Shortening the time to confirm or to rebut **A**dverse events of interest related to innovative **T**herapies for immune-mediated inflamm**AT**ory d**I**seases: cross-talking between different data s**OUR**ces. **SATURATIOn study**.

Summary table of persons involved in the project:

Partner	Name	First name	Current position	Role & responsibilities in the project (4 lines max)	Involvement (person.month) throughout the project's total duration
UPEC	SBIDIAN	Emilie	PU-PH	Coordinator WP2	15p.month
UPEC	LE CLEACH	Laurence	PU-PH	Partner's scientific leader WP 1	8p.month
UPEC	VO	Thang	Pr Junior	Partner's scientific leader WP3	8p.month
UPEC	HOISNARD	Léa	Post-doc	Data management and Data analysis WP 3>Task3.2, partner's scientific WP2	12p.month
UPEC	El AARBAOUI	Tarik	MCF	Partner's scientific WP 2, Data management and Data analysis WP3	24p.month
UPEC	LEBRUN-VIGNES	Bénédicte	PH	Partner's scientific WP1	1p.month
UPEC	MAISON	Patrick	PU-PH	Partner's scientific WP2	2p.month
UPEC	BETTUZZI	Thomas	CCA	Data analysis	1p.month
UPEC	AFACH	Sivem	Engineer	Data management and data analysis WP1	12p.month
UPEC	PENSO	Laetitia	Post-doc	Data management and Data analysis WP2	12p.month
UPEC	GUELIMI	Robin	PhD	Data management and Data analysis WP 1	12p.month
UPEC	ABBOUD	Mounya	PhD	Data management and Data analysis WP2	36p.month
UPEC	To be recruited		Data manager	Data management WP1	24p.month
UPEC	To be recruited		Post-doc	Data analysis WP1	12p.month
UPEC	To be recruited		Bio-statistician	Data management and data analysis WP3	24p.month

1. Objectives and research hypothesis

The global prevalence of overall immune-mediated inflammatory diseases (IMIDs) is estimated around 5 to 7% of the general population.[1] Tumor necrosis factors inhibitors (TNFi) have been approved since the 2000's to treat patients with IMIDs and have considerably improved the prognosis of psoriasis, inflammatory arthritis or inflammatory bowel diseases, which all share common pathophysiological mechanisms through the TNF alpha pathway. Therefore, nowadays, treatments targeting molecules involved in the immune and inflammatory process, including TNFi, are becoming the standard of care in patients with IMIDs. However, due to their immunosuppressive nature, safety concerns were raised early, including risk of infections, malignancies, demyelinating diseases, autoimmune disorders, or heart failure. Twenty years later, the link between such adverse events (AEs) and TNFi is still unclear. Moreover, since 2015, a growing number of therapies have become available to treat patients with IMIDs[2] : biologic therapies targeting different pathways (interleukin 17 inhibitors, IL17i, and IL23i), as well as targeted therapies (Janus Kinase inhibitors, JAKi). Identifying AEs related to these new therapies as quickly as possible and with the best level of evidence is crucial for assessing benefit-risk ratios and for informing physicians and patients. Since IMIDs are chronic diseases with a prolonged therapeutic exposure, collecting long-term safety data is particularly important. Moreover, these are rare events.

It is therefore essential to study them regardless of the underlying pathology, to increase power and the ability to identify risk factors.

Data from randomized clinical trials (RCTs) are frequently used to assess AEs. This first step provides a partial detection. In 2011, the Cochrane Collaboration published a systematic review and a network meta-analysis (NMA) on AEs of biologics in RCTs with their extension periods when available, irrespectively of the underlying IMIDs.[3] In this study, the authors reported a positive association between certain biologics and specific AEs compared with controls. Even though these results are important, the generalizability to the overall population treated in routine practice is questionable since safety evaluations from RCTs are based on highly selected populations. In addition, although it may be circumvented by pooling results in NMAs, RCTs are also underpowered to detect rare events. Moreover, RCTs do not provide long-term follow-up, and reporting of AEs remains widely incomplete.[4]

If RCTs data are limited, observational data are mandatory to confirm a signal detection of AE as well as to estimate its effect-size. Observational data come from unselected populations, with long-term exposure and provide sufficient power to detect rare and serious AEs. Currently, several databases based on different recording methods are used in pharmacovigilance and pharmacoepidemiology to detect AEs.[5] For Harpaz et al, jointly analysing multiple data sources (**integrative approach**, including both RCTs and observational data) may improve detection of AEs.[6] However, synthesizing all these replicative results is highly time consuming, requires a heavy workload, and leads to delayed results. Indeed, the mean estimated time to complete a systematic review from registered project start to publication date was 67.3 weeks (IQR=42), for reviews in 2014 including a mean number of studies for the qualitative synthesis of 15 (from 0 to 291)[7]. In the light of the ever-increasing volume of published studies, and considering the large expected number of references for the IMIDs field, such integrative approach will allow results within a 2-year period. In order to improve knowledge about the benefit-risk ratio for a growing number of patients who could be treated by new biologics for their IMIDs, reliable and prompt analyses are needed. However, the automation of meta-analyses is still far from being able to significantly facilate the work of researchers, even though machine learning approaches, and tools to reduce the time required for a meta-analysis, have already been proposed.[8] Thus, our hypothesis is that assessing AEs related to biologics/targeted therapies **using a unique database, with large and exhaustive observational data** would allow to obtain earlier results as reliable as those obtained by an integrative approach which involves systematic reviews and meta-analyses of both RCTs and observational studies. Indeed, using a unique database will shorten the process of systematic reviews and meta-analysis including the following tasks: search, deduplication, selection, data extraction, bias assessments, summarization and synthesis of data.

Thus, the French National Health Data System (Système National des Données de Santé, SNDS) is a large and exhaustive database, which contains data regarding health care reimbursement of approximately 67 million individuals (98.8% of the French population) and which is linked to the national hospital discharge database (SNDS-PMSI) by a unique anonymous identifier. The SNDS has already been used in France to conduct real-life studies on large, unbiased and nationally representative samples, particularly regarding the use, safety and effectiveness of drugs.

All in all, treatment uncertainty may be highly detrimental and hinder patient's care. On the one hand, it deprives them from beneficial treatments by irrational fear of AEs. On the other hand, it exposes them to avoidable AEs. Thus, uncertainty may deeply disbalance the benefit-risk ratio and large health insurance database, such as the SNDS, could constitute a new corner stone for assessing AEs.

Thus, the **aim of SATURATIOn is to shorten the time to confirm adverse events of interest related to innovative therapies for immune-mediated inflammatory diseases using the French National health-insurance data.** To achieve this objective, we propose a 4-year programme to assess AEs of interest that might be missed in RCTs by (i) pooling RCTs data with observational data from registries, health-insurance database in an integrative approach, (ii) using the French medico-administrative data SNDS as a unique database, (iii) comparing the results obtained with the two methods to validate our hypothesis that SNDS could be useful to reduce time to assess AEs of biologics.

The SATURATIOn study will help clinicians to choose and select the biologic with the best benefit-risk ratio for patients with IMIDs.

2. Position of the project as it relates to the state of the art

Numerous studies have been conducted to identify AEs related to TNFi according to the underlying diseases and by using data from each of the following data sources: RCTs, registries, health-insurance databases. Nonetheless, we observed discrepancies between results. Since JAKi are recent therapies, as well as IL17 or IL23i, AEs related to their administration have been sparsely assessed and reported.
A previous systematic review and meta-analysis, which assessed the safety of biologics irrespective of the underlying IMIDs, only included data from RCTs (and not observational studies) until 2010.[3] It concerned only 5 TNFi, as other biologics were not yet developed. Certolizumab and infliximab were associated with a significantly higher risk of serious AEs, and certolizumab with a higher risk of serious infections. Data were limited for tuberculosis reactivation, lymphoma, and congestive heart failure. Generally speaking, the overall numbers of AEs of interest were too small for indirect comparisons for all the outcomes. Indeed, we already mentioned that clinical trials are not underpowered to assess safety outcomes[9,10]. RCTs have also limited external validity. For example, 30% to 80% of psoriasis patients receiving biologics in national cohorts are ineligible for randomized controlled trials. Moreover, ineligible patients are more likely to develop serious adverse events including serious infections than eligible patients.[11–13] National and international registries, while being relevant sources for providing complementary evidence regarding the short- and longer-term safety of biologics, use however different methodologies and can therefore provide diverging results. For example, Dávila-Seijo et al. and Yiu et al. showed no increased risk of serious infection with biologics versus non-biologics,[14] whereas Kalb et al. showed an increased risk with adalimumab and infliximab but not ustekinumab or etanercept as compared with retinoids or phototherapy.[15] More recently, a US cohort study of 107 707 psoriasis patients who were biologic-new-users showed lower risk of serious infection with etanercept and ustekinumab but not infliximab or adalimumab versus methotrexate.[16] In addition, only limited data are available on the most recent biologics (IL-17 and IL-23 inhibitors and JAKi).[17] Using the SNDS database, we have recently shown that the risk of serious infections was increased in new users of infliximab and adalimumab versus etanercept, whereas ustekinumab users had lower risk of having a serious infection but not new users of IL-17 among 40,000 and 12,000 patients with psoriasis and psoriatic arthritis treated with biologics, respectively .[18,19] Our findings were important because we identified the risk of infections at drug level (and not class level), including the most recent ones (IL17i, secukizumab). However, power was missing for the most recent drugs (few exposed patients for other IL17i or IL23i). In total, there is no available which pools all RCTs and observational studies regardless the of the IMIDS (integrative approach), while it would be the only way to reconcile discordant results and to increase statistical power and precision of treatments' effect sizes. Also, worth mentioning is the absence of a large observational study assessing all the AEs irrespective of the underlying diseases. Such study would be the only way to increase the statistical power in order to identify risk factors.
Medico-administrative data from SNDS have been widely used in France to conduct safety drug studies across various medications. However, there is no comparison available between SNDS studies and integrative approaches regarding the estimation of the risks of AEs.
Moreover, in order to strengthen validity of the results from medico-administrative studies, emulation of clinical trials with such data is particularly useful (see WP2>Task 2.2). It is important to understand in what context findings from medico-administrative studies match RCTs results.[20] To our knowledge, no such data are available regarding biologics regardless the underlying diseases. Emulated studies from medico-administrative data should apply adequate statistical adjustment to account for confounding. The high-dimensional propensity score (hdPS) is an automated data-driven or empirical approach to deriving variables from administrative data for inclusion in propensity score models.[21] Even though the use of high dimensional propensity scores does not replace a randomization, emulated studies from real-world data allow to infer from a larger population receiving the biologic treatment in clinical routine, during a longer follow-up compared with RCTs.
In conclusion, the **SATURATIOn study will contain 3 Work Packages**: In WP1, we will use an integrative approach in order to identify AEs related to biologics/targeted therapies; ii) In WP2, we will identify AEs related to biologics/targeted therapies using the French health-insurance database; machine

learning will be used for improving high-dimensional proxy confounder adjustment; iii) In WP3, we will compare results from the integrative approach and the French health-insurance data.

3. Methodology and risk management

Data sources

- **Published data** from RCTs, quasi-randomized controlled trials and observational studies (including registry, health-insurance database, clinical routine data-based studies) will be included in the integrative approach. For RCTs, phase I trials and cross-over trials will not be eligible. Single-arm, single-center observational studies, and observational studies with less than 200 participants will not be eligible. Indeed, these latter are less likely to detect any of the adverse events of interest given their incidence rate. Based on our preliminary data[18]; we identified more than 1,600 serious infections out of 42,000 patients with psoriasis under biologics. There were 10 different biologics. The number of participants in one cohort was very low (n=180) leading to a small number of events (2 serious infections during the follow up); making any conclusion impossible in this group.
- **French National Health Data System (Système National des Données de Santé, SNDS)**, which covers almost the totality (>99%) of the French population—68 million residents. The SNDS contains individual and pseudonymized outpatient data (age, sex, vital status, reimbursed drugs and procedures) that can be linked with public and private hospitalization data (admission date; discharge diagnoses according to the International Classification of Diseases, 10th revision [ICD-10] codes for the main, principal, related or accompanying diagnosis; medical procedures) from the French Hospital Discharge database (Programme de médicalisation des systèmes d'information [PMSI]). The SNDS also contains information on place of residence, complementary universal health insurance (CSS – Complémentaire Santé Solidaire, a system providing free access to healthcare for people with an annual income below 50% of the poverty threshold) and quintiles of deprivation index (coded from 1 to 5, 1 being the least deprived). Patients' status for a 100% reimbursement of care related to a severe and costly long-term disease (LTD) is recorded and LTD diagnosis is coded according to ICD-10. Due to the medico-administrative nature of this database, clinical information such as treatment indication is not systematically recorded.

Study populations and interventions:

Intervention group: Patients receiving TNFi for psoriasis (PsO), psoriatic arthritis (PsA), ankylosis spondylitis (AS), inflammatory bowel diseases (IBD)

Comparator group: Patients receiving other biological/targeted therapies or placebo (only for RCTs) for the same diseases, with the same severity as in the intervention group to avoid selection bias.

Details of the two groups and preliminary data are available in Table 1.

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Table1. Intervention and comparator groups

Groups	Class-level	Drug (year of first release in France)	**Preliminary data** on SNDS database (see *General scientific risks* paragraph below*)* **Number of sequences* per intervention**
Intervention	TNFi	adalimumab (2005); certolizumab pegol (2010); etanercept (2003); golimumab (2012); infliximab (2004)	205,000; 30,000; 109,000; 42,000; 95,000; respectively
Comparators	JAKi	baricitinib (2017); tofacitinib (2017); upadacitinib (2020)	11,000; 10,000; 9,000 respectively
	IL12/23i	ustekinumab (2010)	40,000
	IL17i	brodalumab (2018); ixekizumab (2016); secukinumab (2016)	2,000; 12,000; 33,000 respectively
	IL23i	guselkumab (2019); Risankizumab-rzaa (2020); tildrakizumab (2020)	9,500; 5,800; 1,200 respectively

*from 2010 to 2023, a total of 341,574 patients with IMIDS and new-users of biologic/targeted therapy were identified using the SNDS database. The number of sequences represents the number of patients who received at least one line of biological/targeted therapies during the study period.

Outcomes

Primary outcomes will be the following incident AEs of interest:

- Heart failures and Major Adverse Cardiovascular Events (MACEs) (including nonfatal stroke, nonfatal myocardial infarction or cardiovascular death),
- Serious infections (any infection meeting the regulatory definition of a serious adverse event, SAE)
- Malignancies excluding non-melanoma skin cancer (NMSC) and carcinoma in situ of the cervix,
- Psychiatric disorders (depression, suicidal ideation behaviour; neurotic, stress-related, or somatoform disorders; and personality and behavioural disorders)

Secondary outcomes

- NMSC and carcinoma in situ of the cervix,
- Demyelinating diseases and auto-immune diseases
- Pulmonary embolism and leg veinous thrombo-embolic events
- All reported events defined as SAEs.

General scientific risks: *To face a low number of AEs of interest for both datasets. To prevent an insufficient number of cases, we focused on all biologics/targeted therapies, regardless of the underlying diseases. In preliminary results, we have identified a large population, making us confident for the number of AEs of interest (a) For the integrative approach (WP1) we conducted the research equations for one disease (psoriasis) and we identified 7,677 records on MEDLINE and 11,161 on Embase leading to 300 reports (more than 80,000 participants, both RCTs and observational studies). Moreover we already identified the most recent network meta-analyses including all the RCTs for our pre-selected IMIDs and identified 197 RCTs and 68,705 participants with at least one IMID of interest and a biologic/targeted therapy; (b) as we obtained the regulatory authorization for WP2 (see c. Methodology and risk management > Regulatory and ethical consideration), we have been working on the targeted population (IMIDs) on the SNDS, and we identified 341,574 new-users of biologics/targeted therapies with the IMIDs of interest, the median number of different treatments during the follow-up was 2 (IQR_{25-75} 1-3). The total number of severe infections after the index date was estimated at 56,074.*

Work package 1: To identify AEs related to biologics/targeted therapies using an integrative approach

We will perform a systematic review and network meta-analysis assessing the risk of SAE in adult patients receiving **biologics/targeted therapies** for PsO, PsA, AS, or IBD comparing them against each other. Interventions will include infliximab, etanercept, adalimumab, certolizumab pegol and golimumab; only EMA/FDA approved doses will be considered. Comparators will be other biological/targeted therapies including IL12/23i, IL17i, IL23i, JAKi using only approved doses (Table 1),

as well as placebo only for RCTs. Indeed, in RCTs, characteristics of patients in placebo group in terms of phenotype, severity of diseases will be similar to those of the intervention groups. Non-biological treatments will not be included as comparators to minimize the risk of heterogeneity across population: in daily practice, in most countries, biological treatments are prescribed after a failure or a contraindication to a non-biological treatment; thus users of non-biological treatments might have a less severe disease. In multi-arm trials or studies evaluating more than two interventions, study groups assessing drugs other than those mentioned above, or doses that are not EMA or FDA approved, will not be eligible.

We will search all RCTs and observational studies (see Data sources>Published data) with no language or date restriction in the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and LILACS. The search equation will be constructed by the Trial Search co-coordinator of the Cochrane Skin Group (within which we already work on psoriasis disease, see Methodology and risk management>general scientific risk). We will look for additional unpublished data. At least two authors will independently select eligible references using a collaborative online management tool for systemic reviews (covidence) and will extract the data in a standardized form, including any of the AEs of special interest defined previously and any SAE. For RCTs, extraction will be done from clinicaltrials.gov results' database, clinical study reports[22] when available as well as from published data. Regarding the outcomes, in the case of multiple time points for RCTs, we will choose the furthest one from the date of initiation of treatment.

For time-to-event data from observational studies, we will extract the crude and adjusted/weighted hazard ratio (HR) and its 95% confidence interval (CI) from studies. If multiple adjusted estimates of intervention effect are reported, both the one adjusted at least on age and sex (mandatory covariates) and the one that is judged to minimize the risk of bias due to confounding will be chosen. For the RCTs, we will extract data to allow both intention-to-treat and per protocol analyses (as we are assessing safety outcomes). We will extract participants' baseline demographic and clinical characteristics that may act as effect modifiers (age, sex, obesity, duration and severity of the underlying disease, previous specific systemic treatment).

Assessment of risk of bias in included studies (by two authors independently). Risk of bias for each included RCT will be assessed using the Cochrane Risk of bias tool 2. Risk of bias for each observational study included will be assessed using the ROBINS-I tool. More details are available in the Cochrane Handbook for Systematic Reviews of Interventions version 6.3.

Measures of treatment effect. For time-to-event data, the extracted adjusted/weighted HR with 95% CIs will be used as a measure of treatment effect. To pool observational and RCTs data, we will estimate the log (HR) and its standard error from the binomial data of the RCTs.[23] Thus, the conversion of RRs to HRs for RCTs data will allow for later data synthesis. For every treatment, we will estimate the ranking probabilities of being at each possible rank for all outcomes. We will infer treatment hierarchy using the surface under the cumulative ranking curve (SUCRA).

Dealing with missing data. Authors will be contacted to request any missing data.

Assessment of heterogeneity. We will undertake meta-analyses only if we judge participants, interventions, comparisons, and outcomes to be sufficiently similar. Potential sources of heterogeneity will include participants' baseline characteristics (age, sex, weight, previous systemic treatment or not, and duration and severity of the underlying disease). We will investigate the distributions of these characteristics across studies and treatment comparisons to assess transitivity. Transitivity is the assumption required to combine direct and indirect evidence. To do so, it is necessary for direct comparisons to be similar in their distribution of effect modifiers. To reinforce the plausibility of the transitivity assumption, we will include in our analyses only trials and studies not involving co-interventions. In the classical meta-analyses, we will assess statistical heterogeneity by visual inspection of the forest plots and using the I^2 statistic and the estimate of the between-study variance (tau^2). In the network meta-analysis, the assessment of statistical heterogeneity in the entire network will be based on the estimated heterogeneity variance parameter (tau^2) estimated from the network meta-analysis models. We will also estimate the prediction intervals to assess how much the estimated heterogeneity affects the relative effects with respect to the additional uncertainty anticipated in

future studies. If important heterogeneity is detected, we will investigate the possible sources by conducting subgroup analyses (e.g., randomized versus non-randomized studies; for each underlying disease) and network meta-regressions.

***Assessment of reporting biases for randomized evidence and non-randomized evidence*.** To assess reporting biases, we will use 'comparison-adjusted funnel plots' by study design (for RCTs and observational studies) for all comparisons of an active treatment against placebo. If substantial funnel plot asymmetry is detected, we will investigate the presence of small study-effects in the network meta-regression.

***Data synthesis*.** For data synthesis, as recommended by the Cochrane handbook, we will exclude from analysis any non-randomized studies judged to be at critical risk of bias according to the ROBINS-I tool and will only include studies that are at serious, moderate or low risk of bias.

Network meta-analysis. After conducting pairwise meta-analysis, and if there is no evidence of important intransitivity, we will conduct a NMA combining the data from the randomized and non-randomized studies, for all outcomes and comparisons (both class- and drug-level analyses), to estimate the relative effects for all possible comparisons between any pair of treatments within a frequentist framework. We will conduct a NMA combining both randomized and non-randomized evidence for all outcomes and comparisons (both class- and drug-level analyses, see Table 1.) to estimate the relative effects for all possible comparisons between any pair of treatments within a frequentist framework. We will assess inconsistency, which is the potential disagreement between the different sources of evidence (RCTs or observational studies), both locally and globally. We will use the side-splitting method, and the design-by-treatment interaction model to evaluate the presence of inconsistency in the whole network.

Sensitivity analysis. To assess the robustness of our results, we will perform several sensitivity analyses for the primary outcomes: excluding studies with high risk of bias; including only studies with naïve-biological treatment patients or with previous-biological treatment patients; including only studies with an optimal adjustment.

Summary of findings and assessment of the certainty of the evidence. We will assess the confidence of the evidence from the network meta-analysis based on CINeMa (Confidence In Network Meta-Analysis).

Expected results: By applying the highest standard of methodology as described in the Cochrane Handbook, this integrative approach (both RCTs and observational studies) will provide the best estimate of the relative safety of biologics and targeted therapies.

Risk Management. Considering that participants in RCTs are highly selected, with a higher proportion of males, younger with less comorbidities that patients included in observational studies,[11,24] *we could face a problem of heterogeneity across populations from RCTs and observational studies. We chose as comparators other biological treatments, allowing us to compare populations with similar severity of the diseases, thus minimizing this risk of heterogeneity. In case of persistent intransitivity, we will conduct two separate NMA for (i) randomized and (ii) non-randomized evidence. Then, we will also standardize the results of the RCTs and observational studies using multilevel network meta-regression for population-adjusted treatment comparisons.*[25] *Standardization will help to reduce the heterogeneity between RCTs and observational studies. This will be possible by using individual-patient-data from RCTs, we asked using dedicated data sharing platforms such as vivli, yoda and clinical study sata request. Currently, we have already obtained the access to the Individual Patient Data (IPD) of 67 RCTs out of 82 listed on these platforms for psoriasis (including 30,465 participants).*

Work package 2: To identify AEs related to biologics/target therapies using the French National health-insurance data

Nationwide "exposed/unexposed" cohort study using the SNDS (see Data sources>French National Health Data System).

Study population and exposure definition

All adults (≥ 18 years old) with at least one prescription of TNFi for PsO, PsA/AS or IBD between January 1st 2010 and December 31 2022, will be eligible for inclusion. TNFi will include infliximab, etanercept, adalimumab, certolizumab pegol and golimumab (as in WP1). Drugs will be identified by using their Anatomical Therapeutic Chemical (ATC) classification codes. Algorithms used to identify PsO, PsA/AS or IBD in the SNDS have already been published.[26] Next, we will select TNFi new users, defined as those who have not received a prescription for these drugs for 1 year. Patients will be considered exposed to TNFi during the time from initiation (index date) to discontinuation. We will define the discontinuation of treatment as 1) a period of >60 days without a dispensation of the same treatment after the period covered by the previous reimbursement or 2) a switch to other biologics. The period covered by a prescription will be from 30 days to 82 days depending on the molecules. The discontinuation date will be defined either as the end of the 60-day period, or as the date on which another biologic is reimbursed. Only the first therapeutic exposure will be considered in this analysis. Lastly, we will exclude patients with a history of AEs of special interest (depending on the outcomes) within 5 years before the index date.

Definition of the unexposed population

The definition of the unexposed population will have to meet one important criterion: the severity of PsO, PsA/AS or IBD has to be comparable with the one of the exposed cohort. Thus, the PsO, PsA/AS or IBD population receiving other biological treatments including IL12/23i, IL23i and IL17i is candidate in the unexposed population (Table 1). These biologics are also the comparators used in the WP1. We will determine the time period from the initiation to the discontinuation as mentioned above. Preliminary data on the number of exposed and unexposed individuals are available in Table 1.

Outcomes

The different endpoints will be the occurrence of AEs of special interest listed in Table 2 which have already been used and validated in the SNDS.[27–32] Events will be identified by either hospital discharge diagnoses or a specific prescription or by an appointment to a long-term disease status after the index date.

Follow-up

Patients will be followed up to the **AEs of special interest** (Table 2), death from any-cause, exposure discontinuation (treatment discontinuation or switch), lost to follow-up (defined by the absence of any reimbursement for 12 consecutive months) or December 31, 2023, whichever came first.

Covariates

At baseline, covariates will include age, sex, comorbidities (diabetes, hypertension, dyslipidemia, chronic obstructive pulmonary disease [COPD], acute myocardial infarction, ischemic stroke, chronic renal failure, cancer, hepatic insufficiency/cirrhosis, hepatitis B, C and HIV infections, tobacco and obesity), and vital status. Definitions of these covariates have already been published.[26] For example, comorbidities will be identified according to algorithms developed by the French National Health Insurance Fund.[33] These algorithms have been developed to identify 58 health conditions (grouped into 15 categories) from the medical information available in SNDS using a lookback period of up to 5 years. Available medical information include diagnosis coded during hospital stays, long-term diseases, and specific drugs. We will also base our comorbidities' definitions on algorithms used for the adapted Charlson comorbidity index to a large health care database.[34] The number of hospital admissions in the 6 months preceding the index date will also be considered, as well as the number and type of other specific systemic treatments (cyclosporin, methotrexate, acitretin, phototherapy, sulfalazine, leflunomide, azathioprine, non-steroidal anti-inflammatory drugs (NSAIDs), specific topical treatments and systemic corticosteroids) in the 2 years preceding the index date. Specific covariates related to the AE of interest will be defined and extracted at baseline, but also during the follow-up.

Table 2. Definition of adverse events of special interest using the French health-insurance database

	ICD-10 codes for hospital discharge or long-term diseases	**Specific prescriptions (ATC)**
Hear failure Major Adverse Cardiovascular Events[28]	I50 I21, I24, I63, I64, I20.0, G45 (except G45.4)	
Serious infections[27]	A00-B99, ICD-10 codes specific to organs	
Malignancies excluding non-melanoma skin cancer (NMSC) and carcinoma in situ of the cervix[31]	C00 to C26, C30 to C34, C37 to C41, C43, C45 to C58, C60 to C76, C81 to C85, C88, C90 to C97, D05, Z08, Z511, Z512, C77 to C80	
Psychiatric disorders[29]	F20 to F25, F28 to F34, F38 to F45, F48	N05AN01, N06A, N05A, N03AG01/NO3AG02
NMSC and carcinoma in situ of the cervix[31]	C44, D06	
Demyelinating diseases and auto-immune diseases[30]	G35, M05 to M09, L93, L94, L95, M30 to M35, M360	
Pulmonary embolism and leg veinous thrombo-embolic events[32]	I26, I80 and I83	
SAEs	Any hospitalisation	

Statistical analyses

Regarding descriptive statistics of the study population, categorical data will be reported as counts (and percentages), quantitative data as mean ± standard deviation (SD) in the case of a normal distribution or otherwise, as median with its interquartile range (IQR).

As primary analysis, we will compute cause-specific Cox proportional hazards regression models to estimate the hazard ratio (HR) and 95% confidence interval (CI) of the occurrence of AEs of interest (one analysis per AE of interest) associated with exposure to TNFi, compared with other class of biologics/targeted therapies. The proportional-hazards assumption will be tested formally by using Schoenfeld residuals. To control for confounding by baseline covariates, HR_w values will be adjusted by using inverse probability of treatment weighting (IPTW).[35] Weights will be first based on the propensity score, which will be estimated with multinomial logistic regression including the covariates collected at the index date. Stabilized weights will be computed to preserve the sample size of the original data and produce an appropriate estimation of the main effect variance.[36] The balance between baseline covariates will be compared with standardized differences, before and after weighting.

If researchers are increasingly using administrative healthcare data to estimate the effects of interventions and treatment thanks to coverage of entire populations and nominal cost, concerns have been raised as to whether administrative healthcare data contain sufficient patient characteristics to make adequate statistical adjustment to account for confounding. The high-dimensional propensity score (hdPS) is an automated data-driven or empirical approach to deriving variables from administrative data for inclusion in propensity score models[37]. Therefore, we will use two different propensity score to apply IPTW method: one containing variables selected with empirical approach (hdPS) and one containing variables selected according to literature (PS) for sensitivity analysis.

For hdPS, we will use the steps described in Schneeweiss et al[37], who hypothesized that the large number of measured covariates available in health insurance databases may be used as proxies of unobserved confounding factors. The first step will be to identify different data dimensions, including inpatient diagnoses, medical or surgical procedures, and medications dispensed. In this project, we will consider three different dimensions: (a) diagnoses made on hospitalized patients; (b) procedures and interventions performed in hospital; and (c) unique medications dispensed to patients by outpatient pharmacies. The temporal window will be one year prior to study entry. The second step is to identify candidate covariates, thanks to prevalence of the codes, i.e proportion of patients having a specific code at least once during the 1-year period prior to study entry, we will select *n* codes for which prevalence will be between 50% and 100% with at least 100 patients. Numbers of digits of the codes used to calculate prevalence will depend on the diagnoses, procedures and drugs. Third, we will assess

how frequently each code is recorded for each patient during the baseline period. We will divide each code into three binary variables: code occurred ≥ 1 time, ≥ median number of times, and ≥ 75th percentile of the number of times. The next step is to combine information from all three dimensions (diagnoses, procedures and drugs) to reduce the total number of covariates. Prioritization of covariates will be done taking into account their marginal association with the outcome of interest and the expositions, and which may be used for building the hdPS.
Additionally, as some research have suggested that the hdPS approach could be improved when completed with other machine learning algorithms, a hybrid approach will also be attempted where the pool of covariates selected by the hdPS will be further refined using either the "Least Absolute Shrinkage and Selection Operator" (LASSO) or the more flexible Elastic-Net.[38,39]
For PS, the following variables will be included : age, sex, use of (i) biological agents, (ii) non-biological systemic and previously listed comorbidities will be systematically included in the propensity score. Depending on the AE of interest, additional covariates will be added. In the cases presenting a low number of events, we will use a linearized variance estimator that accounts for the fact that weights are estimated rather than known, allowing a correction of the variance estimation.
We will perform pre-specified subgroup analyses depending on the underlying disease. To assess the sensitivity of the estimated HR_w with respect to several possible models, we will perform the following additional analyses: 1) Fine-Gray competing risks analysis, computing IPTW sub-hazard ratios to account for the competing risk between all-cause of death and other AEs of interest; and 2) conventional multivariate Cox model computing adjusted HRs; 3) defining treatment discontinuation as >90 days without filling a prescription for the same treatment after the period covered by the previous prescription.

Expected results: For each AE of interest, we will provide an estimate of the relative safety of biologics/targeted therapies using the French health-insurance data. Such results will be available for each underlying disease separately. We will select covariates for high-dimensional propensity score thanks to machine learning tools ("least absolute shrinkage and selection operator" [LASSO] or Elastic-Net).
Risk Management: ***Identification of some AEs*** *of interest using the French health-insurance data could be challenging due to its administrative origin. Since 2017, REDSIAM, a network organized into thematic working groups by pathological domains, has aimed to develop and to validate pathology-specific algorithms based on the French health-insurance data. As the head of the skin REDSIAM group, we will easily be able to work with other groups for the most complicated AEs of interest (especially NMSC and carcinoma in situ of the cervix).* ***For competing events as death****, we need to assess (case-by-case) if a patient's death is due to the AE of interest or due to unrelated reason. This might be challenging as the SNDS contains reasons of death (Cépi-DC), but with a 3-year delay. As sensitivity analyses, we will use cause-specific hazard models to address this issue.* ***Loss to follow-up*** *over the time that is related to the AEs (i.e., informative censoring) could induce bias over time even if we use survival analyses. According to the proportion of loss to follow-up, analyses would be repeated with a marginal structural model (MSM) with inverse probability of censoring weights.*[40] *Inverse probability of censoring weighting (IPCW) is a semiparametric method for estimation of the model of interest that adjusts for censoring that is Missing at Random (MAR), meaning that censoring may depend on the observed past, but not on the future prognosis. However, less than 1% lost to follow-up are expected due to the French health system organization.* ***AEs of interest are severe, but rare AEs****. To obtain accurate estimation of the relative safety of biologics/targeted therapies, we need a large exposed population, thus, we assessed the safety of biologics/targeted therapies* regardless of the underlying diseases*.* ***Limits****. Using administrative healthcare data, variables regarding the disease phenotype or severity will be missing. However, we will select patients with similar disease activity as all biologics/targeted therapies are indicated for moderate to severe IMIDs. To avoid bias due to the selection of patients who are already treated by the drugs studied and possibly affected by the treatment at their entry in the study, we will include patients initiating treatments in both groups. As random assignment is not possible in observational studies, we will adjust for all confounding factors at baseline using hybrid approaches*

combining the high-dimensional propensity score with machine learning algorithms to minimize the residual confounding. Nevertheless, residual confounding will probably remain as administrative healthcare data do not enable us to adjust on some factors such as disease activity, lifestyle, or family history of events. Moreover, some variables recorded at baseline will rely on proxies (no available quantitative data on tobacco use or clinical data on obesity for example). However, other listed co-variables (co-morbidities, previous therapeutic lines or co-medication) are reliable structured variables defined thanks to ICD-10 codes, long-term disease status, or specific medications.[27–34]

Work package 3: To compare results from the integrative approach (WP1) and the French health-insurance data (WP2)

RCTs have limited external validity due to growing non-inclusion criteria over time. About 80% of participants of the French national cohort of psoriasis would not be eligible for phase III moderate to severe psoriasis trials whereas incidence of adverse events is higher among them .[24] In order to compare the results of the integrative approach with those from the more representative French health insurance database population have to be comparable. To do so, we will use two different methods: standardization and emulation.

Task 3.1. Standardization

First, we will standardize the results of the integrative approach (obtained in WP1) over the patients' characteristics of the French health-insurance data (obtained in WP2). Standardization will help to reduce the heterogeneity in terms of case-mix before directly comparing their results. As an example, men represent 70% of the RCTs population for psoriasis whereas the sex ratio of patients receiving TNFi for the same indication is 1:1 in France. To standardize results of one trial over the case-mix of the others, more than 10 different approaches exist: plug-in, inverse probability weighting, augmented inverse probability weighting or doubly robust approaches.[41] We will focus on 10 important prognostic variables that will be collected across all studies: age, sex, underlying diseases, associate-inflammatory diseases, biologic-naïve or not, previous non-biologic systemic treatment, obesity, heart failure, liver failure or kidney failure. We will standardize results of the SNDS study over the case-mix of the integrative approach by using the standard inverse probability weighting (IPW) approach. When the individual participant data of these trials are accessible, we will also consider other advanced approaches such as (i) the doubly robust approach and (ii) the augmented inverse probability weighting (AIPW) approach. A two-random-effect model can then be used to summarize the standardized results, and to quantify the case-mix heterogeneity between different trials and the SNDS database.[41]

Task 3.2. Emulating the RCT design from French health-insurance data

The second method will be to emulate trials[20] by using the French health-insurance data. Among the RCTs identified in the WP1, for each underlying diseases (PsO, PsA/AS or IBD), we will select RCTs with at least an active comparator (no placebo). Indeed, active comparator could allow us to study patients with the same severity of the underlying diseases. For each selected RCT, inclusion and non-inclusion criteria as well as specific prior treatments will be recorded according to protocols available on ClinicalTrials.gov or supplemental materials from published data. Patients from the French health-insurance data who had continuous enrollment in the database for 6 months before initiation of treatment studied and who met the inclusion criteria will be included. We will exclude patients meeting exclusion criteria. To control for confounding by baseline covariates, we will adjust models by using inverse probability of treatment weighting (IPTW). As in WP2, we will use two different propensity score: one containing variables selected with an empirical approach (hdPS combined LASSO/Elastic-Net) and one containing variables selected according to literature (PS) for sensitivity analysis. For PS, confounders will include demographics, previous specific systemic treatments, associated-IMIDs, comorbidities, and relevant disease-specific variables, including procedures, and indicators of health care utilization as proxy for overall disease state, care intensity, and surveillance which will be measured during the two years before drug initiation. Outcomes will be the AEs of interest. Lastly, we will calculate the treatment effect as detailed in the WP2 and compare it to what is reported in trials. We will use as a conclusion the 3 binary agreement metrics proposed by Franklin

et al : (1) “regulatory agreement” defined as the ability of the French health-insurance data study to replicate the direction and statistical significance of the RCT finding; (2) “estimate agreement” defined as a HR estimate from French health-insurance data that is within the 95% CI of the RCT estimate , (3) we will conduct hypothesis tests to evaluate whether there is a difference in findings by calculating the standardized difference between the RCTs and French health-insurance data effect estimates.

Expected results. We will compare these results to those from the integrative approach using challenging and innovative methods: If the results based from the SNDS are proven to be at least as good as those from the integrative approach, this will allow future studies to be based solely on the SNDS. Therefore compared to the lengthy and time-consuming approaches based on meta-analyses estimated at 67 months from the registered project start to publication date,[7] the one from SNDS will shorten the time required to reach conclusion regarding AEs. Additionally, with the use of the SNDS, we will improve the external validity of the results, as we will assess the safety of biologics/targeted therapies in an unbiased population including specific population usually excluded (or under-represented) from RCTs: women, elderly patients, and patients with comorbidities.[24]

Risk Management:

***Identification of some AEs** of interest using the French health-insurance data could be less accurate than into RCTs due to the lack of clinical data. However, SNDS database provides, among others, data coded by physicians during the hospital stay which correspond to proper diagnosis of disease. Indeed, these codes rely on all clinical, biological and imaging data brought to the attention of the physicians. Moreover, most of the adverse events studied are coded either during hospital stay or as long-term diseases**. AEs of interest are severe, but rare AEs**. To obtain estimation of the relative safety of biologics/targeted therapies, we need a large exposed population. By using emulated study on SNDS, we will decrease the total number of exposed patients included due to inclusion/exclusion criteria. However preliminary results indicated that from 2010 to 2023 341,574 patients with IMIDs of interest received at least one biologic/targeted therapy in France, with a total number of 56,074 severe infections after the index date (see Methodology and risk management > General scientific risks paragraph and Table 1). This high number of exposed patients make us confident regarding the feasibility of trials emulation thanks to SNDS data. **Risk in applying the target trial emulation framework.** Because treatment assignment is neither blind nor random, valid causal treatment effects are estimated if the identification principles of causal inference are satisfied. We will pay attention to the design of the emulated trial in terms of eligibility criteria, treatment assignment, outcomes, baseline and follow-up; we will justify the causal inference assumptions including exchangeability, consistency and non-interference.*

Regulatory and ethical considerations

This research falls within the framework of the “Reference Methodology for the processing of personal data implemented in the context of research in the health field” (MR-004 modified).

For this protocol, the CNIL authorization will not be necessary for the WP1 because we will use aggregated data (WP1) from already published RCTs or observational studies. The project on SNDS data (WP2) is the subject of an agreement between Paris-Est Créteil University and the French National Agency for the Safety of Medicines and Health Products (ANSM) which allows us to benefit from CNIL authorization from ANSM to use health insurance data (convention n°2022S063). This permanent access is given according the French Decree No. 2016-1871 of December 26, 2016 relating to the processing of personal data called "National Health Data System" and French law articles Art. R. 1461-13 and 14. For this protocol, the Committee for Public Protection (CPP) agreement will not be necessary because NMA will synthesize data from already published studies and will address research questions closed to those to which participants originally consented.

This research will follow the French National Charter for Research Integrity (https://www.inserm.fr/en/our-research/scientific-integrity/), including the registration of our protocol on the Open Science Framework database. All discrepancies with the protocol will be justify.

This research belongs to the concept of social responsibility as it will provide the best safety profile according to the current advances.[42] All the researchers that will work on SATURATIOn project have no financial conflict of interest following the National Institute of Health requirement to promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct, and reporting is free from bias resulting from investigator financial conflicts of interest.

Open science practices

Data from WP1 (integrative approach). An editable file containing all extracted data and analytical codes will be available on a dedicated platform.

Data from SNDS database (WP2). All algorithms used for IMIDs diagnosis, identification of severe adverse events, therapeutic sequences and co-morbidities will be made available on a dedicated website. The statistical programming used on the SNDS (scripts on SAS and R softwares) will also be open source. Data sharing is not applicable for raw SNDS data. According to data protection and the French regulation, the authors cannot publicly release the data from the French national health data system (SNDS). However, any person or structure, public or private, for-profit or nonprofit, is able to access SNDS data upon authorization from the French Data Protection Office (CNIL Commission Nationale de l'Informatique et des Libertés) to carry out a study, research, or an evaluation of public interest (https://www.snds.gouv.fr/SNDS/Processus-d-acces-aux-donnees and https://www.indsante.fr/). However, aggregated data will be available on request.

I. Organisation and implementation of the project

a. Scientific coordinator and its consortium / its team

Emilie Sbidian is a full Professor in Therapeutics and a dermatologist with an extensive experience in pharmacoepidemiology. She is the author of more than 180 articles, including senior author of publications in Ann Rheum Dis, Arthritis Rheumatol, J Allergy Clin Immunol, JAMA Dermatology, J Clin Epidemiol (Index H: 40). She is head of EpiDermE, a research team dedicated to pharmacoepidemiology. Her research work is dedicated to the benefit-risk ratio of systemic treatment for psoriasis. Indeed, she is the lead author of the living Cochrane SR and NMA of systemic pharmacological treatments for chronic plaque psoriasis. She also has a strong experience in the use of the French health-insurance database (SNDS) by developing and validating algorithms to identify patients with PsO/PsA (PMID: 32911531, 32364321, 29791721, 33585948), and assessing effectiveness and safety of biologics for these patients (PMID: 36198438, 34287624, 34244706, 33894022, 34279061, 34310699, 31758801, 31991503, 31021438). Emilie Sbidian has a solid experience in the coordination of research programs. Her implication in SATURATIOn ANR (30% of her time) will ensure the efficient collaboration between EpiDermE's members and will provide the global scientific direction. Considering her experience in the use of SNDS, she will lead WP2 and will work with Laetitia Penso and Mounya Abboud for the statistical analyses. **Laetitia Penso** defended her PhD in 2022, which aimed to assess severe infectious risks of new immunomodulatory therapeutics in psoriasis using SNDS data. After a postdoctoral year in 2023 at EREN (U1153 Inserm/U1125 Inrae/Cnam/Université Sorbonne Paris Nord), Laetitia Penso will come back to EpiDermE as a full-time researcher. **Mounya Abboud** is a PhD student who has obtained funding from the National Agency for Safety of Medicines and Health products to conduct a three-year PhD program (November 2023) to conduct the WP2 of SATURATIOn project. **Laurence Le Cleach** is a professor in Therapeutic and the co-director of EpiDermE. As head of the Cochrane skin group, she has a strong experience in the coordination of research programs of systematic reviews and meta-analyses (more than 10 in the dermatology field) as well as in the coordination of meta-research programs. Indeed, she developed meta-research works using the identification of recurrent shortcomings and biases brought to light during the realization of Cochrane's systematic reviews and meta-analyses. As a consequence, she will lead the WP1 and work with **Robin Guelimi**, a PhD student and **Sivem Afach**, a research engineer who defended her thesis under the supervision of Laurence Le Cleach in 2021. Her PhD was dedicated to the methodological and ethical relevance of the placebo group in randomized controlled trials evaluating systemic therapy

in moderate to severe plaque psoriasis. **Thang Vo** has been a Pr Junior in the team since 2023. His topic of interest consists in the development of novel approaches regarding causal inference in meta-analysis and heterogeneity assessment. He is working on mediation analyses methods for systematic reviews and meta-analyses, which are techniques commonly used to assess the causal mechanisms by which a treatment may affect an outcome. He joined the team to develop statistical techniques that combined aggregated and individual patient data (IPD) data in causally interpretable meta-analysis and extension to network meta-analysis. Thus, he will lead the WP3. **Lea Hoisnard** is a public health physician and postdoc, who has a solid experience in the use of SNDS. She defended her thesis which aimed to assess the safety of JAKi in 2023. She also received a funding for a research program, which aims to emulate a safety trial for JAKi compared with TNFi in the SNDS database (MESSIDORE grant, Inserm) and will start a 1-year post-doc in the team SOFA (INRIA) to increase her knowledge on deep learning methods. She will work on WP3> Task 3.2 with **Tarik El Aarbaoui**, who is an associate professor in Drug Science and Other Health Products. He joined EpiDermE in 2021, with a research program dedicated to the safety profil of JAKi used for IMIDs. Lastly, the team will beneficiate from the expertise of **Patrick Maison**, head of the scientific delegation and data office of the French Agency for the Safety of Medicines and Health Products (ANSM) and professor of Pharmacology; **Benedicte Lebrun-Vignes**, head of the regional pharmacovigilance centers in Île-de-France area, whose research interests focused on drug adverse effects, especially cutaneous adverse effects, particularly using national and worldwide pharmacovigilance databases; and **Thomas Bettuzzi**, fellow in the dermatology department with a research activity focused on serious cutaneous adverse drug reactions and pharmacovigilance.
Monthly meetings will be organized between the team members to reciprocally communicate the main results of the research project. Teleconferences will be held for scientific discussion whenever necessary.

Gantt diagram

			Year1			Year 2			Year 3			Year 4		
			Q1	Q2	Q3	Q1	Q2	Q3	Q1	Q2	Q3	Q1	Q2	Q3
WP 1: To identify AEs related to biologics/targeted therapies using an integrative approach		selection extraction assessement risk of bias assessment of heterogeneity data synthesis valorisation												
WP 2: To identify AEs related to biologics/targeted therapies using the French health-insurance data (PhD program already funded)		identification of the study population (already done) identification of the exposures (already done) identification of the outcomes statistical analyses valorisation												
WP 3: To compare results from the integrative data and the French health-insurance data	**Task 3.1. Standardization**	identification of the variables statistical analyses data synthesis : compare the 2 approaches valorisation												
	Task 3.2 Emulate trials	identification of RCTs extraction of variables from posted protocols statistical analyses data synthesis : compare the 2 approaches valorisation												

Q: quadrimester; WP: work package; AEs: adverse events; RCTs : randomized controlled trials

need funding

II. Impact and benefits of the project

Adverse events (AEs) related to treatments have a major impact on global health. In OECD (Organisation for Economic Co-operation and Development) countries, 15% of total hospital activity and expenditure is a direct result of AEs. 'Medication Without Harm' which aims to reduce the level of severe, avoidable harm related to medications globally by 50% over five years, is one of the 3 goals of the global health priority of the WHO initiative Patient Safety.[43,44] The main interests of SATURATIOn are (i) to assess the properties of the SNDS in the detection of AEs compared with the integrative NMAs approach and (ii) to shorten the time to confirm adverse events of interest related to innovative therapies for immune-mediated inflammatory diseases using the National French health-insurance. Our **preliminary data** focused on serious infectious events in psoriasis. Based on more than 40,000 psoriasis patients with psoriasis under biologics identified using the SNDS database, we have recently shown that the risk of serious infections that the risk of serious infections was increased in new users of infliximab and adalimumab versus etanercept, whereas ustekinumab users had lower risk of having a serious infection but not new users of IL-17 and IL-23 inhibitors.[18] This study was published in July 2021, with a first submission in January 2021. As a demonstration of the relative short time scale made possible by using the SNDS data, this project was started in January 2020 and was therefore carried out in one year. In parallel, we have started a systemic review and meta-analysis on the efficacy and safety of biologics for psoriasis since 2018, secondarily focusing on severe infectious risks.[4] Because of the small number of events, we used alternative statistical methods, with the binomial-normal model for all biological treatments, and we found an excess risk of serious infection for TNFi, but not for other biologics. However, the small number of events prevented us to perform a drug-level analysis such as the one we did when using the SNDS data. Moreover, initially we did not include the observational studies in the systematic review. This integrative approach (equivalent to WP1) for psoriasis has been ongoing for one year (300 reports were identified, see > ***General scientific risks***), and extraction is ongoing. These preliminary data confirm that systematic reviews and meta-analyses take a long time to complete (estimated at 1.5 years for smaller SRs)[7] and require a large number of workers. The next step is now to include a higher number of exposed patients to these treatments to reach the number of events needed to validate our future results as the link between AEs of interest and biologics is still unclear (> ***background***). The SATURATION project will therefore concern all IMIDs related with the use of biologics/targeted therapies. The interest of WP3 is to ensure that a method using a unique country's health insurance data (here the SNDS, WP2) yields results similar to the pooled data from all the trials and observational studies published on the subject at the time of analysis all over the world. **If we confirm our hypothesis, our conclusions may be applicable to other countries.** That's why we think SATURATIOn project is a valuable project that could allow the fast generation of appropriate analyses in order to confirm other AE-drug associations if needed. **This model, if fully applicable for other drug classes, aims to broadly strengthen existing pharmacovigilance systems,** even if other drugs will probably lead to new diseases' and outcomes identification. Indeed, the transposability of this project to all different therapeutic classes will require a significant generalization work and could be more easily achieved by relying on the scripts and methods we will provide on an accessible platform (>***Open science practices***).

Although AEs related to drugs are mainly a concern for medical reasons, they also interact deeply with the civil society and may generate judiciary affairs, press scandals, as in the valproate or the mediator affairs. In addition, with regard to patients and prescribers, confidence into a treatment could be altered by the risk of AEs even though the drug might be highly beneficial. On the opposite, exposition to avoidable serious AE is highly detrimental for patients. Therefore, in case of medical or societal suspicion of AEs, the access to reliable analyses with prompt, rapid identification and confirmation of AEs via the SNDS, associated with their respective incidence and risk factors, would be of prime interest. SATURATIOn will focus on chronic inflammatory diseases with a global prevalence ranging from 5 to 7% of the general population. Biologics are the second biggest drug expenditure reimbursed by the French health insurance, just after anti-neoplastic drugs (close to 2 billion euros in 2019, https://assurance-maladie.ameli.fr/). As the SNDS covers 99% of the French population and all

biologics are reimbursed, every new patient receiving them could easily be identified and included in the analyses. Moreover, the SNDS allows an extended duration of follow-up compared with RCTs. SATURATIOn aims also to assess the accuracy of the SNDS in identifying AEs for innovative therapeutics in IMIDs compared with an integrative approach (using already published data, both RCTs and observational studies). The different sources commonly used to detect and assess the frequency of AEs have never been compared. SNDS has been extensively used in France to conduct safety drugs studies, but no data is available regarding the accuracy of the results for estimating the risk of AEs when compared with other methods, such as meta-analyses. Recently, the use of exhaustive high-dimensional propensity scores allowed to achieve emulations of RCT using real world evidence data and enabled to assess and predict patient outcomes, including AEs.[21] Moreover, this approach could be improved using machine learning algorithms for variable selection which are especially adapted to high dimension databases such as the SNDS. Consistent findings between an RCT and an emulated one with real world evidence particularly strengthen their validity.[20] Conversely, to our knowledge, no data are available regarding biologics. Although our approach would be limited to IMIDs and biologics, the confirmation that the SNDS is as efficient as the integrative approach in unravelling AEs for these drugs and indications, could allow the fast generation of appropriate analyses in order to confirm other AE-drug associations if needed. The next step will be to (1) prevent avoidable AEs by identifying their respective risk factors, including socio-economic characteristics, both at the individual level (with the complementary universal health insurance as a proxy) and the area level (deprivation index); as well as (2) assess their global impact in terms of costs. This prompt identification of AEs, estimation of their incidence and risk factors could prop a quick public health response. By modifying the target populations according to identified risk factors, the prevention of AEs would be possible. Moreover, finding that socioeconomic status is a strong driver of AEs paves the way for future expenditures in therapeutical education in order to improve the understanding of IMIDs by patients, such as their treatment and early AE recognition. If the SATURATIOn study validates the method of identifying AEs via the SNDS, the data will be updated on a regular basis. National communications via the French Agency for the Safety of Medicines and Health Products to clinicians would be the most appropriate dissemination model for informing clinicians quickly and accurately. The SATURATIOn study will contribute to provide data which help clinicians to choose and select the biologic with the best benefit-risk ratio for patients with IMIDs.

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