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Oral Janus kinase inhibitors and venous thromboembolic events in atopic dermatitis: protocols for a case-time control study and a nested case-control study based on the French national health insurance (SNDS) cohort.

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Title: Oral Janus kinase inhibitors and venous thromboembolic events in atopic dermatitis: protocols for a case-time control study and a nested case-control study based on the French national health insurance (SNDS) cohort.

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Abbreviations

Ankylosing spondylitis (AS)

Atopic dermatitis (AD)

Anatomical Therapeutic Chemical (ATC)

Confidence interval (CI)

Crohn's disease (CD)

European Medicines Agency (EMA)

Incidence rate (IR)

International Classification of Diseases, 10th Revision (ICD-10)

Odds ratio (OR)

Psoriatic arthritis (PsA)

Rheumatoid arthritis (RA)

Signal transducer and activator of transcription (STAT)

Système National des Données de Santé (SNDS)

Ulcerative colitis (UC)

Venous thromboembolic event (VTE)

Abstract

Introduction:

Atopic dermatitis (AD) is a highly prevalent, chronic, inflammatory skin disease. Recent advances in understanding its pathogenesis have greatly expanded the therapeutic armamentarium. Several orally administered Janus kinase inhibitors (JAKis, including baricitinib, upadacitinib and abrocitinib) have received a marketing authorization for AD.

Clinical trials in rheumatoid arthritis (RA) have flagged up a potential risk of JAKi-induced venous thromboembolic events (VTEs). Accordingly, the summary of product characteristics for a JAKi must mention VTEs as potential adverse drug reactions. In contrast to RA, AD per se is not associated with an elevated risk of VTEs. Assessing this potential risk among AD patients would shed further light on the putative underlying relationship between JAKis and VTEs.

Methods and analysis:

Our objective is to investigate the association between JAKis prescribed for AD and VTEs. We will address the following two questions: (i) is the risk of VTEs higher in adults with AD exposed to JAKis than in AD adults not exposed to JAKis, and (ii) does the initiation of treatment with a JAKi trigger VTEs? Hence, we have designed (i) a nested case-control study and (ii) a case-time-control study in a cohort of adults with AD with data from the French national health insurance system (2017-2025).

Here, we describe the study protocol, our methodological choices, and certain novel aspects - including the combined value of the two assumptions, and the use of an exhaustive national health insurance database with potentially greater statistical power for studying rare events in the population of AD patients at a low risk of VTEs (thus limiting the influence of confounding factors).

Ethics and dissemination:

The protocol has been approved by an independent ethics committee and registered with the French National Data Protection Commission. The study's findings will be published in peer-reviewed scientific journals and presented at international conferences.

Article Summary: strengths and limitations of this study

A population-based study using the exhaustive French national health insurance database would provide additional insight into the risk of venous thromboembolic events (VTEs). Advantageously, this nationwide study should be able to exhaustively identify VTEs, the time of their occurrence, and prescriptions of JAK inhibitors.

By studying atopic dermatitis (AD), we hope to avoid a major source of confounding bias; in contrast to rheumatoid arthritis, AD is not associated *per se* with an elevated risk of VTEs.

The limitations of this study protocol (based on the use of French national health insurance database) include a lack of data on certain risk factors for VTEs (including obesity and a family history of thromboembolic disease) and a potential lack of statistical power.

INTRODUCTION

Atopic dermatitis (AD) is a highly prevalent, pruritic, inflammatory disease skin that occurs in both adults (3 to 10%) (1–3) and children (15 to 20%) (1,4,5). Approximately 2 to 8% of adults with AD have severe forms; the associated impairments in quality of life make AD a disabling disease. Severe AD is frequently associated with other atopic comorbidities (e.g. asthma, allergic rhinitis, allergic conjunctivitis, and food allergy), and may be associated with psychiatric disorders.

The European guidelines on the management of AD in adults recommend first-line treatment with topical anti-inflammatory drugs (topical corticosteroids and tacrolimus) and then (if the treatment fails) systemic immunosuppressants (6,7). In late 2017, the management of treatment-refractory AD was revolutionized by the marketing of the first biologic drug, dupilumab (a subcutaneously administered monoclonal antibody against the interleukin -4 and -13 receptors) (8,9). Other systemic treatments have since received (or are awaiting) marketing authorization: baricitinib (an orally administered Janus kinase (Jak) 1 and 2 inhibitor (JAKi) (10–13), upadacitinib (an orally administered JAK1 inhibitor) (14–16), abrocitinib (another orally administered JAK1 inhibitor) (17–19), and tralokinumab (a subcutaneously administered anti-interleukin-13 monoclonal antibody) (20,21).

JAKis constitute a new family of orally administered molecules that target the JAK-signal transducer and activator of transcription (STAT) pathway. Janus kinases are involved in the transduction of intracellular signals in response to various cytokines and growth factors involved in haematopoiesis, inflammation, and immune functions.

In the European Union, baricitinib was approved for the treatment of active, moderate-to-severe rheumatoid arthritis (RA) in adults in 2017 and for moderate-to-severe AD in adults who are candidates for systemic drug treatment in 2021. Upadacitinib was approved for the treatment of adults with moderate-to-severe active RA, psoriatic arthritis (PsA), or ankylosing spondylitis (AS) in 2020 and 2021 and for the treatment of moderate-to-severe AD in adults and adolescents (aged 12 or over) who are candidates for systemic drug treatment in August 2021. Lastly, abrocitinib was approved very recently by the European Medicines Agency (EMA) for the systemic treatment of moderate-to-severe AD in adults and adolescents.

Clinical trials in RA have flagged up a potential risk of JAKi-induced venous thromboembolic events (VTEs, including deep vein thrombosis and pulmonary embolism) (22–26). Although the EMA approved low (2 mg) and high (4 mg) doses of baricitinib, the FDA only approved the 2 mg dose because of the VTE risk. On a broader scale, the summary of product

characteristics for a JAKi must mention VTEs as potential adverse drug reactions. The safety profiles of baricitinib and upadacitinib in patients with RA have been described in nine and five clinical studies, respectively. The estimated incidence of VTEs ranged from 0.3 to 0.6 per 100 person-years (22,27).

Due to the presence of systemic inflammation, RA *per se* can induce thromboembolic events, and the treatment of RA with anti-inflammatory drugs helps to reduce the cardiovascular and thromboembolic risk (25,28). Furthermore, most patients with RA are aged over 50 at diagnosis and have higher prevalence of obesity and a higher incidence of VTEs. In this case, the interplay between RA, JAKis and thromboembolic risk is particularly difficult to characterize.

The pathogenic links between JAKis and a potentially greater risk of thromboembolic disease are poorly understood, and the literature data are contradictory. The potential thromboembolic risk might be related to an imbalance between pro and anti-thrombotic signals, including the inhibition of pro-inflammatory signals (such as interferon-dependant pathways) and the paradoxical inhibition of JAK-STAT-dependant anti-inflammatory pathways (such as the IL-10 pathway that helps to limit clot formation under normal conditions) (29,30). JAKis that influence JAK2-dependent signalling (such as baricitinib) might also promote platelet formation from megakaryocytes, as evidenced by a transient increase in the platelet count following JAKi initiation. Nonetheless, a causal link between transient thrombocytosis and VTE has never been proven (22).

The results of meta-analyses of the links between JAKis and the risk of thromboembolic and/or cardiovascular events are summarized in Table 1. Most of the meta-analyzed data came from clinical trials, rather than real-life studies with a longer follow-up period. The meta-analyses concluded that although the JAKi treatment is associated with an elevated risk of VTEs, the association is not statistically significance. Lastly, the meta-analyses did not encompass data on VTEs treated in primary care facilities (i.e. on an outpatient basis). Two analyses of US medical-administrative databases did not find a difference in the VTE risk between patients with RA taking tofacitinib and those taking an anti-tumour necrosis factor agent (hazard ratio [95% confidence interval (CI)] = 1.13 [0.77-1.65] and 1.33 [0.78-2.24], respectively) (31,32). However, the researchers could not rule out such a risk, and only considered VTEs leading to hospital admission (31,32).

A population-based study of a health insurance database (the *Système National des Données de Santé*, SNDS) would provide additional insights by focusing on the VTE risk. The advantages of studying a health insurance database include the precise, national-level identification of JAKi

prescriptions, VTEs, and the time of occurrence (relative to treatment initiation, for example). Furthermore, studying AD avoids a major source of confounding bias; in contrast to RA and inflammatory bowel disease, AD is not associated with an increased risk of VTE (33) and predominantly affects a younger population with a lower prevalence of concomitant cardiovascular comorbidities or obesity.

Here, we describe the protocol for the "JAK inhibitors and ThromboEmbolic Risk" (JAKTER) study of the association between JAKis and VTEs in AD, using real-world evidence from an exhaustive French medical-administrative database. We also discuss our methodological choices. We will address the following two questions, using two different methodological approaches: (i) is the risk of VTEs higher in adults with AD exposed to JAKis than in adults with AD not exposed to JAKis, and (ii) does the initiation of treatment with a JAKi trigger VTEs?

METHODS AND ANALYSIS

Overall study design

The literature data on the temporal relationship between the initiation of treatment with a JAKi and the occurrence of a VTE are contradictory. Some studies suggest that the incidence rates of VTEs are consistent over time (22), whereas other indicate that the incidence rates are clustered soon after the start of exposure (34). We will therefore use two different methodological approaches to investigate the VTEs and the JAKis prescribed for AD: (i) a nested case-control study in a cohort of adults with AD (analysis #1) and (ii) a case-time-control study (analysis #2).

The overall study design is summarized in Figure 1.

Place and study time

The analysis period will run from January 1st, 2017, to August 31st, 2025, in France.

Data sources

We will analyze the French national health insurance database (*Système National des Données de Santé*, SNDS), which covers 98% of the 66 million people in France. The SNDS database contains anonymous data on individuals' demographic characteristics (sex, dates of birth, and (of applicable) date of death); all healthcare reimbursements, including drugs (with the

prescription filling date, the prescriber's medical speciality, laboratory tests, outpatient care/visits, all hospital stays, and the associated diagnoses (coded according to the International Classification of Diseases, 10th Revision (ICD-10), all causes of death (classified according to the ICD-10 codes), and the attribution or not of "chronic disease" status ("*affection de longue durée*" (ALD), giving entitlement to the full coverage of related healthcare costs, and again coded according to ICD-10 codes).

Selection criteria and constitution of the target cohort

To avoid indication bias and form a homogeneous group of patients in terms of medical care, we will build up a cohort of adults with AD and who start systemic immunomodulatory treatment for this disease.

In France, AD is a chronic condition that is mostly managed in outpatient settings and not during hospital stays. Furthermore, AD does not give entitlement to ALD chronic disease status. All eligible adults (aged 18 or over) with *a priori* AD will be identified as follows:

- adults (aged 18 or over) with an initial fulfilment of a prescription for dupilumab, cyclosporine, methotrexate, tralokinumab, or a JAKi (baricitinib, upadacitinib, or abrocitinib), two or more fulfilments of topical corticosteroids, and a consultation with a dermatologist between January 1st, 2017, and December 31st, 2024.
- adults with no fulfilments of dupilumab, cyclosporine, methotrexate, tralokinumab or JAKi (baricitinib, upadacitinib, or abrocitinib) prescriptions in the year prior to cohort entry.
- adults with no other indications for dupilumab, cyclosporine, methotrexate, tralokinumab, or the JAKis baricitinib, upadacitinib, or abrocitinib (i.e. RA, PsA, AS, ulcerative colitis, lupus, organ or bone marrow transplant, nephrotic syndrome, and psoriasis) identified through "ALD" chronic disease status or the hospital discharge ICD-10 codes, between January 1st, 2016, and December 31st, 2024.
- adults with follow-up starting on the date of the first filled prescription of a JAKi (baricitinib, upadacitinib, or abrocitinib), dupilumab, tralokinumab, cyclosporine, or methotrexate, up until August 31st, 2025.

Outcomes

The cases will be adults with AD and incident deep vein thrombosis or pulmonary embolism, managed in an outpatient setting, a hospital, or an emergency department.

VTEs managed in hospital or an emergency department will be identified through the hospital discharge ICD-10 code (Table 2). VTEs managed in outpatient settings will be identified by applying the validated EPIGETBAM algorithm (manuscript under submission).

The index date is the date of the VTE.

To study cases of "unprovoked" VTEs, we will exclude the following cases of adults with "provoked" VTEs (35):

- initiation of oral oestroprogestative contraception in the three months before the index date.
- pregnancy (including a two-month postpartum period) before the index date.
- surgery (orthopaedic surgery involving long bones or the pelvis, or other major surgery) in the four weeks before the index date.
- prolonged hospitalisation (>72 hours) in the four weeks before the index date.
- a diagnosis of cancer (including haematological malignancies but not including non-melanoma skin cancer) before the index date.
- fulfilment of one or more prescriptions for preventive or curative treatments with anticoagulants, including heparins, anti-vitamin K agents, and direct oral anticoagulant (ensuring the exclusion of patients with a history of VTEs and persistent risk factors for VTE recurrence) before the index date (for VTEs managed in hospital or in an emergency department) or before the index date minus 7 days (for adults starting an anticoagulant treatment before hospitalization for VTE).

Data analysis

The characteristics of the JAKis-treated population of patients with AD will be described, together with the time interval between JAKi initiation and the occurrence of the VTE. We will explore the risk function and the potential time-varying association.

Analysis #1: a nested case-control study of a cohort of adults with AD

The association between exposure to JAKis and the occurrence of VTEs will be investigated in a nested case-control study of a cohort of adults with AD requiring systemic treatment.

Adults with AD will be considered to have been exposed to JAKis if they have at least one fulfilled prescription for a JAKi prior to the index date. Adults with AD will be assigned to a "JAKi user" category or a "JAKi never-user" category, based on the prior fulfilment closest to the index date. Subgroups of JAKi users will be defined as follows: for current JAKis users, the last prescription will have been fulfilled in the month before the index date: for recent JAKis users, the last prescription will have been fulfilled between one and four months before the index date; and for past JAKis users, the last prescription will have been fulfilled more than four months before the index date. Furthermore, for current JAKis users; the number of JAKi prescription fulfilments and the total cumulative dose of JAKis received before the index date will be calculated.

References will be adults with AD whose most recent prescription fulfilment before the index date (regardless of how long before) will have been for another systemic treatment for AD.

For each case (adults with AD having experienced a VTE), four controls will be selected from the target AD cohort. Controls must not have experienced a VTE at the time of their selection. Cases and controls will be matched for age, sex, and length of exposure at the case's index date. The inclusion and exclusion criteria applied to cases will be applied to the matched controls. It will be possible for a control to become a case after his/her selection (density sampling) (36). We will estimate odds ratios (ORs) using conditional logistic regression. We will consider systemic treatment of AD as a binary variable: JAKi users (baricitinib, upadacitinib, or abrocitinib) vs. users of other systemic drugs (dupilumab, tralokinumab, cyclosporine, or methotrexate). We will consider drug exposure as a continuous variable. The primary analysis will compare current JAKi users with JAKi never-users. The secondary analyses will cover "recent JAKi user" status, "past JAKi user" status, and use of each individual JAKi (baricitinib, upadacitinib, and abrocitinib). A Schneeweiss diagram for analysis #1 is shown in Figure 2 (37).

Analysis #2. A case-only design: a nested case-time-control study of a cohort of adults with AD.

To evaluate whether or not initiation of a JAKi increases the risk of VTE in the following three months (i.e. a "triggering effect"), we will perform a case-time-control analysis.

In the field of pharmacoepidemiology, case-time-control studies can be used to study an acute, early-onset adverse event during treatment (38). A VTE is sudden (with a short time interval between the pathophysiological cause and the clinical manifestations) and is easy to date by

screening for specific treatments and additional investigations (including Doppler ultrasound). The majority of the VTEs observed in clinical trials (22) or reported in pharmacovigilance databases (34) occurred within three to four months of JAKi initiation (39). Furthermore, the case-only design can control for potential confounding factors (such as obesity and physical activity) not recorded in the French health insurance database.

Only AD patients exposed to a JAKi and having experienced a VTE (i.e. cases) will be analyzed. The case-time-control design compares the exposure status immediately before the event (the risk period) with exposure during a designated (earlier) reference period. Each VTE case will serve as his/her own control during a comparison of the risk period (0 to 3 months before occurrence of the VTE) with the reference period (3 to 6 months before occurrence of the VTE). Each VTE case will be assessed for exposure (yes/no) during the risk period and during the reference period. Only participants whose status differs when comparing the two periods (i.e. discordants) will be considered in our estimation of the OR. To take account of the expected increase in JAKi prescription, the case-time-control analysis will include a selection of controls matched with VTE cases. Each VTE case will be matched for age and sex with 5 controls without VTEs and who will be randomly selected from the AD target cohort. The date of the VTE will be used as the index date for the matched controls. The above-defined risk and reference periods will be screened for JAKi initiation among the controls in the same way as among the cases, and a case-crossover OR for controls will be computed. The case-time-control OR [95%CI] will be estimated with a conditional logistic model by considering the interaction term between the exposure of interest (JAKi initiation) and the participant's status (case or control). The case-time-control OR will correspond to the ratio between the respective case-crossover ORs obtained in cases and controls.

Sensitivity analyses in which the durations of the risk and reference period are modified will be performed as follows: the risk period will be defined as 0 to 2 months or 0 to 4 months before the VTE, and the control period will be defined as 2 to 4 months or 4 to 8 months before the VTE. Furthermore, sensitivity analysis will be performed for analyses #1 and #2 by changing the patient selection criteria and excluding patients with asthma. Lastly, we shall exclude patients having initiated oral oestroprogestative contraception in the 6 months or the 12 months before the date of the VTE in cases or the corresponding date in controls.

Covariates

We used a directed acyclic graph (Figure 3) to describe covariates, mediators, and potential confounding factors in the relationship between JAKis and VTEs.

The results will be adjusted for several covariates, including the patient's chronic comorbidities (using Bannay et al.'s algorithm for use of the Charlson Comorbidity Index with an electronic healthcare database (40,41)) and the use of systemic corticosteroids (42). Obesity is either not documented or only partially documented in the SNDS database; in Europe, most adults with AD are not obese (43). The case-only design approach (analysis #2) avoids this potential confounding factor, since the patient is his/her own control. The SNDS database does not contain identifiable information on a family history of venous thromboembolic disease.

Asthma (the most important atopic comorbidity in AD) will be assessed and defined as follows: an ICD-10 code J45-J46 and/or at least two fulfilments of a drug for the treatment of obstructive airway diseases (an Anatomical Therapeutic Chemical (ATC) code of R03). The study variables are listed in Table 2.

Sample size

Based on a frequency of exposure to JAKi among the targeted cohort of 25%, a 1:4 case to control ratio, and a statistical significance threshold of 0.05, the sample sizes required for a power of 80% in a comparison of JAKi exposure in cases vs. controls are as follows: 1836 participants (306 cases and 1530 controls) for detecting an OR of 1.5, 618 participants (103 cases and 515 controls) for detecting an OR of 2, 354 participants (59 cases and 295 controls) for detecting an OR of 2.5, 246 participants (41 cases and 205 controls) for detecting an OR of 3, and 192 participants (32 cases and 160 controls) for detecting an OR of 3.5. These calculations do not take account of matching, which will tend to increase the power in an unknown manner. The estimated power calculation is given in Table 3. A final power calculation will be performed at the end of the study.

The estimated incidence of thromboembolic diseases in France is one per 1000 per year; approximately 50,000 adults with a follow-up of three years are required. The target population for baricitinib/upadacitinib has been estimated at between 26,500 and 42,500 by the French High Authority for Health (44); this is almost certainly an underestimate, given that courses of treatment with cyclosporine are short.

ETHICS AND DISSEMINATION

In accordance with French legislation, the protocol has been approved by an independent ethics committee (*Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé*, Paris, France; reference: 4523600, dated June 17th, 2021) and has been registered with the French National Data Protection Commission (*Commission Nationale de l'Informatique et des Libertés*, Paris, France; reference: 921265, dated June 28th, 2021). The study's findings will be published in peer-reviewed scientific journals and presented at international conferences

The data will be consulted via the French national health insurance system's (*Caisse Nationale de l'Assurance Maladie*) portal; the investigators' access is restricted to the scope of the study. The data were not extracted from the main database but were analyzed in a dedicated project area on the server. The investigators will comply with the reference framework applicable to the SNDS database (as set out in the government act dated March 22nd, 2017).

The study protocol has been registered at France's Health Data Hub (www.health-data-hub.fr). The statistical analysis plan and data management book will now be drafted. The first results are expected in late 2025. The study's findings will be published in peer-reviewed scientific journals and presented at international conferences

DISCUSSION

A population-based study of a cohort of AD adults documented in the SNDS French national health insurance database should provide additional insights on the potential association between VTE and JAKis (baricitinib, upadacitinib, and abrocitinib).

There are several possible pathophysiological explanations for an elevated risk of VTE during treatment with a JAKi. Firstly, the leading hypothesis states that the thrombogenic effect is related to the thrombocytosis associated with baricitinib use (22). However, a clear time-domain or quantitative association between the platelet count and the occurrence of VTE has not been observed (22). Furthermore, elevation of the platelet count is not observed in people treated with other JAKis, including upadacitinib (45). Secondly, the JAK 2 pathway has an important role in haematopoiesis and might promote VTE. Paradoxically, inhibition of the JAK2 pathway by JAKis does not account for the occurrence of VTE: in Vaquez disease and essential thrombocythemia, an activating mutation in JAK 2 increases the risk of arterial and venous thrombotic events (46). Data from mouse models suggest that JAK V617F expression induces hypersensitivity to fibrinogen, thrombopoietin, and other endogenous pro-thrombogenic factors (47).

The literature data on the potential risk are contradictory and do not enable a firm conclusion about the association between JAKis and VTE to be drawn. A false association might result from methodological bias. For example, selection bias occurs when including patients who have received several courses of systemic treatment (and so might have more severe disease and a higher thromboembolic risk) are included in clinical trials (especially in open-label trials in RA) (22,24). Confounding bias may occur because the disease treated with JAKi is itself associated with a higher risk of VTE; this is particularly true for RA. Indeed, the thromboembolic risk is known to be two to three times higher in patients with RA (25) than in the general population (28,48). The baseline risk also appears to be elevated other systemic inflammatory diseases, including inflammatory bowel disease (49,50). In contrast, adults managed for moderate-to-severe AD are not known to have an elevated thromboembolic risk and are also younger than patients with RA; hence, the baseline risk of VTEs is lower. Published data on this indication are scarce: the only two meta-analyses included data from four randomized clinical trials evaluating the efficacy of baricitinib and abrocitinib in AD (51). The lack of a significant association might have several explanations: (i) a lack of power would apply if the number of JAKi-exposed patients experiencing a VTE is low; meta-analyses have provided inconclusive results, due the rarity of the event and the predominant inclusion of clinical trial data; (ii) insufficient follow-up in clinical trials (given the latency between JAKi initiation and VTE occurrence); and (iii) a lack of specific detection of VTEs (requiring a targeted initial assessment and follow-up, and perhaps a longer follow-up period). Lastly, it is unclear whether the published studies considered only VTEs leading to a hospitalization or, in contrast, all VTEs. In France, the majority of VTEs are managed in an outpatient setting (52).

Our implementation of two complementary methodological approaches should shed more light on this question. The case-control study is carried out on a population of AD patients with similar disease severity levels and receiving similar intensities of systemic treatment. This design assumes that after initiation of a JAKi, the risk of a VTE is constant. The case-time-control design will be applied to address (i) the assumption whereby a JAKi triggers a VTE, and (ii) the issue of residual confounding factors. This study design is particularly suitable when the outcome is sudden and easily dated, as is the case here (53–55). The hypothetical triggering effect is based on (i) the transient thrombocytosis observed with baricitinib early after treatment initiation (56,57), (ii) pharmacovigilance data from France and North America (34,39), where more than half of the reported VTEs occurred within 120 days of JAKi initiation (39), and (iii) the fact that other drugs (such as contraceptives) can trigger VTEs (58–62). An increase over the study period in the prevalence of JAKi use for AD is expected; the case-time-control design

considers time-trends in the prevalence of exposure that might introduce a confounding effect in a case-crossover design. We chose to study "unprovoked" VTEs by excluding well-known risk factors for thromboembolic disease (63), such as cancer (64), surgery (65), immobilisation (proxy marker: a hospital stay), hospital admission (66), and the initiation of hormone therapy (67). Furthermore, we will adjust for the Charlson Comorbidity Index, which includes diabetes (68–71). However, obesity, black ethnicity (72), and a family history of thromboembolic disease are not documented in the SNDS database, and so we cannot rule out residual confounding in analysis #1 (the nested case-control study). In analysis #2 (the case-only design), cases serve as their own controls, which can mitigate the potential confounding factors (such as diet, smoking, the level of physical activity, and a family history of thromboembolic disease) not documented in healthcare databases (38,73).

Our study has several potential strengths, including the exhaustive nationwide coverage of the French population (thereby enabling an assessment of rare events and providing potentially greater statistical power); the theoretical absence of selection bias, given our use of the SNDS database; the quality of the recorded data (enabling estimation of the time of occurrence of VTEs); the implementation of two complementary methodological approaches; and the definitions of outcomes that encompass VTEs managed in out- and inpatient settings.

The study's potential limitations include the difficulty of tracking all VTEs (the use of an algorithm for the identification of inpatient and outpatient diagnoses of VTE in the health insurance database is, however, currently being validated); potential information bias on hormone therapy, since a proportion of these treatments are not reimbursed and therefore cannot be detected in the SNDS; a potential lack of statistical power; and inability to take account of some risk factors for VTEs (including obesity, and a family history of thromboembolic disease) in the case-control design – although we believe that these potential confounding factors should affect cases and controls to the same extent.

FIGURE AND TABLE LEGENDS

Figure 1: Overall study design

Figure 2: Schneeweiss diagram for analysis #1 (37)

Figure 3: A directed acyclic graph of the relationship between JAKis, AD, and VTEs

Table 1: List of meta-analyses on the risk of VTEs during treatment with JAKis

Table 2: List of variables

Table 3: Power calculation for analysis #1

STATEMENTS

Contributorship statement

PB and CD wrote the first draft of the manuscript. PB, LMS, AL, DSS, GC, PG, AD, EO and CD conceived the scoping review and developed the research questions and the search strategy. All authors critically reviewed drafts and edited the manuscript.

Competing interests

There are no competing interests for any author.

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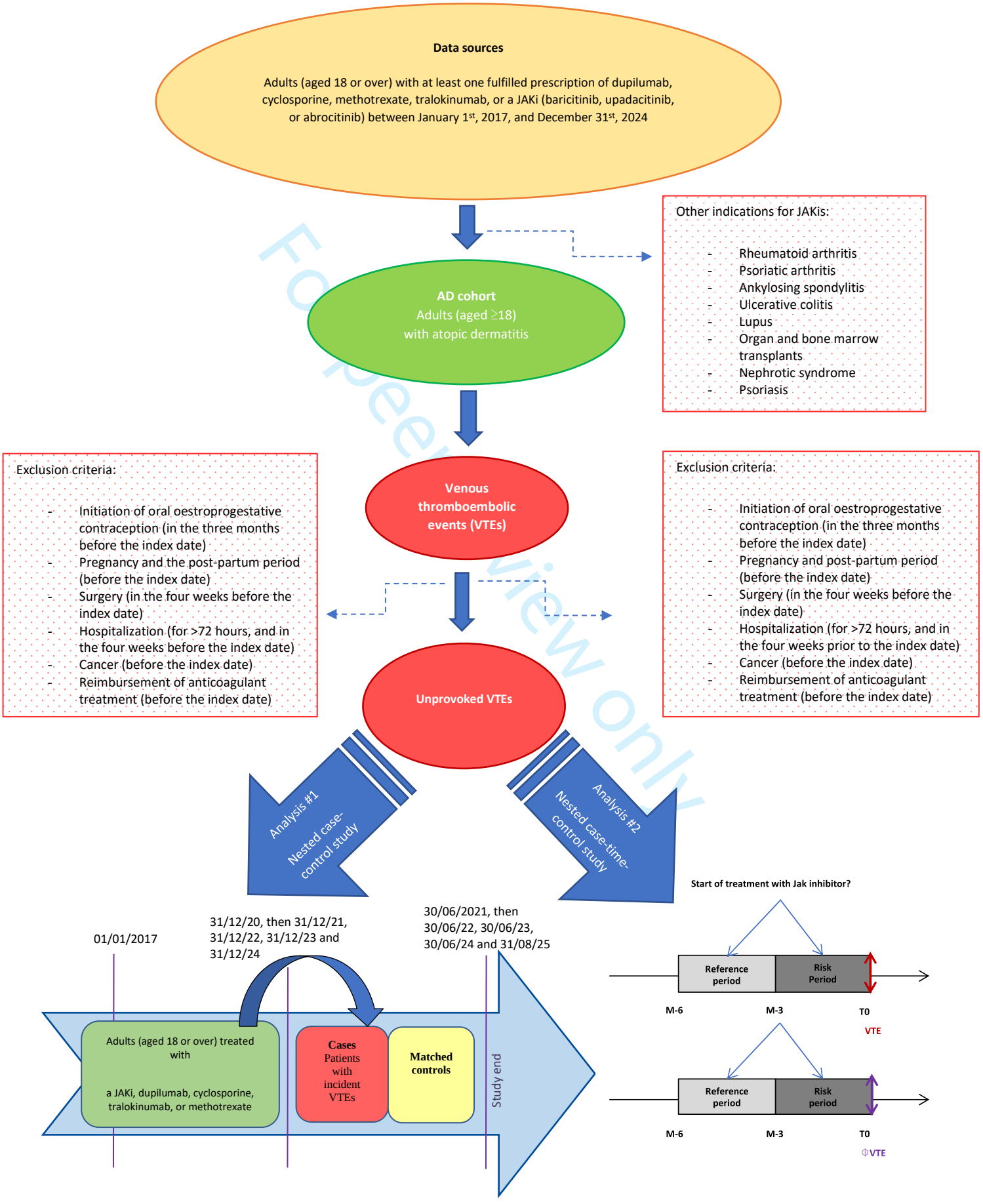
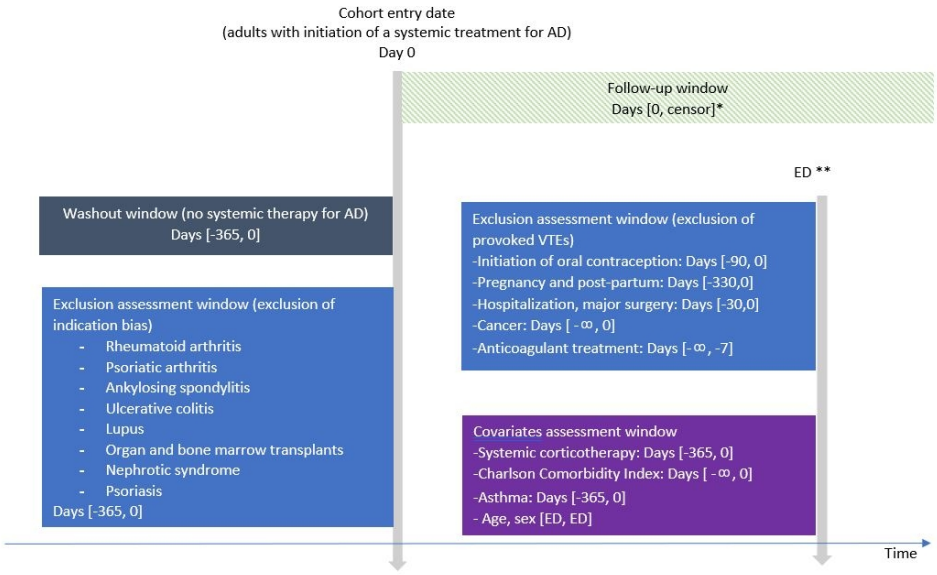
- Nested case-control study (analysis #1)
- Nested case-time-control study (analysis #2): in patients with a VTE, we shall compare the frequency of JAKi initiation in the risk period (before VTE) with the frequency of JAKi initiation in the reference period (prior to the risk period).

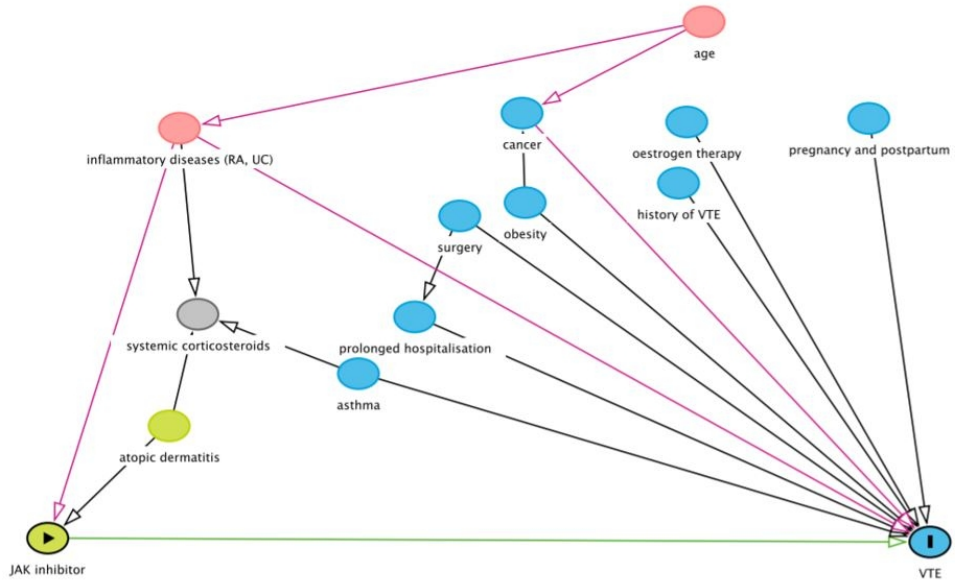




Abbreviations: AD, atopic dermatitis; ED, event date; VTE, venous thromboembolic event
*Censored at the date of the first VTE, death, emigration, or the end of the study period
** ED: the date of the first VTE (the index date)

Schneeweiss diagram for analysis #1

192x121mm (144 x 144 DPI)



Abbreviations: RA, rheumatoid arthritis; UC, ulcerative colitis; VTE, venous thromboembolic event

A directed acyclic graph of the relationship between JAKis, AD, and VTEs

168x105mm (144 x 144 DPI)

First Author	Date of publication	JAK inhibitor	Indication	Number of studies included	Type of studies included	Number of patients included	Median follow-up (weeks)	Number of events among exposed participants	Number of events among nonexposed participants	Results OR (95%CI)	Methods used
Xie (74)	2019	Tofacitinib Baricitinib Upadacitinib Peficitinib Decernotinib	RA	26	RCT	11799	Placebo-controlled period: 12 Dose-comparison period: 24	12	3	All JAKis: 1.16 (0.48-2.81) Tofacitinib: 0.17 (0.03–1.05) Baricitinib: 2.33 (0,62–8,75) Upadacitinib: 1.77 (0.20–16.00)	Mantel-Haenszel fixed-effect method
Xie (75)	2019	Tofacitinib	RA, PsA, CPP, UC, CD, AS	27	RCT	13611	Placebo-controlled period: 12 Dose-comparison period: 24	1	5	0.03 (0.00-0.21)	Peto method
Olivera (76)	2020	Tofacitinib Upadacitinib Filgotinib Baricitinib	RA, AS, UC, CD, CPP	10	RCT Cohorts	5143	26	12	3	All JAKis: 0.90 (0.32-2.54)	Random-effects model
Giménez Poderos (51)	2020	Tofacitinib Baricitinib	RA, KT, UC, CPP, CD, PsA, AD, DKD, SLE, JIA, SS	59	RCT Cohorts	25947	16	24	23	Tofacitinib: 0.29 (0.10-0.84) Baricitinib: 3.39 (0.82-14.04)	Fixed-effects or random-effects model, with application of the most conservative model in each case
Yates (77)	2020	Tofacitinib Baricitinib Upadacitinib Filgotinib	RA, PsA, AS, UC, CD, CPP	42	RCT	17269	unavailable	15	4	All JAKis: 0.68 (0.36-1.29)	Mantel-Haenszel fixed-effect method
Wang (78)	2020	Upadacitinib	RA	3	RCT	2852	unavailable	3	1	2.34 (0.15-15.02)	Random-effects model
Bilal (79)	2021	Abrocitinib, Baricitinib, Decernotinib, Filgotinib, Peficitinib, Ruxolitinib, Tofacitinib	RA, AD, SLE, CPP, AS, PsA, UC, Pancreatic cancer, Breast cancer	29	RCT	13910	48	50	27	All JAKis: 0.91 (0.57-1.47) Baricitinib: 1.12 (0.27-4.69) Decernotinib: 1.07 (0.18-6.43) Filgotinib: 2.13 (0.22-20.64) Ruxolitinib: (0.31-2.29) Upadacitinib: 2.25 (0.55-9.25) Tofacitinib: 0.27 (0.08-0.89)	Random-effects model

Abbreviations: AD, atopic dermatitis; AS, ankylosing spondylarthritis; CD, Crohn's disease; CI, confidence interval; CPP, Chronic Plaque Psoriasis; DKD, diabetic kidney disease; IR, incidence rates; JAKi, Janus kinase inhibitor; JIA, juvenile idiopathic arthritis; KT, kidney transplantation; OR, odds ratio; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomized clinical trial; SLE, systemic lupus erythematosus; SS, systemic sclerosis; UC, ulcerative colitis.

Variables	Registry	Code
Atopic dermatitis		
Atopic dermatitis	PMSI	ICD-10 code L20
Topical corticosteroids	DCIR	ATC codes D07AB01, D07AB02, D07AB03, D07AB04, D07AB05, D07AB06, D07AB07, D07AB08, D07AB09, D07AB10, D07AB11, D07AB19, D07AB21, D07AB30, D07AC01, D07AC02, D07AC03, D07AC04, D07AC05, D07AC06, D07AC07, D07AC08, D07AC09, D07AC10, D07AC11, D07AC12, D07AC13, D07AC14, D07AC15, D07AC16,D07AC17, D07AC18, D07AC19, D07AC20, D07AC21, D07AD01, D07AD02
Consultation with a dermatologist	DCIR	PFS_SPE_COD or PFE_SPE_COD code 05
Exposure		
Baricitinib	DCIR	ATC code L04AA37
Upadacitinib	DCIR	ATC code L04AA44
Abrocitinib	DCIR	ATC code D11AH08
Dupilumab	DCIR	ATC code D11AH05
Tralokinumab	DCIR	ATC code D11AH07
Cyclosporine	DCIR	ATC code L04AD01
Methotrexate	DCIR	ATC code L01BA01
Venous thromboembolic events		
Venous thromboembolic events	PMSI, DCIR	EPIGETBAM algorithm under submission
Exclusion criteria		
Oral oestroprogestative	DCIR	ATC codes G03AA01, G03AA02, G03AA03, G03AA04, G03AA05, G03AA06, G03AA07, G03AA08, G03AA09, G03AA10, G03AA11, G03AA12, G03AA13, G03AA14, G03AA15, G03AA16, G03AB01, G03AB02, G03AB03, G03AB04, G03AB05, G03AB06, G03AB07, G03AB08
Pregnancy	PMSI	ICD-10 code Z321
Hospital stay >72 hours, with or without surgery	PMSI	ICD-10 codes
Cancer and haematological malignancies	PMSI	ICD-10 codes C00 to C43 and C45 to C97, D00 to D03, D05 to D09, D37 to D48, or ALD n°30
Anticoagulant treatment	DCIR	ATC codes B01AA01, B01AA02, B01AA03, B01AA04, B01AA07, B01AA08, B01AA09, B01AA10, B01AA11, B01AA12, B01AB01, B01AB02, B01AB04, B01AB05, B01AB06, B01AB07, B01AB08, B01AB09, B01AB10, B01AB11, B01AB12, B01AB51, B01AE01, B01AE02, B01AE03, B01AE04, B01AE05, B01AE06, B01AE07, B01AF01, B01AF02, B01AF03, B01AX01, B01AX04, B01AX05
Rheumatoid arthritis	PMSI DCIR	ICD-10 codes M069, M0690, M0691, M0692, M0693, M0694, M0695, M0696, M0697, M0698, M0699, M06 or ALD n°22
Psoriatic arthritis	PMSI DCIR	ICD-10 codes M0700, M0701, M0702, M0703, M0704, M0705, M0706, M0707, M0708, M0709, M072, M0720, M0721, M0722, M0723, M0724, M0725, M0726, M0727, M0728, M0729, M073, M0730, M0734, M0732, M0733, M0734, M0735, M0736, M0737, M0738, M0739

Ulcerative colitis	PMSI DCIR	ICD-10 codes K519 or ALD n°24
Lupus	PMSI DCIR	ICD-10 codes L93, M32 or ALD n°21
Organ and bone marrow transplants	PMSI DCIR	ICD-10 codes Z940, Z941, Z942, Z943, Z944, Z945, Z946, Z947, Z948, Z9480, Z94800, Z94801, Z9481, Z9482, Z94802, Z94803, Z94804, Z94809, Z949
Nephrotic syndrome	PMSI DCIR	ICD-10 code N04 or ALD n°19
Psoriasis	PMSI DCIR	ICD-10 code L40, L400, L401, L402, L403, L404, L405, L408, L409
Ankylosing spondylitis	PMSI	ICD-10 codes M45, M450, M451, M452, M453, M454, M455, M456, M457, M458, M459 or ALD n°27
Covariates		
Charlson Comorbidity Index	PMSI	Algorithm developed by Bannay et al. (40)
Systemic corticosteroids	DCIR	ATC codes H02A and H02B
Asthma	PMSI DCIR	ICD-10 codes J45, J450, J451, J458, J459, J46 ATC code R03

Abbreviations: ALD, *affection longue durée* long-term chronic disease status giving entitlement to full coverage of related healthcare costs; ATC, Anatomical Therapeutic Chemical; DCIR, Données de Consommation Inter Régimes; ICD-10, International Classification of Diseases 10th Revision; PMSI, Programme de Médicalisation des Systèmes d'Information.

Frequency of exposure to JAKis in the targeted cohort	Odds ratio	Nominal power	Number of controls	Number of cases	Total number of participants
0.50	1.5	0.8	1275	255	1530
0.50	2.0	0.8	465	93	558
0.50	3.0	0.8	205	41	246
0.25	1.5	0.8	1530	306	1836
0.25	2.0	0.8	515	103	618
0.25	2.5	0.8	295	59	354
0.25	3.0	0.8	205	41	246
0.25	3.5	0.8	160	32	192

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Oral Janus kinases inhibitors and venous thromboembolism in atopic dermatitis: Protocol of a case-time control study and a nested case-control study based on French SNDS cohort

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	p. 8
1.1.2 End of data collection[2]	☒	☐	☐	p. 8
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	p.14

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	p. 8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	p. 7
2.1.2 The objective(s) of the study?	☒	☐	☐	p. 8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	p. 8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	p. 8
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	p. 8-13
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	p. 9
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	p. 11-12
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	p. 11-12
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	p. 9-10
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	p. 8

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
	4.2.2 Age and sex	☒	☐	☐	p. 9
	4.2.3 Country of origin	☒	☐	☐	p. 9
	4.2.4 Disease/indication	☒	☐	☐	p. 9
	4.2.5 Duration of follow-up	☒	☐	☐	p. 10
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	p. 9-10

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	p. 9
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	p. 9
5.3	Is exposure categorised according to time windows?	☒	☐	☐	p. 11
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	p. 11
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	p. 9

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	p. 10
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	p. 10
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	p. 10
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	p. 13
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	p.16
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	p.16

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	p. 13

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	p. 9
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	p. 10
9.1.3 Covariates and other characteristics?	☒	☐	☐	p. 13
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	p. 9
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	p. 10
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	p. 13
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	p.50
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	p.50
9.3.3 Covariates and other characteristics?	☒	☐	☐	p. 51

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	p. 8, 12, 17
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	p. 13, 14
10.3 Are descriptive analyses included?	☒	☐	☐	p.11
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	p. 16, 17
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	p. 13
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	p. 13

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	p. 14
11.2 Are methods of quality assurance described?	☐	☐	☒	
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	p. 14

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	p. 15-16
12.1.2 Information bias?	☒	☐	☐	p. 15-16
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	p. 16

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	p. 13

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	p. 14
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	p. 14

Comments:

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

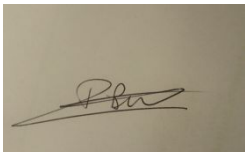
Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	p. 14
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	p. 14

Comments:

Name of the main author of the protocol: BERTHE Pauline

Date: 07/12/2021

Signature: 

BMJ Open

Oral Janus kinase inhibitors and venous thromboembolic events in atopic dermatitis: protocols for a case-time control study and a nested case-control study based on the French national health insurance (SNDS) cohort.

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Title: Oral Janus kinase inhibitors and venous thromboembolic events in atopic dermatitis: protocols for a case-time control study and a nested case-control study based on the French national health insurance (SNDS) cohort.

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Conflicts of Interest: None with regard to the present work.

Keywords: JAK inhibitor, venous thromboembolic event, health insurance database

Abbreviations

Ankylosing spondylitis (AS)

Atopic dermatitis (AD)

Anatomical Therapeutic Chemical (ATC)

Confidence interval (CI)

Crohn's disease (CD)

European Medicines Agency (EMA)

Incidence rate (IR)

International Classification of Diseases, 10th Revision (ICD-10)

Odds ratio (OR)

Psoriatic arthritis (PsA)

Rheumatoid arthritis (RA)

Signal transducer and activator of transcription (STAT)

Système National des Données de Santé (SNDS)

Ulcerative colitis (UC)

Venous thromboembolic event (VTE)

Abstract

Introduction:

Atopic dermatitis (AD) is a highly prevalent, chronic, inflammatory skin disease. Several orally administered Janus kinase inhibitors (JAKis, including baricitinib, upadacitinib and abrocitinib) have received a marketing authorization for AD.

Clinical trials in rheumatoid arthritis (RA) have flagged up a potential risk of JAKi-induced venous thromboembolic events (VTEs). Accordingly, the summary of product characteristics for a JAKi must mention VTEs as potential adverse drug reactions. In contrast to RA, AD per se is not associated with an elevated risk of VTEs. Assessing this potential risk among AD patients would shed further light on the putative underlying relationship between JAKis and VTEs.

Our objective is to investigate the association between JAKi prescribed for AD and VTEs, using data from the French national health insurance system between 2017 and 2025. We will address two research questions: (i) is the risk of VTEs higher in adults with AD exposed to JAKis than in AD adults not exposed to JAKis, and (ii) does the initiation of treatment with a JAKi trigger VTEs?"

Methods and analysis:

Hence, we have designed (i) a nested case-control study and (ii) a case-time-control study in a cohort of adults with AD with data from the French national health insurance system (2017-2025).

Here, we describe the study protocol, our methodological choices, and certain novel aspects - including the combined value of the two assumptions, and the use of an exhaustive national health insurance database with potentially greater statistical power for studying rare events in the population of AD patients at a low risk of VTEs (thus limiting the influence of confounding factors).

Ethics and dissemination:

The protocol has been approved by an independent ethics committee and registered with the French National Data Protection Commission. The study's findings will be published in peer-reviewed scientific journals and presented at international conferences.

Article Summary: strengths and limitations of this study

A population-based study using the exhaustive French national health insurance database would provide additional insight into the risk of venous thromboembolic events (VTEs). Advantageously, this nationwide study should be able to exhaustively identify VTEs, the time of their occurrence, and prescriptions of JAK inhibitors.

By studying atopic dermatitis (AD), we hope to avoid a major source of confounding bias; in contrast to rheumatoid arthritis, AD is not associated *per se* with an elevated risk of VTEs.

The limitations of this study protocol (based on the use of French national health insurance database) include a lack of data on certain risk factors for VTEs (including obesity and a family history of thromboembolic disease) and a potential lack of statistical power.

INTRODUCTION

Atopic dermatitis (AD) is a highly prevalent, pruritic, inflammatory disease skin that occurs in both adults (3 to 10%) (1–3) and children (15 to 20%) (1,4,5). Approximately 2 to 8% of adults with AD have severe forms; the associated impairments in quality of life make AD a disabling disease. Severe AD is frequently associated with other atopic comorbidities (e.g. asthma, allergic rhinitis, allergic conjunctivitis, and food allergy), and may be associated with psychiatric disorders.

The European guidelines on the management of AD in adults recommend first-line treatment with topical anti-inflammatory drugs (topical corticosteroids and tacrolimus) and then (if the treatment fails) systemic immunosuppressants (6,7). In late 2017, the management of treatment-refractory AD was revolutionized by the marketing of the first biologic drug, dupilumab (a subcutaneously administered monoclonal antibody against the interleukin -4 and -13 receptors) (8,9). Other systemic treatments have since received (or are awaiting) marketing authorization: baricitinib (an orally administered Janus kinase (Jak) 1 and 2 inhibitor (JAKi) (10–13), upadacitinib (an orally administered JAK1 inhibitor) (14–16), abrocitinib (another orally administered JAK1 inhibitor) (17–19), and tralokinumab (a subcutaneously administered anti-interleukin-13 monoclonal antibody) (20,21).

JAKis constitute a new family of orally administered molecules that target the JAK-signal transducer and activator of transcription (STAT) pathway. Janus kinases are involved in the transduction of intracellular signals in response to various cytokines and growth factors involved in haematopoiesis, inflammation, and immune functions.

In the European Union, baricitinib was approved for the treatment of active, moderate-to-severe rheumatoid arthritis (RA) in adults in 2017 and for moderate-to-severe AD in adults who are candidates for systemic drug treatment in 2021. Upadacitinib was approved for the treatment of adults with moderate-to-severe active RA, psoriatic arthritis (PsA), or ankylosing spondylitis (AS) in 2020 and 2021 and for the treatment of moderate-to-severe AD in adults and adolescents (aged 12 or over) who are candidates for systemic drug treatment in August 2021. Lastly, abrocitinib was approved very recently by the European Medicines Agency (EMA) for the systemic treatment of moderate-to-severe AD in adults and adolescents.

Clinical trials in RA have flagged up a potential risk of JAKi-induced venous thromboembolic events (VTEs, including deep vein thrombosis and pulmonary embolism) (22–26). Although the EMA approved low (2 mg) and high (4 mg) doses of baricitinib, the FDA only approved the 2 mg dose because of the VTE risk. On a broader scale, the summary of product

characteristics for a JAKi must mention VTEs as potential adverse drug reactions. The safety profiles of baricitinib and upadacitinib in patients with RA have been described in nine and five clinical studies, respectively. The estimated incidence of VTEs ranged from 0.3 to 0.6 per 100 person-years (22,27).

Due to the presence of systemic inflammation, RA *per se* can induce thromboembolic events, and the treatment of RA with anti-inflammatory drugs helps to reduce the cardiovascular and thromboembolic risk (25,28). Furthermore, most patients with RA are aged over 50 at diagnosis and have higher prevalence of obesity and a higher incidence of VTEs. In this case, the interplay between RA, JAKis and thromboembolic risk is particularly difficult to characterize.

The pathogenic links between JAKis and a potentially greater risk of thromboembolic disease are poorly understood, and the literature data are contradictory. The potential thromboembolic risk might be related to an imbalance between pro and anti-thrombotic signals, including the inhibition of pro-inflammatory signals (such as interferon-dependant pathways) and the paradoxical inhibition of JAK-STAT-dependant anti-inflammatory pathways (such as the IL-10 pathway that helps to limit clot formation under normal conditions) (29,30). JAKis that influence JAK2-dependent signalling (such as baricitinib) might also promote platelet formation from megakaryocytes, as evidenced by a transient increase in the platelet count following JAKi initiation. Nonetheless, a causal link between transient thrombocytosis and VTE has never been proven (22).

The results of meta-analyses of the links between JAKis and the risk of thromboembolic and/or cardiovascular events are summarized in Table 1 (31–37).

Table 1: List of meta-analyses on the risk of VTEs during treatment with JAKis

First Author	Date of publication	JAK inhibitor	Indication	Number of studies included	Type of studies included	Number of patients included	Median follow-up (weeks)	Number of events among exposed participants	Number of events among nonexposed participants	Results OR (95%CI)	Methods used
Xie (31)	2019	Tofacitinib Baricitinib Upadacitinib Peficitinib Decernotinib	RA	26	RCT	11799	Placebo-controlled period: 12 Dose-comparison period: 24	12	3	All JAKis: 1.16 (0.48-2.81) Tofacitinib: 0.17 (0.03–1.05) Baricitinib: 2.33 (0,62–8,75) Upadacitinib: 1.77 (0.20–16.00)	Mantel-Haenszel fixed-effect method
Xie (32)	2019	Tofacitinib	RA, PsA, CPP, UC, CD, AS	27	RCT	13611	Placebo-controlled period: 12 Dose-comparison period: 24	1	5	0.03 (0.00-0.21)	Peto method
Olivera (33)	2020	Tofacitinib Upadacitinib Filgotinib Baricitinib	RA, AS, UC, CD, CPP	10	RCT Cohorts	5143	26	12	3	All JAKis: 0.90 (0.32-2.54)	Random-effects model
Giménez Poderos (34)	2020	Tofacitinib Baricitinib	RA, KT, UC, CPP, CD, PsA, AD, DKD, SLE, JIA, SS	59	RCT Cohorts	25947	16	24	23	Tofacitinib: 0.29 (0.10-0.84) Baricitinib: 3.39 (0.82-14.04)	Fixed-effects or random-effects model, with application of the most conservative model in each case
Yates (35)	2020	Tofacitinib Baricitinib Upadacitinib Filgotinib	RA, PsA, AS, UC, CD, CPP	42	RCT	17269	unavailable	15	4	All JAKis: 0.68 (0.36-1.29)	Mantel-Haenszel fixed-effect method
Wang (36)	2020	Upadacitinib	RA	3	RCT	2852	unavailable	3	1	2.34 (0.15-15.02)	Random-effects model
Bilal (37)	2021	Abrocitinib, Baricitinib, Decernotinib, Filgotinib, Peficitinib, Ruxolitinib, Tofacitinib	RA, AD, SLE, CPP, AS, PsA, UC, Pancreatic cancer, Breast cancer	29	RCT	13910	48	50	27	All JAKis: 0.91 (0.57-1.47) Baricitinib: 1.12 (0.27-4.69) Decernotinib: 1.07 (0.18-6.43) Filgotinib: 2.13 (0.22-20.64) Ruxolitinib: (0.31-2.29) Upadacitinib: 2.25 (0.55-9.25) Tofacitinib: 0.27 (0.08-0.89)	Random-effects model

Abbreviations: AD, atopic dermatitis; AS, ankylosing spondylarthritis; CD, Crohn's disease; CI, confidence interval; CPP, Chronic Plaque Psoriasis; DKD, diabetic kidney disease; IR, incidence rates; JAKi, Janus kinase inhibitor; JIA, juvenile idiopathic arthritis; KT, kidney transplantation; OR, odds ratio; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomized clinical trial; SLE, systemic lupus erythematosus; SS, systemic sclerosis; UC, ulcerative colitis.

Most of the meta-analyzed data came from clinical trials, rather than real-life studies with a longer follow-up period. The meta-analyses concluded that although the JAKi treatment is associated with an elevated risk of VTEs, the association is not statistically significance. Lastly, the meta-analyses did not encompass data on VTEs treated in primary care facilities (i.e. on an outpatient basis). Two analyses of US medical-administrative databases did not find a difference in the VTE risk between patients with RA taking tofacitinib and those taking an anti-tumour necrosis factor agent (hazard ratio [95% confidence interval (CI)] = 1.13 [0.77-1.65] and 1.33 [0.78-2.24], respectively) (38,39). However, the researchers could not rule out such a risk, and only considered VTEs leading to hospital admission (38,39).

A population-based study of a health insurance database (the *Système National des Données de Santé*, SNDS) would provide additional insights by focusing on the VTE risk. The advantages of studying a health insurance database include the precise, national-level identification of JAKi prescriptions, VTEs, and the time of occurrence (relative to treatment initiation, for example). Furthermore, studying AD avoids a major source of confounding bias; in contrast to RA and inflammatory bowel disease, AD is not associated with an increased risk of VTE (40) and predominantly affects a younger population with a lower prevalence of concomitant cardiovascular comorbidities or obesity.

Here, we describe the protocol for the "JAK inhibitors and ThromboEmbolic Risk" (JAKTER) study of the association between JAKis and VTEs in AD, using real-world evidence from an exhaustive French medical-administrative database. We also discuss our methodological choices. We will address the following two questions, using two different methodological approaches: (i) is the risk of VTEs higher in adults with AD exposed to JAKis than in adults with AD not exposed to JAKis, and (ii) does the initiation of treatment with a JAKi trigger VTEs?

METHODS AND ANALYSIS

Overall study design

The literature data on the temporal relationship between the initiation of treatment with a JAKi and the occurrence of a VTE are contradictory. Some studies suggest that the incidence rates of VTEs are consistent over time (22), whereas other indicate that the incidence rates are clustered soon after the start of exposure (41). The study null hypotheses are formulated as follows: (i) VTE risk is equal in adults with AD exposed or not exposed to JAKis, (ii) JAKi initiation does not trigger VTE. We will therefore use two different methodological approaches to investigate

the VTEs and the JAKis prescribed for AD: (i) a nested case-control study in a cohort of adults with AD (analysis #1) and (ii) a case-time-control study (analysis #2).
The overall study design is summarized in Figure 1.

Place and study time

The analysis period will run from January 1st, 2017, to August 31st, 2025, in France.

Data sources

We will analyze the French national health insurance database (*Système National des Données de Santé*, SNDS), which covers 98% of the 66 million people in France. The SNDS database contains anonymous data on individuals' demographic characteristics (sex, dates of birth, and (if applicable) date of death); all healthcare reimbursements, including drugs (with the prescription filling date, the prescriber's medical speciality, laboratory tests, outpatient care/visits, all hospital stays, and the associated diagnoses (coded according to the International Classification of Diseases, 10th Revision (ICD-10), all causes of death (classified according to the ICD-10 codes), and the attribution or not of "chronic disease" status ("*affection de longue durée*" (ALD), giving entitlement to the full coverage of related healthcare costs, and again coded according to ICD-10 codes). Information on medical procedures or biological results are not available in the SNDS.

Selection criteria and constitution of the target cohort

To avoid indication bias and form a homogeneous group of patients in terms of medical care, we will build up a cohort of adults with AD and who start systemic immunomodulatory treatment for this disease.

In France, AD is a chronic condition that is mostly managed in outpatient settings and not during hospital stays. Furthermore, AD does not give entitlement to ALD chronic disease status. All eligible adults (aged 18 or over) with *a priori* AD will be identified as follows:

- adults (aged 18 or over) with an initial fulfilment of a prescription for dupilumab, cyclosporine, methotrexate, tralokinumab, or a JAKi (baricitinib, upadacitinib, or abrocitinib), two or more fulfilments of topical corticosteroids, and a consultation with a dermatologist between January 1st, 2017, and December 31st, 2024.

- adults with no fulfilments of dupilumab, cyclosporine, methotrexate, tralokinumab or JAKi (baricitinib, upadacitinib, or abrocitinib) prescriptions in the year prior to cohort entry.
- adults with no other indications for dupilumab, cyclosporine, methotrexate, tralokinumab, or the JAKis baricitinib, upadacitinib, or abrocitinib (i.e. RA, PsA, AS, ulcerative colitis, lupus, organ or bone marrow transplant, nephrotic syndrome, and psoriasis) identified through "ALD" chronic disease status or the hospital discharge ICD-10 codes, between January 1st, 2016, and December 31st, 2024.
- adults with follow-up starting on the date of the first filled prescription of a JAKi (baricitinib, upadacitinib, or abrocitinib), dupilumab, tralokinumab, cyclosporine, or methotrexate, up until August 31st, 2025.

Outcomes

The primary endpoint is VTE; it is a composite endpoint encompassing pulmonary embolism, managed mostly in hospital and identified through hospital discharge ICD-10 code (Table 2), and deep-vein thrombosis managed mostly in an outpatient setting and identified through a dedicated and validated algorithm (manuscript under review). The cases will be adults with AD and incident deep vein thrombosis or pulmonary embolism, managed in an outpatient setting, a hospital, or an emergency department.

The index date is the date of the VTE.

To study cases of "unprovoked" VTEs, we will exclude the following cases of adults with "provoked" VTEs (42):

- initiation of oral oestroprogestative contraception in the three months before the index date.
- pregnancy (including a two-month postpartum period) before the index date.
- surgery (orthopaedic surgery involving long bones or the pelvis, or other major surgery) in the four weeks before the index date.
- prolonged hospitalisation (>72 hours) in the four weeks before the index date.
- a diagnosis of cancer (including haematological malignancies but not including non-melanoma skin cancer) before the index date.
- fulfilment of one or more prescriptions for preventive or curative treatments with anticoagulants, including heparins, anti-vitamin K agents, and direct oral anticoagulant

(ensuring the exclusion of patients with a history of VTEs and persistent risk factors for VTE recurrence) before the index date (for VTEs managed in hospital or in an emergency department) or before the index date minus 7 days (for adults starting an anticoagulant treatment before hospitalization for VTE).

Data analysis

The characteristics of the JAKis-treated population of patients with AD will be described, together with the time interval between JAKi initiation and the occurrence of the VTE. We will explore the risk function and the potential time-varying association.

Analysis #1: a nested case-control study of a cohort of adults with AD

The association between exposure to JAKis and the occurrence of VTEs will be investigated in a nested case-control study of a cohort of adults with AD requiring systemic treatment.

Adults with AD will be considered to have been exposed to JAKis if they have at least one fulfilled prescription for a JAKi prior to the index date. Adults with AD will be assigned to a "JAKi user" category or a "JAKi never-user" category, based on the prior fulfilment closest to the index date. Subgroups of JAKi users will be defined as follows: for current JAKis users, the last prescription will have been fulfilled in the month before the index date: for recent JAKis users, the last prescription will have been fulfilled between one and four months before the index date; and for past JAKis users, the last prescription will have been fulfilled more than four months before the index date. Furthermore, for current JAKis users; the number of JAKi prescription fulfilments and the total cumulative dose of JAKis received before the index date will be calculated.

References will be adults with AD whose most recent prescription fulfilment before the index date (regardless of how long before) will have been for another systemic treatment for AD.

For each case (adults with AD having experienced a VTE), four controls will be selected from the target AD cohort. Controls must not have experienced a VTE at the time of their selection. Cases and controls will be matched for age, sex, and length of exposure at the case's index date. The inclusion and exclusion criteria applied to cases will be applied to the matched controls. It will be possible for a control to become a case after his/her selection (density sampling) (43). We will estimate odds ratios (ORs) using conditional logistic regression. We will consider systemic treatment of AD as a binary variable: JAKi users (baricitinib, upadacitinib, or

abrocitinib) vs. users of other systemic drugs (dupilumab, tralokinumab, cyclosporine, or methotrexate). We will consider drug exposure as a continuous variable. The primary analysis will compare current JAKi users with JAKi never-users. The secondary analyses will cover "recent JAKi user" status, "past JAKi user" status, and use of each individual JAKi (baricitinib, upadacitinib, and abrocitinib). A Schneeweiss diagram for analysis #1 is shown in Figure 2 (44).

Analysis #2. A case-only design: a nested case-time-control study of a cohort of adults with AD.

To evaluate whether or not initiation of a JAKi increases the risk of VTE in the following three months (i.e. a "triggering effect"), we will perform a case-time-control analysis.

In the field of pharmacoepidemiology, case-time-control studies can be used to study an acute, early-onset adverse event during treatment (45). A VTE is sudden (with a short time interval between the pathophysiological cause and the clinical manifestations) and is easy to date by screening for specific treatments and additional investigations (including Doppler ultrasound). The majority of the VTEs observed in clinical trials (22) or reported in pharmacovigilance databases (41) occurred within three to four months of JAKi initiation (46). Furthermore, the case-only design can control for potential confounding factors (such as obesity and physical activity) not recorded in the French health insurance database.

Only AD patients exposed to a JAKi and having experienced a VTE (i.e. cases) will be analyzed. The case-time-control design compares the exposure status immediately before the event (the risk period) with exposure during a designated (earlier) reference period. Each VTE case will serve as his/her own control during a comparison of the risk period (0 to 3 months before occurrence of the VTE) with the reference period (3 to 6 months before occurrence of the VTE). Each VTE case will be assessed for exposure (yes/no) during the risk period and during the reference period. Only participants whose status differs when comparing the two periods (i.e. discordants) will be considered in our estimation of the OR. To take account of the expected increase in JAKi prescription, the case-time-control analysis will include a selection of controls matched with VTE cases. Each VTE case will be matched for age and sex with 5 controls without VTEs and who will be randomly selected from the AD target cohort. The date of the VTE will be used as the index date for the matched controls. The above-defined risk and reference periods will be screened for JAKi initiation among the controls in the same way as among the cases, and a case-crossover OR for controls will be computed. The case-time-control

OR [95%CI] will be estimated with a conditional logistic model by considering the interaction term between the exposure of interest (JAKi initiation) and the participant's status (case or control). The case-time-control OR will correspond to the ratio between the respective case-crossover ORs obtained in cases and controls.

Sensitivity analyses in which the durations of the risk and reference period are modified will be performed as follows: the risk period will be defined as 0 to 2 months or 0 to 4 months before the VTE, and the control period will be defined as 2 to 4 months or 4 to 8 months before the VTE. Furthermore, sensitivity analysis will be performed for analyses #1 and #2 by changing the patient selection criteria and excluding patients with asthma. Lastly, we shall exclude patients having initiated oral oestroprogestative contraception in the 6 months or the 12 months before the date of the VTE in cases or the corresponding date in controls.

Covariates

We used a directed acyclic graph (Figure 3) to describe covariates, mediators, and potential confounding factors in the relationship between JAKis and VTEs.

The results will be adjusted for several covariates, including the patient's chronic comorbidities (using Bannay et al.'s algorithm for use of the Charlson Comorbidity Index with an electronic healthcare database (47,48)) and the use of statins (49) or systemic corticosteroids (50). Obesity is either not documented or only partially documented in the SNDS database; in Europe, most adults with AD are not obese (51). The case-only design approach (analysis #2) avoids this potential confounding factor, since the patient is his/her own control. The SNDS database does not contain identifiable information on a family history of venous thromboembolic disease.

Asthma (the most important atopic comorbidity in AD) will be assessed and defined as follows: an ICD-10 code J45-J46 and/or at least two fulfilments of a drug for the treatment of obstructive airway diseases (an Anatomical Therapeutic Chemical (ATC) code of R03). The study variables are listed in Table 2.

Table 2: List of variables

Variables	Registry	Code
Atopic dermatitis		
Atopic dermatitis	PMSI	ICD-10 code L20
Topical corticosteroids	DCIR	ATC codes D07AB01, D07AB02, D07AB03, D07AB04, D07AB05, D07AB06, D07AB07, D07AB08, D07AB09, D07AB10, D07AB11, D07AB19, D07AB21, D07AB30, D07AC01, D07AC02, D07AC03, D07AC04, D07AC05, D07AC06, D07AC07, D07AC08, D07AC09, D07AC10, D07AC11, D07AC12, D07AC13, D07AC14, D07AC15, D07AC16,D07AC17, D07AC18, D07AC19, D07AC20, D07AC21, D07AD01, D07AD02
Consultation with a dermatologist	DCIR	PFS_SPE_COD or PFE_SPE_COD code 05
Exposure		
Baricitinib	DCIR	ATC code L04AA37
Upadacitinib	DCIR	ATC code L04AA44
Abrocitinib	DCIR	ATC code D11AH08
Dupilumab	DCIR	ATC code D11AH05
Tralokinumab	DCIR	ATC code D11AH07
Cyclosporine	DCIR	ATC code L04AD01
Methotrexate	DCIR	ATC code L01BA01
Venous thromboembolic events		
Venous thromboembolic events	PMSI, DCIR	EPIGETBAM algorithm under submission
Exclusion criteria		
Oral oestroprogestative	DCIR	ATC codes G03AA01, G03AA02, G03AA03, G03AA04, G03AA05, G03AA06, G03AA07, G03AA08, G03AA09, G03AA10, G03AA11, G03AA12, G03AA13, G03AA14, G03AA15, G03AA16, G03AB01, G03AB02, G03AB03, G03AB04, G03AB05, G03AB06, G03AB07, G03AB08
Pregnancy	PMSI	ICD-10 code Z321
Hospital stay >72 hours, with or without surgery	PMSI	ICD-10 codes
Cancer and haematological malignancies	PMSI	ICD-10 codes C00 to C43 and C45 to C97, D00 to D03, D05 to D09, D37 to D48, or ALD n°30
Anticoagulant treatment	DCIR	ATC codes B01AA01, B01AA02, B01AA03, B01AA04, B01AA07, B01AA08, B01AA09, B01AA10, B01AA11, B01AA12, B01AB01, B01AB02, B01AB04, B01AB05, B01AB06, B01AB07, B01AB08, B01AB09, B01AB10, B01AB11, B01AB12, B01AB51, B01AE01, B01AE02, B01AE03, B01AE04, B01AE05, B01AE06, B01AE07, B01AF01, B01AF02, B01AF03, B01AX01, B01AX04, B01AX05
Rheumatoid arthritis	PMSI DCIR	ICD-10 codes M069, M0690, M0691, M0692, M0693, M0694, M0695, M0696, M0697, M0698, M0699, M06 or ALD n°22
Psoriatic arthritis	PMSI DCIR	ICD-10 codes M0700, M0701, M0702, M0703, M0704, M0705, M0706, M0707, M0708, M0709, M072, M0720, M0721, M0722, M0723, M0724, M0725, M0726, M0727, M0728, M0729, M073, M0730, M0734, M0732, M0733, M0734, M0735, M0736, M0737, M0738, M0739
Ulcerative colitis	PMSI DCIR	ICD-10 codes K519 or ALD n°24
Lupus	PMSI DCIR	ICD-10 codes L93, M32 or ALD n°21
Organ and bone marrow transplants	PMSI DCIR	ICD-10 codes Z940, Z941, Z942, Z943, Z944, Z945, Z946, Z947, Z948, Z9480, Z94800, Z94801, Z9481, Z9482, Z94802, Z94803, Z94804, Z94809, Z949
Nephrotic syndrome	PMSI DCIR	ICD-10 code N04 or ALD n°19
Psoriasis	PMSI DCIR	ICD-10 code L40, L400, L401, L402, L403, L404, L405, L408, L409
Ankylosing spondylitis	PMSI	ICD-10 codes M45, M450, M451, M452, M453, M454, M455, M456, M457, M458, M459 or ALD n°27
Covariates		
Charlson Comorbidity Index	PMSI	Algorithm developed by Bannay et al. (47)
Systemic corticosteroids	DCIR	ATC codes H02A and H02B
Asthma	PMSI DCIR	ICD-10 codes J45, J450, J451, J458, J459, J46 ATC code R03
Statins	DCIR	ATC codes C10AA, C10B

Abbreviations: ALD, *affection longue durée* long-term chronic disease status giving entitlement to full coverage of related healthcare costs; ATC, Anatomical Therapeutic Chemical; DCIR, Données de Consommation Inter Régimes; ICD-10, International Classification of Diseases 10th Revision; PMSI, Programme de Médicalisation des Systèmes d'Information.

Sample size

Based on a frequency of exposure to JAKi among the targeted cohort of 25%, a 1:4 case to control ratio, and a statistical significance threshold of 0.05, the sample sizes required for a power of 80% in a comparison of JAKi exposure in cases vs. controls are as follows: 1836 participants (306 cases and 1530 controls) for detecting an OR of 1.5, 618 participants (103 cases and 515 controls) for detecting an OR of 2, 354 participants (59 cases and 295 controls) for detecting an OR of 2.5, 246 participants (41 cases and 205 controls) for detecting an OR of 3, and 192 participants (32 cases and 160 controls) for detecting an OR of 3.5. These calculations do not take account of matching, which will tend to increase the power in an unknown manner. The estimated power calculation is given in Table 3. A final power calculation will be performed at the end of the study.

Table 3: Power calculation for analysis #1

Frequency of exposure to JAKis in the targeted cohort	Odds ratio	Nominal power	Number of controls	Number of cases	Total number of participants
0.50	1.5	0.8	1275	255	1530
0.50	2.0	0.8	465	93	558
0.50	3.0	0.8	205	41	246
0.25	1.5	0.8	1530	306	1836
0.25	2.0	0.8	515	103	618
0.25	2.5	0.8	295	59	354
0.25	3.0	0.8	205	41	246
0.25	3.5	0.8	160	32	192

Abbreviations: JAKis, Janus kinase inhibitors

The estimated incidence of thromboembolic diseases in France is one per 1000 per year; approximately 50,000 adults with a follow-up of three years are required. The target population for baricitinib/upadacitinib has been estimated at between 26,500 and 42,500 by the French High Authority for Health (52); this is almost certainly an underestimate, given that courses of treatment with cyclosporine are short.

Patient and Public Involvement

A patient will join the independent scientific committee and will participate in the discussion of the results. This patient is Stéphanie Mehrand who is the President of the French Eczema

Association (https://www.associationeczema.fr/). Once the study will be published, patients with AD who are members of the association will be informed of the results in the form of newsletter suitable for a non-specialist audience, through the website of the association.

ETHICS AND DISSEMINATION

In accordance with French legislation, the protocol has been approved by an independent ethics committee (*Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé*, Paris, France; reference: 4523600, dated June 17th, 2021) and has been registered with the French National Data Protection Commission (*Commission Nationale de l'Informatique et des Libertés*, Paris, France; reference: 921265, dated June 28th, 2021). The study's findings will be published in peer-reviewed scientific journals and presented at international conferences

The data will be consulted via the French national health insurance system's (*Caisse Nationale de l'Assurance Maladie*) portal; the investigators' access is restricted to the scope of the study. The data were not extracted from the main database but were analyzed in a dedicated project area on the server. The investigators will comply with the reference framework applicable to the SNDS database (as set out in the government act dated March 22nd, 2017).

The study protocol has been registered at France's Health Data Hub (www.health-data-hub.fr). The statistical analysis plan and data management book will now be drafted. The first results are expected in late 2025. The study's findings will be published in peer-reviewed scientific journals and presented at international conferences

DISCUSSION

A population-based study of a cohort of AD adults documented in the SNDS French national health insurance database should provide additional insights on the potential association between VTE and JAKis (baricitinib, upadacitinib, and abrocitinib).

There are several possible pathophysiological explanations for an elevated risk of VTE during treatment with a JAKi. Firstly, the leading hypothesis states that the thrombogenic effect is related to the thrombocytosis associated with baricitinib use (22). However, a clear time-domain or quantitative association between the platelet count and the occurrence of VTE has not been observed (22). Furthermore, elevation of the platelet count is not observed in people treated with other JAKis, including upadacitinib (53). Secondly, the JAK 2 pathway has an important

role in haematopoiesis and might promote VTE. Paradoxically, inhibition of the JAK2 pathway by JAKis does not account for the occurrence of VTE: in Vaquez disease and essential thrombocythemia, an activating mutation in JAK 2 increases the risk of arterial and venous thrombotic events (54). Data from mouse models suggest that JAK V617F expression induces hypersensitivity to fibrinogen, thrombopoietin, and other endogenous pro-thrombogenic factors (55).

The literature data on the potential risk are contradictory and do not enable a firm conclusion about the association between JAKis and VTE to be drawn. A false association might result from methodological bias. For example, selection bias occurs when including patients who have received several courses of systemic treatment (and so might have more severe disease and a higher thromboembolic risk) are included in clinical trials (especially in open-label trials in RA) (22,24). Confounding bias may occur because the disease treated with JAKi is itself associated with a higher risk of VTE; this is particularly true for RA. Indeed, the thromboembolic risk is known to be two to three times higher in patients with RA (25) than in the general population (28,56). The baseline risk also appears to be elevated other systemic inflammatory diseases, including inflammatory bowel disease (57,58). In contrast, adults managed for moderate-to-severe AD are not known to have an elevated thromboembolic risk and are also younger than patients with RA; hence, the baseline risk of VTEs is lower. Published data on this indication are scarce: the only two meta-analyses included data from four randomized clinical trials evaluating the efficacy of baricitinib and abrocitinib in AD (34). The lack of a significant association might have several explanations: (i) a lack of power would apply if the number of JAKi-exposed patients experiencing a VTE is low; meta-analyses have provided inconclusive results, due the rarity of the event and the predominant inclusion of clinical trial data; (ii) insufficient follow-up in clinical trials (given the latency between JAKi initiation and VTE occurrence); and (iii) a lack of specific detection of VTEs (requiring a targeted initial assessment and follow-up, and perhaps a longer follow-up period). Lastly, it is unclear whether the published studies considered only VTEs leading to a hospitalization or, in contrast, all VTEs. In France, the majority of VTEs are managed in an outpatient setting (59).

Our implementation of two complementary methodological approaches should shed more light on this question. The case-control study is carried out on a population of AD patients with similar disease severity levels and receiving similar intensities of systemic treatment. This design assumes that after initiation of a JAKi, the risk of a VTE is constant. The case-time-control design will be applied to address (i) the assumption whereby a JAKi triggers a VTE,

and (ii) the issue of residual confounding factors. This study design is particularly suitable when the outcome is sudden and easily dated, as is the case here (60–62). The hypothetical triggering effect is based on (i) the transient thrombocytosis observed with baricitinib early after treatment initiation (63,64), (ii) pharmacovigilance data from France and North America (41,46), where more than half of the reported VTEs occurred within 120 days of JAKi initiation (46), and (iii) the fact that other drugs (such as contraceptives) can trigger VTEs (65–69). An increase over the study period in the prevalence of JAKi use for AD is expected; the case-time-control design considers time-trends in the prevalence of exposure that might introduce a confounding effect in a case-crossover design. We chose to study "unprovoked" VTEs by excluding well-known risk factors for thromboembolic disease (70), such as cancer (71), surgery (72), immobilisation (proxy marker: a hospital stay), hospital admission (73), and the initiation of hormone therapy (74). Furthermore, we will adjust for the Charlson Comorbidity Index, which includes diabetes (75–78). However, obesity, black ethnicity (79), and a family history of thromboembolic disease are not documented in the SNDS database, and so we cannot rule out residual confounding in analysis #1 (the nested case-control study). In analysis #2 (the case-only design), cases serve as their own controls, which can mitigate the potential confounding factors (such as diet, smoking, the level of physical activity, and a family history of thromboembolic disease) not documented in healthcare databases (45,80).

Our study has several potential strengths, including the exhaustive nationwide coverage of the French population (thereby enabling an assessment of rare events and providing potentially greater statistical power); the theoretical absence of selection bias, given our use of the SNDS database; the quality of the recorded data (enabling estimation of the time of occurrence of VTEs); the implementation of two complementary methodological approaches; and the definitions of outcomes that encompass VTEs managed in out- and inpatient settings.

The study's potential limitations include the difficulty of tracking all VTEs (the use of an algorithm for the identification of inpatient and outpatient diagnoses of VTE in the health insurance database is, however, currently being validated); potential information bias on hormone therapy, since a proportion of these treatments are not reimbursed and therefore cannot be detected in the SNDS; a potential lack of statistical power; and inability to take account of some risk factors for VTEs (including obesity, and a family history of thromboembolic disease) in the case-control design – although we believe that these potential confounding factors should affect cases and controls to the same extent.

FIGURE AND TABLE LEGENDS

Figure 1: Overall study design

Figure 2: Schneeweiss diagram for analysis #1 (44)

Figure 3: A directed acyclic graph of the relationship between JAKis, AD, and VTEs

Table 1: List of meta-analyses on the risk of VTEs during treatment with JAKis

Table 2: List of variables

Table 3: Power calculation for analysis #1

STATEMENTS

Contributorship statement

PB and CD wrote the first draft of the manuscript. PB, LMS, AL, DSS, GC, PG, AD, EO and CD conceived the scoping review and developed the research questions and the search strategy. All authors critically reviewed drafts and edited the manuscript.

Competing interests

There are no competing interests for any author.

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- Nested case-control study (analysis #1)
- Nested case-time-control study (analysis #2): in patients with a VTE, we shall compare the frequency of JAKi initiation in the risk period (before VTE) with the frequency of JAKi initiation in the reference period (prior to the risk period).

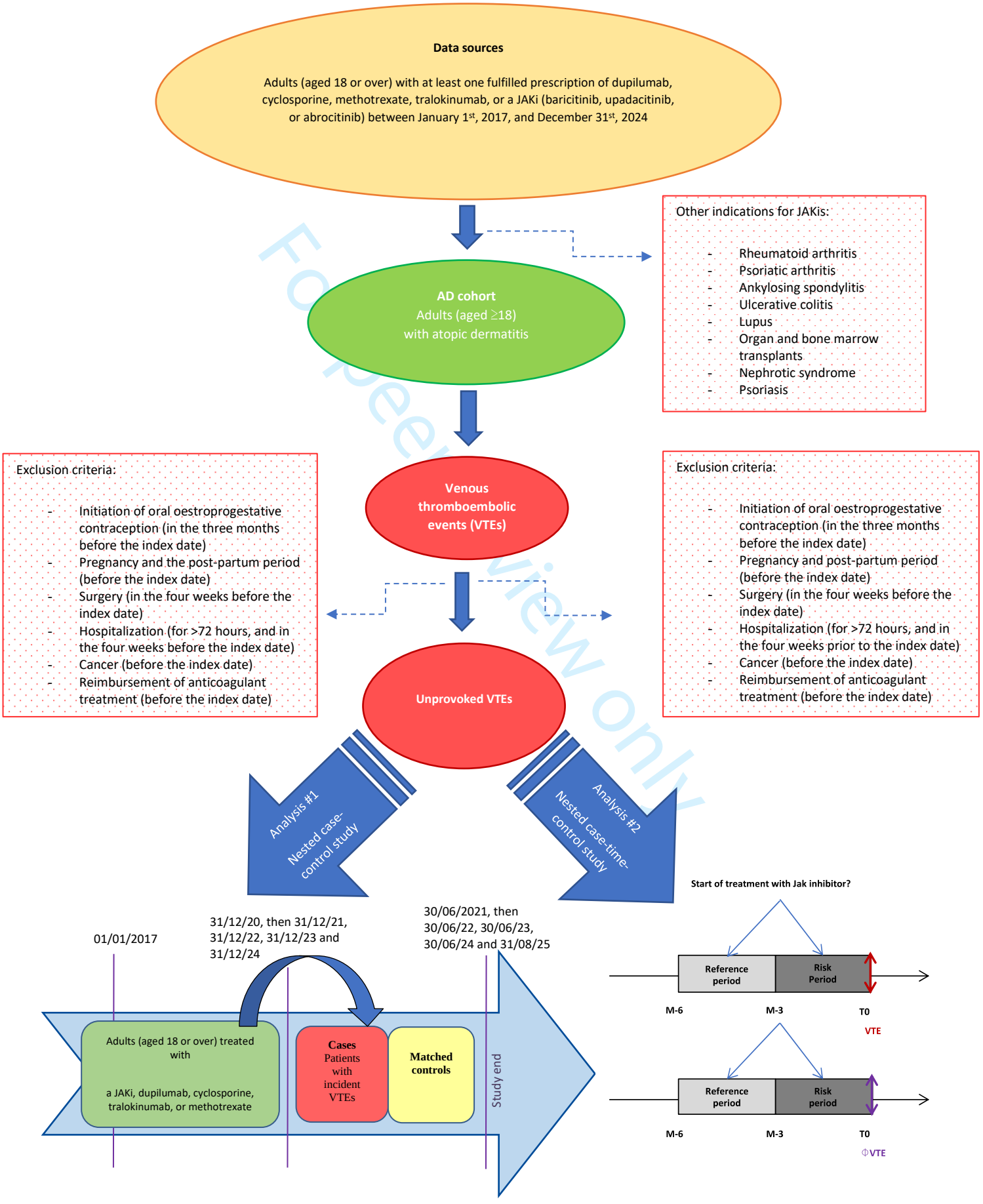
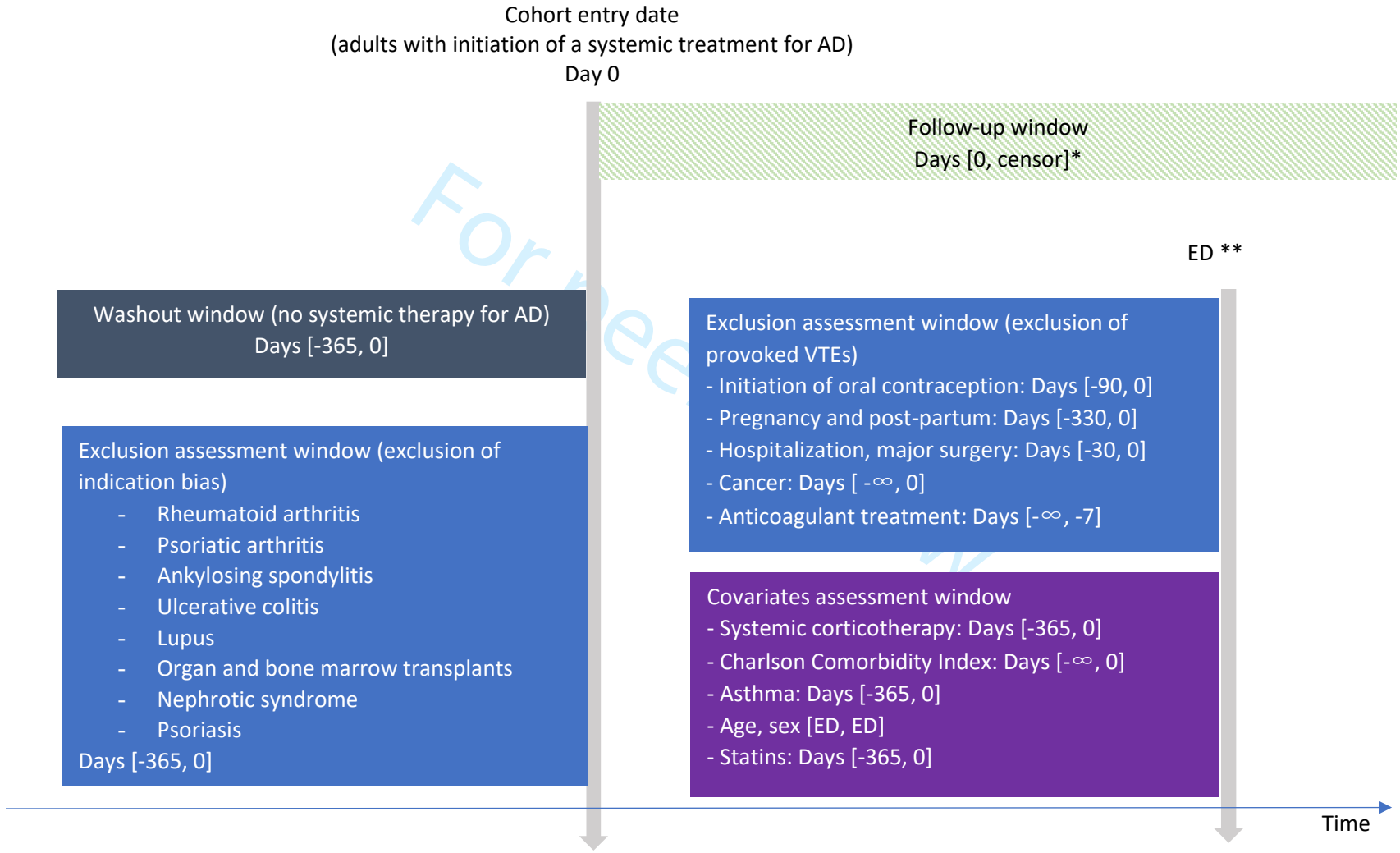
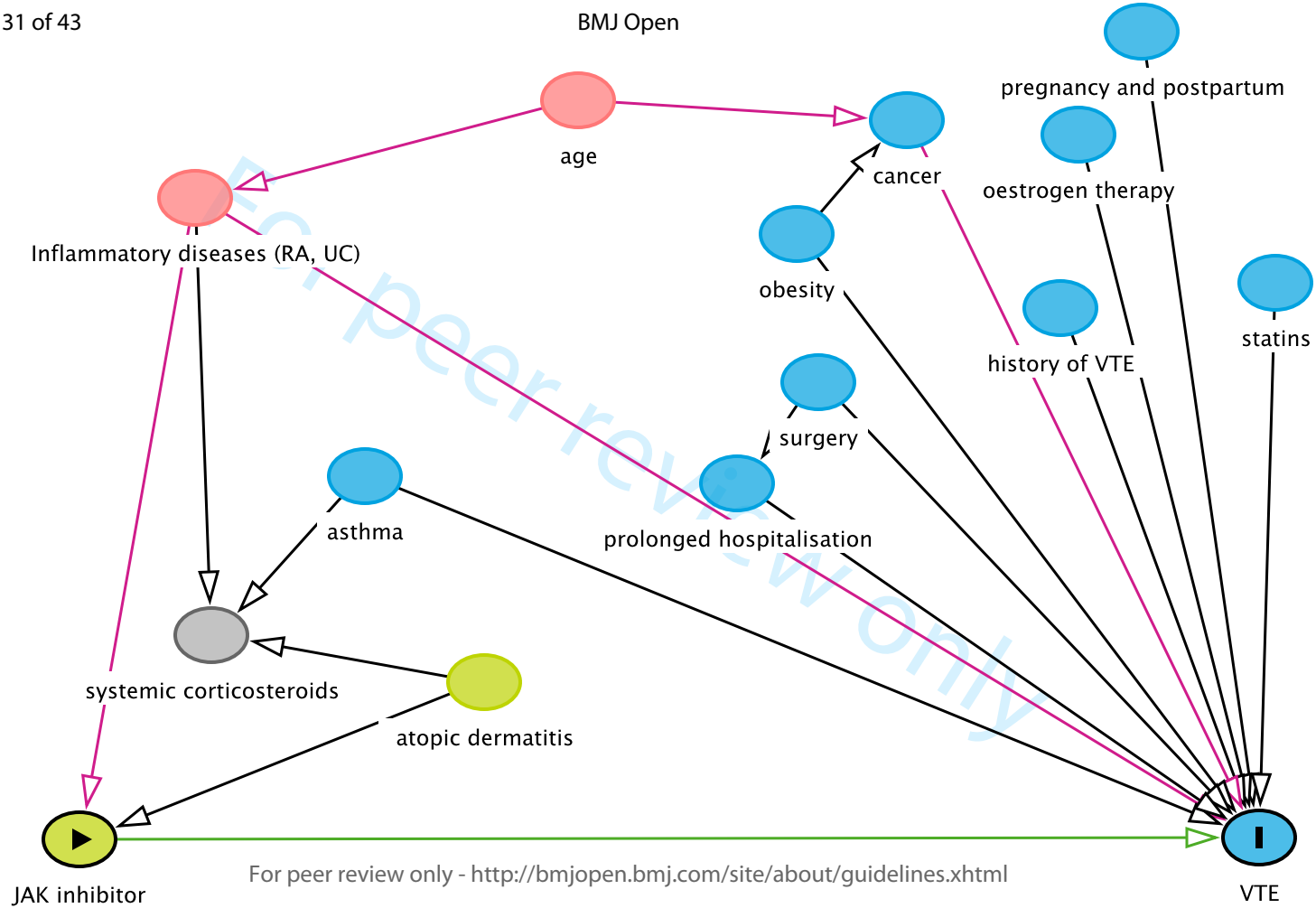


Figure 2: Schneeweiss diagram for analysis #1



Abbreviations: AD, atopic dermatitis; ED, event date; VTE, venous thromboembolic event
*Censored at the date of the first VTE, death, emigration, or the end of the study period
** ED: the date of the first VTE (the index date)



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European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Oral Janus kinases inhibitors and venous thromboembolism in atopic dermatitis: Protocol of a case-time control study and a nested case-control study based on French SNDS cohort

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	p. 10
1.1.2 End of data collection[2]	☒	☐	☐	p. 10
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	p.17

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	p. 6-8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	p. 6-8
2.1.2 The objective(s) of the study?	☒	☐	☐	p. 9-10
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	p. 9
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	p. 9
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	p. 9-14
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	p. 10-11
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	p. 12-13
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	p. 12-13
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	p. 10-11
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	p. 10

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
	4.2.2 Age and sex	☒	☐	☐	p. 10
	4.2.3 Country of origin	☒	☐	☐	p. 10
	4.2.4 Disease/indication	☒	☐	☐	p. 10
	4.2.5 Duration of follow-up	☒	☐	☐	p. 10-11
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	p. 10-11

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	p. 10-11
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	p. 10-11
5.3	Is exposure categorised according to time windows?	☒	☐	☐	p. 10-11
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	p. 10-11
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	p. 10-11

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	p. 11
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	p. 11-12
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	p. 11
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	p. 14
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	p.18
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	p.18

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	p. 14

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	p. 10-11
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	p. 11-12
9.1.3 Covariates and other characteristics?	☒	☐	☐	p. 14
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	p. 10-11
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	p. 11-12
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	p. 14
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Table 2
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Table 2
9.3.3 Covariates and other characteristics?	☒	☐	☐	Table 2

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	p. 9, 12, 13, 14
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	p. 16
10.3 Are descriptive analyses included?	☒	☐	☐	p.12-13
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	p. 18, 19
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	p. 19
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	p. 14

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	p. 17
11.2 Are methods of quality assurance described?	☐	☐	☒	
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	p. 17

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	p. 18-19
12.1.2 Information bias?	☒	☐	☐	p. 18-19
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	p. 19

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	p. 16

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	p. 17
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	p. 17

Comments:

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

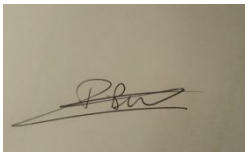
Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	p. 17
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	p. 17

Comments:

Name of the main author of the protocol: BERTHE Pauline

Date: 07/04/2022

Signature: 

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Pages 1 and 4
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Pages 6, 7 and 8
Objectives	3	State specific objectives, including any prespecified hypotheses			Page 9
Methods					
Study Design	4	Present key elements of study design early in the paper			Pages 9 and 10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Pages 10, 11 and 12

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Pages 10 and 11, and in table 2
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Pages 10, 11, 12, 14 and in table 2
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			Pages 10 to 14

Bias	9	Describe any efforts to address potential sources of bias			Pages 9, 10
Study size	10	Explain how the study size was arrived at			Page 16
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Pages 12, 13, and 14
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			Pages 12, 13 and 14
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Pages 10, 11 and 12

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure			

		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			
Discussion					
Key results	18	Summarise key results with reference to study objectives			
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page 19
Interpretation	20	Give a cautious overall interpretation of results considering objectives,			

		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results			
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			Page 20
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

Oral Janus kinase inhibitors and venous thromboembolic events in atopic dermatitis: protocols for a case-time control study and a nested case-control study based on the French national health insurance (SNDS) cohort.

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Primary Subject Heading:	Dermatology
Secondary Subject Heading:	Epidemiology, Pharmacology and therapeutics
Keywords:	Adult dermatology < DERMATOLOGY, Eczema < DERMATOLOGY, Thromboembolism < CARDIOLOGY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, CLINICAL PHARMACOLOGY

Title: Oral Janus kinase inhibitors and venous thromboembolic events in atopic dermatitis: protocols for a case-time control study and a nested case-control study based on the French national health insurance (SNDS) cohort.

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Conflicts of Interest: None with regard to the present work.

Keywords: JAK inhibitor, venous thromboembolic event, health insurance database

Abbreviations

Ankylosing spondylitis (AS)

Atopic dermatitis (AD)

Anatomical Therapeutic Chemical (ATC)

Confidence interval (CI)

Crohn's disease (CD)

European Medicines Agency (EMA)

Incidence rate (IR)

International Classification of Diseases, 10th Revision (ICD-10)

Odds ratio (OR)

Psoriatic arthritis (PsA)

Rheumatoid arthritis (RA)

Signal transducer and activator of transcription (STAT)

Système National des Données de Santé (SNDS)

Ulcerative colitis (UC)

Venous thromboembolic event (VTE)

Abstract

Introduction:

Atopic dermatitis (AD) is a highly prevalent, chronic, inflammatory skin disease. Several orally administered Janus kinase inhibitors (JAKis, including baricitinib, upadacitinib and abrocitinib) have received a marketing authorization for AD.

Clinical trials in rheumatoid arthritis (RA) have flagged up a potential risk of JAKi-induced venous thromboembolic events (VTEs). Accordingly, the summary of product characteristics for a JAKi must mention VTEs as potential adverse drug reactions. In contrast to RA, AD per se is not associated with an elevated risk of VTEs. Assessing this potential risk among AD patients would shed further light on the putative underlying relationship between JAKis and VTEs.

Our research question is to investigate whether JAKis administration increases the risk of VTEs in adults with AD. Our primary objective is to assess the risk of VTEs in adults with AD exposed to JAKis comparing to AD adults not exposed to JAKis, and our secondary objective is to evaluate whether JAKis initiation acts as a trigger of VTEs in adults with AD within three months.

Methods and analysis:

Hence, we have designed (i) a nested case-control study and (ii) a case-time-control study in a cohort of adults with AD with data from the French national health insurance system (2017-2025).

Here, we describe the study protocol, our methodological choices, and certain novel aspects - including the combined value of the two assumptions, and the use of an exhaustive national health insurance database with potentially greater statistical power for studying rare events in the population of AD patients at a low risk of VTEs (thus limiting the influence of confounding factors).

Ethics and dissemination:

The protocol has been approved by an independent ethics committee and registered with the French National Data Protection Commission. The study's findings will be published in peer-reviewed scientific journals and presented at international conferences.

Article Summary: strengths and limitations of this study

The strengths of this study protocol are:

- a population-based study using the exhaustive French national health insurance database would provide additional insight into the risk of venous thromboembolic events (VTEs). Advantageously, this nationwide study should be able to exhaustively identify VTEs, the time of their occurrence, and prescriptions of JAK inhibitors.
- By studying atopic dermatitis (AD), we hope to avoid a major source of confounding bias; in contrast to rheumatoid arthritis, AD is not associated *per se* with an elevated risk of VTEs.

The limitations of this study protocol (based on the use of French national health insurance database) include:

- a lack of data on certain risk factors for VTEs (including obesity and a family history of thromboembolic disease)
- a potential lack of statistical power.

INTRODUCTION

Atopic dermatitis (AD) is a highly prevalent, pruritic, inflammatory disease skin that occurs in both adults (3 to 10%) (1–3) and children (15 to 20%) (1,4,5). Approximately 2 to 8% of adults with AD have severe forms; the associated impairments in quality of life make AD a disabling disease. Severe AD is frequently associated with other atopic comorbidities (e.g. asthma, allergic rhinitis, allergic conjunctivitis, and food allergy), and may be associated with psychiatric disorders.

The European guidelines on the management of AD in adults recommend first-line treatment with topical anti-inflammatory drugs (topical corticosteroids and tacrolimus) and then (if the treatment fails) systemic immunosuppressants (6,7). In late 2017, the management of treatment-refractory AD was revolutionized by the marketing of the first biologic drug, dupilumab (a subcutaneously administered monoclonal antibody against the interleukin -4 and -13 receptors) (8,9). Other systemic treatments have since received (or are awaiting) marketing authorization: baricitinib (an orally administered Janus kinase (Jak) 1 and 2 inhibitor (JAKi) (10–13), upadacitinib (an orally administered JAK1 inhibitor) (14–16), abrocitinib (another orally administered JAK1 inhibitor) (17–19), and tralokinumab (a subcutaneously administered anti-interleukin-13 monoclonal antibody) (20,21).

JAKis constitute a new family of orally administered molecules that target the JAK-signal transducer and activator of transcription (STAT) pathway. Janus kinases are involved in the transduction of intracellular signals in response to various cytokines and growth factors involved in haematopoiesis, inflammation, and immune functions.

In the European Union, baricitinib was approved for the treatment of active, moderate-to-severe rheumatoid arthritis (RA) in adults in 2017 and for moderate-to-severe AD in adults who are candidates for systemic drug treatment in 2021. Upadacitinib was approved for the treatment of adults with moderate-to-severe active RA, psoriatic arthritis (PsA), or ankylosing spondylitis (AS) in 2020 and 2021 and for the treatment of moderate-to-severe AD in adults and adolescents (aged 12 or over) who are candidates for systemic drug treatment in August 2021. Lastly, abrocitinib was approved very recently by the European Medicines Agency (EMA) for the systemic treatment of moderate-to-severe AD in adults and adolescents.

Clinical trials in RA have flagged up a potential risk of JAKi-induced venous thromboembolic events (VTEs, including deep vein thrombosis and pulmonary embolism) (22–26). Although the EMA approved low (2 mg) and high (4 mg) doses of baricitinib, the FDA only approved the 2 mg dose because of the VTE risk. On a broader scale, the summary of product

characteristics for a JAKi must mention VTEs as potential adverse drug reactions. The safety profiles of baricitinib and upadacitinib in patients with RA have been described in nine and five clinical studies, respectively. The estimated incidence of VTEs ranged from 0.3 to 0.6 per 100 person-years (22,27).

Due to the presence of systemic inflammation, RA *per se* can induce thromboembolic events, and the treatment of RA with anti-inflammatory drugs helps to reduce the cardiovascular and thromboembolic risk (25,28). Furthermore, most patients with RA are aged over 50 at diagnosis and have higher prevalence of obesity and a higher incidence of VTEs. In this case, the interplay between RA, JAKis and thromboembolic risk is particularly difficult to characterize.

The pathogenic links between JAKis and a potentially greater risk of thromboembolic disease are poorly understood, and the literature data are contradictory. The potential thromboembolic risk might be related to an imbalance between pro and anti-thrombotic signals, including the inhibition of pro-inflammatory signals (such as interferon-dependant pathways) and the paradoxical inhibition of JAK-STAT-dependant anti-inflammatory pathways (such as the IL-10 pathway that helps to limit clot formation under normal conditions) (29,30). JAKis that influence JAK2-dependent signalling (such as baricitinib) might also promote platelet formation from megakaryocytes, as evidenced by a transient increase in the platelet count following JAKi initiation. Nonetheless, a causal link between transient thrombocytosis and VTE has never been proven (22).

The results of meta-analyses of the links between JAKis and the risk of thromboembolic and/or cardiovascular events are summarized in Table 1 (31–37).

Table 1: List of meta-analyses on the risk of VTEs during treatment with JAKis

First Author	Date of publication	JAK inhibitor	Indication	Number of studies included	Type of studies included	Number of patients included	Median follow-up (weeks)	Number of events among exposed participants	Number of events among nonexposed participants	Results OR (95%CI)	Methods used
Xie (31)	2019	Tofacitinib Baricitinib Upadacitinib Peficitinib Decernotinib	RA	26	RCT	11799	Placebo-controlled period: 12 Dose-comparison period: 24	12	3	All JAKis: 1.16 (0.48-2.81) Tofacitinib: 0.17 (0.03–1.05) Baricitinib: 2.33 (0,62–8,75) Upadacitinib: 1.77 (0.20–16.00)	Mantel-Haenszel fixed-effect method
Xie (32)	2019	Tofacitinib	RA, PsA, CPP, UC, CD, AS	27	RCT	13611	Placebo-controlled period: 12 Dose-comparison period: 24	1	5	0.03 (0.00-0.21)	Peto method
Olivera (33)	2020	Tofacitinib Upadacitinib Filgotinib Baricitinib	RA, AS, UC, CD, CPP	10	RCT Cohorts	5143	26	12	3	All JAKis: 0.90 (0.32-2.54)	Random-effects model
Giménez Poderos (34)	2020	Tofacitinib Baricitinib	RA, KT, UC, CPP, CD, PsA, AD, DKD, SLE, JIA, SS	59	RCT Cohorts	25947	16	24	23	Tofacitinib: 0.29 (0.10-0.84) Baricitinib: 3.39 (0.82-14.04)	Fixed-effects or random-effects model, with application of the most conservative model in each case
Yates (35)	2020	Tofacitinib Baricitinib Upadacitinib Filgotinib	RA, PsA, AS, UC, CD, CPP	42	RCT	17269	unavailable	15	4	All JAKis: 0.68 (0.36-1.29)	Mantel-Haenszel fixed-effect method
Wang (36)	2020	Upadacitinib	RA	3	RCT	2852	unavailable	3	1	2.34 (0.15-15.02)	Random-effects model
Bilal (37)	2021	Abrocitinib, Baricitinib, Decernotinib, Filgotinib, Peficitinib, Ruxolitinib, Tofacitinib	RA, AD, SLE, CPP, AS, PsA, UC, Pancreatic cancer, Breast cancer	29	RCT	13910	48	50	27	All JAKis: 0.91 (0.57-1.47) Baricitinib: 1.12 (0.27-4.69) Decernotinib: 1.07 (0.18-6.43) Filgotinib: 2.13 (0.22-20.64) Ruxolitinib: (0.31-2.29) Upadacitinib: 2.25 (0.55-9.25) Tofacitinib: 0.27 (0.08-0.89)	Random-effects model

Abbreviations: AD, atopic dermatitis; AS, ankylosing spondylarthritis; CD, Crohn's disease; CI, confidence interval; CPP, Chronic Plaque Psoriasis; DKD, diabetic kidney disease; IR, incidence rates; JAKi, Janus kinase inhibitor; JIA, juvenile idiopathic arthritis; KT, kidney transplantation; OR, odds ratio; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomized clinical trial; SLE, systemic lupus erythematosus; SS, systemic sclerosis; UC, ulcerative colitis.

Most of the meta-analyzed data came from clinical trials, rather than real-life studies with a longer follow-up period. The meta-analyses concluded that although the JAKi treatment is associated with an elevated risk of VTEs, the association is not statistically significance. Lastly, the meta-analyses did not encompass data on VTEs treated in primary care facilities (i.e. on an outpatient basis). Two analyses of US medical-administrative databases did not find a difference in the VTE risk between patients with RA taking tofacitinib and those taking an anti-tumour necrosis factor agent (hazard ratio [95% confidence interval (CI)] = 1.13 [0.77-1.65] and 1.33 [0.78-2.24], respectively) (38,39). However, the researchers could not rule out such a risk, and only considered VTEs leading to hospital admission (38,39).

A population-based study of a health insurance database (the *Système National des Données de Santé*, SNDS) would provide additional insights by focusing on the VTE risk. The advantages of studying a health insurance database include the precise, national-level identification of JAKi prescriptions, VTEs, and the time of occurrence (relative to treatment initiation, for example). Furthermore, studying AD avoids a major source of confounding bias; in contrast to RA and inflammatory bowel disease, AD is not associated with an increased risk of VTE (40) and predominantly affects a younger population with a lower prevalence of concomitant cardiovascular comorbidities or obesity.

Here, we describe the protocol for the "JAK inhibitors and ThromboEmbolic Risk" (JAKTER) study of the association between JAKis and VTEs in AD, using real-world evidence from an exhaustive French medical-administrative database. We also discuss our methodological choices. Our primary objective is to assess the risk of VTEs in adults with AD exposed to JAKis comparing to AD adults not exposed to JAKis, and our secondary objective is to evaluate whether JAKis initiation acts as a trigger of VTEs in adults with AD within three months, corresponding to two different methodological approaches.

METHODS AND ANALYSIS

Overall study design

The literature data on the temporal relationship between the initiation of treatment with a JAKi and the occurrence of a VTE are contradictory. Some studies suggest that the incidence rates of VTEs are consistent over time (22), whereas other indicate that the incidence rates are clustered soon after the start of exposure (41). The study null hypotheses are formulated as follows: (i) VTE risk is equal in adults with AD exposed or not exposed to JAKis, (ii) JAKi initiation does not trigger VTE. We will therefore use two different methodological approaches to investigate

the VTEs and the JAKis prescribed for AD: (i) a nested case-control study in a cohort of adults with AD (analysis #1) and (ii) a case-time-control study (analysis #2).
The overall study design is summarized in Figure 1.

Place and study time

The analysis period will run from January 1st, 2017, to August 31st, 2025, in France.

Data sources

We will analyze the French national health insurance database (*Système National des Données de Santé*, SNDS), which covers 98% of the 66 million people in France. The SNDS database contains anonymous data on individuals' demographic characteristics (sex, dates of birth, and (if applicable) date of death); all healthcare reimbursements, including drugs (with the prescription filling date, the prescriber's medical speciality, laboratory tests, outpatient care/visits, all hospital stays, and the associated diagnoses (coded according to the International Classification of Diseases, 10th Revision (ICD-10), all causes of death (classified according to the ICD-10 codes), and the attribution or not of "chronic disease" status ("*affection de longue durée*" (ALD), giving entitlement to the full coverage of related healthcare costs, and again coded according to ICD-10 codes). Information on medical procedures or biological results are not available in the SNDS.

Selection criteria and constitution of the target cohort

To avoid indication bias and form a homogeneous group of patients in terms of medical care, we will build up a cohort of adults with AD and who start systemic immunomodulatory treatment for this disease.

In France, AD is a chronic condition that is mostly managed in outpatient settings and not during hospital stays. Furthermore, AD does not give entitlement to ALD chronic disease status. All eligible adults (aged 18 or over) with *a priori* AD will be identified as follows:

- adults (aged 18 or over) with an initial fulfilment of a prescription for dupilumab, cyclosporine, methotrexate, tralokinumab, or a JAKi (baricitinib, upadacitinib, or abrocitinib), two or more fulfilments of topical corticosteroids, and a consultation with a dermatologist between January 1st, 2017, and December 31st, 2024.

- adults with no fulfilments of dupilumab, cyclosporine, methotrexate, tralokinumab or JAKi (baricitinib, upadacitinib, or abrocitinib) prescriptions in the year prior to cohort entry.
- adults with no other indications for dupilumab, cyclosporine, methotrexate, tralokinumab, or the JAKis baricitinib, upadacitinib, or abrocitinib (i.e. RA, PsA, AS, ulcerative colitis, lupus, organ or bone marrow transplant, nephrotic syndrome, and psoriasis) identified through "ALD" chronic disease status or the hospital discharge ICD-10 codes, between January 1st, 2016, and December 31st, 2024.
- adults with follow-up starting on the date of the first filled prescription of a JAKi (baricitinib, upadacitinib, or abrocitinib), dupilumab, tralokinumab, cyclosporine, or methotrexate, up until August 31st, 2025.

Outcomes

The primary endpoint is VTE; it is a composite endpoint encompassing pulmonary embolism, managed mostly in hospital and identified through hospital discharge ICD-10 code (Table 2), and deep-vein thrombosis managed mostly in an outpatient setting and identified through a dedicated and validated algorithm (manuscript under review). The cases will be adults with AD and incident deep vein thrombosis or pulmonary embolism, managed in an outpatient setting, a hospital, or an emergency department.

The index date is the date of the VTE.

To study cases of "unprovoked" VTEs, we will exclude the following cases of adults with "provoked" VTEs (42):

- initiation of oral oestroprogestative contraception in the three months before the index date.
- pregnancy (including a two-month postpartum period) before the index date.
- surgery (orthopaedic surgery involving long bones or the pelvis, or other major surgery) in the four weeks before the index date.
- prolonged hospitalisation (>72 hours) in the four weeks before the index date.
- a diagnosis of cancer (including haematological malignancies but not including non-melanoma skin cancer) before the index date.
- fulfilment of one or more prescriptions for preventive or curative treatments with anticoagulants, including heparins, anti-vitamin K agents, and direct oral anticoagulant

(ensuring the exclusion of patients with a history of VTEs and persistent risk factors for VTE recurrence) before the index date (for VTEs managed in hospital or in an emergency department) or before the index date minus 7 days (for adults starting an anticoagulant treatment before hospitalization for VTE).

Data analysis

The characteristics of the JAKis-treated population of patients with AD will be described, together with the time interval between JAKi initiation and the occurrence of the VTE. We will explore the risk function and the potential time-varying association.

Analysis #1: a nested case-control study of a cohort of adults with AD

The association between exposure to JAKis and the occurrence of VTEs will be investigated in a nested case-control study of a cohort of adults with AD requiring systemic treatment.

Adults with AD will be considered to have been exposed to JAKis if they have at least one fulfilled prescription for a JAKi prior to the index date. Adults with AD will be assigned to a "JAKi user" category or a "JAKi never-user" category, based on the prior fulfilment closest to the index date. Subgroups of JAKi users will be defined as follows: for current JAKis users, the last prescription will have been fulfilled in the month before the index date: for recent JAKis users, the last prescription will have been fulfilled between one and four months before the index date; and for past JAKis users, the last prescription will have been fulfilled more than four months before the index date. Furthermore, for current JAKis users; the number of JAKi prescription fulfilments and the total cumulative dose of JAKis received before the index date will be calculated.

References will be adults with AD whose most recent prescription fulfilment before the index date (regardless of how long before) will have been for another systemic treatment for AD.

For each case (adults with AD having experienced a VTE), four controls will be selected from the target AD cohort. Controls must not have experienced a VTE at the time of their selection. Cases and controls will be matched for age, sex, and length of exposure at the case's index date. The inclusion and exclusion criteria applied to cases will be applied to the matched controls. It will be possible for a control to become a case after his/her selection (density sampling) (43). We will estimate odds ratios (ORs) using conditional logistic regression. We will consider systemic treatment of AD as a binary variable: JAKi users (baricitinib, upadacitinib, or

abrocitinib) vs. users of other systemic drugs (dupilumab, tralokinumab, cyclosporine, or methotrexate). We will consider drug exposure as a continuous variable. The primary analysis will compare current JAKi users with JAKi never-users. The secondary analyses will cover "recent JAKi user" status, "past JAKi user" status, and use of each individual JAKi (baricitinib, upadacitinib, and abrocitinib). A Schneeweiss diagram for analysis #1 is shown in Figure 2 (44).

Analysis #2. A case-only design: a nested case-time-control study of a cohort of adults with AD.

To evaluate whether or not initiation of a JAKi increases the risk of VTE in the following three months (i.e. a "triggering effect"), we will perform a case-time-control analysis.

In the field of pharmacoepidemiology, case-time-control studies can be used to study an acute, early-onset adverse event during treatment (45). A VTE is sudden (with a short time interval between the pathophysiological cause and the clinical manifestations) and is easy to date by screening for specific treatments and additional investigations (including Doppler ultrasound). The majority of the VTEs observed in clinical trials (22) or reported in pharmacovigilance databases (41) occurred within three to four months of JAKi initiation (46). Furthermore, the case-only design can control for potential confounding factors (such as obesity and physical activity) not recorded in the French health insurance database.

Only AD patients exposed to a JAKi and having experienced a VTE (i.e. cases) will be analyzed. The case-time-control design compares the exposure status immediately before the event (the risk period) with exposure during a designated (earlier) reference period. Each VTE case will serve as his/her own control during a comparison of the risk period (0 to 3 months before occurrence of the VTE) with the reference period (3 to 6 months before occurrence of the VTE). Each VTE case will be assessed for exposure (yes/no) during the risk period and during the reference period. Only participants whose status differs when comparing the two periods (i.e. discordants) will be considered in our estimation of the OR. To take account of the expected increase in JAKi prescription, the case-time-control analysis will include a selection of controls matched with VTE cases. Each VTE case will be matched for age and sex with 5 controls without VTEs and who will be randomly selected from the AD target cohort. The date of the VTE will be used as the index date for the matched controls. The above-defined risk and reference periods will be screened for JAKi initiation among the controls in the same way as among the cases, and a case-crossover OR for controls will be computed. The case-time-control

OR [95%CI] will be estimated with a conditional logistic model by considering the interaction term between the exposure of interest (JAKi initiation) and the participant's status (case or control). The case-time-control OR will correspond to the ratio between the respective case-crossover ORs obtained in cases and controls.

Sensitivity analyses in which the durations of the risk and reference period are modified will be performed as follows: the risk period will be defined as 0 to 2 months or 0 to 4 months before the VTE, and the control period will be defined as 2 to 4 months or 4 to 8 months before the VTE. Furthermore, sensitivity analysis will be performed for analyses #1 and #2 by changing the patient selection criteria and excluding patients with asthma. Lastly, we shall exclude patients having initiated oral oestroprogestative contraception in the 6 months or the 12 months before the date of the VTE in cases or the corresponding date in controls.

Covariates

We used a directed acyclic graph (Figure 3) to describe covariates, mediators, and potential confounding factors in the relationship between JAKis and VTEs.

The results will be adjusted for several covariates, including the patient's chronic comorbidities (using Bannay et al.'s algorithm for use of the Charlson Comorbidity Index with an electronic healthcare database (47,48)) and the use of statins (49) or systemic corticosteroids (50). Obesity is either not documented or only partially documented in the SNDS database; in Europe, most adults with AD are not obese (51). The case-only design approach (analysis #2) avoids this potential confounding factor, since the patient is his/her own control. The SNDS database does not contain identifiable information on a family history of venous thromboembolic disease.

Asthma (the most important atopic comorbidity in AD) will be assessed and defined as follows: an ICD-10 code J45-J46 and/or at least two fulfilments of a drug for the treatment of obstructive airway diseases (an Anatomical Therapeutic Chemical (ATC) code of R03). The study variables are listed in Table 2.

Table 2: List of variables

Variables	Registry	Code
Atopic dermatitis		
Atopic dermatitis	PMSI	ICD-10 code L20
Topical corticosteroids	DCIR	ATC codes D07AB01, D07AB02, D07AB03, D07AB04, D07AB05, D07AB06, D07AB07, D07AB08, D07AB09, D07AB10, D07AB11, D07AB19, D07AB21, D07AB30, D07AC01, D07AC02, D07AC03, D07AC04, D07AC05, D07AC06, D07AC07, D07AC08, D07AC09, D07AC10, D07AC11, D07AC12, D07AC13, D07AC14, D07AC15, D07AC16,D07AC17, D07AC18, D07AC19, D07AC20, D07AC21, D07AD01, D07AD02
Consultation with a dermatologist	DCIR	PFS_SPE_COD or PFE_SPE_COD code 05
Exposure		
Baricitinib	DCIR	ATC code L04AA37
Upadacitinib	DCIR	ATC code L04AA44
Abrocitinib	DCIR	ATC code D11AH08
Dupilumab	DCIR	ATC code D11AH05
Tralokinumab	DCIR	ATC code D11AH07
Cyclosporine	DCIR	ATC code L04AD01
Methotrexate	DCIR	ATC code L01BA01
Venous thromboembolic events		
Venous thromboembolic events	PMSI, DCIR	EPIGETBAM algorithm under submission
Exclusion criteria		
Oral oestroprogestative	DCIR	ATC codes G03AA01, G03AA02, G03AA03, G03AA04, G03AA05, G03AA06, G03AA07, G03AA08, G03AA09, G03AA10, G03AA11, G03AA12, G03AA13, G03AA14, G03AA15, G03AA16, G03AB01, G03AB02, G03AB03, G03AB04, G03AB05, G03AB06, G03AB07, G03AB08
Pregnancy	PMSI	ICD-10 code Z321
Hospital stay >72 hours, with or without surgery	PMSI	ICD-10 codes
Cancer and haematological malignancies	PMSI	ICD-10 codes C00 to C43 and C45 to C97, D00 to D03, D05 to D09, D37 to D48, or ALD n°30
Anticoagulant treatment	DCIR	ATC codes B01AA01, B01AA02, B01AA03, B01AA04, B01AA07, B01AA08, B01AA09, B01AA10, B01AA11, B01AA12, B01AB01, B01AB02, B01AB04, B01AB05, B01AB06, B01AB07, B01AB08, B01AB09, B01AB10, B01AB11, B01AB12, B01AB51, B01AE01, B01AE02, B01AE03, B01AE04, B01AE05, B01AE06, B01AE07, B01AF01, B01AF02, B01AF03, B01AX01, B01AX04, B01AX05
Rheumatoid arthritis	PMSI DCIR	ICD-10 codes M069, M0690, M0691, M0692, M0693, M0694, M0695, M0696, M0697, M0698, M0699, M06 or ALD n°22
Psoriatic arthritis	PMSI DCIR	ICD-10 codes M0700, M0701, M0702, M0703, M0704, M0705, M0706, M0707, M0708, M0709, M072, M0720, M0721, M0722, M0723, M0724, M0725, M0726, M0727, M0728, M0729, M073, M0730, M0734, M0732, M0733, M0734, M0735, M0736, M0737, M0738, M0739
Ulcerative colitis	PMSI DCIR	ICD-10 codes K519 or ALD n°24
Lupus	PMSI DCIR	ICD-10 codes L93, M32 or ALD n°21
Organ and bone marrow transplants	PMSI DCIR	ICD-10 codes Z940, Z941, Z942, Z943, Z944, Z945, Z946, Z947, Z948, Z9480, Z94800, Z94801, Z9481, Z9482, Z94802, Z94803, Z94804, Z94809, Z949
Nephrotic syndrome	PMSI DCIR	ICD-10 code N04 or ALD n°19
Psoriasis	PMSI DCIR	ICD-10 code L40, L400, L401, L402, L403, L404, L405, L408, L409
Ankylosing spondylitis	PMSI	ICD-10 codes M45, M450, M451, M452, M453, M454, M455, M456, M457, M458, M459 or ALD n°27
Covariates		
Charlson Comorbidity Index	PMSI	Algorithm developed by Bannay et al. (47)
Systemic corticosteroids	DCIR	ATC codes H02A and H02B
Asthma	PMSI DCIR	ICD-10 codes J45, J450, J451, J458, J459, J46 ATC code R03
Statins	DCIR	ATC codes C10AA, C10B

Abbreviations: ALD, *affection longue durée* long-term chronic disease status giving entitlement to full coverage of related healthcare costs; ATC, Anatomical Therapeutic Chemical; DCIR, Données de Consommation Inter Régimes; ICD-10, International Classification of Diseases 10th Revision; PMSI, Programme de Médicalisation des Systèmes d'Information.

Sample size

Based on a frequency of exposure to JAKi among the targeted cohort of 25%, a 1:4 case to control ratio, and a statistical significance threshold of 0.05, the sample sizes required for a power of 80% in a comparison of JAKi exposure in cases vs. controls are as follows: 1836 participants (306 cases and 1530 controls) for detecting an OR of 1.5, 618 participants (103 cases and 515 controls) for detecting an OR of 2, 354 participants (59 cases and 295 controls) for detecting an OR of 2.5, 246 participants (41 cases and 205 controls) for detecting an OR of 3, and 192 participants (32 cases and 160 controls) for detecting an OR of 3.5. These calculations do not take account of matching, which will tend to increase the power in an unknown manner. The estimated power calculation is given in Table 3. A final power calculation will be performed at the end of the study.

Table 3: Power calculation for analysis #1

Frequency of exposure to JAKis in the targeted cohort	Odds ratio	Nominal power	Number of controls	Number of cases	Total number of participants
0.50	1.5	0.8	1275	255	1530
0.50	2.0	0.8	465	93	558
0.50	3.0	0.8	205	41	246
0.25	1.5	0.8	1530	306	1836
0.25	2.0	0.8	515	103	618
0.25	2.5	0.8	295	59	354
0.25	3.0	0.8	205	41	246
0.25	3.5	0.8	160	32	192

Abbreviations: JAKis, Janus kinase inhibitors

The estimated incidence of thromboembolic diseases in France is one per 1000 per year; approximately 50,000 adults with a follow-up of three years are required. The target population for baricitinib/upadacitinib has been estimated at between 26,500 and 42,500 by the French High Authority for Health (52); this is almost certainly an underestimate, given that courses of treatment with cyclosporine are short.

Patient and Public Involvement

A patient will join the independent scientific committee and will participate in the discussion of the results. This patient is Stéphanie Mehrand who is the Director of the French Eczema

Association (https://www.associationeczema.fr/). Once the study will be published, patients with AD who are members of the association will be informed of the results in the form of newsletter suitable for a non-specialist audience, through the website of the association.

ETHICS AND DISSEMINATION

In accordance with French legislation, the protocol has been approved by an independent ethics committee (*Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé*, Paris, France; reference: 4523600, dated June 17th, 2021) and has been registered with the French National Data Protection Commission (*Commission Nationale de l'Informatique et des Libertés*, Paris, France; reference: 921265, dated June 28th, 2021). The study's findings will be published in peer-reviewed scientific journals and presented at international conferences

The data will be consulted via the French national health insurance system's (*Caisse Nationale de l'Assurance Maladie*) portal; the investigators' access is restricted to the scope of the study. The data were not extracted from the main database but were analyzed in a dedicated project area on the server. The investigators will comply with the reference framework applicable to the SNDS database (as set out in the government act dated March 22nd, 2017).

The study protocol has been registered at France's Health Data Hub (www.health-data-hub.fr). The statistical analysis plan and data management book will now be drafted. The first results are expected in late 2025. The study's findings will be published in peer-reviewed scientific journals and presented at international conferences

DISCUSSION

A population-based study of a cohort of AD adults documented in the SNDS French national health insurance database should provide additional insights on the potential association between VTE and JAKis (baricitinib, upadacitinib, and abrocitinib).

There are several possible pathophysiological explanations for an elevated risk of VTE during treatment with a JAKi. Firstly, the leading hypothesis states that the thrombogenic effect is related to the thrombocytosis associated with baricitinib use (22). However, a clear time-domain or quantitative association between the platelet count and the occurrence of VTE has not been observed (22). Furthermore, elevation of the platelet count is not observed in people treated with other JAKis, including upadacitinib (53). Secondly, the JAK 2 pathway has an important

role in haematopoiesis and might promote VTE. Paradoxically, inhibition of the JAK2 pathway by JAKis does not account for the occurrence of VTE: in Vaquez disease and essential thrombocythemia, an activating mutation in JAK 2 increases the risk of arterial and venous thrombotic events (54). Data from mouse models suggest that JAK V617F expression induces hypersensitivity to fibrinogen, thrombopoietin, and other endogenous pro-thrombogenic factors (55).

The literature data on the potential risk are contradictory and do not enable a firm conclusion about the association between JAKis and VTE to be drawn. A false association might result from methodological bias. For example, selection bias occurs when including patients who have received several courses of systemic treatment (and so might have more severe disease and a higher thromboembolic risk) are included in clinical trials (especially in open-label trials in RA) (22,24). Confounding bias may occur because the disease treated with JAKi is itself associated with a higher risk of VTE; this is particularly true for RA. Indeed, the thromboembolic risk is known to be two to three times higher in patients with RA (25) than in the general population (28,56). The baseline risk also appears to be elevated other systemic inflammatory diseases, including inflammatory bowel disease (57,58). In contrast, adults managed for moderate-to-severe AD are not known to have an elevated thromboembolic risk and are also younger than patients with RA; hence, the baseline risk of VTEs is lower. Published data on this indication are scarce: the only two meta-analyses included data from four randomized clinical trials evaluating the efficacy of baricitinib and abrocitinib in AD (34). The lack of a significant association might have several explanations: (i) a lack of power would apply if the number of JAKi-exposed patients experiencing a VTE is low; meta-analyses have provided inconclusive results, due the rarity of the event and the predominant inclusion of clinical trial data; (ii) insufficient follow-up in clinical trials (given the latency between JAKi initiation and VTE occurrence); and (iii) a lack of specific detection of VTEs (requiring a targeted initial assessment and follow-up, and perhaps a longer follow-up period). Lastly, it is unclear whether the published studies considered only VTEs leading to a hospitalization or, in contrast, all VTEs. In France, the majority of VTEs are managed in an outpatient setting (59).

Our implementation of two complementary methodological approaches should shed more light on this question. The case-control study is carried out on a population of AD patients with similar disease severity levels and receiving similar intensities of systemic treatment. This design assumes that after initiation of a JAKi, the risk of a VTE is constant. The case-time-control design will be applied to address (i) the assumption whereby a JAKi triggers a VTE,

and (ii) the issue of residual confounding factors. This study design is particularly suitable when the outcome is sudden and easily dated, as is the case here (60–62). The hypothetical triggering effect is based on (i) the transient thrombocytosis observed with baricitinib early after treatment initiation (63,64), (ii) pharmacovigilance data from France and North America (41,46), where more than half of the reported VTEs occurred within 120 days of JAKi initiation (46), and (iii) the fact that other drugs (such as contraceptives) can trigger VTEs (65–69). An increase over the study period in the prevalence of JAKi use for AD is expected; the case-time-control design considers time-trends in the prevalence of exposure that might introduce a confounding effect in a case-crossover design. We chose to study "unprovoked" VTEs by excluding well-known risk factors for thromboembolic disease (70), such as cancer (71), surgery (72), immobilisation (proxy marker: a hospital stay), hospital admission (73), and the initiation of hormone therapy (74). Furthermore, we will adjust for the Charlson Comorbidity Index, which includes diabetes (75–78). However, obesity, black ethnicity (79), and a family history of thromboembolic disease are not documented in the SNDS database, and so we cannot rule out residual confounding in analysis #1 (the nested case-control study). In analysis #2 (the case-only design), cases serve as their own controls, which can mitigate the potential confounding factors (such as diet, smoking, the level of physical activity, and a family history of thromboembolic disease) not documented in healthcare databases (45,80).

Our study has several potential strengths, including the exhaustive nationwide coverage of the French population (thereby enabling an assessment of rare events and providing potentially greater statistical power); the theoretical absence of selection bias, given our use of the SNDS database; the quality of the recorded data (enabling estimation of the time of occurrence of VTEs); the implementation of two complementary methodological approaches; and the definitions of outcomes that encompass VTEs managed in out- and inpatient settings.

The study's potential limitations include the difficulty of tracking all VTEs (the use of an algorithm for the identification of inpatient and outpatient diagnoses of VTE in the health insurance database is, however, currently being validated); potential information bias on hormone therapy, since a proportion of these treatments are not reimbursed and therefore cannot be detected in the SNDS; a potential lack of statistical power; and inability to take account of some risk factors for VTEs (including obesity, and a family history of thromboembolic disease) in the case-control design – although we believe that these potential confounding factors should affect cases and controls to the same extent.

FIGURE AND TABLE LEGENDS

Figure 1: Overall study design

Figure 2: Schneeweiss diagram for analysis #1 (44)

Figure 3: A directed acyclic graph of the relationship between JAKis, AD, and VTEs

Table 1: List of meta-analyses on the risk of VTEs during treatment with JAKis

Table 2: List of variables

Table 3: Power calculation for analysis #1

STATEMENTS

Contributorship statement

PB and CD wrote the first draft of the manuscript. PB, LMS, AL, DSS, GC, PG, AD, EO and CD conceived the scoping review and developed the research questions and the search strategy. All authors critically reviewed drafts and edited the manuscript.

Competing interests

There are no competing interests for any author.

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- Nested case-control study (analysis #1)
- Nested case-time-control study (analysis #2): in patients with a VTE, we shall compare the frequency of JAKi initiation in the risk period (before VTE) with the frequency of JAKi initiation in the reference period (prior to the risk period).

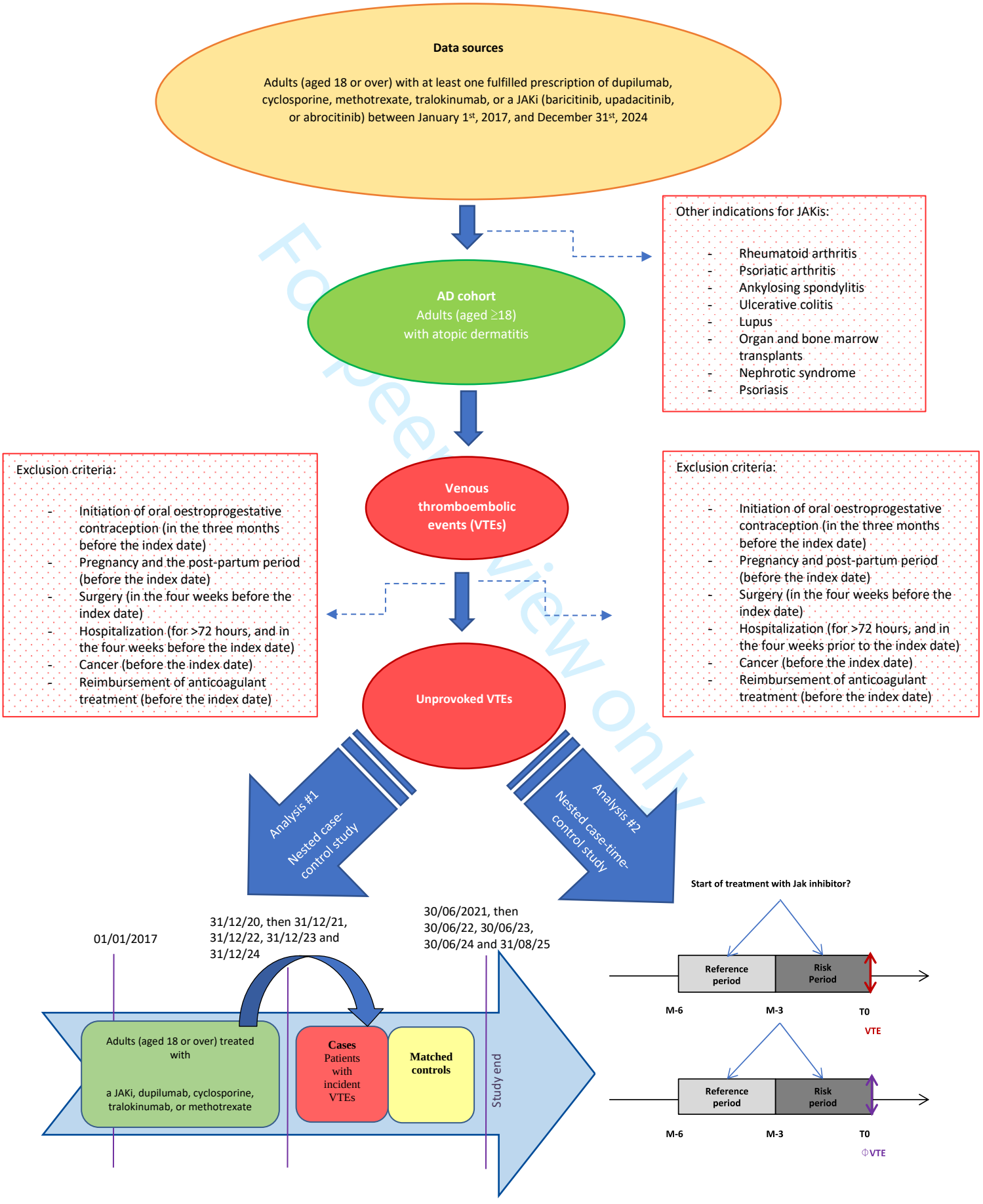
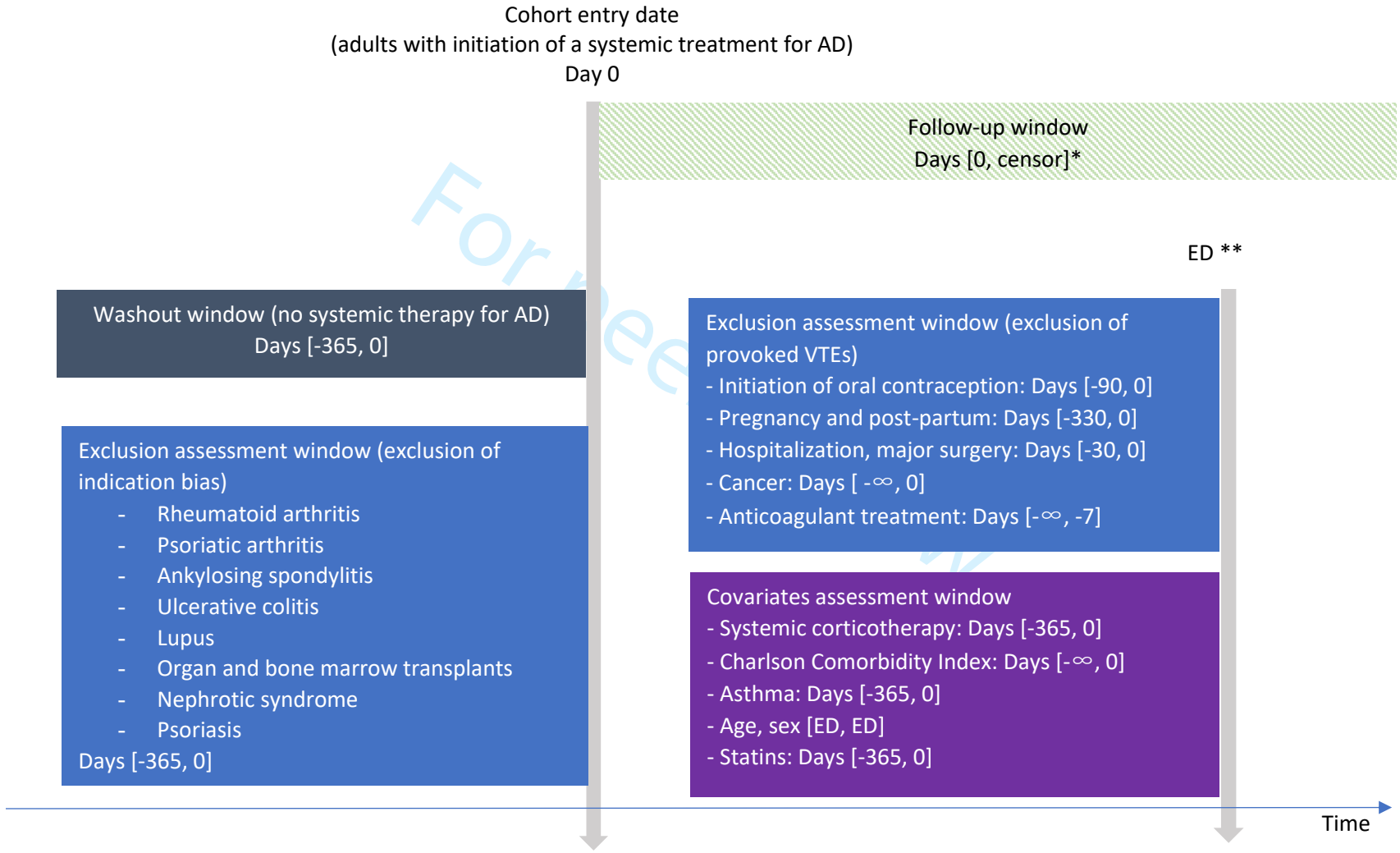
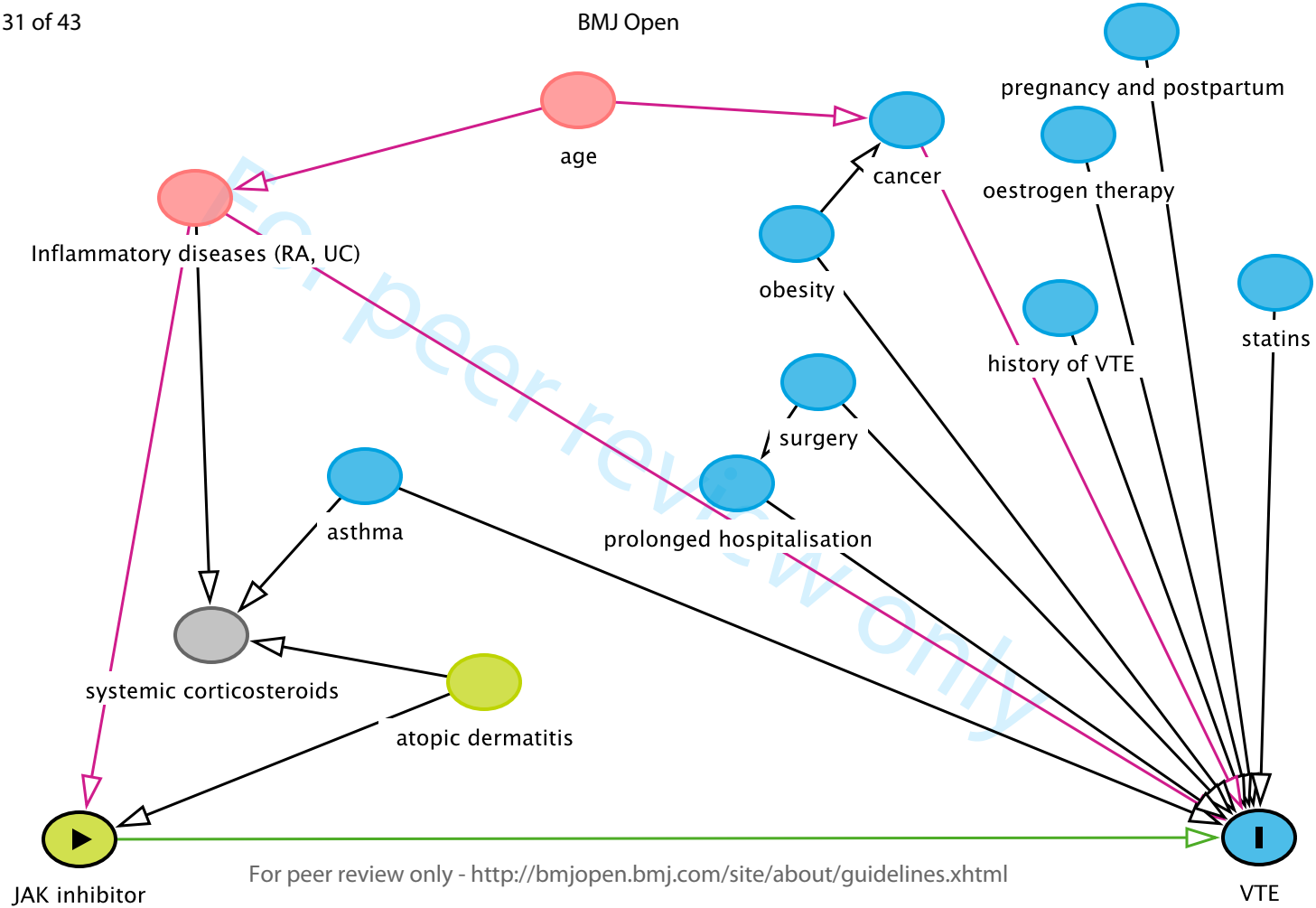


Figure 2: Schneeweiss diagram for analysis #1



Abbreviations: AD, atopic dermatitis; ED, event date; VTE, venous thromboembolic event
*Censored at the date of the first VTE, death, emigration, or the end of the study period
** ED: the date of the first VTE (the index date)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Oral Janus kinases inhibitors and venous thromboembolism in atopic dermatitis: Protocol of a case-time control study and a nested case-control study based on French SNDS cohort

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	p. 10
1.1.2 End of data collection[2]	☒	☐	☐	p. 10
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	p.17

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	p. 6-8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	p. 6-8
2.1.2 The objective(s) of the study?	☒	☐	☐	p. 9-10
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	p. 9
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	p. 9
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	p. 9-14
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	p. 10-11
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	p. 12-13
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	p. 12-13
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	p. 10-11
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	p. 10

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
	4.2.2 Age and sex	☒	☐	☐	p. 10
	4.2.3 Country of origin	☒	☐	☐	p. 10
	4.2.4 Disease/indication	☒	☐	☐	p. 10
	4.2.5 Duration of follow-up	☒	☐	☐	p. 10-11
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	p. 10-11

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	p. 10-11
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	p. 10-11
5.3	Is exposure categorised according to time windows?	☒	☐	☐	p. 10-11
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	p. 10-11
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	p. 10-11

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	p. 11
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	p. 11-12
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	p. 11
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	p. 14
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	p.18
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	p.18

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	p. 14

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	p. 10-11
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	p. 11-12
9.1.3 Covariates and other characteristics?	☒	☐	☐	p. 14
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	p. 10-11
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	p. 11-12
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	p. 14
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Table 2
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Table 2
9.3.3 Covariates and other characteristics?	☒	☐	☐	Table 2

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	p. 9, 12, 13, 14
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	p. 16
10.3 Are descriptive analyses included?	☒	☐	☐	p.12-13
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	p. 18, 19
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	p. 19
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	p. 14

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	p. 17
11.2 Are methods of quality assurance described?	☐	☐	☒	
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	p. 17

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	p. 18-19
12.1.2 Information bias?	☒	☐	☐	p. 18-19
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	p. 19

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	p. 16

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	p. 17
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	p. 17

Comments:

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

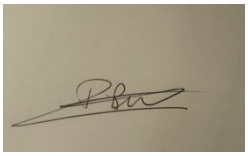
Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	p. 17
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	p. 17

Comments:

Name of the main author of the protocol: BERTHE Pauline

Date: 07/04/2022

Signature: 

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Pages 1 and 4
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Pages 6, 7 and 8
Objectives	3	State specific objectives, including any prespecified hypotheses			Page 9
Methods					
Study Design	4	Present key elements of study design early in the paper			Pages 9 and 10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Pages 10, 11 and 12

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Pages 10 and 11, and in table 2
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Pages 10, 11, 12, 14 and in table 2
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			Pages 10 to 14

Bias	9	Describe any efforts to address potential sources of bias			Pages 9, 10
Study size	10	Explain how the study size was arrived at			Page 16
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Pages 12, 13, and 14
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			Pages 12, 13 and 14
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Pages 10, 11 and 12

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure			

		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			
Discussion					
Key results	18	Summarise key results with reference to study objectives			
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page 19
Interpretation	20	Give a cautious overall interpretation of results considering objectives,			

		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results			
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			Page 20
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.