Primary outcome: The incidence of serious infections requiring hospitalization will be estimated as the number of events that occurred out of the total number of person-years and will be reported per 1000 person-years for ease of interpretation. As reported in the index trial, the number and proportion of events among the total number of patients within each treatment group of the pseudo populations will be calculated, along with the relative risk (RR), which will be estimated using a log-binomial model. To statistically assess whether the RR differs significantly from that reported in the index trial, a single log-binomial model will be performed, using aggregate counts as the dependent variable (see also section 1.9). This model will include treatment, trial, and the treatment-by-trial interaction term. The significance of the interaction term will be evaluated to determine if there is a statistically significant difference.

The effect of secukinumab with respect to the adalimumab (as the reference drug) on the incidence of serious infections requiring hospitalizations at one year of follow-up will be estimated in the pseudo populations using the Cox Proportional-Hazards (PH) model with a sandwich (robust) variance estimator. Risks will be reported as Hazard ratios (HR) and their 95% confidence interval (CI). Based on the scaled Schoenfeld residuals, the PH assumption will be checked using statistical tests and graphical diagnostics. Kaplan-Meier curves will be plotted to estimate the cumulative number of events among secukinumab and adalimumab users.

Secondary outcome: Kaplan-Meier curves will be plotted to estimate the cumulative survival of persistent secukinumab and adalimumab users at one year after the index date in the pseudo

populations. The number and proportion of patients discontinuing secukinumab and adalimumab at one year of follow-up compared to the total number of patients in the pseudo populations will be calculated, as well as the RR, using a log-binomial model. The two RRs will be compared using the same methods reported for the primary outcome.

A p-value < 0.05 will be used to denote statistical significance. All statistical analyses and plots will be performed using R, version 4.3 (R Foundation for Statistical Computing, Vienna, Austria).

1.8 Sensitivity analysis

Primary and secondary outcome: the following stratification will be performed:

- Patients only with a previous record of PsA
- Stratification according to presence of a previous record of NSAIDs in the look-back period:
    - Rationale: To assess if this variable that was decided to be excluded can have affected our study results.
- Censoring those patients with a cDMARD in the follow-up period for primary and secondary outcome

1.9 Agreement between the index trial and the replicated trial

The evaluation of the agreement between the results of the index trial and the replicated trial cannot rely solely on the statistical significance or the overlap of confidence intervals, as there may be a lack of statistical power in one or both trial estimates. Therefore, in accordance with the DUPLICATE[7] initiative, the following metrics will be assessed:

- (1) **Full statistical significance agreement:** This is defined by whether the estimates and their confidence intervals fall on the same side of the null hypothesis.
- (2) **Estimate agreement**: This refers to whether the estimates from the replicated trial fall within the 95% CI of the index trial's results; additionally, a log-binomial model was also used to statistically confirm the observed agreement.
- (3) **Standardized difference agreement:** This measures the agreement between treatment effect estimates from the index and replicated trials. This measure quantifies the difference in effect size between two trials relative to the pooled standard deviation.

2.0 Extending the study design

If there is agreement (at least 2 out of 3 measures) between the results of the index trial replication and the index trial, the study design will be "extended" to answer questions that could not be explored in the index trial.

- **2.1 Exposures not assessed in the index trial**

Using the calibrated study design (study design of the index trial replication in which results were tested against the index trial), new users (no previous use of the drug before the index date, i.e., the first dispensation) of biological drugs approved for PsO or PsA will be added to the study cohort (the index trial included only secukinumab and adalimumab users).

In particular, the following exposures approved for PsA and PsO will be added: etanercept (anti-TNF-alpha), ustekinumab (anti-interleukin 12/23) and ixekizumab (anti-interleukin 17)

All inclusion and exclusion criteria used in the index replication will be maintained in the extended trial to maintain the original study design. The PS fine stratification model will be used to balance the baseline characteristics between groups. Pairwise comparisons will be made between adalimumab (reference drug) and the other included exposures for the primary and secondary outcomes.
Moreover, we decided to maintain the same study period used in the index trial replication despite it was chosen according to the secukinumab authorization (2015-2021). This choice will not impact in case of drugs were approved before 2014 since both drugs were on the market on starting of the study period (e.g., ustekinumab, infliximab). However, drugs approved after 2015 their utilization can start only after that date (e.g., ixekizumab – approval date 04/2016). Nevertheless, a PS fine stratification model will be used to weight patients also according to calendar year and adalimumab patients using the drug before approval of the comparator will have a null or marginal weight.

- **2.2 Assessment of the longer-term primary and secondary outcomes**

The primary and secondary outcomes will be evaluated at one year in the replicated trial as previously specified and according to the index trial. Additionally, the primary (serious infections rate) and secondary (discontinuation) outcomes will be evaluated at a longer follow-up (3 years)

- **2.3 Older patients' stratification**

The primary and secondary outcomes will be assessed by including only older patients (≥65 years)

	Primary				Secondary			
	1 year	3 years	Old 1 y	Old 3 y	1 year	3 years	Old 1 y	Old 3 y
ADALIMUMAB								
IR/ %*								
HR	REF	REF	REF	REF	REF	REF	REF	REF
ETANERCEPT								
IR / %*								
HR								
INFLIXIMAB								
IR / %*								
HR								
GOLIMUMAB								
IR / %*								
HR								
CERTOLIZUMAB								
IR / %*								
HR								
…								

*: IR: incident rate 1000 py for primary outcome / % of discontinuers;

References

1. McInnes et al. IB, Behrens F, Mease PJ, Kavanaugh A, Ritchlin C, Nash P, Masmitja JG, Goupille P, Korotaeva T, Gottlieb AB, Martin R, Ding K, Pellet P, Mpofu S, Pricop L; EXCEED Study Group. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. Lancet. 2020 May 9;395(10235):1496-1505.
2. Pazzagli L, Linder M, Zhang M, Vago E, Stang P, Myers D, Andersen M, Bahmanyar S. Methods for time-varying exposure related problems in pharmacoepidemiology: An overview. Pharmacoepidemiol Drug Saf. 2018 Feb;27(2):148-160. doi: 10.1002/pds.4372. Epub 2017 Dec 28.
3. Adas MA, Alveyn E, Cook E, Dey M, Galloway JB, Bechman K. The infection risks of JAK inhibition. Expert Rev Clin Immunol. 2022 Mar;18(3):253-261. doi: 10.1080/1744666X.2022.2014323.
4. Desai RJ, Rothman KJ, Bateman BT, Hernandez-Diaz S, Huybrechts KF. A Propensity-score-based Fine Stratification Approach for Confounding Adjustment When Exposure Is Infrequent. Epidemiology. 2017 Mar;28(2):249-257. doi: 10.1097/EDE.0000000000000595.
5. Sawilowsky, S (2009). "New effect size rules of thumb". Journal of Modern Applied Statistical Methods. 8 (2): 467–474
6. Wang SV, Schneeweiss S, RCT-DUPLICATE Initiative. Emulation of Randomized Clinical Trials With Nonrandomized Database Analyses: Results of 32 Clinical Trials. *JAMA*. 2023;329(16):1376–1385. doi:10.1001/jama.2023.4221

Table A1. Inclusion and exclusion criteria

	Criteria	EXCEED Study Protocol	Replication	References/Rational	Limitation of the replication
Wash out	WASHOUT	Any subjects who are receiving a cDMARD will be allowed to enter the study only after cDMARD discontinuation and appropriate wash-out e.g. 4 weeks prior to randomization visit except for leflunomide, which has to be discontinued for 8 weeks prior to randomization unless a cholestyramine wash-out has been performed	Record of cDMARDs: Days [-90;0]	We will use a larger time window due to the administrative nature of datasource	–
Inclusion criteria	INCL1	Informed consent must be obtained before any assessment is performed.	NA	–	–
	INCL2	**Male or non-pregnant, non-lactating female subjects at least 18 years of age.**	Patients +18 years old at first use of adalimumab or secukinumab and female without a CEDAP record. Days [-450;0]	A maximum of 15 months was chosen considering 9 months of pregnancy + 6 months after end of pregnancy to avoid the inclusion of lactating women.	Some regions don't have available CEDAP records thus stratification CEPAD y/n need to be performed
	INCL3	**Diagnosis of PsA as classified by CASPAR criteria and with symptoms for at least 6 months and with active PsA at baseline defined as ≥3 tender joints out of 78 and ≥3 swollen joints out of 76 (dactylitis of a digit, counts as one joint each).**	Record of psoriatic arthritis / psoriasis through a validated META-algorithm	Psoriasis and psoriatic arthritis are usually concomitant diseases and the specific indication for which the biological drug is dispensed could be difficult to identify in claims data. Thus, PsO/PsA algorithm used in the definition of the META-algorithm will be used. *"Spini A, L'Abbate L, Ingrasciotta Y, et al. Development and validation of a META-algorithm to identify the indications of use of biological drugs approved for the treatment of immune-mediated inflammatory diseases from claims databases: insights from the VALORE Project. Clinical Epidemiology. Volume 2024:16 Pages 395—407- https://doi.org/10.2147/CLEP.S445120"*	The cited article reported some issues in distinguishing between psoriatic arthritis and psoriasis using claims data: PsO: Acc 0.84 Se 0.89 Sp 0.83 PPV 0.48 NPV 0.98 PsA: Acc 0.82 Se 0.48 Sp 0.95 PPV 0.78 NPV 0.83 However, PsO/or PsA algorithm
	INCL4	**Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibodies negative at screening**	NA	–	–
	INCL5	**Diagnosis of active plaque psoriasis, with at least one psoriatic plaque of ≥2 cm diameter or nail changes consistent with psoriasis or documented history of plaque psoriasis.**	See Replication INCL3	See Reference /Rational INCL3	See limitation INCL 3
	INCL6	**Subjects with PsA should have taken NSAIDs for at least 4 weeks prior to randomization with inadequate control of symptoms or at least one dose if stopped due to intolerance to NSAIDs.**	NA	This inclusion criteria means that all the patients included in the RCT should have an active disease. However patients starting with biological drugs in real-world setting should have active disease and we believe that this criteria did not affected our study results. This choice was taken because the use of NSAIDs is diffultly collected by administrative data due to private purchase and most part of patients were excluded if considering it as an inclusion criteria (>85%). However a sensitivity analysis was conducted to assess if the exclusion of this criteria could have affected the study results by stratifying patients in users vs non-users.	
	INCL7	Subjects who are regularly receiving NSAIDs as part of their PsA therapy are required to be on a stable dose for at least 2 weeks before study randomization and should remain on a stable dose up to Week 52.	NA	–	–
	INCL8	Subjects receiving corticosteroids must be on a stable dose of ≤10 mg/day prednisone or equivalent for at least 2 weeks before randomization and should remain on a stable dose up to Week 52	NA	–	–
	INCL9	**Subjects must have previously been treated with a cDMARD, including but not limited to MTX, with an inadequate response to therapy, or must have stopped treatment due to safety/tolerability problems after at least one administration of the cDMARD.**	History of cDMARD Days [-All Data; -91]	–	Possible underestimation of the cDMARDs utilization in claims data due to private purchase (despite expected to be lower NSAIDs)
Exclusion	EXCL1	**Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the**	See INCL2	–	See limitation of INCL2

criteria		**termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.**			
Exclusion criteria	EXCL2	Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and minimum 16 weeks or longer if local label requires it after the last dose (e.g. 20 weeks for secukinumab, 5 months for adalimumab in EU).	NA	–	–
	EXCL3	**Chest X-ray or chest magnetic resonance imaging (MRI) with evidence of ongoing infectious or malignant process obtained within 3 months prior to screening and evaluated by a qualified physician**	Hospitalization or access to day-hospital due to infection Days [-90, 0] As for malignancy see EXCL21	–	–
	EXCL4	**Previous exposure to any biologic drugs for PsA and PSO, including but not limited to TNFα inhibitors, secukinumab or other biologic drugs targeting IL-17 or IL-17 receptor.**	History of biological drug approved for PsA and PsO Days [-All Data, 0]		–
	EXCL5	Subjects receiving high-potency opioid analgesics, including but not limited to, methadone, hydromorphone, and morphine.	NA	–	Not information on these drugs in the VALORE dictionary
	EXCL6	**Ongoing use of prohibited psoriasis treatments/medications (e.g., topical corticosteroids or ultraviolet (UV) therapy at randomization). The following wash out periods need to be observed: • Oral or topical retinoids: 4 weeks. • Photochemotherapy (e.g., PUVA): 4 weeks. • Phototherapy (UVA or UVB): 2 weeks. • Topical skin treatments (except in face, eyes, scalp and genital area during screening; only corticosteroids with mild to moderate potency): 2 weeks.**	Record of oral or topical retinoids or phototherapy. Days [-30, 0]		Cannot find PUVA, topical corticosteroids in the VALORE dictionary. Some regions don't have available outpatients encounter data (OED)
	EXCL7	**Previous treatment with any cell-depleting therapies, including but not limited to antiCD20 or investigational agents (e.g., alemtuzumab (Campath®), anti-CD4, anti-CD5, antiCD3, and anti-CD19).**	History of anti-CD20 (rituximab) Days [-All Data, 0]	–	No information from other cell-depleting therapies
	EXCL8	Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days until the expected pharmacodynamic effect has returned to baseline, whichever is longer.	NA	–	–
	EXCL9	History of hypersensitivity to any of the study drugs or excipients or to drugs of similar chemical classes	NA	–	–
	EXCL10	Any intramuscular or intravenous corticosteroid treatment within 4 weeks before randomization.	Record of systemic corticosteroids Days [-30, 0]		Exclusion also of those patients with a oral corticosteroid in the 4 weeks before index date
	EXCL11	Any therapy by intra-articular injections (e.g., corticosteroid) within 4 weeks before randomization.	See EXCL 10	–	See limitation of EXCL10
	EXCL12	Active ongoing inflammatory diseases other than PsA that might confound the evaluation of the benefit of secukinumab therapy.	History of rheumatoid arthritis, chron's disease, ulcerative colitis, hidradenitis suppurativa or uveitis before index date. Days [-All Data, 0]	Since they all are chronic diseases, all look-back period will be considered All algorithms will be retrieved from the following publication: *"Spini A, L'Abbate L, Ingrasciotta Y, et al. Development and validation of a META-algorithm to identify the indications of use of biological drugs approved for the treatment of immune-mediated inflammatory diseases from claims databases: insights from the VALORE Project. Clinical Epidemiology. Volume 2024:16 Pages 395—407- https://doi.org/10.2147/CLEP.S445120"*	–
	EXCL13	Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator	NA	–	–

		immunocompromises the subject and/or places the subject at unacceptable risk for participation in an immunomodulatory therapy			
	EXCL14	Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥160/95 mmHg), congestive heart failure (New York Heart Association status of class III or IV) and uncontrolled diabetes.	History of heart failure (primary diagnosis) Days [-All Data, 0]	Heart failure (not congestive): *Lorenzoni G, Baldi I, Soattin M, Gregori D, Buja A. A Systematic Review of Case-Identification Algorithms Based on Italian Healthcare Administrative Databases for Three Relevant Diseases of the Cardiovascular System: Hypertension, Heart Failure, and Congenital Heart Diseases. Epidemiol Prev. 2019 Jul-Aug;43(4 Suppl 2):51-61. doi: 10.19191/EP19.4.S2.P051.092. PMID: 31650806.*	No information about the congestive nature of heart failure neither uncontrolled hypertension and uncontrolled diabetes. However, in the PS comorbidities such as hypertension and diabetes will be included
	EXCL15	History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests (LFTs) such as aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/ serum glutamic pyruvic transaminase (ALT/SGPT), alkaline phosphatase or serum bilirubin.	History of hospitalization due to autoimmune hepatitis, viral hepatitis, other hepatitis, acute hepatic failure or transaminase elevation Days [-All Data, -1]	–	No lab values data are available in the VALORE distribuited database
Exclusion criteria	EXCL16	History of renal trauma, glomerulonephritis, or subjects with one kidney only, or a serum creatinine level exceeding 1.5 mg/dL (132.6 µmol/L).	History of glomerulonephritis Days [-All Data, -1]	–	No lab values, renal trauma, or information about patients with only one kidney are available in the VALORE distribuited database
	EXCL17	Screening total white blood cell (WBC) count	NA	–	
	EXCL18	Active systemic infections during the last two weeks (exception: common cold) prior to randomization.	Use of antibiotics, antiviral or anti-fungine Days [-15, 0] See also EXCL3		Limitation due to private purchase (not reimbursement) of the drugs. No information if this is a systemic infection
	EXCL19	History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5mm or according to local practice/guidelines), or a positive QuantiFERON TB-Gold test. Subjects with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated prior to enrollment.	History of tuberculosis infection Days [-All Data, -1]	–	–
	EXCL20	Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at screening or randomization	History of hospitalization due to HIV, HBV or HCV infection Days [-All Data, -1]	–	Patients with these conditions not hospitalized cannot be found
	EXCL21	History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).	History of malignancy Days [-All Data, -1]		
	EXCL22	Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the subject unsuitable for the trial.	NA		
	EXCL23	Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins).	NA		
	EXCL24	Any medical or psychiatric condition which, in the investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol.	NA		

	EXCL25	Donation or loss of 400 mL or more of blood within 8 weeks before randomization	NA		
	EXCL26	History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization.	NA		
	EXCL27	Plans for administration of live vaccines during the study period or within 6 weeks preceding randomization	NA		The VALORE database do not collect information on vaccines

Bold: Key inclusion and exclusion criteria reported in clinicaltrials.gov

Tabella A2. Flow chart

	Less excluded patients from selected cohort (n=76,431) by single criteria	**Remaining patients from selected cohort (n=76,431) by single criteria**	**Excluded patients (cumulative)**	**Remaining patients (cumulative)**
New users of secukinumab and adalimumab (after December 31, 2014, and before January 1, 2022) with at least 1-year of look-back		76,431		76,431 (100)
Exclusion of patients with a record of cDMARDs; Days [-90;0] (WASHOUT)	-13,267 (17.4)	63,164	-13,267 (17.4)	63,164 (82.6)
Selection of patients +18 years old at the index date and female without a CEDAP record; Days [-450;0] (INCL2)	-3,181 (4.2)	73,250	-15,634 (20.5)	60,797 (79.5)
Selection of patients with a record of psoriatic arthritis / psoriasis; Days [-All Data; + All Data] (INCL3)	**-44,804 (58.6)**	31,627	-51,903 (67.9)	24,528 (32.1)
Selection of patients with history of cDMARD; Days [-All Data; -91] (INCL9)	**-34,039 (44.5)**	42,392	-60,312 (78.9)	16,119 (21.1)
Exclusion of patients with a record d of hospitalization or access to day-hospital due to infection; Days [-90, 0] (EXCL3)	-835 (1.1)	75,596	-60,382 (79)	16,049 (21)
Exclusion of patients with a history of biological drug approved for PsA and PsO; Days [-All Data, 0] (EXCL4)	**-18,607 (24.3)**	57,824	-65,547 (85.8)	10,884 (14.2)
Exclusion of patients with a record of oral or topical retinoids or phototherapy. Days [-90, 0] (EXCL6)	-169 (0.2)	76,262	-65,608 (85.8)	10,823 (14.2)
Exclusion of patients with a history of anti-CD20 (rituximab); Days [-All Data, 0] (EXCL7)	-183 (0.2)	76,248	-65618 (85.9)	10,813 (14.1)
Exclusion of patients with a record of systemic corticosteroids; Days [-30, 0] (EXCL10)	-3,723 (4.9)	72,708	-66,028 (86.4)	10,403 (13.6)
Exclusion of patients with a history of rheumatoid arthritis, chron's disease, ulcerative colitis, hidradenitis suppurativa or uveitis; Days [-All Data, 0] (EXCL12)	**-28,786 (37.7)**	47,645	-66,823 (87.4)	9,608 (12.6)
Exclusion of patients with a history of heart failure; Days [-All Data, 0] (EXCL14)	-517 (0.8)	75,914	-66,889 (87.5)	9,542 (12.5)
Exclusion of patients with a history of hospitalization due to autoimmune hepatitis, viral hepatitis, other hepatitis, acute hepatic failure or transaminase elevation; Days [-All Data, -1] (EXCL15)	-368 (0.5)	76,063	-66,935 (87.6)	9,496 (12.4)
Exclusion of patients with a history of glomerulonephritis Days [-All Data, -1] (EXCL16)	-170 (0.2)	76,261	-66,946 (87.6)	9,485 (12.4)
Exclusion of patients with use of antibiotics, antiviral or anti-fungine Days [-90, 0] (EXCL18)	-2,787 (3.6)	73,644	-67,243 (88)	9,188 (12)
Exclusion of patients with a history of tuberculosis infection; Days [-All Data, -1] (EXCL19)	-17 (0.02)	76,414	-67,244 (88)	9,187 (12)
Exclusion of patients with a history of hospitalization due to HIV, HBV or HCV infection Days [-All Data, -1] (EXCL20)	-354 (0.5)	76,077	-67,244 (88)	9,187 (12)
Exclusion of patients with a history of malignancy; Days [-All Data, -1] (EXCL21)	-4,003 (5.2)	72,428	-67678 (88.5)	8,753 (11.5)

Bold: Criteria excluding more than 20% of the initial cohort

Table A3. Codes for infections (primary outcome)

Description	**ICD-9CM Codes**
Herpes simplex	054
Herpes zoster	053
Primary tuberculosis	010
Pulmonary tuberculosis	011, 012
Extra-pulmonary tuberculosis	013, 014, 015, 016, 017, 018, 137
Non-invasive candidiasis	1120, 1121, 1122, 1223
Invasive candidiasis	1124, 1125, 1228, 1129
Sepsis	99591, 99592, 78552, 7907, 038, 77181,77183
Endocarditis	03642, 07422, 0932, 09884, 421, 42292
Viral hepatitis	070
Pneumonia	480-486, 07889, 4870
Non-invasive fungal infections	0390, 0394
Invasive fungal infections	0391, 0392, 0393, 0398, 0399, 114, 115, 116, 117, 118, 4846, 4847, 7116
Infections of conjunctiva	077
Infections of the eye	3731, 3732, 3734, 3735, 3736
COVID-19	4803, 07982
Osteomyelitis/infection of joints	730, 711, 00323, 05671, 0985, 00324, 37603, 5264
Cystitis (UTI)	5950, 5954, 597, 5990
Infections of kidney	590
Infections of skin and subcutaneous tissue	686, 035, 0400, 56961, 681, 682, 72886, 7854
Intestinal infectious diseases	001-009, 567, 566
Other bacterial infections	020,021,022,023,024,025,026,027,030,031,032,033,034,035,036,037,038,039,041,042,0980,0999,0880,670,7907,77181,0419
Nervous system infections	00321,0360,0361,045,046,047,048,049,0530,0543,05472,05601,05821,05829,062,063,064,06641,0721,0722,09181,0942,09481,09882,10081,130,320,321,3230,3231,3232,3234,3236,324
Urinary tract infections	5950,5954,597,5990
Gynecological infections	6140,6142,6143,6145,6149
Infections of upper respiratory tract	460,461,462,463,464,465,466,4871