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Methodology of the brodalumab assessment of hazards: a multicentre observational safety (BRAHMS) study

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ABSTRACT

Introduction Safe and effective pharmacological treatment is of paramount importance for treating severe psoriasis. Brodalumab, a monoclonal antibody against interleukin (IL) 17 receptor A, was granted marketing authorisation in the EU in 2017. The European Medicines Agency requested a postauthorisation safety study of brodalumab to address potential safety issues raised during drug development regarding major adverse cardiovascular events, suicidal conduct, cancer and serious infections.

Methods and analysis BRodalumab Assessment of Hazards: A Multinational Safety is a multicentre observational safety study of brodalumab running from 2017 to 2029 using population-based healthcare databases from Denmark, Sweden, Norway, Netherlands, Germany and three different centres in Italy. A distributed database network approach is used, such that only aggregate data are exchanged between sites.

Two types of designs are used: a case-time-control design to study acute effects of transient treatment and a variation of the new user active comparator design to study the effects of transient or chronic treatment. As comparators, inhibitors of TNF-α, inhibitors of IL-12 and IL-23, and other inhibitors of cytokine IL-17A are included.

In the self-controlled case-time-control design, the risk of developing the outcome of interest during periods of brodalumab use is compared within individuals to the risk in periods without use.

In the active comparator cohort design, new users of brodalumab are identified and matched to new users of active comparators. Potential baseline confounders are adjusted for by using propensity score modelling.

For outcomes that potentially require large cumulative exposure, an adapted active comparator design has been developed.

Ethics and dissemination The study is approved by relevant authorities in Denmark, Norway, Sweden, the Netherlands, Germany and Italy in line with the relevant legislation at each site. Data confidentiality is secured by the distributed network approach. Results will be published in peer-reviewed journals.

Trial registration number EUPAS30280.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ An important strength of the BRodalumab Assessment of Hazards: A Multinational Safety (BRAHMS) study is the establishment of a collaboration across 6 European countries with data sources covering approximately 50 million people thus allowing investigation of potential safety issues related to use of brodalumab with best achievable statistical precision.

⇒ The BRAHMS study uses multiple designs, applying both the self-controlled, case-time-control design and variations of the active comparator cohort design, thereby also accounting for diverse biological mechanisms behind potential associations and for unique strengths and limitations in each design.

⇒ To mitigate heterogeneity of data sources and coding practices across participating countries, a comprehensive infrastructure has been built including a BRAHMS common data model and a component-composite framework for study variable definitions.

⇒ As an important collateral benefit of the study, we build network, experience, methodology and infrastructure, which allows for a timely and scientifically rigorous investigation of future safety issues, especially in the area of biological drug use in psoriasis and other immune mediated inflammatory diseases.

INTRODUCTION

Psoriasis is a chronic immune mediated inflammatory skin disease affecting 2%–3% of adults in western countries.[1 2] Safe and efficacious pharmacological treatments of moderate to severe psoriasis is important to improve quality of life and prevent serious comorbidities in these patients.

An increasing number of biological therapies for the treatment of moderate to severe psoriasis have become available over the last two decades. The patients can profit from this as treatment switches between approved drugs are often needed due to

lack of response, tolerability issues or treatment fatigue.[3] Brodalumab is indicated for the treatment of moderate to severe plaque psoriasis in adults and was granted marketing authorisation in the European Union (EU) in 2017. It is a fully human immunomodulatory monoclonal antibody that binds to human interleukin 17 receptor A (IL17 A).

The safety of brodalumab has been investigated in clinical trials including the two pivotal phase III clinical trials AMAGINE-2 and AMAGINE-3.[4–6] In the regulatory processing of the marketing authorisation, specific aspects of long-term safety were agreed to be further investigated as part of the risk management plan for brodalumab. This included the risk of serious infections, suicidal ideation and behaviour, major adverse cardiovascular event (MACE) and malignancies. The concern for serious infections, MACE and cancer are shared by other biologics approved for the treatment of immune-mediated inflammatory diseases and originate from the products' immunomodulatory activity.[7] As brodalumab binds to IL-17 A, the role of IL-17 and the correspondent IL-17 RA in the host defence against bacterial and fungal infections prompts for investigation of the risk of infections in brodalumab treated patients.[8] Some instances of suicidal conduct were observed during the development programme,[4] but due to the rarity of these events, trial data were inconclusive as to whether brodalumab treated individuals had an excess risk. Psychiatric comorbidity, including suicidality, is well known in psoriasis patients,[9 10] and a potential association between suicidal conduct and brodalumab is not substantiated by any known underlying biological mechanism.[11] Psoriasis patients have an increased risk of cardiovascular events.[12] However, the impact of treatment with systemic biologics on the general cardiovascular comorbidity in psoriasis patients is debated[13] and no specific evidence exists for brodalumab. While the results from most studies of the risk of malignancies in psoriasis patients treated with systemic biologics are reassuring, evidence from long-term studies is limited.[14] These risks are therefore to be investigated in a postauthorisation safety study, that is, the BRodalumab Assessment of Hazards: A Multinational Safety (BRAHMS) study.

METHODS AND ANALYSIS

The BRAHMS study is a European multinational observational study using electronic healthcare data covering the period from the first authorisation date of brodalumab in Europe (July 2017) until the extraction of the final dataset in 2029. The study intends to evaluate a potential excess risk of serious infections, suicidal conduct (including death by suicide and suicide attempt), MACE and cancer associated with brodalumab treatment in patients with psoriasis by applying the case-time-control design and variations of the active comparator cohort design adapted to new use, current use, ever-use and high cumulative use.

Data sources

The BRAHMS study is conducted in a collaboration between research groups from Denmark (University of Southern Denmark), Sweden (Karolinska Institute), Norway (Norwegian Institute of Public Health), Germany (Leibniz Institute for Prevention Research and Epidemiology-BIPS), the Netherlands (PHARMO Database Network), and Italy (Tuscany (Agenzia Regionale di Sanità), Caserta local health unit (University of Verona) and Lazio (Lazio Regional Health Service)). Table 1 provides an overview of local population-based electronic healthcare databases included in the study.

Common to all collaborating sites is the availability of inpatient hospital data or hospital discharge diagnoses as well as pharmacy claims data with at least 10 years of coverage leading up to study start. Other relevant data sources such as outpatient and primary care data are included but may differ between sites in terms of availability or level of coverage. Linkage between data sources is possible within each site through unique and pseudonymised person identifiers. Depending on the site, local clinical data are encoded using either the Internation Classification of Disease-9th Revision-Clinical Modification, International Classification of Disease 10th revision or International Classification of Primary Care-2 (primary care) classifications. The Anatomical Therapeutic Classification (ATC) is generally used to code drug dispensing at all sites. Since dispensing, registration and coding practices for biologics differ by country, some sites will also use procedure codes to identify these dispensing from hospital data.

In total, the participating sites have access to data covering a population of approximately 50 million people from 6 European countries.

Study design

A major challenge of the BRAHMS study is the inherently increased risk of comorbidities, such as psychiatric and cardiovascular diseases, among psoriasis patients relative to the background population, which may induce confounding by indication. For example, rates of suicidal acts are 42% higher in this patient population than in healthy individuals.[10] To mitigate unmeasured confounding by underlying psoriasis severity, two designs are used; a self-controlled, case-time-control design[15] and variations of an active comparator cohort design.[16]

The case-time-control design is appropriate in studies of a transient effect of ongoing exposure related to an abrupt outcome, for example, in the analysis of suicidal conduct, where a potential risk hereof is expected to increase directly after initiation of the drug and fade immediately after discontinuation. The choice of the case-time-control design among the self-controlled designs was motivated by the fact that some of the outcomes carry a high mortality, which invalidates the bidirectional self-controlled designs, such as the self-controlled case series or symmetry design.[17] In addition, exposure to a given biologic is likely to be chronic, which in a classic

Table 1 Overview of data sources from each participating site

	Denmark	Sweden	Norway	Netherlands	Germany	Tuscany	Caserta	Lazio
Individuals covered (% of country pop)	5.7 mill (100%)	10 mill (100%)	5.2 mill (100%)	4 mill (25%)	20 mill (25%)	3.6 mill (6%)	1.1 mill (1.8%)	5.7 mill (9.5%)
Data source name/data owner	The Danish Health Data Authority	National Board of Health and Welfare	Norwegian Health and socioeconomic data authorities*	PHARMO	GePaRD†	Tuscany regional claims database	Caserta LHU claims databases	Lazio regional claims database
Included data types/settings								
Inpatient hospital care	Yes	Yes	Yes	Yes‡	Yes	Yes	Yes	Yes
Outpatient hospital care	Yes	Yes	Yes	Yes‡	Yes§	No	No	No
Emergency room care	Yes	Yes	Yes	No	Yes¶	Yes	Yes	Yes
Non-hospital specialist care	No	No	Yes	No	Yes	No	No	No
General practice care	No	No	Yes	Yes‡	No	No	No	No
Inpatient drug dispensings	Yes**	No	Yes	Yes‡	Yes**	No	No	No
Outpatient pharmacy dispensed prescription drugs	Yes	Yes	Yes	Yes‡	Yes	Yes	Yes	Yes
Civil registration data	Yes	Yes	Yes	Yes‡	Yes	Yes	Yes	Yes
Cancer register	Yes	Yes	Yes	No	No	No	No	No
Causes of death register	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Socioeconomy	No	Yes	Yes	Yes‡	Yes	Yes	Yes	Yes
Pathology register	No	No	No	No	No	No	No	No
Exemption from copayment register (Italy)	No	No	No	No	No	Yes	Yes	Yes
Data availability prior to start of study period†† (Years)	15+	12+	10+	15+	10–15	10+	10+	10+
Coding systems used								
Diagnoses	ICD10	ICD10	ICD10, ICPC-2	ICD10, ICD9-CM, ICPC-2	ICD10	ICD9-CM	ICD9-CM	ICD9-CM
Medication	ATC	ATC	ATC	ATC	ATC	ATC	ATC	ATC
Procedures	Nomesco (SKS), Custom	Nomesco (KVÅ), Custom	Nomesco, Custom	Custom	Custom	ICD9-CM	ICD9-CM	ICD9-CM

*Linked nationwide data from different register holders in Norway.
†Based on claims data from four German statutory health insurance providers.
‡Data collection periods, catchment area and overlap between PHARMO data sources differ.
§Excluding endoscopic and surgical procedures.
¶Cannot be distinguished from other hospital care.
**Possible to identify some drugs dispensings such as biologics from procedure codes with limited dosing information.
††Covered by at least drug dispensing and inpatient hospital data.
ATC, Anatomical Therapeutic Classification; ICD10, International Classification of Disease 10th revision; ICD9-CM, Internation Classification of Disease-9th Revision-Clinical Modification; ICPC, International Classification of Primary Care; Nomesco, Nordic classification of surgical procedures.

Table 2 Overview of design choices for the Brodalumab Assessment of Hazards; a Multinational Safety study

	Serious infections	Suicidal conduct	MACE	Cancer
New use, comparative cohort design	X	X	X	
Current use, comparative cohort design	X	X	X	
Ever-use, comparative cohort design			X	X
Cumulative use, comparative cohort design			X	X
Case-time-control design	X	X	X	

See text for specifications.

case-crossover design would induce persistent user bias.[18] The case-time-control design has been shown to adjust for persistent user bias.[19]

To address the diverse nature of the outcomes, we use variations of the active comparator cohort design. From a biological reasoning, a serious infection is likely to be a short-term outcome of brodalumab exposure that can be investigated by employing the new user, active comparator cohort design. Cancer, on the other hand, is more likely to be caused by a cumulative effect. Hence, neither the case-time-control design nor the new user, active comparator cohort design is suitable to investigate the association of brodalumab use and cancer. Instead, we employ an ever-user approach of the active comparator cohort design and we have developed a comparative design, which is specifically adapted to analysis of cumulative exposures (see below). An overview of the designs employed for each of the outcomes is shown in table 2. Specifications of each design are detailed under 'Analysis section'.

Study cohorts

For the wide range of analyses in the BRAHMS study, different study cohorts are created in a two step-process; the first step is the creation of a general study cohort while the second step is the creation of analysis-specific cohorts.

Individuals enter the general study cohort on the date of the earliest recording within the study period of a biologic used in the treatment of psoriasis. Individuals are censored if another probable indication for receiving biological therapy is registered, if two or more biologics are registered on the same date, in case of loss of data coverage, death or end of study period. This step creates an eligibility period for every included individual during which any occurring treatment episode and outcome may contribute to a specific analysis. Inclusion and exclusion criteria for the general study cohort are described in box 1 and visualised in figure 1.

The analysis-specific cohorts are then created from the general study cohort by applying analysis-specific inclusion and exclusion criteria, which vary across analyses. For the active comparator cohort studies, inclusion and exclusion criteria are implemented relative to the cohort entry date (CED); for the case-time-control studies, they are implemented relative to the event date for cases and the index dates for controls. Inclusion and exclusion criteria for study-specific cohorts are described in box 2 and visualised in figure 2.

Study drugs

Brodalumab is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy. The recommended dose is 210 mg administered by subcutaneous injection at weeks 0, 1 and 2, followed by 210 mg every 2 weeks. Brodalumab is usually administered in a hospital setting or in specialist practice, but patients may self-inject after careful instruction.[20]

Comparator drugs used in the active-comparator cohort design include the following:

1. Inhibitors of IL-12 and IL-23 (ustekinumab, including biosimilars whenever available).
2. Inhibitors of TNF-α (etanercept and adalimumab, including biosimilars whenever available).
3. Other inhibitors of cytokine IL-17A (secukinumab and ixekizumab, including biosimilars whenever available).

Similar to brodalumab, comparator drugs are all administered by subcutaneous injection. For this reason,

Box 1 Inclusion and exclusion criteria for the general study cohort. Due to data source heterogeneity, site-specific adaptations are allowed.

Inclusion criteria

Probable psoriasis diagnosis. The general study cohort entry date (CED) must be preceded by, or coincide with, a record of a psoriasis diagnosis code or other method of ascertainment of psoriasis, for example, use of topical vitamin D3 derivatives or a recording of a disease-specific copayment exemption code.

Qualification of indication for receiving biological therapy (optional). If relevant, each site may impose additional criteria that ascertain that psoriasis is the most likely indication for the biological treatment dispensed at the CED. This could, for example, be a requirement for dermatological specialty associated to the encounter or prescriber.

Exclusion criteria

Probable other indication for receiving biological therapy. The general study CED must not be preceded by any diagnosis (or other means of ascertainment) of clinical conditions that could lead to treatment with any of the drugs evaluated in the BRAHMS study, for example, Crohn's disease, ulcerative colitis, suppurative hidradenitis or inflammatory arthritis. Psoriasis arthritis does not lead to exclusion but is to be adjusted for in the statistical analysis.

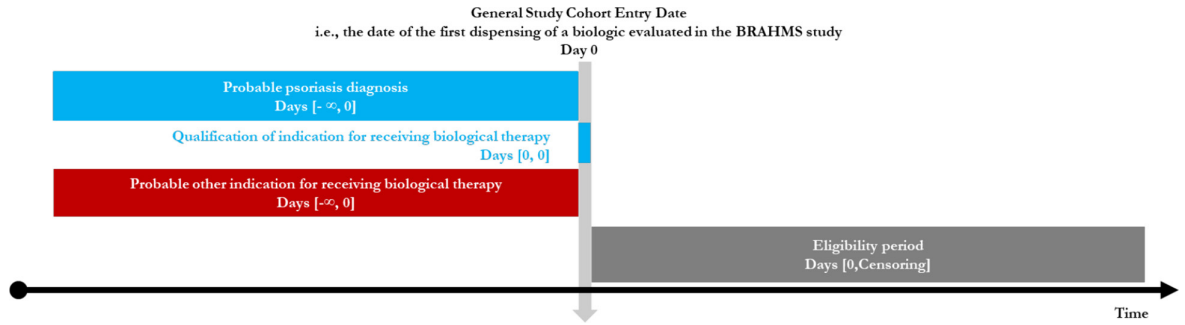

Figure 1 Design diagram for the building of the general study cohort. Light blue: inclusion criteria; red: exclusion criteria; grey: eligibility period. The cohort entry date must lie within the study period, and it must be the earliest possible date that fulfils all inclusion and exclusion criteria.

infliximab is not included among the TNF-α inhibitor study drugs as it is solely given intravenously. This could introduce selection bias by restricting to hospital-treated patients. The dosing interval varies from once a week for TNF-α inhibitors to every 12 weeks for ustekinumab.

Exposure definition

Episodes covered by treatment with study drugs are created for every individual in the general study cohort within the individual's eligibility period by assigning a dispensing duration corresponding to the expected time covered by that dispensing. Dispensing durations of the same biologic are then combined into continuous treatment episodes if there are no gaps between them. Finally, overlapping time in treatment episodes of different biologics are resolved by formally terminating any treatment episode when a treatment episode with another biological begins (figure 3). The result is a non-overlapping sequence of treatment episodes for each individual. At no point in time are persons considered exposed to more than one study drug. This is in line with the dominating treatment regimen in psoriasis, where biologics are prescribed as monotherapy or in combination with topical treatments.[21 22]

Dispensing durations are estimated separately for each biologic at each site using the waiting time distribution (WTD) method, which is a data-driven approach.[23] The WTD method estimates the interarrival density function, that is, the distribution of gap time between dispensings inside a treatment episode for patients in continuous treatment. For this distribution, we will use the time corresponding to the 95th percentile as dispensing duration. This approach mitigates challenges resulting from the heterogeneous availability of data on dispensing durations for biologics, such as recordings of dose or days covered, across sites.

Box 2 Inclusion and exclusion criteria for analysis-specific cohorts (may vary across analyses) in the active comparator cohort design and the case-time-control design.

Inclusion criteria

Minimum registry coverage. Only individuals with a minimum medical and drug coverage of 183 days prior to the cohort entry date (CED) (730 days for cancer) are included in the active comparator cohort studies, whereas 365 days are required in the case-time-control studies to ensure coverage before the first reference date.

Age. Only individuals who are 18 years or older on the CED are included in the active comparator cohort studies, whereas a minimum age of 21 is required in the case-time-control studies to ensure that individuals are at least 18 years on the first reference date.

Non-bionaïve. Only individuals with at least one prior treatment of another biologic than the drug of interest are included in the active comparator studies. A prior treatment must be recorded at least once within 365 days before the CED. Of note, to avoid potential carry-over effect, prior treatment with brodalumab is not allowed when considering CEDs for active comparators.

At least one period of brodalumab use. Specific criterion for the case-time-control studies. Only inclusion of individuals in the case-time-control studies who have a period of use of brodalumab within 730 days prior to the event date/index date.

Exclusion criteria

History of outcome. Individuals with a recording of the outcome (or part of the outcome or history related to the outcome) prior to the CED are excluded.

Previous use of drug of interest. Individuals who have been using the drug of interest (evaluated at substance level) prior to the CED are excluded from the active comparator cohort design, for example, prior users of brodalumab are excluded from the brodalumab treatment group.

Outcome

Study outcomes include

Serious infections, that is, the composite of serious acute infections and incident serious chronic infections. A serious acute infection is defined as any community-acquired acute bacterial, viral or fungal infection that is severe enough to lead to hospitalisation or death. An incident serious chronic infection is defined as a new infection with tuberculosis, hepatitis B or C, or other severe viral hepatitis infections, or osteomyelitis either leading to hospitalisation or treated at outpatient specialist visits.

Suicidal conduct, that is, the composite of death by suicide or suicide attempt leading to hospitalisation or treatment at outpatient visits.

MACE, that is, the composite of hospital admissions due to acute myocardial infarction, stroke (including

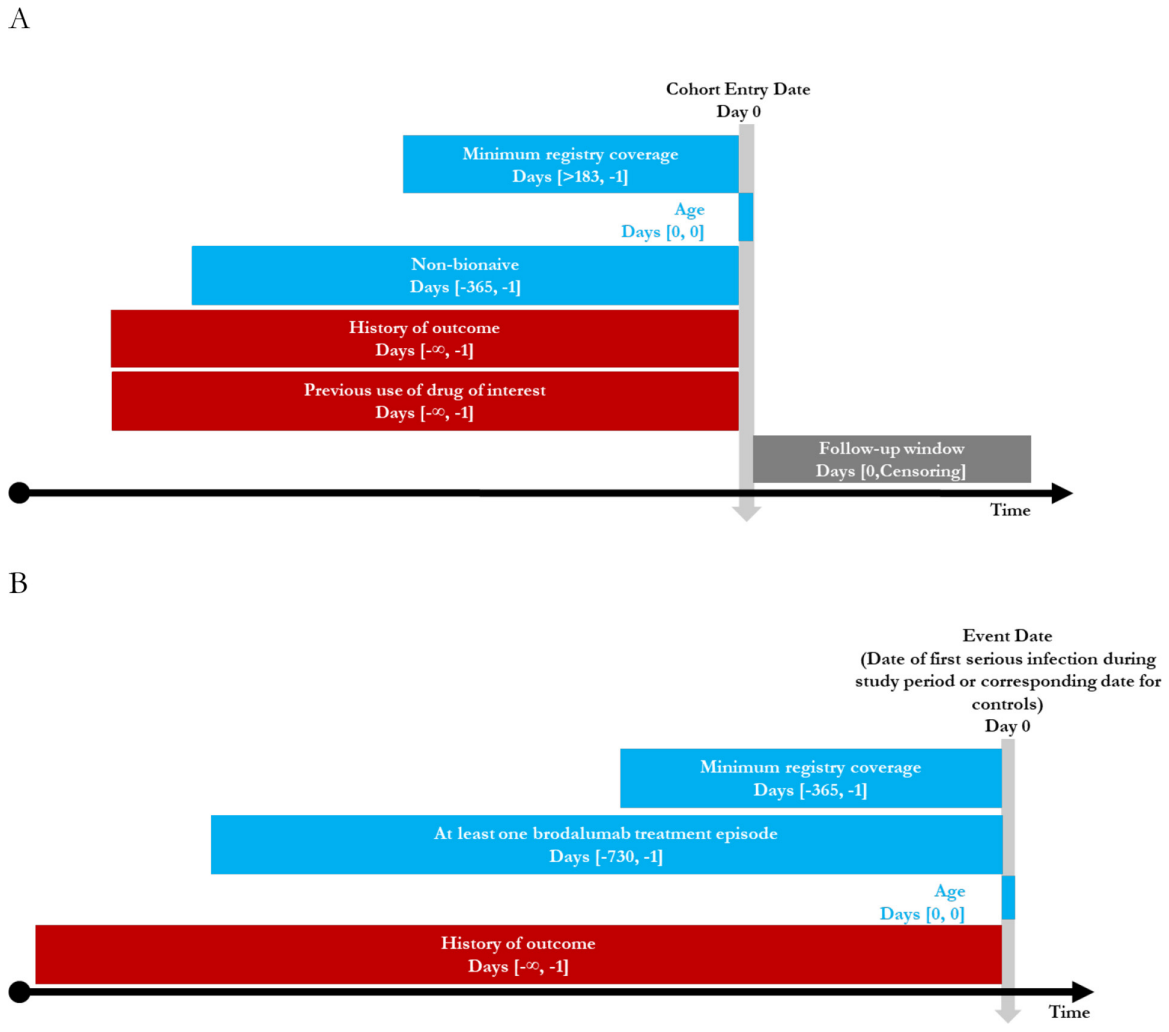

Figure 2 Design diagrams for inclusion and exclusion criteria implemented in (A) the active comparator cohort studies and (B) the case-time-control studies. Light blue: inclusion criteria; red: exclusion criteria; grey: follow-up window.

ischaemic stroke and haemorrhagic stroke but excluding transient ischaemic attack) or cardiovascular death inside or outside hospital.

Cancer, that is, a diagnosis of malignant neoplasms.

The exact definition of these outcomes may vary across sites, according to availability and structure of data.

Analysis

Case-time-control design specifications

In the case-time-control design, each individual's exposure status at the index date is compared with four reference dates in the same individual's past. The index date is the date of the outcome. Control individuals without outcomes are sampled 4:1 by a risk set sampling strategy, matched by age and sex and assigned an index date identical to their corresponding case. Only cases and controls who have been exposed to brodalumab either at the index date or at least at one of the reference dates contribute to the analysis. An individual is considered exposed to brodalumab at an index or reference date if they occurred within a brodalumab treatment episode.

Consistent with standard recommendations regarding case-time-control design, a washout interval is interspersed between the index date and the latest of the reference dates to minimise carry over between index and reference dates.[17] We chose a fairly long interval between each index date and reference point, 4 months, to minimise autocorrelation by exposure.[24] The case-time-control design employed is illustrated in figure 4.

Due to the inherently matched nature of this design, conditional logistic regression is used to calculate ORs.[15]

Active comparator cohort design specifications

The active comparator cohort design addresses the pragmatic, clinical question of whether the outcome association is stronger for brodalumab than for comparable drugs, as rates of events are compared between users of brodalumab and users of other biological treatments.

Adaptations of the active comparator cohort design are used to investigate the effects of both new use, ongoing use without restricting to new users, ever use and cumulative duration of use of brodalumab depending on the expected biological mechanism behind a potential association between use of brodalumab and the outcome.

For serious infections and suicidal conduct, the potential effect of brodalumab is likely to emerge shortly after

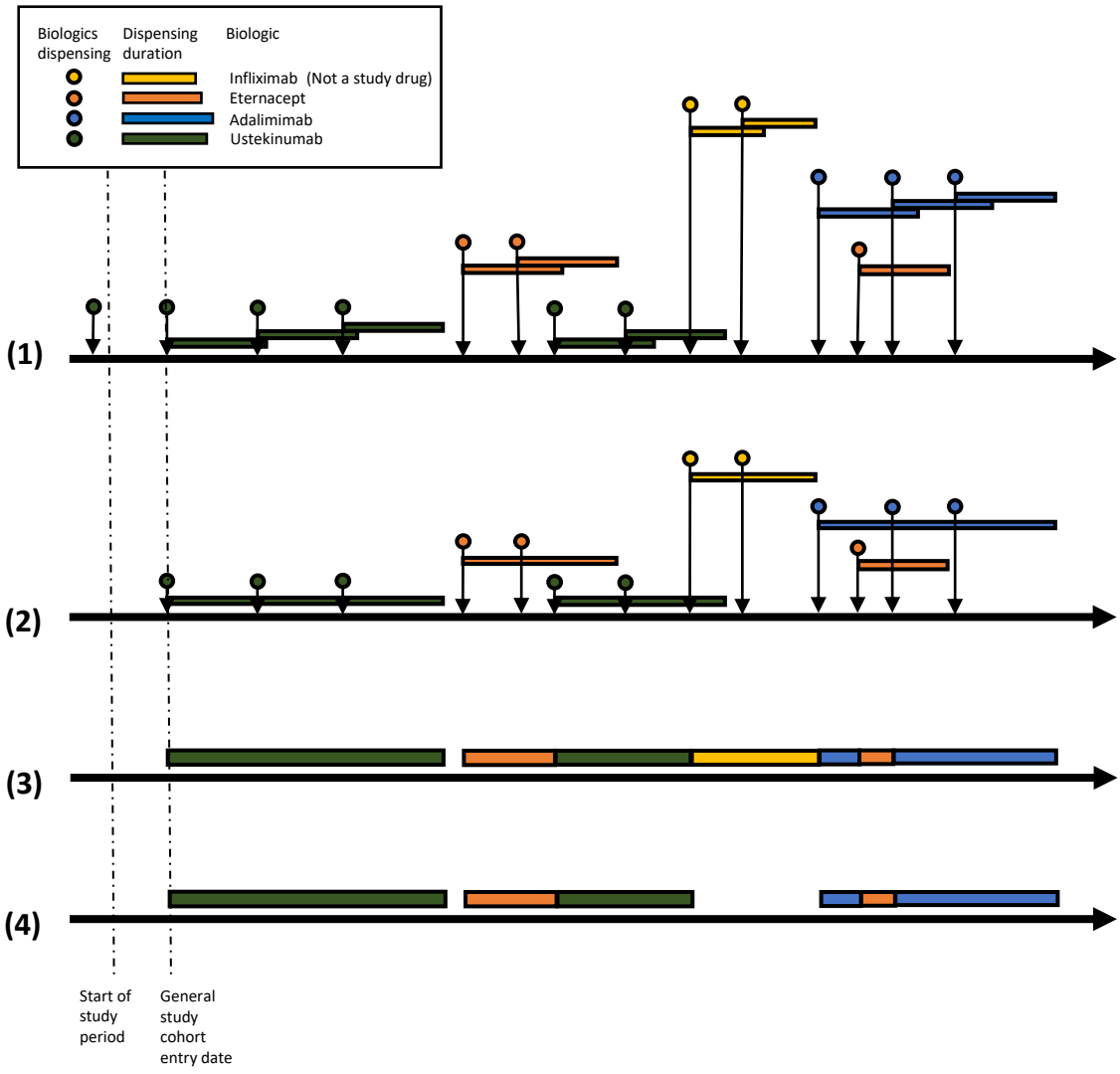

Figure 3 Illustration of the process of creating treatment episodes for a person in the general study cohort. Each color in the four panels represent a specific biological substance used in the treatment of psoriasis. Infliximab (yellow) is not a study drug but dispensing of Infliximab effects episode creation anyway. Circles represent dispensing time points and lines represent dispensing duration. (1) All dispensing of biologics used to treat psoriasis within the eligibility window are identified. A dispensing duration is added to each dispensing. (2) Within each drug, overlapping durations are combined. (3) Between drugs, non-overlapping episodes are created by always truncating a previous episode when it is interrupted by a dispensing by another drug (including non-study drugs). (4) Episodes for non-study biologics are removed. The result is six treatment episodes for three different study drugs.

initiation and is expected to persist during ongoing exposure. The associations are therefore investigated using the active comparator, new user cohort design as well as the variation hereof adapted to ongoing use without restriction to new users. In the active comparator, new user cohort analysis only incident treatment episodes of the drug of interest are included. That is, individuals are only considered exposed while being treated with the drug of interest for the first time. Subsequent treatment episodes with the same drug do not contribute to the analysis. The analysis adapted to ongoing use without restricting to new users only differs by also allowing subsequent treatment episodes.

For cancer as the outcome, an effect of brodalumab may manifest with some latency, possibly even after termination of treatment. Therefore, the active comparator study adapted to ever use is applied. In this analysis, an individual's exposure status remains unchanged even if the drug of interest is discontinued or another biologic is initiated. To avoid unduly complicated histories of exposure patterns in this analysis and undue assumptions, the comparison is with all active comparators without making distinctions at substance level or substance group level.

When investigating a potential association with cancer, it is also reasonable to assume a cumulative dose response association, that is, users with high cumulative doses

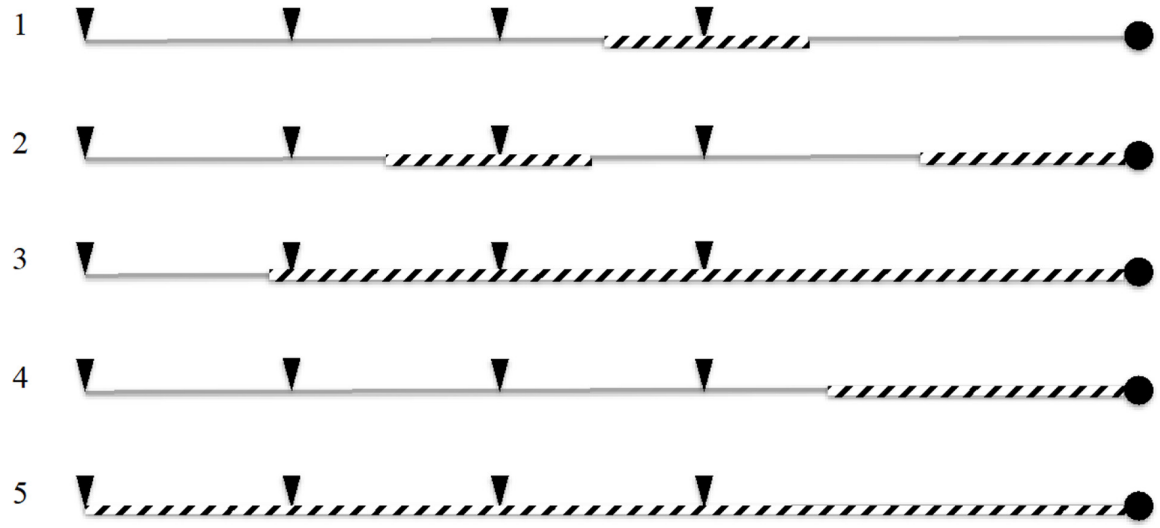

Figure 4 In the case-time-control design, exposure status is compared on event/index date and reference dates. The first four individuals are discordant (ie, they have periods of both non-use and use of brodalumab) while individual number five is concordant (ie, has the same exposure status in all windows, either consistently use or consistently non-use of brodalumab), and therefore, does not contribute to the analysis. The black dots represent the date of the outcome event (for cases) or the index date (for controls), while the black arrows mark the reference dates. The shaded areas indicate the time exposed to brodalumab.

have higher risk than users with low cumulative doses, all things being equal. A methodological challenge is in the comparative element; to assess whether the cumulative dose-response effect is more pronounced for brodalumab than for its active comparators. For this purpose, we developed an active comparator cohort design, adapted to cumulative exposure effects. We establish running cumulative accounts of exposed person-time from brodalumab treatment episodes as well as running accounts of exposed person-time from treatment episodes of any study biologics, including brodalumab. Only incident treatment episodes with a starting date within an individual's eligibility period contributes to the analysis (figure 5).

For MACE as the outcome, the underlying biological mechanisms behind a potential association are unknown, that is, neither an immediate effect of ongoing exposure nor a delayed effect of long-term use can be ruled out. Thus, all four variations of the active comparator cohort design are used to investigate a potential association between brodalumab and the risk of MACE.

For the analysis adapted to cumulative exposure effects, a Cox regression is performed with cumulative exposure to any biologic and to brodalumab included in parallel

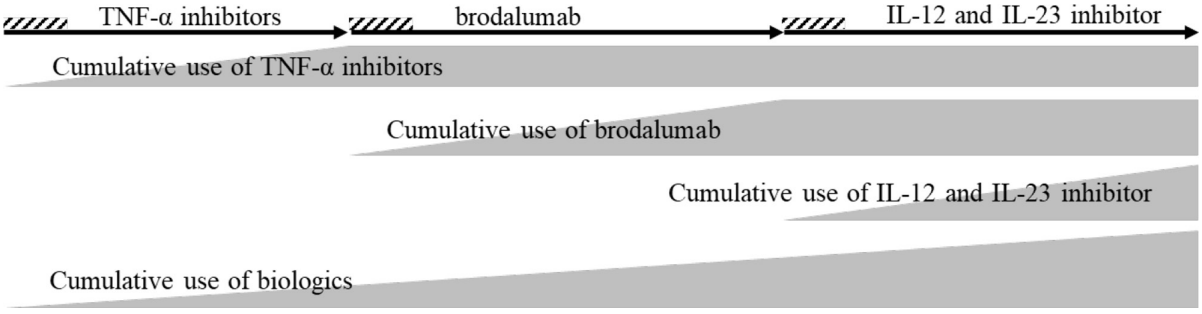

Figure 5 Methods of the cumulative comparative cohort design. The graph illustrates the accumulation of doses during the study period of an individual who is given three different drugs: TNF-α inhibitors, brodalumab, and IL-12 and IL-23 inhibitors. For each time point, a running account of the cumulative dosing of each drug is worked up. For example, when the IL-12 and IL-23 inhibitor is initiated, the individual has a cumulative dose of TNF-α inhibitors, stemming from the first interval and a cumulative dose of brodalumab stemming from the second interval. As the third interval passes, the individual gradually increases the cumulative dose of IL-12 and IL-23 inhibitor while the cumulative doses for brodalumab and TNF-α inhibitors remain constant. At no point in time during exposure the cumulative amount of these three drugs is identical to another point in time. In the analytic dataset, all non-brodalumab biologics are to be grouped together, and a running account of cumulative brodalumab and cumulative non-brodalumab biologics are to be calculated. The metric used for the cumulative analysis is cumulative time treated, rather than a cumulative dose in mg or defined daily doses. The shaded boxes illustrate the lag-time with respect to any biological exposure (ie, the time interval where any occurrence of a cancer cannot be expected to be caused by time spent in a given cumulative exposure).

as time-dependent variables. The potential incremental effect associated with brodalumab cumulative exposure, above and beyond the cumulative exposure to study biologics in general, is estimated by the coefficient for the cumulative dose of brodalumab in that regression. The model allows for concurrent adjustment for other relevant covariates if they are available.

A standard meta-analysis, including country-specific estimates from the main analysis of each outcome, is performed for both the active comparator cohort design and the case-time-control design.

Potential limitations

The active comparator cohort design is vulnerable to confounding due to differences in patient characteristics between the brodalumab and active comparator groups. This is accounted for in several ways. First, to optimise comparability between users of brodalumab and users of active comparators, only treatment episodes that are incident or preceded by an incident treatment episode within an individual's eligibility period are included. A minimum look-back of 183 days is required to ensure incident use. Also, as brodalumab is considered a second-line treatment, we require all users of comparator drugs to have switched from another biological antipsoriatic drug before cohort entry. Finally, in the standard active comparator analyses, measured confounding is addressed by using propensity score matching as the main tool.[25] Inverse probability of treatment weighting is applied in a sensitivity analysis.

In both the active comparator cohort design and the case-time-control design, analyses are performed with and without restriction to individuals without a history of the outcome of interest to limit confounding by indication. Time-dependent confounding by disease activity is handled by adjusting for measures of disease activity and proxies hereof whenever this is possible.

Considerable heterogeneity in the structure, quality, availability (eg, cause of death) and coding practice across sites is expected. Some of these problems might be mitigated by using a common data model (CDM) and a centralised development of analysis. In addition, there will be validation studies of suicidal conduct in selected regions, although no general case validation is planned.

The mapping of exposure status involves critical decisions with an inherent risk of misclassification. This may threaten the validity of both designs. Consequently, the estimation of dispensing durations using the WTD is subject to several sensitivity analyses.

The range of subgroup, sensitivity and supplementary analyses performed to elucidate potential biases are described in online supplemental table 1.

Data management

The data infrastructure of the BRAHMS study is based on a distributed database network which applies a CDM designed specifically for the study. The BRAHMS CDM provides a detailed specification of an agreed data structure and codebook, that each site must transform their local register data into. A quality assurance programme is used to confirm compliance. The result of data transformation is a locally populated instance of the BRAHMS CDM containing all relevant study data structured identically across sites, but accessible only by the local site. The coordinating site creates analytical programmes to be run locally at each site. Only aggregate results from these programmes are shared across sites. This strategy is described in the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, in the section on multidatabase studies.[26]

The heterogeneity of for example, available data sources, coding practices and validity of codes across sites is a limitation that necessitates a flexible method of adapting study variable definitions (required codes, settings, number of occurrences, assessment windows, etc) to the requirement of each site. A component-composite framework is implemented.[27 28] In this framework, each study variable is defined locally as a logical composite of one or more components. Each component is a specification of codes, for example, diagnoses codes or ATC codes, and contextual conditions, for example, 'only inpatient contacts', that records in the CDM must fulfil.[27 28]

Other

Study sponsorship: monitoring, audit, quality control and quality assurance

The study sponsor is the University of Southern Denmark, which undertakes quality assurance. The study is funded by Leo Pharma, the market authorisation holder of brodalumab, as part of an EMA mandated Post Authorisation Safety Study.[29]

Access to data

Data will be available for local investigators only. Data extraction and analyses are performed locally, and results are transferred at an aggregate level to SDU. Individual-level data will be unavailable across the other sites and to third parties outside the BRAHMS collaboration.

ETHICS AND DISSEMINATION

The BRAHMS study is performed in accordance with International Society of Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology Practice guidance.[30] The study is approved by relevant authorities in Denmark, Norway, Sweden, the Netherlands, Germany and Italy in line with the relevant legislation at each site (detailed statements can be found in online supplemental appendix A. The general data protective regulation will be followed, and data confidentiality will be ensured by the distributed network approach to data exchange. The results of the study will be published in peer-reviewed scientific journals and presented at relevant conferences.

Patient and public involvement

Patients and/or the public were not involved in this study.

DISCUSSION

The BRAHMS study design and innovative data infrastructure serves as an example of how a large multidatabase safety study can be conducted by efficiently using data sources and IT, including follow-up of patients by record linkage. Through the distributed network methodology, the CDM and the centralised programming, the risk for breach of data confidentiality is minimal and a high analytical standard is achieved.

The results from the BRAHMS study will be of substantial interest to patients with moderate to severe psoriasis and their treating physicians, irrespective of its findings. If the BRAHMS study reveals associations with any of the outcomes, further regulatory actions would be initiated to limit their impact. If BRAHMS identifies no associations with any of the outcomes, brodalumab can be used confidently at its proper position in the armamentarium of biological antipsoriatic agents. Treatment failure occurs frequently with biological psoriasis treatment,[31] and it is vital to have multiple medications that offers new treatment alternatives when others have failed.

As an important collateral benefit of the study, we build network, experience, methodology and infrastructure which allows for a timely and scientifically rigorous investigation of future safety issues, especially in the area of biological drug use in psoriasis and other immune mediated inflammatory diseases.

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