PASS INFORMATION

Title	Association between use of desloratadine and risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter: A Nordic register-based study
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Research question and objectives	To describe the use of desloratadine in the general population; to describe the incidence rates of first seizure, supraventricular tachycardia, and atrial fibrillation or flutter; and to examine the associations between desloratadine exposure and risk of first seizure, supraventricular tachycardia, and atrial fibrillation or flutter.
Country(-ies) of study	Denmark, Finland, Norway, Sweden

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1 ABSTRACT

Title

Association between use of desloratadine and risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter: A Nordic register-based study

Keywords

desloratadine, atrial fibrillation or flutter, supraventricular tachycardia, seizure, Nordic register-based study

Rationale and background

A post-authorization safety study was conducted to assess the potential risk of desloratadine (DL) exposure on seizures, supraventricular tachycardia (SVT), and atrial fibrillation or flutter (A-fib/flu).

Post-authorization safety study (PASS) P203 was submitted and the regulatory commitment was accepted as complete using data from Denmark, Finland, and Sweden in January 2020. Although the original commitment and its associated protocol (P203) included analyses on four countries, the data for Norway were very delayed and the European Medicines Agency (EMA) subsequently allowed MSD to provide a final report without these data.

This protocol (P205) is a voluntary PASS including a subset of analyses as intended in the original study protocol (P203) of the Norway data both alone and in combination with the original three countries.

Research question and objectives

The objectives of this study were to explore the use of DL in the general population (Substudy 1); to describe the incidence rate of first seizure (Substudy 2A); to examine the associations between DL exposure and risk of first seizure (Substudy 2B); to describe the incidence rate of SVT (Substudy 3A); to examine the association between DL exposure and SVT (Substudy 3B); to describe the incidence rate of A-fib/flu (Substudy 4A); and to examine the associations between DL exposure and A-fib/flu (Substudy 4B).

Study design

This study is an observational, nationwide, register-based study using person-specific linkage of data from the national population registers from Denmark, Finland, Norway, and Sweden ("Nordic countries") including all individuals who redeemed a prescription of DL and all individuals with a registered diagnosis of seizure, SVT, or A-fib/flu.

Setting

The study population consists of a cohort of DL users, where presumed time using DL is compared with time presumed not using DL. Three cohorts were created: a cohort of individuals under investigation for seizures, a cohort of individuals under investigation for SVT, and a cohort of individuals under investigation for A-fib/flu. The general population of the four Nordic countries was used to derive estimates of the background risk by age, year, and country.

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Subjects and study size, including dropouts

The sample size is fixed, as it consisted of all individuals in four Nordic countries (Denmark (2001–2015), Finland (2001–2015), Norway (2010-2015), and Sweden (2006–2015)) who redeemed at least one prescription for DL or who received a diagnosis of seizure, SVT, or A-fib/flu.

The total number of incident DL users is 2,125,243 individuals. The number of individuals with diagnosis of first seizure is 105,849, first SVT 96,940 and first A-fib/flu 511,503, respectively.

Variables and data sources

The exposure variable of interest is desloratadine for which current use (i.e., exposed period) will be defined as the period after each redeemed prescription equal to the number of days' supply plus a 4-week grace period to account for intermittent use and a possible wash-out effect. To minimize exposure misclassification, we propose to use person time at least 26 weeks beyond the dispensing date of the last prescription as the "unexposed" reference period.

The outcome variables are first seizure, first SVT diagnosis, and first A-fib/flu diagnosis. Directed acyclic graphs (DAGs) were developed to identify the minimum sufficient adjustment set of confounders to include in the association analysis of each outcome.

Data were obtained from nationwide population registers, including the national patient registers, the civil registration systems, and the prescription registers.

Results

The incidence rate (IR) of DL users was 754.8 per 100,000 person-years. The IR per 100,000 person-years in the general population of: first seizure was 37.6, first SVT was 34.4, and first A-fib/flu was 181.7.

The results of the main analysis found a higher rate of first seizure in DL exposed person-time compared with DL unexposed person-time. Across all age groups, the magnitude of the adjusted incidence rate ratio (aIRR) for seizure is small (aIRR 1.20, 95% CI 1.08; 1.33) adjusted for age, country, sex, calendar year, seasonality, asthmatic status, and chronic urticaria status. The overall finding of increased risk of first seizure is driven by increased IR of first seizure in the 0-4 year-old (aIRR 1.65, 95% CI 1.34; 2.03) and in the 5-19 year-old (aIRR 1.34, 95% CI 1.12; 1.61) age categories when comparing DL exposed and DL unexposed person-time. DL exposure status was not associated with first seizure in patients 20 years old or older.

This PASS found no association between DL exposure status and incident SVT in main analysis (aIRR 1.01 95% CI 0.91; 1.13) or in supplementary analyses.

This study also found a slightly higher rate of first A-fib/flu in DL exposed compared with DL unexposed person-time (aIRR 1.08, 95% CI 1.03; 1.14), adjusted for age, country, sex, calendar year, seasonality, asthmatic status, chronic urticaria status and severe rhinitis. The overall finding of increased rate of first A-fib/flu is driven by increased IR of first A-fib/flu in the ≥65 years age category (aIRR 1.10, 95% CI 1.03; 1.17) when comparing DL exposed and

DL unexposed person-time. The association of DL with first Afib/flu was consistent across sensitivity analyses that varied the exposure definition but was attenuated in an analysis that adjusted for an alternative set of confounders (aIRR 1.04, 95% CI 0.99; 1.09).

Discussion

There was an association between the IR of first seizure and first A-fib/flu during the DL exposed person-time as compared to the DL unexposed person-time in the age-, sex-, country- and calendar-year adjusted analyses as well as in the fully confounder-adjusted analyses. Adjustment for confounding variables (asthma, rhinitis, chronic urticaria) had only a small effect on the estimates.

This PASS found no association between exposed DL person-time and risk of first SVT.

For first seizure, this association was largely driven by the younger (0-4 and 5-19 year old) age groups. The aIRR is about 1.7 for 0-4 year-olds and 1.3 for 5-19 year-old age groups comparing DL exposed person-time to unexposed person-time. The associations were largely consistent across sensitivity analyses. Taken together with prior pharmacovigilance data, there is reasonable evidence to suggest that seizure should be considered an adverse reaction to DL. Even if causality is assumed, however, the adjusted absolute rate difference is 56 per 100,000 person year (PY) in the 0-4 and 10 per 100,000 PY in the 5-19-year age groups, indicating absolute increases in risk are small.

For first A-fib/flu, the association with DL persisted after adjustment for preselected confounders (aIRR 1.08, 95% CI 1.03; 1.14). In age-stratified analyses, the association was strongest for patients aged ≥65 years (aIRR 1.10, 95% CI 1.03; 1.17) in whom baseline risk of this outcome is known to be highest. Sensitivity analyses adjusting for an alternative set of confounders attenuated the aIRR. Thus, residual confounding could plausibly explain the association between DL and A-fib/flu. Evidence is insufficient to conclude that the association between current DL use and A-fib/flu is causal.

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2 LIST OF ABBREVIATIONS

AE	Adverse event
A-fib	Atrial fibrillation
A-flu	Atrial flutter
A-fib/flu	Atrial fibrillation or atrial flutter
aIRR	Adjusted incidence rate ratio
ApHER	Institute of Applied Economics and Health Research
ATC	Anatomical Therapeutic Chemical Classification System
CHF	Chronic heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DAG	Directed acyclic graph
DDD	Defined daily dose
DL	Desloratadine
DSUR	Development safety update report
EMA	European Medicines Agency
EU	European Union
ICD	International Classification of Diseases
IR	Incidence rate
IRR	Incidence rate ratio
MAH	Marketing authorization holder
MSD	Merck Sharp & Dohme, a subsidiary of Merck & Co., Inc.
NIPH	National Institute of Public Health, University of Southern Denmark
NSAE	Non-serious adverse event
PASS	Post-authorisation safety studies
PBRER	Periodic Benefit Risk Evaluation Report
PIC	Personal identification code
PPV	Positive predictive value
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
PV	Pharmacovigilance
PY	Person-years
OTC	Over-the-counter
QBA	Quantitative Bias Analysis
RAI	Regulatory Affairs International
RSI	Request for Supplementary Information
SAE	Serious adverse event
SAP	Statistical analysis plan
SCRID	Self-controlled risk interval design
SD	Standard deviation
SVT	Supraventricular tachycardia

3 INVESTIGATORS

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4 OTHER RESPONSIBLE PARTIES

Not applicable

5 MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	31-Jul-2020	31-Jul-2020	
End of data collection	15-Aug-2020	30-Sep-2020	
Registration in the EU PAS register	15-Jul-2020	19-Jun-2020	
Final report of study results	30-Dec-2020	13-Oct-2020	

6 RATIONALE AND BACKGROUND

The European Medicines Agency (EMA) had previously requested that Merck Sharp and Dohme (MSD) consider options for a post-authorization safety study (PASS; Category 3 PV activity) to investigate whether there is an association between desloratadine (DL) use and seizures, supraventricular tachycardia (SVT) , and atrial fibrillation or flutter (A-fib/flu) in the general population. That PASS (P203) was submitted and the regulatory commitment was accepted as complete using data from Denmark, Finland, and Sweden in January 2020. Although the original commitment and its associated protocol (P203) included analyses on four countries, the data for Norway were very delayed and the EMA subsequently allowed MSD to provide a final report without these data.

This protocol (P205) is a voluntary PASS including analyses as intended in the original study protocol (P203) of the Norway data both alone and in combination with the original three countries. The findings for the analyses for all four countries (P205) will be submitted to the EU health authorities with the next Periodic Safety Update Report. The only change from the original protocol's (P203) study methods/design is the removal of the secondary analyses. The final report for this protocol (P205) builds upon the report with the three countries to be inclusive of all four as was the intent of the original PASS.

7 RESEARCH QUESTION AND OBJECTIVES

The research question is to examine the associations between DL use and seizures, SVT, and A-fib/ flu in the general population.

Primary hypotheses (stated as null-hypotheses)

- There is no association between current DL use and first seizure.
- There is no association between current DL use and SVT.
- There is no association between current DL use and A-fib/flu.

Primary objectives

- Describe the use of DL during the study period in the general population overall and stratified by country, age, gender, calendar year, seasonality, severity of rhinitis, asthmatic status, and chronic urticaria status.
- Describe the IRs of the following outcomes in the general population:
    - Incident diagnosis of seizure;
    - Incident diagnosis of SVT; and
    - Incident diagnosis of A-fib/flu.
- Compare the risk of incident seizure among persons while currently exposed to DL to the risk among the same persons while unexposed to DL for the total DL population and stratified by age, while adjusting for relevant confounding factors.
- Compare the risk of incident SVT among persons while currently exposed to DL to the risk among the same persons while unexposed to DL for the total DL population and stratified by age, while adjusting for relevant confounding factors.
- Compare the risk of incident A-fib/flu among persons while currently exposed to DL to the risk among the same persons while unexposed to DL for the total DL population and stratified by age, while adjusting for relevant confounding factors.

8 AMENDMENTS AND UPDATES

None

9 RESEARCH METHODS

Text that came directly from the protocol are shown in grey text boxes.

9.1 Study design

The proposed study will be an observational (non-experimental), nationwide, register-based study using data from the Nordic national population registers. The associations between current DL use and seizures, current DL use and SVT, and current DL use and A-fib/flu will be assessed in analyses using person-specific linkage of data [Table 1]. The cohort of all DL users will be used for describing DL use (Substudy 1). The cohorts of individuals who have had first seizure, SVT, or A-fib/flu will be used to examine the IRs of first seizure, SVT, and A-fib/ flu in the general population (Substudies 2A, 3A, and 4A, respectively). A cohort study design among all DL users (i.e. a risk interval design including the DL-only cohort [Ref. 5.4: 03QPDQ]) will be used for the association between current DL exposure and first seizure, SVT, and A-fib/flu (Substudies 2B, 3B, and 4B, respectively).

Table 1. Overview of Substudies.

Primary objectives	
Substudy	**Aim**
1	Descriptive analysis of DL use in the general population
2A	Descriptive analysis of IR of first seizure in the general population
2B	Association between DL exposure and risk of first seizure
3A	Descriptive analysis of IR of first SVT in the general population
3B	Association between DL exposure and risk of first SVT
4A	Descriptive analysis of IR of first A-fib/flu in general population
4B	Association between DL exposure and risk of A-fib/flu

Pharmacoepidemiological studies typically use dispensed days' supply as a surrogate for current drug exposure, assuming they are used every day. However, in contrast to medications for many chronic diseases, antihistamines may be used intermittently, as needed for symptoms. For the main analyses in the present study of the association between current DL use and outcomes of interest (Substudies 2B, 3B, and 4B), person time exposed to DL will be determined from dispensing records. "Current use" (i.e., "exposed" period) will be defined for each prescription as the sum of days' supply plus a 4 week grace period to account for intermittent use and a possible wash-out effect. If a new DL prescription redemption occurs during an exposed period (either during the period equal to the sum of the days' supply or the 4 week grace period), the exposure period extends from that date with a period equal to the sum of days' supply in the newly redeemed prescription plus a 4 week grace period. Note: Days' supply will be calculated from the quantity of tablets or amount of solution dispensed and the standard daily dose based on the age of the patient (i.e., 6-11 months: 1 mg/day; 12 months-5 years: 1.25 mg/day; 6-11 years: 2.5 mg/day; ≥12 years: 5 mg/day). Because the drug is used "as needed", it is quite possible that there may still be exposed days in the period after the latest exposed period (i.e., after the exposed period that includes the sum of the days' supply plus a 4 week grace period). To minimize exposure misclassification, we propose to use person time at least 26 weeks beyond the dispensing date of the prior prescription as the "unexposed"

reference period. The "unexposed" period is actually a period with remote exposure to DL because dispensing of DL is a condition of entering the study population. We will refer to the "remote exposure" period as "unexposed" (For more details, see section 9.4.1 and Figure 1). The time between the exposed period and the unexposed period is considered neither exposed nor unexposed.

The advantage of using this design restricted to DL users, in which the same persons may have both exposed and unexposed periods, is that we reduce confounding due to time-independent factors associated with DL use.

The study is divided into six parts described below (For more details, see section 9.9).

1. Substudy 1

A descriptive analysis of DL use in the general population. To describe DL use in the general population, we will identify both prevalent and incident users of DL and describe the distribution of the number of redeemed DL prescriptions for the total population and stratified by country, age, sex, calendar year, seasonality, severity of rhinitis, asthmatic status, and chronic urticaria status.

2. Substudies 2A and 2B

A descriptive analysis of the IR of first seizure overall in the general population and stratified by country, sex, and age will be conducted (2A).

Among persons ever dispensed DL, the association between exposure to DL use and first seizure will be evaluated using Poisson regression of the IR of first seizure for the total population and stratified by age when accounting for confounding factors (2B).

3. Substudies 3A and 3B

Descriptive analysis of the IR of SVT overall in the general population and stratified by country, sex, and age will be conducted (3A).

Among persons ever dispensed DL, the association between exposure to DL use and first SVT will be evaluated using Poisson regression of the IR of first SVT for the total population and stratified by age when accounting for confounding factors (3B).

4. Substudies 4A and 4B

Descriptive analysis of the IR of A-fib/flu overall in the general population and stratified by country, sex, and age will be conducted (4A).

Among persons ever dispensed DL, the association between exposure to DL use and first A-fib/flu will be evaluated using Poisson regression of the IR of first A-fib/flu for the total population and stratified by age when accounting for confounding factors (4B).

5. Supplementary analyses

In total, 10 supplementary analyses will be performed to examine the robustness of the results. These are described in further details in section 7.7.6 of the protocol as well as in the SAP.

9.2 Setting

The cohort of individuals with redeemed DL prescriptions will be identified from the four Nordic national prescription registers. Similarly, the cohort of all individuals with seizures (first seizure), the cohort of individuals with SVT, and the cohort of individuals with A-fib/flu will be identified from the four Nordic national patient registers. The population is comprised of all individuals with DL prescriptions and of all individuals with seizures, SVT, or A-fib/flu in the four Nordic countries in the period 2001–2015 in Denmark and Finland, 2008–2015 in Norway, and July 2005–2015 in Sweden [Table 5]). Individuals for Substudies 2B, 3B, and 4B become eligible for the study cohort upon first dispensing of DL (See sections 9.3.1 and 9.3.2). Data will be available until and including 2015 for all countries.

9.3 Subjects

9.3.1 Inclusion criteria

Substudy 1

- Individuals who have redeemed at least one prescription of DL during the study period (DL cohort) and have residential location in Denmark, Finland, Norway, or Sweden.
- General population living in Denmark, Finland, Norway, and Sweden on 01 January of each year.

Substudy 2A

- Individuals who have experienced a seizure during the study period (seizure cohort) and have residential location in Denmark, Finland, Norway, or Sweden.
- General population living in Denmark, Finland, Norway, and Sweden on 01 January of each year.

Substudy 2B

- Individuals who have redeemed at least one prescription of DL during the study period (DL cohort) and have residential location in Denmark, Finland, Norway, or Sweden.

Substudy 3A

- Individuals who have experienced a SVT during the study period (SVT cohort) and have residential location in Denmark, Finland, Norway, or Sweden.
- General population living in Denmark, Finland, Norway, and Sweden on 01 January of each year.

Substudy 3B

- Individuals who have redeemed at least one prescription of DL during the study period (DL cohort) and have residential location in Denmark, Finland, Norway, or Sweden.

Substudy 4A

- Individuals who have had an A-fib/flu diagnosis during the study period (A-fib/flu cohort) and have residential location in Denmark, Finland, Norway, or Sweden.
- General population living in Denmark, Finland, Norway, and Sweden on 01 January of each year.

Substudy 4B

- Individuals who have redeemed at least one prescription of DL during the study period (DL cohort) and have residential location in Denmark, Finland, Norway, or Sweden.

9.3.2 Exclusion criteria

Substudy 2A

- Individuals with a diagnosis of seizure, epilepsy, or prescriptions of antiepileptic medicine before entering the study period, as they have prevalent disease.
- Individuals with a diagnosis of malignant brain tumor or head trauma before the first seizure, as they are at high risk of seizures due to causes other than DL use.

Substudy 2B

- Individuals with a diagnosis of seizures, epilepsy, prescriptions of antiepileptic medicine, malignant brain tumor, or head trauma before redemption of first DL prescription, as they have prevalent disease or are at high risk of seizures due to causes other than DL use.
- Individuals with a brain tumor (benign and malignant), initiation of treatment with antiepileptic medicine, or head trauma occurring after beginning of DL use will be censored at date of first occurrence, as they are at high risk of seizures due to causes other than DL use.

Substudies 3A and 4A

- Individuals with a diagnosis of SVT or A-fib/flu before entering the study period, as they have prevalent disease.
- Individuals with a diagnosis of congenital pre-excitation syndrome (e.g., Wolff Parkinson White) before entering the study period, as they are at high risk of cardiac SVT or A-fib/flu due to causes other than DL use.

Substudies 3B and 4B

- Individuals with a diagnosis of SVT or A-fib/flu before use of DL, as they have prevalent disease.
- Individuals with a diagnosis of congenital pre-excitation syndrome (e.g., Wolff Parkinson White) before use of DL, as they are at high risk of SVT or A-fib/flu due to causes other than DL.

9.4 Variables

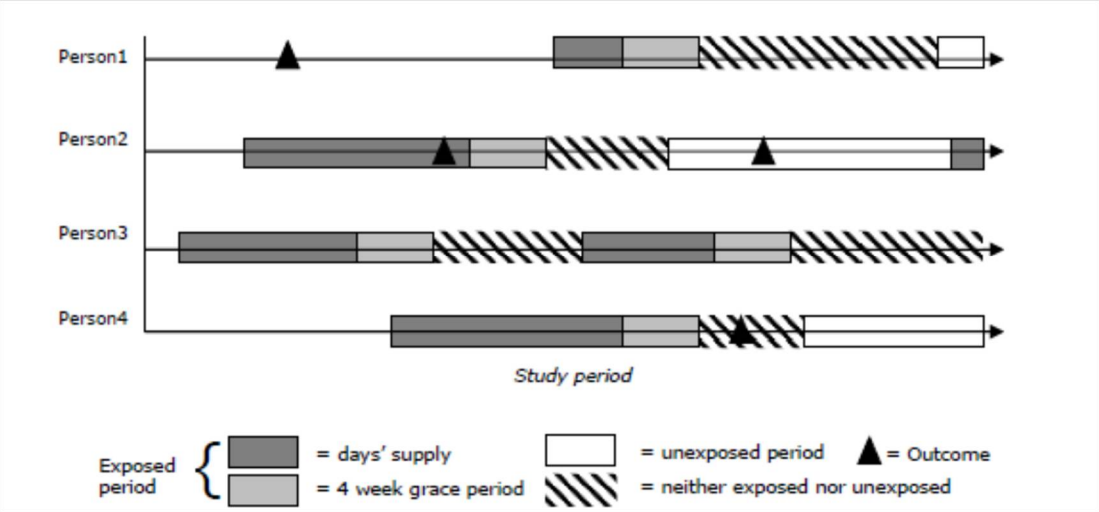
9.4.1 Exposure

The main exposure of interest in the present study is DL use identified in the national prescription registers by use of Anatomical Therapeutic Chemical Classification System (ATC) code R06AX27. The exploratory analysis will describe DL use based on data about persons who have redeemed at least one DL prescription (Substudy 1). In the association studies (Substudies 2B, 3B, and 4B), DL use is considered a time-varying variable, as the same person can be both exposed and unexposed during the study period depending on the time period from last redeemed DL prescription and the amount of days' supply redeemed at the last DL prescription redemption.

For the association analyses, person time exposed to DL will be determined from dispensing records and period of current use will be defined for each prescription as days' supply starting from the date of redemption plus a 4 week grace period to account for intermittent use and a possible wash-out effect. To minimize exposure misclassification, we propose to use person time at least 26 weeks beyond the dispensing date of the prior prescription as the "unexposed" reference period (in supplementary analysis 7, an alternative period of 52 weeks beyond the prior prescription is used to define the unexposed reference period). If a new DL prescription redemption occurs during an exposed period (either during the period equal to the sum of the days' supply or the 4 week grace period), the exposure period extends from that date with a period equal to the sum of days' supply in the newly redeemed prescription plus a 4 week grace period. In addition, a prescription redemption before 26 weeks after previous prescription redemption would mark the start of a new exposed period (and would not result in an unexposed period). [Figure 1] below provides an example of how persons included in the association analyses enter and exit exposure periods during the study period.

Days' supply will be calculated from the quantity of tablets or amount of solution dispensed and the standard daily dose based on the age of the patient (i.e., 6-11 months: 1 mg/day; 12 months-5 years: 1.25 mg/day; 6-11 years: 2.5 mg/day; ≥12 years: 5 mg/day).

Figure 1. Example of current exposed periods versus unexposed periods for study subjects included in the association analyses (Substudies 2B, 3B, and 4B)



[*Figure 1*] *illustrates how subjects in the study population (i.e., restricted to persons with at least one redeemed prescription of DL) enter and exit exposed and unexposed periods. An exposed period is a period starting from the day of redemption of a DL prescription and includes the following period equal to the number of days' supply in the drug packages purchased (illustrated with dark grey boxes) and a 4-week grace period (illustrated with the light grey boxes). Unexposed periods, which start 26 weeks after the dispensing date of the last DL prescription, are depicted with white boxes. The time between the end of the exposed period and the unexposed period is considered neither exposed nor unexposed; these periods are illustrated with shaded boxes. Moreover, the date at which an outcome (i.e., seizure, SVT, or A-fib/flu) occurs (if occurring) is marked with a black triangle. For example, person 1 experienced the outcome before redeeming DL for the first time (date of entering the study); and therefore, this person will be excluded. Person 2 experienced the first outcome while in an exposed period and a recurrent outcome occurred in an unexposed period. Person 3 was exposed to DL twice, but did not experience an outcome. Finally, person 4 was exposed to DL once and experienced the outcome in a period where the person was neither exposed nor unexposed; therefore, this outcome will not count toward the analysis of the association.*

In a supplementary analysis, an individual's exposure status is categorized according to time since last DL dispensing (periods 0–4, 5–8, 9–16, and 17–26 weeks each compared with >26 week since last DL dispensing), and individuals are considered unexposed in the period beyond 26 weeks after a DL prescription redemption until next DL prescription redemption, the end of the study period, death, emigration, or occurrence of the outcome, whichever comes first.

Loratadine, the parent compound of DL, is also available via prescription and over–the-counter in the Nordic countries. We think it is somewhat unlikely that patients would switch between DL and loratadine; however, it is possible that some of the time counted as unexposed in the analyses could actually be time exposed to loratadine. Moreover, other non-sedating prescription antihistamines are available in the Nordic countries, and if the effect on the outcomes is driven by use of non-sedating antihistamines in general rather than the specific

effect of DL exposure, these drugs should be examined to elucidate potential misclassification of exposure. To explore exposure misclassification (i.e., the influence of loratadine and other non-sedating prescription antihistamines), on the associations under study), we will conduct supplementary analyses, which will be specified in the statistical analysis plan.

Regarding missing values in variables from the prescription registers, normally no registration is interpreted as the person does not use the drug (e.g., no registration of DL use is interpreted as the person has not used DL)). Prescription drugs are not available from sources other than the pharmacies, and all drugs purchased at pharmacies are included in the prescription register (the only exception are drugs supplied from hospitals, however less than 1% of DL is supplied by the hospitals). We do not expect missing information for data in the prescription registry that will be used to determine DL exposure (e.g., number of packs per redemption). However, we will examine data to see whether missing information occurs. Missing data handling will be determined after review of the data, but before data from different registers are linked together (e.g. handling of missing values for exposure data is blinded to outcome status and vice versa) and will be described in a data control report, which will be submitted with the study report.

9.4.2 Outcome

Three outcome variables will be used in the present study: first seizure (Substudy 2B), first SVT (Substudy 3B), and first A-fib/flu (Substudy 4B). Except where noted, the case definition of seizure excludes febrile seizure, a condition in infancy and early childhood attributed to fever. However, supplementary analysis 2 will evaluate the outcomes of febrile and non-febrile seizures in children. (The diagnosis of febrile seizure is generally not used in adults.) Information on outcome variables will be obtained from the Nordic national patient registers, including diagnostic and treatment information for patients treated at the secondary and tertiary hospital level in all four Nordic countries using International Classification of Diseases (ICD)-10 codes. We will exclude seizure cases if they are registered with brain tumor (benign and malignant), stroke, or acute drug intoxication or overdose of drugs during the same hospitalization as the seizure. [Table 2] gives an overview of the outcome variables in the study. For all outcome variables, we will include the primary diagnoses from the emergency room or inpatient settings registered in the Nordic national patient registers.

The National Patient Registers are used for reimbursement of services to the hospitals. It is mandatory to enter specific information (such as name, date, main diagnosis) for the record to be established. Due to the requirements of the national registries, we do not expect missing data on the outcome variables. In Denmark and Finland, it is only possible to register hospitalizations into the Nordic national patient registers if complete information on the primary diagnosis, date, and hospital department is entered into the registration system. Therefore, no missing values should occur for these variables. This procedure is most likely the same for Sweden and Norway. Data in the Danish National Patient Register is automatically checked for missing codes, inconsistencies between diagnosis and gender, incorrect digits and errors in the personal identification code (PIC). If an error is detected, the record is returned to the source hospital for correction [Ref. 5.4: 04C0C2].No studies have examined the validity of seizures in the total population, but Vestergaard et al (2006) examined

the validity of the discharge diagnosis of febrile seizure in children the National Patient Register (ICD-10 code R56.0) [Ref. 5.4: 04C0C7]. The positive predictive value (PPV) was 92.8% (95%CI: 88.8-95.7%). The sensitivity (defined as completeness by the authors) is 71.5% (95% CI: 66.3-76.4%) [Ref. 5.4: 04C0C7]. The diagnosis of atrial fibrillation and atrial flutter has been validated in the Danish National Patient Register [Ref. 5.4: 04C0BZ]. The PPV for the combined diagnosis of atrial fibrillation and atrial flutter (I48) was 92.6%. Other studies have found even higher PPVs [Ref. 5.4: 04C0BS] [Ref. 5.4: 04C0BQ]. No studies have validated the diagnosis for supraventricular tachycardia (I47); however, we find it likely that this diagnosis has approximately the same validity in the National Patient Register as seen for atrial fibrillation and atrial flutter.

Table 2. Overview of the Outcome Variables in the Study

Substudy	Aim
Substudy 2B	First seizure: An incident case of seizure is a person with the first diagnosis of seizure
Substudy 3B	Supraventricular tachycardia (SVT): An incident case of SVT is a person with first diagnosis of SVT
Substudy 4B	Atrial fibrillation or atrial flutter (A-fib/flu): An incident case of A-fib/flu is a person with first diagnosis of A-fib or first diagnosis of A-flu. These two diagnoses will be combined into a composite endpoint

ICD-10 codes are listed in Annex 6 of the protocol. Note that the case definition of seizure in these substudies excludes febrile seizures.

9.4.3 Covariates

In the present study, we have used directed acyclic graphs (DAGs), also called causal diagrams, for confounder selection. DAGs are a well-accepted methodology for using causal knowledge and a set of formal mathematical principles for selecting which variables to adjust for when performing association analyses [Ref. 5.4: 045RCQ]. They provide a systematic way to explore the relationships between the exposures, outcomes, and covariates (unidirectional, bidirectional, causal) and facilitate dealing with a large number of potential confounders. DAGs help make the assumptions underlying an analysis explicit. The selection of variables needed for confounder adjustment to obtain an unbiased estimate of the association under study is called the minimum sufficient adjustment set of confounders. We used the open source and freely available software DAGitty for the development of the DAGs [Ref. 5.4: 045WX9]. DAGitty helps the researcher visualize the structure of relevant variables for the association under study included in the DAG, as well as to identify the minimum sufficient adjustment sets available for confounder adjustment. In the following paragraphs, we present a brief description of the DAG process; however, the full DAG process is described in Annex 8 of the protocol.

The factors listed in the left-hand column of [Table 3] were considered potential confounders (i.e., candidate variables) for the association between DL use and seizures, SVT, and/or A-

fib/flu based on the literature, as well as consultation with a group of clinical experts. The potential confounders were reviewed during a DAG meeting held on January 6, 2015. At this meeting, the relationships among the different factors were discussed, and DAGitty was used to help identify the minimum sufficient adjustment set of confounders to include in the association analysis of each outcome. Three DAGs including potential confounders of the association between DL use and seizures, SVT, and A-fib/flu, respectively, were developed by the Danish national investigators, MSD, ApHER, and two clinical experts. After the DAG meeting, we consulted a dermatologist to confirm the correctness of the developed DAGs, especially regarding the relationships between urticaria and the other potential confounders. The DAGs helped clarify whether the potential confounders listed were confounders, colliders, or intermediate variables and which of the potential confounders constituted a minimum sufficient adjustment set. We selected the final minimum sufficient adjustment set, which will be used to adjust for confounding factors in the association studies based on whether we found that a given combination of confounders would be obtainable from the registers. The final minimum sufficient adjustment set for the association studies (i.e., 2B, 3B, and 4B) are seen in the right-hand columns of [Table 3].

Persons with risk time in two age categories are counted in both age-categories.

Table 3. Information on whether potential confounding factors are included in the DAGs and the minimum sufficient adjustment sets, which will be used for confounder adjustment in the association studies.

Potential confounding factors	Potential confounder included in the DAG			Confounders included in the selected minimum sufficient adjustment set for each association study		
	Seizures	SVT	A-fib/flu	Seizures	SVT	A-fib/flu
Age (age will be derived as a categorical and a continuous variable: Age groups [0–4 years, 5–19 years, 20–64 years, ≥65 years] and years)	Yes	Yes	Yes	Yes	Yes	Yes
Sex (male versus female)	Yes	Yes	Yes	Yes	Yes	Yes
Country of residence (Denmark, Finland, Norway, Sweden)	Yes	Yes	Yes	Yes	Yes	Yes
Calendar year (years ranging from 2001–2015)	Yes	Yes	Yes	Yes	Yes	Yes
Drug overdose (other than desloratadine)	Yes	Yes	Yes	No	No	No
Drug and alcohol abuse	Yes	Yes	Yes	No	No	No
Diabetes (both type 1 and type 2)	Yes	Yes	Yes	No	No	No
Use of hypoglycemic agents (oral anti-diabetics, insulin)	Yes	No	No	No	No	No
Hypertension	No	Yes	Yes	No	No	No
Thyroidism (both hypo- and hyperthyroidism, e.g., Grave's disease, thyrotoxicosis)	No	Yes	Yes	No	No	No
Structural heart disease: Left ventricular hypertrophy, left ventricular systolic dysfunction, chronic heart failure (CHF)	No	Yes	Yes	No	No	No
Seasonality (i.e., winter [December-February], spring [March – May], summer [June-August], and autumn [September-November])	Yes	Yes	Yes	Yes	Yes	Yes
Asthmatic status	Yes	Yes	Yes	Yes	Yes	Yes
Disease severity of rhinitis	Yes	Yes	Yes	Yes	Yes	Yes
Chronic obstructive pulmonary disease (COPD)	Yes	Yes	Yes	No	No	No
Smoking	Yes	Yes	Yes	No	No	No
Inflammatory disease	No	Yes	Yes	No	No	No

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

Potential confounding factors	Potential confounder included in the DAG			Confounders included in the selected minimum sufficient adjustment set for each association study		
	Seizures	SVT	A-fib/flu	Seizures	SVT	A-fib/flu
Metastatic disease	Yes	No	No	No	No	No
Infections	No	Yes	Yes	No	No	No
Stroke	Yes	Yes	Yes	No	No	No
Chronic urticaria	Yes	Yes	Yes	Yes	Yes	Yes
Unspecific autoimmune disease	Yes	Yes	Yes	No	No	No
Type 1 allergy	Yes	Yes	Yes	No	No	No
Antihypertensive treatment	No	Yes	Yes	No	No	No

[Table 4] below shows the variables included in the minimum sufficient adjustment sets in all four association analyses. In addition to being confounders included in the association analyses, the variables in the minimum sufficient adjustment sets will be used to characterize the population using DL in the descriptive study of DL use (Substudy 1). The table describes how each of the variables will be operationalized. ICD-10 codes and ATC codes that will be used for the definition of the variables can be found in Annex 6 of the protocol.

Table 4. Definition of confounders included in the minimum sufficient adjustment sets that will be used for confounder adjustment in the association studies.

Confounders included in the minimum sufficient adjustment sets	Definition	Data source
Age	For the descriptive analyses of DL use, age will be defined as the age of the purchaser at the date of prescription redemption and stratified into age groups (0–4 years, 5–19 years, 20–64 years, ≥65 years). In the association studies, age is a time varying confounder; and therefore, risk time will be split up in years of age. We will evaluate whether age can be included as a continuous variable by examining the assumption of linearity. Alternatively, age will be included as a categorical variable.	Civil registration system
Sex	Sex is a time-independent confounder and will be included as males versus females in both the descriptive and association analyses.	Civil registration system
Country	Country of residence is a time-independent confounder, as persons will be excluded if emigrating the country. Country of residence will be included with four categories, i.e. Denmark, Finland, Norway, or Sweden in both the descriptive and association analyses.	Civil registration system
Calendar year	For the descriptive analyses of DL use, calendar year is defined as the year of prescription redemption. In the association studies, calendar year is a time varying confounder; and therefore, risk time will be split up in calendar years.	Prescription register
Seasonality	For the descriptive analyses of DL use, seasonality is defined as the season (i.e., winter [December-February], spring [March – May], summer [June-August], and autumn [September-November]) when the DL prescriptions are redeemed. In the association studies, seasonality is a time varying confounder; and therefore, risk time will be split up in seasons defined as winter (December–February), spring (March–May), summer (June–August), and autumn (September–November).	Prescription register
Asthma status	Both for the descriptive and association analyses, asthmatic status is defined as a binary variable indicating whether or not a person has redeemed treatment for asthma defined as at least two prescriptions of inhalant steroids within a six-month period and/or contacts hospitals with a diagnosis of asthma (including both primary and secondary diagnoses) during a five-year period before first DL exposure. To distinguish persons treated for chronic obstructive pulmonary disease from those treated for asthma, first registered asthma treatment has to be redeemed when the purchaser was 45 years or younger.	National patient register and prescription register

Confounders included in the minimum sufficient adjustment sets	Definition	Data source
Disease severity of rhinitis	Both for the descriptive and association analyses, severity of rhinitis will be defined as binary variable indicating whether or not a person has received treatment for severe rhinitis. Persons with severe rhinitis will be identified from the prescription register as persons who have redeemed immunotherapy at least once during a five-year period before first DL exposure.	Prescription register
Chronic urticaria	Both for the descriptive and association analyses, chronic urticaria status is defined as a binary variable indicating whether or not a person has a registered diagnosis of chronic urticaria in the five-year period before first DL exposure.	National patient register

9.4.4 Other variables

We will also obtain information on immigration and emigration, as well as date of birth and death status from the civil registration systems to be able to calculate the IRs in Substudies 2B, 3B, and 4B.

The interpretation of register-based variables with regard to missing information was discussed in section 9.4.1 and 9.4.2. For a few of the included register-based variables (e.g., sex and date of birth), all included persons should have information. We do not expect missing information on these variables; however, we will examine data to see whether missing information occurs. Missing data handling will be determined after review of the data, but before data from different registers are linked together (blinded to exposure to DL and outcome status) and will be described in a data control report, which will be submitted along with the study report.

9.5 Data sources and measurement

The DL study will include register information from four Nordic countries – Denmark, Finland, Norway, and Sweden. In addition to a long history of collecting high quality information on births, deaths, immigration and emigration, disease incidence, and activities in the healthcare sector [Ref. 5.4: 00W4D0], exceptional opportunities to perform register-based research are driven by the unique PIC introduced in the Nordic countries in the 1960's and available to all persons with permanent residence in the Nordic countries [Ref. 5.4: 00W4G3]. The PIC makes it possible to link information at the individual level from several registers for scientific research purposes. The national prescription registers and national patient registers within each of the Nordic countries capture all the individual encounters of purchasing prescribed DL and allow sufficient longitudinal data to differentiate between first and recurrent seizures, as only first seizure will be analyzed, and to identify incident SVT and A-fib/flu cases. Person-specific use of DL will be elucidated from the national prescription registers by obtaining information on redemption of DL prescription for each person [Ref. 5.4: 00W4CX]. Person-specific information on seizures, SVT, and A-fib/flu will be derived from the Nordic national patient registers.

[Table 5] presents key information on the population-based health registers in the Nordic countries of relevance for the present study. Data will be available until and including 2015 for all countries. The data extraction period refers to the longest period for which data on exclusion variables (e.g., seizures, SVT, or A-fib/flu before baseline) can be obtained for.

Table 5. Overview of national health registers in the Nordic countries of relevance for the present study.

Register	Country			
	Denmark	**Finland**	**Norway**	**Sweden**
National prescription register	1995–2015	1994–2015	2004–2015	2005–2015
National patient register	1977–2015 (1)	1967–2015 (2)	2008–2015	1987–2015 (3)
Civil registration system	1968–2015	1967–2015	1964–2015	1965–2015
Study period	2001–2015 (15 years)	2001–2015 (15 years)	2008–2015 (8 years)	July 2005–2015 (11 years)
Data extraction period	1977–2015	1967–2015	2008–2015	1987–2015

(1) Contacts with outpatient clinics (incl. emergency departments) since 1995.
(2) Contacts with outpatient clinics (incl. emergency departments) since 1998.
(3) Contacts with outpatient clinics (incl. emergency departments) since 2001.

The national prescription registers include information on the date of prescription redemption, information on the purchaser, and information on the drug redeemed (e.g., ATC code, number of pills, daily dose, pack size, and number of packs purchased) [Ref. 5.4: 045TYK]. The Nordic national patient registers include diagnostic and treatment information for patients treated at the secondary and tertiary hospital level [Ref. 5.4: 045TZL] [Ref. 5.4: 045W09]. Clinical experts have been consulted on how to include information from the prescription and patient registers. Information on date of birth, immigration, emigration, and death will be obtained from the civil registration systems [Ref. 5.4: 00W4G3] [Ref. 5.4: 045W09].

9.5.1 Study Procedures

This is an observational, register-based study and pre-existing health-related national register data will be the sole data source. According to Danish, Finnish, Norwegian, and Swedish law, register-based studies can be carried out without consent from the individual subjects where the processing takes place for the sole purpose of carrying out statistical or scientific studies of significant public importance and where such processing is necessary in order to carry out these studies. It is an absolute requirement that the publication of statistical or scientific results may never reveal the identity of individuals or otherwise compromise data subjects. We will obtain approval by the data agencies in the four countries before data management and data analyses will be performed.

9.6 Bias

The present study utilizes observational data from nationwide population registers covering the entire population meaning the total population is included and that loss to follow-up is minimal, limiting the impact of selection bias on results. Furthermore, observational data are extracted from health registers which are established and operated for purposes not immediately related to the present study. This minimizes information bias related to the differential misclassification of outcomes, but introduces other types of limitations with respect to quantifying exposure, outcome, and confounders as outlined below:

Exposure: Use of DL

- The prescription registers capture information on purchasing of drugs from pharmacies. The actual adherence of prescribed drugs and consumption cannot be established in these databases. This is a major limitation because the drugs concerned are taken on an as needed basis to treat symptomatic disease. Thus, it is difficult to establish when persons are truly exposed to the drug. Therefore, supplementary analyses will be performed to characterize the relationship of prescribing and timing of events of interest by categorizing time since DL prescription to the outcomes of interest and by using 52 instead of 26 weeks beyond previous prescription redemption as start of an unexposed period.

- Left-truncation is a potential bias in the study meaning that we have no information on DL use before the start of registration of prescriptions in each country. Left-truncation bias in relation to DL use is only a relevant issue for Sweden and Norway since DL was available from 2001, but the prescription registers in Norway and Sweden were established in 2004 and 2005, respectively [Table 4]. Therefore, we do not know whether a DL user in the first year of registration in Norway and Sweden is a long-term user (prevalent user) or a first-time user (incident user). To account for this potential bias, a person with prescription redemption of DL in Norway and Sweden within the first 6 months after establishment of the prescriptions registers will not be included. This is not a limitation in Denmark and Finland since DL was first approved in 2001 and the prescription registers in Denmark and Finland were established in 1995 and 1994, respectively. However, left-truncation bias might also occur when persons are immigrating into the study population. Therefore we also exclude persons with DL prescription redemptions within 6 months after immigrating to Denmark, Finland, Norway, or Sweden.

- There is a possibility that patients could purchase DL over-the-counter; however, because of reimbursement systems in the Nordic countries, it is actually less expensive to purchase prescription DL. In Norway and Sweden DL has only been allowed for prescription sale; However, in Denmark, DL has been available for over-the-counter sale since 2013, but over-the-counter sales only counted for less than 4 % of the total amount of DL purchased in 2013. A supplementary analysis will examine the associations under consideration restricting the time period to include only years where DL was not allowed for OTC sale.

- Loratadine, the parent compound of DL, is also available via prescription and over-the counter in the Nordic countries. We think it is somewhat unlikely that patients would switch between DL and loratadine. However, it is possible that some of the time counted as unexposed in the analyses could actually be time exposed to loratadine or over-the-counter DL. Moreover, other non-sedating prescription antihistamines are available in the Nordic countries, and if the effect on the outcomes is driven by non-sedating prescription antihistamines in general, rather than the specific effect of desloratadine exposure only, these drugs should be examined to elucidate potential misclassification of exposure. To explore exposure misclassification (i.e., the influence of loratadine and other non-sedating prescription antihistamines on the associations under study), we will conduct supplementary analyses, which will be specified in the statistical analysis plan.

Outcome: Episodes of seizures, SVT, and A-fib/flu

- Seizures, SVT, or A-fib/flu not registered with a relevant diagnosis code in the national patient registers will not be included in the study. However, the completeness of registration is assumed high, since both a procedure for data control of information in the national patient registers is established, and hospitals have an incentive to register patients, as the financing of hospitals is based on the registration of patients treated and procedures performed. If under-recording exists, it would reduce the number of outcomes evaluated, but this under-recording is not likely to be differential (i.e. associated with periods of use or nonuse of DL) and introduce bias.

- The coverage of calendar years in the national patient registers differ between the Nordic countries and may be insufficient to capture the complete history of seizures, SVT, or A-fib/ flu at the individual level. Regarding seizures, recurrent seizures would be studied as primary seizures, if first seizure happened before start of registration.

- Truncation is a potential bias in the study meaning that we have no information on seizures, SVT, and A-fib/flu before the start of registration of each of these variables. For Denmark, Finland, and Sweden, information on seizures, SVT, and A-fib/flu is available from 1977, 1967, and 1987, respectively. Thus, the impact of truncation bias on results from these countries is limited. However, information on seizures, SVT, and A-fib/flu in Norway is only available from 2008, which limits the study period of the Norwegian data further and increases the risk of truncation bias.

- The present study aims at studying incident outcomes occurring in the community setting. To differentiate between incident and prevalent disease, we exclude persons with registered disease before baseline. In addition, we used surrogates of prevalence (i.e., redeemed prescriptions of antiepileptic medicine) to exclude persons with prevalent disease. To capture disease cases emerging in the community setting, we limit ascertainment to those sites of care where incident presentation would be present and use only primary diagnoses of hospitalization, as secondary diagnoses often represent conditions emerging during hospitalization.

Confounders

In the present study, we expect complete information on the central confounders of age, sex, calendar year, country, and seasonality, as these are measured as key variables in the registers and information on these variables has to be entered into the system to establish a record file.

Information on the three confounders of severity of rhinitis, asthmatic status, and chronic urticaria status is challenging to obtain from the nationwide registers for many reasons. First of all, these conditions in general emerge in the primary health care sector where patients normally seek care from their general practitioner for treatment of symptoms. Second, truncation bias may, as with regard to the measures of exposure and outcome, also occur in relation to these three confounders in Norway as the patient register was established in 2008, making the follow-up period rather short. Third, different issues regarding codes and use of drugs for the three conditions have to be realized and discussed to understand the potential impact of residual confounders in the present study. We have discussed these issues with clinical experts and the essence of the discussion is given below.

- Severity of rhinitis is measured as use of immunotherapy and the binary measure of severity of rhinitis will not capture different levels of disease severity. Therefore, we expect the sensitivity of the measure to be rather low and severity of rhinitis to be underreported in the present study. However, we do not expect misclassification of those persons who received immunotherapy, as it is assumed that persons receiving immunotherapy also have severe rhinitis. A quantitative bias analysis examining the impact of misclassification of severity of rhinitis on the results will be performed.

- Identifying persons with asthma by use of register data is challenging due to the fact that the drugs used for treatment of asthma overlap with the treatment of chronic obstructive pulmonary disease (COPD). In order not to misclassify persons with COPD into the group of persons with asthma, we identify persons with asthma as those initiating asthma treatment before the age of 45 years. However, this means that for the part of the population aged 45 years or older, we will only have information on asthmatic status from the patient register in which hospitalized cases are registered. These cases are more likely to have severe asthma than those identified through the prescription register meaning that residual confounders may be more likely to occur among the population older than 45 years than those younger. A quantitative bias analysis examining the impact of misclassification of asthma on the results will be performed.

- Chronic urticaria is a very rare diagnosis given at highly specialized hospital units. This means that we expect a delay from onset of symptoms of chronic urticaria and the diagnosis of chronic urticaria of approximately 2-5 years. In the period between onset of disease and diagnosis, persons may receive antihistamines, including DL prescribed by the general practitioner, for their symptoms. Therefore, chronic urticaria may be underreported in the hospital register and the sensitivity of the measure is expected to be somewhat low. To get an impression of how important this misclassification will be in the present study, we will look at how many of the persons with a diagnosis of chronic urticaria have redeemed prescriptions of

DL during the five years prior to the date of diagnosis. A quantitative bias analysis examining the impact of misclassification of chronic urticaria on the results will be performed.

- As in any association study, there is always the possibility of unmeasured confounders or residual confounding resulting from roughly categorized confounders that could affect the results of the study.

Variables used for inclusion and exclusion criteria

In Substudy 2B, seizure outcomes for which a drug overdose is also registered at the same hospitalization are excluded. In general, drug overdoses are likely to be underreported in the registries, as the registries often do not have sufficient detail to differentiate between overdoses from different types of drugs. Therefore, it is not possible to distinguish between overdoses from DL and overdoses from other drugs. Because overdoses of DL are rare compared to other drug overdoses, persons with any drug overdose registered during the same hospitalization as the seizure are excluded from analysis 2B. As a result, this study cannot determine whether the seizure outcomes are specifically associated with DL overdoses.

Sample size

Based on the assumptions made, the sample size is not adequate in the youngest age group for the assessment of the potential association between DL use and A-fib. In this age group only relatively strong associations (IRR>=8.2) can be properly assessed for the association between DL use and SVT.

9.7 Study size

The proposed study will be performed in the framework of an observational design with the use of register-based data. The primary interest is to assess the association between current DL exposure in the general population and the outcomes (i.e., first seizure [Substudy 2B], first SVT [Substudy 3B], and first A-fib/flu [Substudy 4B]). For Substudies 2B, 3B, and 4B, a cohort study design among DL users will be used. The sample size in the present study will be fixed, as the study population for the association studies 2B, 3B, and 4B consists of all individuals in the four Nordic countries who have redeemed a DL prescription at least once. Hence, the aim of this section is to calculate the minimum detectable incidence rate ratio (IRR). Calculations concern Substudy 2B evaluating the association between DL use and first seizure, Substudy 3B evaluating the association between DL use and first SVT event, and Substudy 4B evaluating the association between DL use and first A-fib/flu. The actual annual IR of seizures, SVT, and A-fib/flu among current DL users is unknown and will be determined in the current study. Minimal detectable IRR were calculated based on a rearranged formula for sample size calculations developed by Bryant & Morganstein [Ref. 5.4: 045WWJ] (Formula provided in Annex 7 of the protocol). The following are the parameters needed to calculate the minimum detectable IRR: the number of DL users in each age group (i.e., the fixed sample size); the proportion of exposed time (current exposure) and unexposed time (non-current/remote exposure) for DL users; the background event rates of seizures, SVT, and A-fib/flu; and the

number of years included in the study along with statistical parameters and assumptions included in the equation (i.e., the significance level, power, and 1-sided versus 2-sided tests).

9.7.1 Fixed sample size

The number of DL users from each country has been estimated based on national drug sale statistics (Annex 1A of the protocol). The annual unique number of DL users in Denmark, Finland, and Sweden for age groups 0–4, 5–19, 20–64, and ≥65 years is estimated to be 20,000, 86,000, 215,000, and 44,500, respectively. Data for Norway on DL prescriptions and seizures/SVT/A-fib/flu are available for a shorter time period; and therefore, Norway is not included in the calculations of the minimum detectable IRR. The number of annual unique DL users in the four countries is thereby slightly underestimated.

9.7.2 Proportion of current and non-current exposure time among DL users for the purpose of calculation of minimum detectable IRR

DL exposure (i.e., current DL use) is time-varying, and each person might have one or more periods as exposed and one or more periods as unexposed. Individuals in the study population (i.e., individuals who have redeemed at least one prescription of DL) are assumed to be exposed in a period following the date of DL purchase (i.e., current users). An estimate of the number of DL prescriptions redeemed per year in each age group was obtained from the feasibility study performed prior to developing the synopsis and the present protocol. For the minimum detectable IRR calculations, the mean number of prescriptions in each age group per year from the Danish data is used as an estimate of the average annual number of redemptions. The exposure period is then calculated as follows: (mean annual number of prescriptions in each age group*4 weeks (standard days' supply)) + 4 weeks grace period to account for intermittent use and a possible wash-out effect. Beyond this period, individuals are assumed to be unexposed (i.e., non-current users). The average number of prescriptions per year was estimated to be 1.50, 1.62, 1.78, and 2.30 for age groups 0–4, 5–19, 20–64, and ≥65 years, respectively[1].

Exposure periods for age groups 0–4, 5–19, 20–64, and ≥65 years were then calculated to be 10.00, 10.48, 11.12, 13.20 weeks, respectively. The proportion of exposed time in each age group is calculated as number of weeks exposed divided by number of weeks in a year (i.e., 52 weeks). For example, for age group 0–4 years, the proportion of exposed time is 10 weeks/52 weeks = 19%, and thus, the proportion of non-exposed or neither exposed nor unexposed time is 81%. Note: A simplified method was used to calculate exposed and unexposed person time for each age group for the purpose of estimating the minimum detectable IRR. The method for

[1] By using Danish figures we might get conservative estimates of the minimal detectable IRR as mean number of prescriptions calculated for the feasibility study showed slightly lower means for Denmark compared to Sweden (figures from Finland and Norway were not available for these calculations). The average number of prescriptions per age group for the 20-64 and ≥65 year's age groups was calculated as the mean number of annual prescriptions (2001-2012) per age group using data from Denmark for ages ≥16 years. For the 5-19 year age group, the calculation was based on data from Denmark for ages 16-19. For the 0-4 year age group, the calculation was based on Swedish data from the feasibility study, which showed a tendency for a lower number of prescriptions in this age group compared to the older age groups.

calculating exposed, unexposed, and neither exposed nor unexposed time for individuals for the study analysis is outlined in section 9.4.1.

9.7.3 Background event rate

The background incidence rate (i.e., IR) of seizures, SVT, and A-fib/flu was obtained from published studies [Ref. 5.4: 00W4CY] [Ref. 5.4: 03XNM4] [Ref. 5.4: 03XNL7]. IRs of seizure among unexposed individuals for age groups 0–4, 5–19, 20–64, and ≥65 years were estimated to be 65, 50, 40, and 40 per 100,000 person-years, respectively [Ref. 5.4: 00W4CY]. The IR of SVT is reported to be 13/100,000 person-years for persons aged 19 years or younger, 27/100,000 person-years for persons aged 20–64 years, and 122/100,000 person-years for persons aged 65 years or older [Ref. 5.4: 03XNM4]. Wilke et al. (2013) [Ref. 5.4: 03XNL7] reported the incidence of A-fib to increase markedly with age with 0.0016 cases/1000 person-years in children (<15 years) and approximately 30 cases/1000 person-years for persons aged 80 years or older. No data on the epidemiology of flutter were available.

9.7.4 Number of years in the study

The maximum number of years (t) that an individual can be included in the study is 5 years for the age group 0–4 years and 12 years for the remaining age groups (≥5 years). The period of 15 years corresponds to the period where DL has been on the market. For the calculations of the minimum detectable IRR, we assume that individuals, on average, will be included in the study for a shorter period; and therefore, the maximum number of years included has been set to 2 years for ages 0–4 years and 6 years for ages ≥5 years.

9.7.5 Statistical parameters and assumptions

The minimum incidence rate ratio, IRR>1, that can be detected is calculated using the following parameter values and assumptions:

Significance level, α: 0.05

Power, 1-β: 0.80

1-sided test

9.7.6 Example of calculating the minimum detectable IRR

The mean number of DL prescriptions in the age group 0–4 years is 1.50 prescriptions. This gives an exposure period of (1.50*4 weeks) + 4 weeks = 10 weeks. In this age group, 20,000 children have redeemed DL (i.e., the fixed sample size for this age group). Due to the exposure period of 10 weeks in this group, the proportion of the time exposed to DL is 10 weeks/52 weeks per year = 19%. The background annual rate of seizures is 65/100,000 in this age group. It is assumed that individuals in this age group will be included in the study for an average of 2 years. When using a 1-sided test, significance level of 5% and power of 80%, the minimum detectable IRR will be 3.0.

Table 6. The minimum detectable incidence rate ratio (IRR>1) was calculated based on the Nordic population of SL users with at least one prescription of DL per year. Incidence rate (IR) of seizures is based on Hauser & Beghi (2008). A 1-sided test, significance level of 5% and power of 80% have been used.

Age group (years)	Annual IR of seizures among unexposed individuals per 100,000 person-years	Mean number of individuals with at least one annual DL prescription in the Nordic countries	Estimated number of weeks exposed based on mean number of DL prescriptions per person	Minimum detectable IRR t=2 and 6 years (for age 0-4 years and age ≥5 years)
0-4	65	20,000	10.00	3.0
5-19	50	86,000	10.48	1.5
20-64	40	215,000	11.12	1.3
≥65	40	44,500	13.20	1.7

Table 7. The minimum detectable incidence rate ratio (IRR>1) was calculated based on the Nordic population of DL users with at least one prescription of DL per year. Incidence rate (IR) of SVT is based on Orejarena et al. (1998). A 1-sided test, significance level of 5% and power of 80% have been used.

Age group (years)	Annual IR of SVT among unexposed individuals per 100,000 person-years	Mean number of individuals with at least one annual DL prescription in the Nordic countries	Estimated number of weeks exposed based on mean number of DL prescriptions per person	Minimum detectable IRR t=2 and 6 years (for age 0-4 years and age ≥5 years)
0-4	13	20,000	10.00	8.2
5-19	13	86,000	10.48	2.1
20-64	27	215,000	11.12	1.4
≥65	122	44,500	13.20	1.4

Table 8. The minimum detectable incidence rate ratio (IRR>1) was calculated based on the Nordic population of DL users with at least one prescription of DL per year. Incidence rates (IR) for atrial flutter were not available; therefore, we base the calculations only on IR of A-fib obtained from Wilke et al. (2013). A 1-sided test, significance level of 5% and power of 80% have been used.

Age group (years)	Annual IR of A-fib among unexposed individuals per 100,000 person-years	Mean number of individuals with at least one annual DL prescription in the Nordic countries	Estimated number of weeks exposed based on mean number of DL prescriptions per person	Minimum detectable IRR t=2 and 6 years (for age 0-4 years and age ≥5 years)
0-4	1.6	20,000	10.00	54.0
5-19	3.8	86,000	10.48	3.4
20-64	168.9	215,000	11.12	1.6
≥65	2154.3	44,500	13.20	1.1

9.8 Data transformation

The outcome variable in Substudy 2 was first seizure, which was defined as a first seizure diagnosed in the study period. Seizure was identified in the patient registers among all inpatient hospitalizations and emergency room encounters or contacts with seizure as the primary diagnosis.

The outcome variable in Substudy 3 was first SVT, which was defined as a first SVT diagnosed in the study period. SVT was identified in the patient registers among all inpatient hospitalization and emergency room encounters or contacts with SVT as the primary diagnosis.

The outcome variable in Substudy 4 was first A-fib/flu, which was defined as a first Afib/flu diagnosed in the study period. A-fib/flu was identified in the patient registers among all inpatient hospitalization and emergency room encounters or contacts with Afib/flu as the primary diagnosis.

The construction of the potential confounding factors is described below:

- Age: Age was categorized into 4 age categories (0-4 years, 5-19 years, 20-64, ≥65 years)
- Calendar time: 1-year categories (2001, 2002, …, 2015)
- Seasonality: Winter (December, January, February), spring (March, April, May), summer (June, July, August) and autumn (September, October, November)
- Country: Denmark, Finland, Norway, Sweden

All diseases included as potential confounders were identified in the patient registers among all hospital encounters (contacts) with specific primary or secondary diagnosis within the last 5 years before the first DL prescription redemption. See Annex 6 of the protocol for the specific ICD-10 codes used. The diseases included were asthma, chronic urticaria, rhinitis, diabetes, hypo/hyper-thyroidism, inflammatory disease, infections, and type 1 allergy.

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All drugs included as potential confounders were identified in the prescription registers among all prescriptions with specific ATC-codes the last 5 years before the first DL prescription redemption. See Annex 6 of the protocol for specific ATC-codes. The drugs included were for treatment of asthma, severe rhinitis, diabetes, hypo/hyper-thyroidism, inflammatory disease and type 1 allergy.

9.8.1 Data management

The handling of data in the DL study involves six steps and requires applications and approvals for access to data in each of the four Nordic countries. In addition to the acquisition and management of data, a primary scientific coordinator will be responsible for the overall study and establishment of a joint Nordic study dataset. Four national scientific coordinators will be responsible for steps 1–4 in each country, whereas the Danish scientific coordinator also will be responsible for steps 5–6.

The handling of data is categorized into the following six steps:

- All national scientific coordinators will apply to the relevant agencies for permission to perform the study and to get access to data.

- All national scientific coordinators will facilitate the construction of the study populations:
  - Study population consisting of all DL users during the study period.
  - Study population consisting of all individuals with seizure during the study period and the years prior to the study period.
  - Study population consisting of all individuals with SVT during the study period and years prior to the study period.
  - Study population consisting of all individuals with A-fib/flu during the study period and years prior to the study period.
- All national scientific coordinators are responsible for acquiring and validating the datasets and will explore how the data can be combined from the registers. Data quality control includes but is not restricted to check for legal values for each categorical variable, check of consistency between dates (at least date of birth before all other dates and date of death after all dates), and check and advise on the handling of missing data. All national scientific coordinators will produce a data control report describing the checks performed. All national scientific coordinators will derive the final dataset from the data obtained from the registers by combining the registers according to the study designs. All national scientific coordinators will produce a data control report describing the checks performed of the final dataset, including reasons for modifications and exclusions. In this process, all national coordinators have to agree on the reasons for exclusion (e.g., missing value on crucial variables, chronological errors in the relation between dates, non-legal values of categorical variables, and extreme values of continuous variables). The national scientific coordinators should send the final data set and the data control reports that describe the data and provide suggestions on how to handle missing values and invalid codes to the Danish scientific coordinator. A template for the data control report will be provided by the Danish scientific coordinator and will include the following requirements:

1. Information on known misclassification of each variable (e.g., underreporting, low sensitivity or specificity, categorization with obvious invalid values, etc.).
2. Check for legal values for each categorical variable. Check for reasonable distribution of variables. Include advice on how to handle unexpected observations.
3. Check for reasonable minimum, maximum, and central tendency (median, mean) for each continuous variable. Check for outliers must be performed (e.g., exploratory plots, such as box-whiskers plot). Include advice on how to handle unexpected observations.
4. Check of chronological relation between date variables: At least date of birth before all other dates and date of death after all dates, but also reasonable relation of dates of diagnoses and prescriptions. Unexpected patterns should be described and solutions for handling such observations should be included.
5. Check of missing information on variables and include advice on how to handle such observations (e.g., delete observations with missing information, put missing observations into a specific category, etc.).

- The final datasets from Finland, Norway, and Sweden are transferred to Statistics Denmark where all subsequent data handling is done by the Danish scientific coordinator.

- The Danish scientific coordinator combines data as described by the document developed by all national scientific coordinators and the datasets from all countries will be joined into a combined analysis dataset. Relevant variables will be derived.

The Danish scientific coordinator will assess the data validity of all countries by logical checks, examination of extreme values, and missing data. It is important that identification numbers are maintained to facilitate linkage back to the original datasets to be able to check the data and for the sake of transparency.

9.9 Statistical methods

9.9.1 Main summary measures

Frequency distributions (number, percentage), mean and standard deviation, minimum, median and maximum values, and incidence rates were used as summary measures for descriptive analyses.

9.9.2 Substudy 1: Descriptive analysis of exposure of DL

A cohort study describing DL use in the general population will be performed. A person with prescription redemption of DL in Norway and Sweden within the first 6 months after establishment of the prescriptions registers will not be included in order to avoid left-truncation bias. In addition, to avoid analogous misclassification of prevalent with incident DL dispensings among immigrants, we exclude persons with DL prescription redemptions within 6 months after immigrating to Denmark, Finland, Norway, or Sweden. Prevalent users will be defined as persons who have at least one prescription of DL in the period of interest (e.g., the entire study period or each year). Incident users are first time users of DL in the period of interest. The following descriptive analyses will be performed:

- The distribution of prevalent and incident users in the total population and stratified by country, age, sex, calendar year, seasonality, severity of rhinitis, asthmatic status, and chronic urticaria status.

- Descriptive information on the mean, standard deviation, median, and maximum and minimum number of redeemed DL prescriptions in the total population and stratified by country, age, sex, calendar year, seasonality, severity of rhinitis, asthmatic status, and chronic urticaria status.

9.9.3 Substudy 2: First seizure

Substudy 2A

A cohort study estimating the incidence of first seizures in the general population will be conducted. The cohort of individuals with seizures and the distribution of the population by age, year , and country will be used to derive estimates for the general population. The number of individuals in the general population on 01 January of each year will be obtained from the NORDCAN database and used as an estimate of the number of person years at risk assuming each person in the population on 01 January of each year contributes one person year at risk [Ref. 5.4: 045VPW]. The IRs of seizure will be shown for the total population and stratified by country, sex, and age. The 95% confidence interval for IRs will be calculated as:

$$IR/\exp(1.96/\sqrt{N_{new\ users}}) \text{ to } IR * \exp(1.96/\sqrt{N_{new\ users}})$$

where IR is the incidence rate, exp is the exponential function, and $N_{new\ users}$ is the number of new users [Ref. 5.4: 045VXZ].

Substudy 2B

A cohort study among ever-DL users analyzing the association between exposed and unexposed time and first seizures will be performed for the total population and stratified by age. Current use (i.e., “exposed” period) will be defined for each prescription as days’ supply plus a 4 week grace period to account for intermittent use and a possible wash-out effect. Unexposed time will be defined as the period starting 26 weeks from the dispensing date of the prior DL prescription until the next DL prescription redemption, if any. A person who has redeemed at least one prescription of DL is included in the cohort and enters the cohort at the date of first prescription redemption. Study individuals are followed until occurrence of a seizure; occurrence of one of the conditions described in section 9.4.2; 31 December 2015; emigration; or death, whichever comes first. The association between exposure to DL and first seizure will be evaluated using Poisson regression of the IR of first seizure, and the measure of effect is the IRR. A person with prescription redemption of DL in Norway and Sweden within the first 6 months after establishment of the prescriptions registers will not be included in order to account for truncation bias. In addition we exclude persons with DL prescription redemptions within 6 months after immigrating to Denmark, Finland, Norway, or Sweden. The analyses will be adjusted for confounders identified from the DAG (i.e., country, age, sex, calendar year, seasonality, severity of rhinitis, asthmatic status, and chronic urticaria status)

[Table 4]). We will evaluate whether age can be included as a continuous variable by examining the assumption of linearity. Alternatively, age will be included as a categorical variable.

9.9.4 Substudy 3: SVT

Substudy 3A

A cohort study estimating the incidence of SVT in the general population will be performed. The cohort of DL users, the cohort of individuals with SVT, and the distribution of the population by age, year, and country will be used to derive estimates in the general population. The number of individuals in the general population on 01 January of each year will be obtained from the NORDCAN database and used as an estimate of the number of person years at risk assuming each person in the population on 01 January of each year contributes one person year at risk [Ref. 5.4: 045VPW]. The IRs of SVT will be shown for the total population and stratified by country, sex, and age. The confidence interval of IRs is calculated as outlined above under Substudy 2A.

Substudy 3B

A cohort study among ever-DL users analyzing the association between exposed and unexposed time (as defined in Substudy 2B) and first SVT will be performed for the total population and stratified by age. A person who has redeemed at least one prescription of DL is included in the cohort and enters the cohort at the date of first prescription redemption. Study individuals are followed until occurrence of a SVT; 31 December 2015; emigration; or death, whichever comes first. The association between exposure to DL use and first SVT will be evaluated using Poisson regression of the IR of first SVT, and the measure of effect is the IRR. A person with prescription redemption of DL in Norway and Sweden within the first 6 months after establishment of the prescriptions registers will not be included in order to account for truncation bias. In addition we exclude persons with DL prescription redemptions within 6 months after immigrating to Denmark, Finland, Norway, or Sweden. The analyses will be adjusted for confounders identified from the DAG (i.e., country, age, sex, calendar year, seasonality, severity of rhinitis, asthmatic status, and chronic urticaria status) [Table 4]. We will evaluate whether age can be included as a continuous variable by examining the assumption of linearity. Alternatively, age will be included as a categorical variable.

9.9.5 Substudy 4: Atrial fibrillation/flutter

Substudy 4A

A cohort study estimating the incidence of A-fib/flu in the general population will be performed. The cohort of individuals with A-fib/flu and the distribution of the population by age, year, and country will be used to derive estimates in the general population. The number of individuals in the general population on 01 January of each year will be obtained from the NORDCAN database and used as an estimate of the number of person years at risk assuming each person in the population on 01 January of each year contributes one person year at risk [Ref. 5.4: 045VPW]. The IRs of A-fib/flu will be shown for the total population and for each

country, sex, and age. The confidence interval of IRs is calculated as outlined above under Substudy 2A.

Substudy 4B

A cohort study among ever-DL users analyzing the association between exposed and unexposed time (as defined in Substudy 2B) and first A-fib/flu diagnosis will be performed for the total population and stratified by age. A person who has redeemed at least one prescription of DL is included in the cohort and enters the cohort at the date of first prescription redemption. Study individuals are followed until occurrence of A-fib/flu; 31 December 2015; emigration or death, whichever comes first. The association between exposure to DL use and first A-fib/flu will be evaluated using Poisson regression of the IR of first A-fib/flu, and the measure of effect is the IRR. A person with prescription redemption of DL in Norway and Sweden within the first 6 months after establishment of the prescriptions registers will not be included in order to account for truncation bias. In addition we exclude persons with DL prescription redemptions within 6 months after immigrating to Denmark, Finland, Norway, or Sweden. The analyses will be adjusted for confounders identified from the DAG (i.e., country, age, sex, calendar years, seasonality, severity of rhinitis, asthmatic status, and chronic urticaria status) [Table 4]. We will evaluate whether age can be included as a continuous variable by examining the assumption of linearity. Alternatively, age will be included as a categorical variable.

9.9.6 Missing values

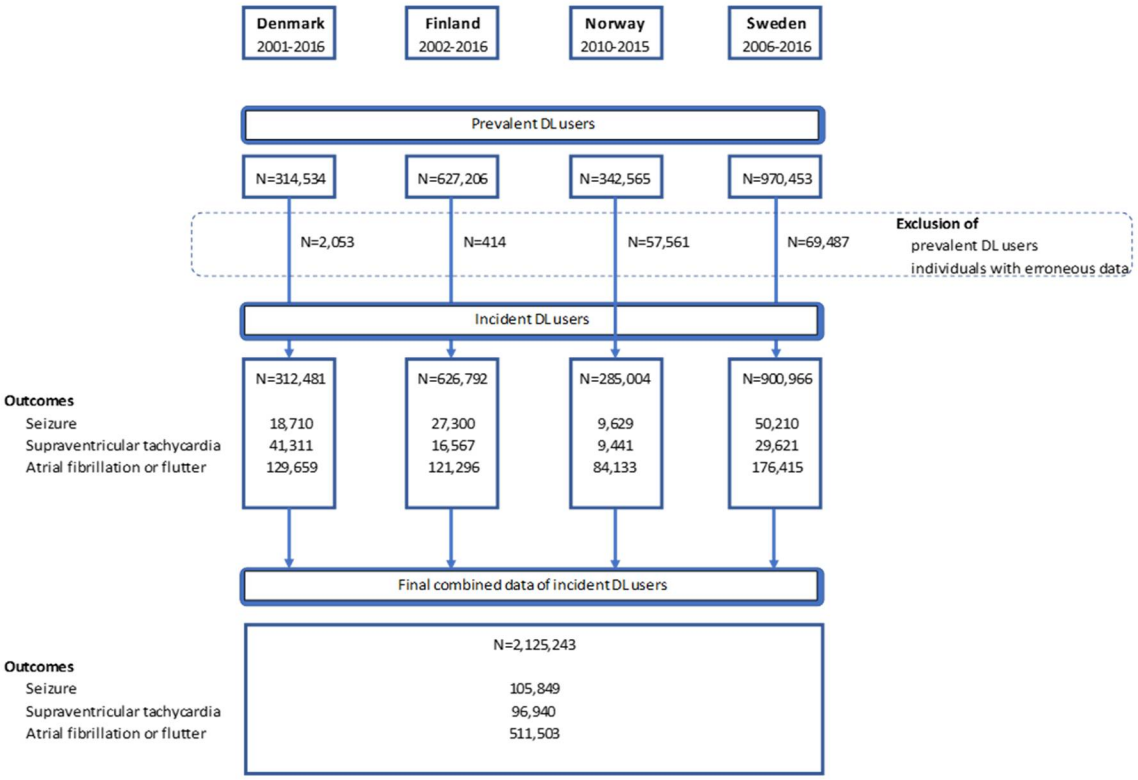
In a register-based study, a missing value in a data set means that a value for an individual is missing because complete information was not entered into the register. Because the current study ascertains only those patient outcomes that present for hospital-based care, it is possible that events that occurred in the community but did not require hospitalization or emergency care would not be captured. Furthermore, although the completeness of the patient registers is high, there is a risk that a hospital contact (encounter) is completely missing if it is not entered into the register. Therefore, there is a theoretical risk of under-ascertainment of study outcomes. However, there is no reason to believe that this under-ascertainment would vary by exposure status.

There are very few observations with missing values identified in the registers, e.g. missing information about strength of the drug.

Similarly, few observations with invalid values were identified, e.g. migration date with the day or month having values “00”.

Observations with missing values or with illegal values were excluded [Figure 2].

Figure 2. Data Flow Diagram



9.9.7 Sensitivity analyses

The following supplementary analyses will be conducted. Unless otherwise specified, supplementary analyses will be performed on the total population (i.e. not stratified by age) and using the primary exposure definition.

- alternative definitions of exposure based on time since last DL dispensing (periods 0-4, 5-8, 9-16, and 17-26 weeks each compared with >26 week since last DL dispensing) for Substudies 2B, 3B, and 4B. Because as-needed medications, such as antihistamines may not be taken daily, this approach reflects the clinical expectation that the probability of actual exposure on a given day is highest shortly after filling a prescription and diminishes with increasing time. Each time a DL prescription is refilled, the time since last dispensing will reset to 0.

- the association analyses in Substudies 2B, 3B, and 4B will be stratified by countries to examine potential differences across countries.

- a supplementary analysis for Substudies 2B, 3B, and 4B will evaluate whether the potential risk of the outcomes is higher following the first ever-DL prescription redemption compared to the second, third prescription redemption etc.

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- a supplementary analysis using an alternative adjustment set to examine the robustness of the study results. This adjustment set consists of age, sex, country, calendar year, seasonality, severity of rhinitis, asthmatic status, diabetes, hypo-/hyperthyroidism, inflammatory disease, infections, type 1 allergy. For the outcomes supraventricular tachycardia and atrial fibrillation or flutter, antihypertensive treatment will also be added.

The following sensitivity analyses were not conducted in the voluntary PASS (4177-205) but were included in the regulatory commitment (4117-203).

- for Substudy 2B, differentiating between febrile and non-febrile seizures for children aged 0–4 years.

- for Substudies 2B, 3B, and 4B, analyses will exclude persons who have been diagnosed with chronic urticaria and/or have redeemed very high doses of DL (dose for chronic urticaria is typically 4 times the standard dose for allergic rhinitis). To operationalize the exclusion of persons with chronic urticaria and/or who redeems high doses of DL, we will exclude person time at risk for a person from the date of a diagnosis of chronic urticaria or date of DL prescription redemption of an amount of pills equal to at least twice the days' supply of DL for the individual's age in the period before next DL prescription redemption.

- additional supplementary analyses, which will be specified in the SAP, will evaluate the potential effect of exposure misclassification in Substudies 2B, 3B, and 4B (i.e. evaluate use of loratadine and other non-sedating prescription antihistamines).

- a supplementary analysis for Substudies 2B, 3B, and 4B for which non-exposed periods start 52 weeks following the last prescription redemption.

- a supplementary analysis restricted to calendar time where misclassification due to over-the counter (OTC) use does not exist.

9.9.8 Post-hoc analyses

A number of post-hoc analyses were performed. Unless otherwise specified, the post-hoc analyses were performed on the total population using the primary exposure definition.

(1) Post-hoc Analysis 1: For Substudy 2, analysis of association between DL exposure and first seizure adjusting for the minimum sufficient confounder set with 5-year age within age category.

(2) Post-hoc Analysis 2: For Substudy 3, analysis of association between DL exposure and first SVT adjusting for the minimum sufficient confounder set with 5-year age within age category.

(3) Post-hoc Analysis 3A: For Substudy 2, number of first seizure cases (alternate seizure definition: febrile, non-febrile or other seizure), risk time and incidence rate across persons currently and not currently exposed to DL with a modified age-group for the youngest age groups to correspond with age after which febrile seizures are not considered febrile.

(4) Post-hoc Analysis 3B: For Substudy 2, analysis of association between DL exposure and first seizure (alternate seizure definition: febrile, non-febrile or other seizure) adjusting for the minimum sufficient confounder set with 5-year age within age category and modified age-group for the youngest age groups to correspond with the age cut off for febrile seizure

(5) Post-hoc Analysis 4: For Substudy 2, analysis of association between DL exposure and first seizure stratified by country adjusting for the minimum sufficient confounder set with 5-year age within age category.

(6) Post-hoc Analysis 5: For Substudy 4, analysis of the association between DL exposure and A-fib/flu overall and when stratified by age category when using an alternative exposure categorization and alternative confounder set.

(7) Post-hoc Analysis 6, analysis to examine the time window for the prevalent disease exclusion criteria of more than two years prior to DL exposure by country for the seizure analysis.

9.9.9 Amendments to the statistical analysis plan

Seizure in the main analyses was defined as non-febrile seizures for Denmark, Finland and Sweden (ICD-10 R56.8). Only the ICD-10 system uses specific codes for febrile and non-febrile seizures. Due to privacy concerns, the Norwegian Health Authority prohibited the release of detailed ICD-10 codes that distinguished between febrile and non-febrile seizures. Instead, the Norwegian Health Authority provided an aggregated general seizure ICD-10 code (R56), which includes all types of seizure (febrile, non-febrile and other seizures; [Annex 2]).

Incident seizures are defined based on data using the ICD-10 system, starting in 1994. As the start of the study period varies by country, the look back period to determine if a seizure is a first seizure differs by country. For Denmark and Finland, where the study period starts in 2001, incident seizure is defined based on having no seizures in the previous six years. For Sweden where the study period starts in 2006 incident seizure is defined based on having no seizures in the previous 11 years. For Norway, where the study period starts in 2010, incident seizure is defined based on having no seizures at minimum during the two previous years to correspond when the patient registry began (2008). For patients who initiated DL later in the study period—after 2010, the look back period would be longer than two years.

For [Table 14], [Table 17], and [Table 20] a person may contribute to more than one age group as they age over time. In this PASS, individuals can contribute to more than one age group. Therefore, the sum of individuals in the four age groups do not add to the total number of individuals.

Statistics Denmark's privacy restrictions mandate suppression of data when there is cell count less than 10. Since the time of submission of the report associated with protocol 4117-203, a new restriction was established. This restriction mandates that total analyses may no longer include sub-groups with cell counts less than 10. This restriction is to prevent back calculation of frequencies for subgroups with small cell counts. Therefore, in this voluntary PASS, the all age group analyses for SVT do not include the 0-4 year old age group and for A-fib/flu the all age group analyses do not include the 0-4 or the 5-19 year age groups. For these outcomes, these exclusions were kept consistent across all analyses, even those not stratified by age, to avoid confusion and allow comparison between main and supplementary analyses. Another consequence of the new Statistics Denmark restriction is that the min and max may no longer be reported in Substudy 1, [Table 9] and [Table 10]. Instead, values for quartiles 1 (q1) and 3 (q3) are reported.

9.10 Quality control

By signing this protocol, all parties agree to following applicable standard operating procedures (SOPs). All parties also agree to ensuring all existing and new study personnel are appropriately trained to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Pharmacoepidemiology Practice (GPP), and all applicable federal, state, and local laws, rules and regulations. All parties should maintain transparency and open communication in order to effectively manage the study and proactively mitigate any risks.

The study is register-based. As a result, data quality is difficult to ascertain directly. However, previous studies have examined the validity and quality of information in the Nordic registers. The Danish National Prescription Registry contains data of high quality, including detailed information on dispensed drugs, and as the register covers all prescription dispensed in Danish pharmacies, loss to follow-up is unlikely for individuals with permanent residence in Denmark [Ref. 5.4: 045TYK]. The completeness of the Norwegian and Swedish prescription registers is characterized as good [Ref. 5.4: 00W4CX] [Ref. 5.4: 046B3C]. Completeness of registration in the Norwegian prescription register is ensured by law and quality checks are carried out monthly to identify possible errors or inconsistencies [Ref. 5.4: 00W4CX]. The patient identity data are only missing for approximately 0.3% of all items in the Swedish prescription register [Ref. 5.4: 046B3C]. The Finnish prescription register has been described in detail and considered as excellent [Ref. 5.4: 0469YG]. Data quality in the Danish National Patient Register is overall assumed to be of high quality; however validity of data depends on the diagnosis under consideration; the positive predictive values for diagnoses similar to those in this study are >90% [Ref. 5.4: 04C0C2]. The Norwegian Patient Register has relatively good agreement with the Norwegian Cancer Register [Ref. 5.4: 0469WT] and the completeness and accuracy of the Finnish Patient Register has been evaluated as varying from satisfactory to very good for common diagnoses with positive predictive values ranging from 75%– 99% [Ref. 5.4: 046B36]. The validity of the Swedish Patient Register is high for many, but not all diagnoses. The positive predictive values of most diagnoses in the Swedish Patient Register compared to medical records ranges from 85–95% [Ref. 5.4: 03RSH6].

The statistical analyses will be performed on servers at Statistics Denmark. The programming will be performed by two researchers independently, limiting programming errors. The statistical programs will be stored on the servers at Statistics Denmark.

The Sponsor may conduct routine or for-cause audits to ensure oversight and conduct of the study are completed in accordance with the protocol, quality standards (e.g. GPP), and applicable laws and regulations. If a significant quality issue (SQI) is identified at any time during the conduct of the study, it must be escalated to the Sponsor immediately. A SQI is any issue with the potential to negatively impact, either directly or indirectly, the rights, safety and well-being of patients or study participants and/or the integrity of the data. In the event an audit or SQI results in corrective or preventive actions, all parties are expected to appropriately implement the action plan in a timely manner.

10 RESULTS

In the results section, the terms “currently DL exposed periods” and “currently DL unexposed periods” have been described as “exposed follow-up time” and “unexposed follow-up time.”

In the results and discussion, the term “association” is used to describe relationships between DL and the study outcome that are statistically significant at the 0.05 level. An effect of similar magnitude, but that is not statistically significant will not be described as “associated”.

Furthermore, person-years have been abbreviated to PY. Incidence rates (IRs) are expressed per 100,000 PY unless otherwise specified.

Prevalent users refer to individuals who have ever had a DL prescription redemption during the study period. The prevalent proportion is defined as the number of prevalent users divided by the population of the country at the midpoint of the year.

10.1 Participants

The flow diagram [Figure 2] shows the selection of subjects in the study. In Substudy 1, individuals redeeming at least one prescription of DL during the study period in Denmark (2001–2015), Finland (2001–2015), Norway (2010-2015) and Sweden (2006–2015) were included, resulting in a total population of 1,912,193 prevalent DL users (Denmark, n=314,534; Finland, n=627,206; Norway, n=342,565; Sweden, n=970,453). From these individuals, patients having erroneous details in the migration registers (e.g., two consecutive immigrations or emigrations, last migration event before redemption of desloratadine being emigration), patients redeeming DL within 6 months of the first immigration event, and (in the case of Sweden or Norway) patients redeeming DL within 6 months of the establishment of the prescription registers were excluded. This resulted in a population of 1,840,239 new users of DL (Denmark, n=312,481; Finland, n=626,792; Norway, n=285,004; Sweden, n=900,966).

10.1.1 Protection of Human Subjects

This is an observational study with no administration of any therapeutic or prophylactic agent. Subjects observed in this study will continue with the normal standard of care as provided by their personal physician. Pre-existing national register data will be the sole data source.

According to Danish, Finnish, Norwegian, and Swedish law, register-based studies can be carried out without consent from the data subjects where the processing takes place for the sole purpose of carrying out statistical or scientific studies of significant public importance and where such processing is necessary in order to carry out these studies. It is an absolute requirement that the publication of statistical or scientific results may never reveal the identity of individuals or otherwise compromise data subjects. We will obtain approval by the data agencies in the four countries before data management and data analyses will be performed.

10.2 Descriptive data

Descriptive analysis of the DL users (incident and prevalent) are described below. For results that had comparable analyses completed as part of 4117-203, the table number is provided in parentheses within the table title of this report. The IR per 100,000 PY, 95% CI of DL users in the general population of the four Nordic countries across 2001 and 2015 was 754.8 (95% CI 753.8; 755.8, [Table 9]). The IRs per 100,000 PY of DL use in the Finnish (839.7), Norwegian (942.1), and Swedish (956.6) populations were more than double that of the Danish (378.8) population. In all four Nordic countries combined, IRs decreased with increasing age. Additionally, IRs per 100,000 PY were slightly higher among females (768.4) than males (740.9) while being considerably higher in spring (1,229.9) and summer (913.0) than in autumn (456.9) and winter (419.3). The IR of DL use, in general, was higher in the later study years, when there were more countries contributing data. The IR per 100,000 PY of DL users in patients having asthma, severe rhinitis, and chronic urticaria was 108.6 (95% CI 108.2; 109.0), 4.1 (95% CI 4.0; 4.2), and 16.0 (95% CI 15.9; 16.2), respectively, [Table 9]. Notably, while the study period started in 2001 for Finland, there was no DL use until 2002.

Table 9. Incidence rates and prevalence proportions of desloratadine (DL) users in the general population between 2001 and 2015 for the total population and stratified by age groups, country, sex, calendar year, seasonality, asthmatic status, severity of rhinitis and chronic urticaria status[$] (Table 1.1)

Number of		Incidence					Prevalence				
		Number of incident users	Person-years at risk*	IR (n/100,000 person-years)**	95 % CI		Number of prevalent users	General population*	PP (n/100,000 persons)	95 % CI	
Total population		2,125,243	281,574,184	754.8	753.8	755.8	2,254,758	289,688,872	778.3	777.3	779.4
Age groups	0–4 years	331,380	16,324,463	2,030.0	2,023.1	2.036.9	336,193	16,777,311	2,003.9	1.997.1	2.010.6
	5–19 years	463,576	50,065,807	925.9	923.3	928.6	556,696	51,734,140	1,076.1	1.073.3	1.078.9
	20–64 years	1,125,425	166,733,203	675.0	673.7	676.2	1,255,397	171,726,897	731.0	729.8	732.3
	65+ years	204,862	48,450,711	422.8	421.0	424.7	252,542	49,450,524	510.7	508.7	512.7
Country	Denmark	312,481	82,498,274	378.8	377.5	380.1	314,534	82,313,321	382.1	380.8	383.5
	Finland	626,792	74,640,876	839.7	837.7	841.8	627,206	74,495,114	841.9	839.9	844.0
	Norway	285,004	30,251,502	942.1	938.7	945.6	342,565	30,069,189	1,139.3	1.135.5	1.143.1
	Sweden	900,966	94,183,532	956.6	954.6	958.6	970,453	102,811,249	943.9	942.0	945.8
Sex	Males	1,034,117	139,570,946	740.9	739.5	742.4	1,089,065	143,541,985	758.7	757.3	760.1
	Females	1,091,126	142,003,238	768.4	766.9	769.8	1,165,713	146,146,887	797.6	796.2	799.1
Calendar year	2001	7,277	5,355,081	135.9	132.8	139.1	7,306	5,346,213	136.7	133.6	139.8
	2002	23,119	10,574,862	218.6	215.8	221.5	25,461	10,558,979	241.1	238.2	244.1
	2003	56,120	10,600,195	529.4	525.1	533.8	63,942	10,587,529	603.9	599.3	608.6
	2004	53,901	10,629,356	507.1	502.8	511,4	76,113	10,614,776	717.1	712.0	722.2
	2005	67,084	10,662,82	629.2	624.4	634.0	163,079	19,657,280	829.6	825.6	833.7
	2006	180,625	19,781,356	913.1	908.9	917.3	264,013	19,736,511	1,337.7	1.332.6	1.342.8
	2007	146,180	19,904,899	734.4	730.6	738.2	278,995	19,843,128	1,406.0	1.400.8	1.411.2
	2008	144,639	20,022,080	722.4	718.7	726.1	300,322	19,963,490	1,504.4	1.499.0	1.509.8
	2009	149,661	20,156,844	742.5	738.7	746.3	323,970	20,089,462	1,612.6	1.607.1	1.618.2
	2010	169,688	25,171,194	674.1	670.9	677.4	394,947	25,076,659	1,575.0	1,570.1	1,579.9
	2011	162,718	25,354,122	641.8	638.7	644.9	407,688	25,262,658	1,613.8	1,608.9	1,618.8
	2012	185,192	25,535,628	725.2	721.9	728.5	430,753	25,444,875	1,692.9	1,687.8	1,698.0
	2013	211,739	25,723,060	823.2	819.7	826.7	507,182	25,629,344	1,978.9	1,973.5	1,984.4
	2014	298,638	25,929,457	1,151.7	1,147.6	1,155.9	671,038	25,826,259	2,598.3	2,592.1	2,604.5

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	2015	268,662	26,173,968	1,026.5	1,022.6	1,030.3	686,654	26,051,713	2,635.7	2,629.5	2,642.0
Seasonality	Winter	295,163	70,393,546	419.3	417.8	420.8	634,463	72,422,218	876.1	873.9	878.2
	Spring	865,752	70,393,546	1,229.9	1,227.3	1,232.5	1,263,041	72,422,218	1,744.0	1,741.0	1,747.0
	Summer	642,709	70,393,546	913.0	910.8	915.3	1,149,726	72,422,218	1,587.5	1,584.6	1,590.4
	Autumn	321,619	70,393,546	456.9	455.3	458.5	691,251	72,422,218	954.5	952.2	956.7
Asthma		305,745	281,574,184	108.6	108.2	109.0	---	---	---	---	---
Severe rhinitis		11,561	281,574,184	4.1	4.0	4.2	---	---	---	---	---
Chronic urticaria		45,108	281,574,184	16.0	15.9	16.2	---	---	---	---	---

IR=incidence rate; PP=prevalence proportion; CI=confidence interval
$ For a complete list of codes, please see Annex 6 of the protocol
* Person-years at risk of DL prescription redemption are estimated by use of the population size on July 1 in each country, for each year in 5-year age groups obtained from the NORDCAN database
# General population size is estimated by use of the population size on January 1 in each country each year in 5-year age groups obtained from the NORDCAN database
**Incidence rates and prevalence proportions are based on different time periods corresponding with when each country started contributing data

The mean defined daily dose (DDD) of DL in the incident DL population was 212.29 (SD=406.19) [Table 10]. The distribution of DDD was very skewed with a median DDD at 90 and interquartile range (quartile 1-quartile 3) ranging from 30 to 200 DDD. Mean DDD was similar in males (210.42) and females (214.06), higher in Norway (241.29) and Sweden (229.73) compared to Denmark (182.74) and Finland (188.77) and increased with increasing age as well as time (calendar year). A higher mean DDD of DL was observed in spring (147.61) and summer (129.98) compared to autumn (120.69) and winter (118.37). As expected from a clinical perspective, the mean DDD of DL used in patients with asthma, severe rhinitis, and chronic urticaria was higher than that in patients without these conditions.

Table 10. Distribution of number of DDD of desloratadine (DL) in the total population and stratified by age, sex, country, calendar year, seasonality, asthmatic status, severity of rhinitis and chronic urticaria status among DL users[$] (Table 1.2)

		Per DL user			
		Mean*	SD	Median	Q_1; Q_3
Total DL population	DDD of DL	212.29	406.19	90.00	30; 200
Age groups	0–4 years	81.69	100.76	48.00	48; 96
	5–19 years	189.28	315.39	90.00	30; 200
	20–64 years	231.98	427.63	100.00	30; 210
	65+ years	233.70	459.09	90.00	30; 200
Country	Denmark	182.74	492.96	48.00	30; 110
	Finland	188.77	363.63	60.00	30; 180
	Norway	241.29	317.88	100.00	60; 300
	Sweden	229.73	423.90	100.00	30; 200
Sex	Males	210.42	393.88	90.00	30; 200
	Females	214.06	417.50	90.00	30; 200
Calendar years	2001	44.13	55.45	30.00	10; 40
	2002	51.35	75.70	30.00	10; 60
	2003	65.02	80.55	30.00	30; 90
	2004	74.27	87.17	30.00	30; 90
	2005	77.34	88.34	40.00	30; 90
	2006	82.88	85.28	60.00	30; 100
	2007	90.67	93.54	60.00	30; 100
	2008	94.89	99.32	60.00	30; 100
	2009	103.13	105.22	72.00	30; 100
	2010	103.00	104.84	90.00	30; 100
	2011	107.11	107.80	90.00	30; 120
	2012	113.39	110.64	100.00	48; 120
	2013	123.77	118.79	100.00	48; 150
	2014	126.24	119.11	100.00	48; 180
	2015	135.32	126.29	100.00	48; 200
Seasonality	Winter	118.37	152.75	90.00	30; 110
	Spring	147.61	178.17	100.00	30; 200
	Summer	129.98	160.88	90.00	30; 150
	Autumn	120.69	159.06	90.00	30; 112
Asthmatic status	No registration	195.66	381.96	80.00	30; 200
	Asthma	311.26	516.90	100.00	48; 330
Severity of rhinitis	No registration	211.28	404.72	90.00	30; 200
	Sever rhinitis	396.98	590.31	200.00	90; 490

		Per DL user			
		Mean*	SD	Median	Q_1; Q_3
Chronic urticaria	No registration	210.64	401.62	90.00	30; 200
	Chronic urticaria	288.34	573.87	100.00	48; 260

SD=Standard deviation Q_1; Q_3: Interquartile range
*Incidence rates and prevalence proportions are based on different time periods corresponding with when each country started contributing data
$ For a complete list of codes, please see Annex 6 in protocol

10.3 Outcome data

In Substudy 2A, the outcome of first seizure within the study period was detected in 105,849 individuals from the general population in Denmark, Finland, Norway and Sweden, with an IR per 100,000 PY of 37.6, 95% CI 37.4; 37.8 [Table 11]. IR of first seizure was also stratified by country, sex, and age. The IR was highest in Sweden (n=50,210; IR 53.3, 95% CI 52.8; 53.8) followed by Finland (n=27,300; IR 36.6, 95% CI 36.1; 37.0), Norway (n=9,629; IR 31.8, 95% 31.2; 32.5) and Denmark (n=18,710; IR 22.7, 95% CI 22.4; 23.0). The IR was higher in males (39.5, 95% CI 39.2; 39.9) than females (35.7, 95% CI 35.4; 36.0). The highest IR of first seizure in the general population was observed in the 0–4 years age group (130.6, 95% CI 128.9; 132.4).

Table 11. Number of persons with a first time diagnoses of seizures, risk time and incidence rate of seizures overall and stratified by age groups, country and sex[$] (Table 2A)

Variable	Level	First ever seizure				
		N	Risk time (person-years) #	IR (per 100,000 person-years)	95% CI	
Overall		105,849	281,574,184	37.6	37.4	37.8
Age groups	0–4	21,326	16,324,463	130.6	128.9	132.4
	5–19	18,420	50,065,807	36.8	36.3	37.3
	20–64	45,401	166,733,203	27.2	27.0	27.5
	≥65	20,702	48,450,711	42.7	42.1	43.3
Country	Denmark	18,710	82,498,274	22.7	22.4	23.0
	Finland	27,300	74,640,876	36.6	36.1	37.0
	Norway*	9,629	30,251,502	31.8	31.2	32.5
	Sweden	50,210	94,183,532	53.3	52.8	53.8
Sex	Males	55,191	139,570,946	39.5	39.2	39.9
	Females	50,658	142,003,238	35.7	35.4	36.0

IR=incidence rate; CI=confidence interval
$ For a complete list of codes, please see Annex 6 of the protocol
# Risk time is estimated by use of the population size on July 1 in each country, for each year in 5-year age groups obtained from the NORDCAN database
*Data for seizures provided from Norway is ICD-10 R56 including all types of seizure and from Denmark, Finland and Sweden is ICD-10 R568 non-febrile seizure

In Substudy 3A, the incidence of first SVT was observed in 96,940 individuals from the general population, with an IR per 100,000 PY of 34.4, 95% CI 34.2; 34.6 [Table 12]. [Table 12] also shows the IRs of first SVT when stratified by country, sex, and age. The IR per 100,000 PY was the highest in Denmark (n=41,311; IR 50.1, 95% CI 49.6; 50.6) followed by Sweden (n=29,621; IR 31.5, 95% CI 31.1; 31.8), Norway (n=9,441; IR=31.2, 95% CI 30.6; 31.8) and Finland (n=16,567; IR 22.2, 95% CI 21.9; 22.5). The IR was similar in males (35.2, 95% CI

34.9; 35.5) and females (33.6, 95% CI 33.3; 33.9). The IR per 100,000 PY of first SVT increased with increasing age and was the highest in the ≥65 year age group (80.7, 95% CI 79.9; 81.5).

Table 12. Number of persons diagnosed with supraventricular tachycardia (SVT), risk time and incidence rate of supraventricular tachycardia overall and stratified by age groups, country and sex[$] (Table 3A)

Variable	Level	First ever SVT				
		N	Risk time (person-years) #	IR (per 100,000 person-years)	95% CI	
Overall		96,940	281,574,184	34.4	34.2	34.6
Age groups	0–4	1,000	16,324,463	6.1	5.8	6.5
	5–19	4,478	50,065,807	8.9	8.7	9.2
	20–64	52,344	166,733,203	31.4	31.1	31.7
	≥65	39,118	48,450,711	80.7	79.9	81.5
Country	Denmark	41,311	82,498,274	50.1	49.6	50.6
	Finland	16,567	74,640,876	22.2	21.9	22.5
	Norway	9,441	30,251,502	31.2	30.6	31.8
	Sweden	29,621	94,183,532	31.5	31.1	31.8
Sex	Males	49,166	139,570,946	35.2	34.9	35.5
	Females	47,774	142,003,238	33.6	33.3	33.9

IR=incidence rate; CI=confidence interval
$ For a complete list of codes, please see Annex 6 of the protocol
# Risk time is estimated by use of the population size on July 1 in each country, for each year in 5-year age groups obtained from the NORDCAN database

In Substudy 4A, the incidence of first A-fib/flu occurred in 511,503 individuals from the general population, with an IR per 100,000 PY of 181.7, 95% CI 181.2; 182.2 [Table 13]. The IR was the highest in Norway (278.1, 95% CI 276.2; 280.0), as compared with Sweden (187.3, 95% CI 186.4; 188.2), Denmark (157.2, 95% CI 156.3; 158.0) and Finland (162.5, 95% CI 161.6; 163.4). Among the incident A-fib/flu cases (n=511,503), 53.3% occurred in males and 46.7% in females. As clinically expected, the IR was higher in males (195.4, 95% CI 194.6; 196.1) than females (168.2, 95% CI 167.5; 168.9), and increased with increasing age. The IR of first A-fib/flu was markedly higher in the oldest (≥65 years) age group (774.7, 95% CI 772.2; 777.2) compared to the younger ones. The IR of first A-fib/flu was lower in the 20–64 years age group (81.2, 95% CI 80.8; 81.7) and considerably lower in the 0–4 years (0.6, 95% CI 0.5; 0.7) and 5–19 years (1.2, 95% CI 1.1; 1.3) age groups.

Table 13. Number of persons diagnosed with atrial fibrillation or flutter (A-fib/flu), risk time and incidence rate of atrial fibrillation of flutters overall and stratified by age groups, country and sex[$] (Table 4A)

Variable	Level	First ever A-fib/flu				
		N	Risk time (person-years) #	IR (per 100,000 person-years)	95% CI	
Overall		511,503	281,574,184	181.7	181.2	182.2
Age groups	0–4	95	16,324,463	0.6	0.5	0.7
	5–19	597	50,065,807	1.2	1.1	1.3
	20–64	135,462	166,733,203	81.2	80.8	81.7
	≥65	375,349	48,450,711	774.7	772.2	777.2
Country	Denmark	129,659	82,498,274	157.2	156.3	158.0
	Finland	121,296	74,640,876	162.5	161.6	163.4
	Norway	84,133	30,251,502	278.1	276.2	280.0
	Sweden	176,415	94,183,532	187.3	186.4	188.2
Sex	Males	272,672	139,570,946	195.4	194.6	196.1
	Females	238,831	142,003,238	168.2	167.5	168.9

IR=incidence rate; CI=confidence interval
# Risk time is estimated by use of the population size on July 1 in each country, for each year in 5-year age groups obtained from the NORDCAN database
$ For a complete list of codes, please see Annex 6 of the protocol

10.4 Main results

The main results of Substudy 2B were that the IR of first seizure per 100,000 PY during exposed follow-up time (i.e., among those currently exposed to DL, 38.8 95% CI 35.4; 42.6) was higher than during unexposed follow-up time (i.e., among those currently not exposed to DL, 29.5, 95% CI 28.2; 30.8 [Table 14]). When analyzed within specific age categories, the IR was higher during exposed follow-up time as compared to during unexposed follow-up time in all the age categories except the 20–64 years age group, where the IRs were similar. The IR of first seizure was the highest among those in the 0–4 years age group comparing DL exposed (141.1, 95% CI 119.4; 166.8) with DL unexposed (79.3, 95% CI 70.8; 88.8).

Table 14. Number of first seizure cases, risk time and incidence rate across persons currently and not currently exposed to desloratadine (DL)[$] (Table 2B1)

Age groups	Exposure status	Level	Persons included (N)#	First seizures* (N)	Risk time**	IR	95% CI
All	Currently DL exposed	Yes	1,812,320	454	1,168,897	38.8	35.4; 42.6
	Not currently DL exposed	No		1,961	6,651,608	29.5	28.2; 30.8
0–4 years	Currently DL exposed	Yes	320,900	137	97,086	141.1	119.4; 166.8
	Not currently DL exposed	No		301	379,495	79.3	70.8; 88.8
5–19 years	Currently DL exposed	Yes	643,176	152	298,713	50.9	43.4; 59.7
	Not currently DL exposed	No		704	1,860,915	37.8	35.1; 40.7
20–64 years	Currently DL exposed	Yes	1,057,843	124	669,330	18.5	15.5; 22.1
	Not currently DL exposed	No		732	3,783,679	19.4	18.0; 20.8
≥65 years	Currently DL exposed	Yes	207,191	41	103,768	39.5	29.1; 53.7
	Not currently DL exposed	No		224	627,520	35.7	31.3; 40.7

IR=incidence rate; CI=confidence interval
$ For a complete list of codes, please see Annex 6 of the protocol
# Age groups N will not sum to total as individuals can contribute to more than one age group.
*Data for seizures provided from Norway is ICD-10 R56 including all types of seizure and from Denmark, Finland and Sweden, is ICD-10 R568 non-febrile
** Risk-time may not sum to total due to rounding

Crude analyses of the association between DL exposure and first seizure indicated that periods of exposed follow-up time were associated with higher incidence of first seizures when compared with periods of unexposed follow-up time (IRR 1.32, 95% CI 1.19; 1.46 [Table 15]). A pre-study exercise using DAGs indicated that age, sex country, calendar year, seasonality, asthmatic status, severe rhinitis, and chronic urticaria status in the fully adjusted models. The adjusted incidence rate ratio (aIRR) of first seizure when comparing exposed and unexposed follow-up time remained greater than 1 in the fully adjusted models, albeit with some attenuation of the estimates (aIRR 1.20, 95% CI 1.08; 1.33). Thus, in the fully adjusted model, a 20% higher IR of first seizure was observed during exposed follow-up time than during unexposed follow-up time. Further adjustment for 5 year age within age categories did not have a meaningful impact on these results (See Post-hoc Analysis 1 [Table 16]).

Table 15. Analysis of association between desloratadine (DL) exposure and first seizure[a**$] (Table 2B2)

Age groups	Exposure status	Level	Crude model			Fully adjusted model*		
			IRR	95% CI	p-value	aIRR*	95% CI	p-value
All	Currently DL exposed	Yes	1.32	1.19; 1.46	<0.001	1.20	1.08; 1.33	0.001
	Not currently DL exposed	No	1	Ref		1	Ref	
0–4 years	Currently DL exposed	Yes	1.78	1.45; 2.18	<0.001	1.65	1.34; 2.03	<0.001
	Not currently DL exposed	No	1	Ref		1	Ref	
5–19 years	Currently DL exposed	Yes	1.35	1.13; 1.60	0.001	1.34	1.12; 1.61	0.002
	Not currently DL exposed	No	1	Ref		1	Ref	
20–64 years	Currently DL exposed	Yes	0.96	0.79; 1.16	0.65	0.92	0.76; 1.12	0.43
	Not currently DL exposed	No	1	Ref		1	Ref	
≥65 years	Currently DL exposed	Yes	1.11	0.79; 1.54	0.55	1.14	0.81; 1.61	0.44
	Not currently DL exposed	No	1	Ref		1	Ref	

IRR= Incidence rate ratio; aIRR= adjusted Incidence rate ratio; CI=confidence interval
$ For a complete list of codes, please see Annex 6 of the protocol
a Years 2001–2004 are combined due to too few observations to obtain convergence
*Adjusted for confounders in the minimum sufficient adjustment set: age (0-4, 5-9, 10-14, …, 70-74, 75-79, 80+), country, sex, calendar year, seasonality, asthmatic status, severe rhinitis, chronic urticaria status. Due to too few individuals with severe rhinitis, no adjustment was performed in the analyses stratified by age group. Analysis adjusted for age categorized into 5-year age categories
**Data for seizures provided from Norway is ICD-10 R56 including both febrile and non-febrile seizure <5 years of age; Seizure includes non-febrile seizure for Denmark, Finland and Sweden for ages <5 years of age. For comparison with submitted PASS report (protocol P203), this table uses the 0-4 age breakdown of the original report. The age <6 age category is shown in post-hoc

Table 16. Post-hoc Analysis 1- Analysis of association between desloratadine (DL) exposure and first seizure with adjustment for 5 year age within age categories[a]

Age groups	Exposure status	Level	Fully adjusted model*		
			aIRR*	95% CI	p-value
All	Currently DL exposed	Yes	1.21	1.09; 1.35	<0.001
	Not currently DL exposed	No	1	Ref	
0–4 years	Currently DL exposed	Yes	1.65	1.34; 2.03	<0.001
	Not currently DL exposed	No	1	Ref	
5–19 years	Currently DL exposed	Yes	1.34	1.12; 1.61	0.002
	Not currently DL exposed	No	1	Ref	
20–64 years	Currently DL exposed	Yes	0.95	0.78; 1.16	0.60
	Not currently DL exposed	No	1	Ref	
≥65 years	Currently DL exposed	Yes	1.17	0.84; 1.65	0.37
	Not currently DL exposed	No	1	Ref	

aIRR=adjusted incidence rate ratio; CI=confidence interval
$ For a complete list of codes, please see Annex 6 of the protocol
a Years 2001–2004 are combined due to too few observations to obtain convergence
*Adjusted for confounders in the minimum sufficient adjustment set: age (0-4, 5-9, 10-14, …, 70-74, 75-79, 80+), country, sex, calendar year, seasonality, asthmatic status, severe rhinitis, chronic urticaria status. Due to too few individuals with severe rhinitis, no adjustment was performed in the analyses stratified by age group. Analysis adjusted for age categorized into 5-year age categories
**Data for seizures provided from Norway is ICD-10 R56 including both febrile and non-febrile seizure <5 years of age; Seizure includes non-febrile seizure (ICD-10 R56.8) for Denmark, Finland and Sweden for ages <5 years of age.

The overall association between first seizure and DL exposure is driven by the association in the age groups of 0–4 years (aIRR 1.65, 95% CI 1.34; 2.03) and 5–19 years (aIRR 1.34, 95% CI 1.12;1.61), as there was no association between exposure status and first seizure in the older age categories (20–64 and ≥65 years).

The main results of Substudy 3B indicate that there was no association between exposure status and the IRs of first SVT per 100,000 PY (exposed follow-up time: 31.2, 95% CI 28.3; 34.3/ unexposed follow-up time: 32.5, 95% CI 31.2; 34.3 [Table 17]). Although the IR of first SVT increased with age within age groups, the IR of first SVT between exposed and unexposed periods was similar in the age-stratified analyses. The IR per 100,000 PY of first SVT was higher in the oldest (≥65 years) age group (exposed follow-up time: 72.4, 95% CI 60.4; 86.7/ unexposed follow-up time: 81.9, 95% CI 76.5; 87.7).

Table 17. Number of supraventricular tachycardia (SVT) cases, risk time and incidence rate across persons currently and not currently exposed to desloratadine (DL)$ (Table 3B1)

Age groups	Exposure status	Level	Persons included (N)*	SVT (N)	Risk time	IR	95% CI
All	Currently DL exposed	Yes	2,006,378	416	1,334,015	31.2	28.3; 34.3
	Not currently DL exposed	No		2,551	7,859,827	32.5	31.2; 34.3
0–4 years #	Currently DL exposed	Yes	0	≤10	-	-	-
	Not currently DL exposed	No		≤10	-	-	-
5–19 years	Currently DL exposed	Yes	683,051	30	321,414	9.3	6.5; 13.4
	Not currently DL exposed	No		200	2,004,191	10.0	8.7; 11.5
20–64 years	Currently DL exposed	Yes	1,275,078	269	850,888	31.6	28.1; 35.6
	Not currently DL exposed	No		1,521	4,842,333	31.4	29.9; 33.0
≥65 years	Currently DL exposed	Yes	305,802	117	161,713	72.4	60.4; 86.7
	Not currently DL exposed	No		830	1,013,303	81.9	76.5; 87.7

IR=incidence rate; CI=confidence interval
# Too few observations to perform the analysis, and not included in all age groups
$ For a complete list of codes, please see Annex 6 of the protocol
*Age groups N will not sum to total as individuals can contribute to more than one age group.

Crude and fully adjusted analyses indicate no association between DL exposure status and IR of first SVT [Table 18].There were too few observations to perform sub-group analyses for the 0–4 years age group and due to Statistics Denmark privacy restrictions this age group was not included in the overall model. Adjustment for age (5-19, 20–64 and ≥65 years), sex, country, seasonality and calendar year, as well as further adjustment for the remaining confounders (asthma, rhinitis, chronic urticaria) had only a minor effect on the effect estimates. Further adjustment for 5 year age within age category did not have a meaningful impact on these results (See Post-hoc Analysis 2 [Table 19]).

Table 18. Analysis of association between desloratadine (DL) exposure and first supraventricular tachycardia (SVT)[a$] (Table 3B2)

Age groups	Exposure status	Level	Crude model			Fully adjusted model*		
			IRR	95% CI	p-value	aIRR*	95% CI	p-value
All	Currently DL exposed	Yes	0.96	0.87; 1.07	0.45	1.01	0.91; 1.13	0.80
	Not currently DL exposed	No	1	Ref		1	Ref	
0–4 years #	Currently DL exposed	Yes	-	-	-	-	-	-
	Not currently DL exposed	No	1	Ref		1	Ref	
5–19 years	Currently DL exposed	Yes	0.94	0.64; 1.37	0.73	1.03	0.69; 1.54	0.88
	Not currently DL exposed	No	1	Ref		1	Ref	
20–64 years	Currently DL exposed	Yes	1.01	0.88; 1.15	0.92	1.06	0.93; 1.21	0.41
	Not currently DL exposed	No	1	Ref		1	Ref	
≥65 years	Currently DL exposed	Yes	0.88	0.73; 1.07	0.20	0.92	0.75; 1.12	0.40
	Not currently DL exposed	No	1	Ref		1	Ref	

IRR= Incidence rate ratio; aIRR= Adjusted incidence rate ratio; CI=confidence interval
a Years 2001–2004 are combined due to too few observations to obtain convergence
*Adjusted for confounders in the minimum sufficient adjustment set: age, country, sex, calendar year, seasonality, asthmatic status, severe rhinitis, chronic urticaria status. Due to too few individuals with severe rhinitis, no adjustment was performed in the analyses stratified by age group. Analysis adjusted for age categorized into 5-year age categories
#0-4 year age group not included due to privacy restrictions
Too few observations to perform the analysis, Age group not included in all group analysis due Statistics Denmark privacy restrictions
$ For a complete list of codes, please see Annex 6 of the protocol

Table 19. Post-hoc Analysis 2- Analysis of association between desloratadine (DL) exposure and first SVT with adjustment for 5 year age within age categories[a, $, #]

Age groups	Exposure status	Level	Fully adjusted model*		
			aIRR*	95% CI	p-value
All	Currently DL exposed	Yes	0.98	0.88; 1.09	0.69
	Not currently DL exposed	No	1	Ref	
0–4 years	Currently DL exposed	Yes	-	-	-
	Not currently DL exposed	No	1	Ref	
5–19 years	Currently DL exposed	Yes	1.00	0.68; 1.50	0.98
	Not currently DL exposed	No	1	Ref	
20–64 years	Currently DL exposed	Yes	1.00	0.87; 1.14	0.98
	Not currently DL exposed	No	1	Ref	
≥65 years	Currently DL exposed	Yes	0.93	0.76; 1.13	0.45
	Not currently DL exposed	No	1	Ref	

aIRR= adjusted incidence rate ratio; CI=confidence interval
$ For a complete list of codes, please see Annex 6 of the protocol
a Years 2001–2004 are combined due to too few observations to obtain convergence
*Adjusted for confounders in the minimum sufficient adjustment set: age (5-9, 10-14, …, 70-74, 75-79, 80+), country, sex, calendar year, seasonality, asthmatic status, severe rhinitis, chronic urticaria status. Due to too few individuals with severe rhinitis, no adjustment was performed in the analyses stratified by age group. Analysis adjusted for age categorized into 5-year age categories
#0-4 year age group not included due to privacy restrictions

The main results of Substudy 4B were that the IR of first A-fib/flu per 100,000 PY during exposed follow-up time (192.3, 95% CI 183.9; 201.1) was higher than during unexposed follow-up time (187.4, 95% CI 183.9, 191.0 [Table 20]).

Table 20. Number of atrial fibrillation or flutter (A-fib/flu) cases, risk time and incidence rate across persons currently and not currently exposed to desloratadine (DL)[$] (Table 4B1)

Age groups	Exposure status	Level	Persons included (N)*	A-fib/flu (N)	Risk time	IR	95% CI
All	Currently DL exposed	Yes	1,464,900	1,929	1,002,932	192.3	183.9; 201.1
	Not currently DL exposed	No		10,859	5,794,115	187.4	183.9; 191.0
0–4 years #	Currently DL exposed	Yes	0	≤10	-	-	-
	Not currently DL exposed	No		≤10	-	-	-
5–19 years #	Currently DL exposed	Yes	0	≤10	-	-	-
	Not currently DL exposed	No		≤10	-	-	-
20–64 years	Currently DL exposed	Yes	1,273,364	674	849,358	79.4	73.6; 85.6
	Not currently DL exposed	No		3,454	4,834,099	71.5	69.1; 73.9
≥65 years	Currently DL exposed	Yes	292,970	1,255	153,574	817.2	773.2; 863.7
	Not currently DL exposed	No		7,405	960,016	771.3	754.0; 789.1

IR=incidence rate; CI=confidence interval
# Too few observations to perform the analysis, and not included in the all age groups total
$ For a complete list of codes, please see Annex 6 of the protocol
*Age groups N will not sum to total as individuals can contribute to more than one age group.

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In fully adjusted analyses, an association between exposure status and first A-fib/flu was observed (aIRR 1.08, 95% CI 1.03, 1.14, [Table 21]). In the age-stratified analysis, fewer than 10 cases of incident first A-fib/flu were observed during exposed or unexposed follow-up time in the 0–4 and 5–19 years age categories. Due to privacy restrictions no further analysis was performed in these two age categories and these age categories are not included in the all age groups results. In the remaining two age categories (20–64 years and ≥65 years), the IR per 100,000 PY of first A-fib/flu [Table 20] was considerably higher in the oldest (≥65 years) age group (exposed 817.2, 95% CI 773.2; 863.7, unexposed 771.3, 95% CI 754.0; 789.1) compared to the 20–64 years age group (exposed 79.4, 95% CI 73.6; 85.6 unexposed 71.5, 95% CI 69.1; 73.9). This finding of higher rates of A-fib/flu in ≥65 years old age group is consistent with the known epidemiology of A-fib/flu, which increases with age.

Table 21. Analysis of association between desloratadine (DL) exposure and first atrial fibrillation or flutter (A-fib/flu)[a$] (Table 4B2)

Age groups	Exposure status	Level	Crude model			Fully adjusted model*		
			IRR	95% CI	p-value	aIRR*	95% CI	p-value
All	Currently DL exposed	Yes	1.03	0.98; 1.08	0.30	1.08	1.03; 1.14	0.002
	Not currently DL exposed	No	1	Ref		1	Ref	
0–4 years #	Currently DL exposed	Yes	-	-	-	-	-	-
	Not currently DL exposed	No	1	Ref		1	Ref	
5–19 years #	Currently DL exposed	Yes	-	-	-	-	-	-
	Not currently DL exposed	No	1	Ref		1	Ref	
20–64 years	Currently DL exposed	Yes	1.11	1.02; 1.21	0.014	1.05	0.97; 1.15	0.23
	Not currently DL exposed	No	1	Ref		1	Ref	
≥65 years	Currently DL exposed	Yes	1.06	1.00; 1.12	0.060	1.10	1.03; 1.17	0.004
	Not currently DL exposed	No	1	Ref		1	Ref	

IRR= Incidence rate ratio; aIRR= adjusted incidence rate ratio; CI=confidence interval
a Years 2001–2006 are combined due to too few observations to obtain convergence
*Adjusted for confounders in the minimum sufficient adjustment set: age (20-24, …, 70-74, 95-79, ≥80), country, sex, calendar year, seasonality, asthmatic status, severe rhinitis, chronic urticaria status
Too few observations to perform the analysis, 0-4 and 5-19 year old age groups were not included in all group analysis due Statistics Denmark privacy restrictions

When adjusting for the minimally sufficient confounder set and 5 year time-varying age within the 20-64 and ≥65 year age categories to account for the increasing incidence of A-fib/flu with increasing age, a similar trend is seen. There is an association between exposure status and first A-fib/flu for the ≥65 years age category, but no association for the 20-64 year age category. In the fully adjusted analysis [Table 21] in the 20-64 years old age group, a 10% higher IR of first A-fib/flu was observed during the exposed follow-up time as compared to the unexposed follow-up time (aIRR 1.10, 95% CI 1.03; 1.17). Adjustment for age (5-year age within age categories), sex, country, seasonality and calendar year, as well as further adjustment for the remaining confounders (asthma, rhinitis, chronic urticaria) had only a minor effect on the IRR.

10.5 Other analyses

10.5.1 Supplementary analyses

The results of the supplementary analyses are provided below. Only a subset of supplementary analyses presented in the final report for the parent study, 4117-203, were conducted for this study. The numbering of the supplementary analyses from the final report for 4117-203 are provided in each table title to ensure that results could easily be compared.

In general, supplementary analyses support the findings of the main analyses.

In the first set of supplementary analyses, an alternative definition of DL exposure based on the time since the last DL redemption was examined with respect to each study outcome. Associations between exposure status and first seizure were observed when comparing follow up time 0–4 weeks with the reference group ≥ 27 weeks since last DL prescription redemption (aIRR 1.29, 95% CI 1.10; 1.40) and when comparing 9–16 weeks with the reference group (aIRR 1.23, 95% CI 1.07; 1.40) [Table 22].

Table 22. Analysis of association between desloratadine (DL) exposure and first seizure when using an alternative exposure categorization[a$] (Supplementary Analysis S1.1)

Age groups	Variable	First seizures** (N)	Risk time	p-value	Crude IRR	95% CI	p-value	aIRR*	95% CI
All	0–4 weeks	174	400,940	<0.001	1.47	1.26; 1.72	0.003	1.29	1.10; 1.50
	5–8 weeks	135	354,550		1.29	1.08; 1.54		1.13	0.95; 1.35
	9–16 weeks	246	596,793		1.40	1.22; 1.60		1.23	1.07; 1.40
	17–26 weeks	215	599,429		1.22	1.06; 1.40		1.03	0.90; 1.19
	≥27 weeks	1,961	6,651,608		1	Ref		1	Ref

IRR- incidence rate ratio; aIRR= adjusted incidence rate ratio; CI=confidence interval
*All analyses adjusted for confounders in the minimum sufficient adjustment set: age (0-4, 5-19, 20-64, 65+), country, sex, calendar year, seasonality, asthmatic status, severity of rhinitis, chronic urticaria status.
a Years 2001–2004 are combined due to too few observations to obtain convergence
$ For a complete list of codes, please see Annex 6 of the protocol
**Data for seizures provided from Norway is ICD-10 R56 including both febrile and non-febrile seizure <5 years of age; Seizure includes non-febrile seizure for Denmark, Finland and Sweden for ages <5 years of age.

As in the main analyses, no association between the alternative DL exposure definition and first SVT was seen [Table 23].

Table 23. Analysis of association between desloratadine (DL) exposure and supraventricular tachycardia (SVT) when using an alternative exposure categorization[a$] (Supplementary Analysis S1.2)

Age groups	Variable	SVT (N)	Risk time	p-value	IRR*	95% CI	p-value	aIRR*	95% CI
All#	0–4 weeks	129	454,170	0.43	0.88	0.73; 1.04	0.14	0.88	0.74; 1.06
	5–8 weeks	119	397,058		0.92	0.77; 1.11		0.97	0.80; 1.16
	9–16 weeks	224	659,731		1.05	0.91; 1.20		1.12	0.97; 1.28
	17–26 weeks	217	646,460		1.03	0.90; 1.19		1.12	0.97; 1.28
	≥27 weeks	2,551	7,859,827		1	Ref		1	Ref

IRR- incidence rate ratio; aIRR= adjusted incidence rate ratio; CI=confidence interval
*All analyses adjusted for confounders in the minimum sufficient adjustment set: age (5-19, 20-64, 65+), country, sex, calendar year, seasonality, asthmatic status, severity of rhinitis, chronic urticaria status.
a Years 2001–2004 are combined due to too few observations to obtain convergence
$ For a complete list of codes, please see Annex 6 of the protocol
#0-4 year age group not included in all groups due to privacy restrictions

Associations between exposure status and first A-fib/flu were observed between 0–4 weeks and the reference group ≥27 weeks (aIRR 1.11, 95% CI 1.03; 1.20) and between 5–8 weeks and ≥27 weeks (aIRR 1.10, 95% CI 1.01; 1.20) since the last DL prescription redemption [Table 24].

Table 24. Analysis of association between desloratadine (DL) exposure and atrial fibrillation or flutter (A-fib/flu) when using an alternative exposure categorization[a$] Supplementary Analysis S1.3)

Age groups	Variable	A-fib/flu (N)	Risk time	p-value	Crude IRR	95% CI	p-value	aIRR*	95% CI
All#	0–4 weeks	716	338,425	<0.001	1.13	1.05; 1.22	0.011	1.11	1.03; 1.20
	5–8 weeks	593	295,840		1.07	0.98; 1.16		1.10	1.01; 1.20
	9–16 weeks	853	486,608		0.94	0.87; 1.00		1.01	0.94; 1.08
	17–26 weeks	792	462,076		0.91	0.85; 0.98		1.06	0.98; 1.14
	≥27 weeks	10,859	5,794,115		1	Ref		1	Ref

IRR- incidence rate ratio; aIRR= adjusted incidence rate ratio; CI=confidence interval
*All analyses adjusted for confounders in the minimum sufficient adjustment set: age (20-24, …, 70-74, 95-79, ≥80, country, sex, calendar year, seasonality, asthmatic status, severity of rhinitis, chronic urticaria status.
a Years 2001–2006 are combined due to too few observations to obtain convergence
$ For a complete list of codes, please see Annex 6 of the protocol
#0-4 and 5-19 year age group not included in all groups due to privacy restrictions

In the next set of supplementary analyses, country-specific analyses showed that associations between exposure status and first seizure were observed only in Finland (aIRR 1.31, 95% CI 1.06; 1.63) and Norway (aIRR 2.28, 95% CI 1.57; 3.31). No associations were observed in Denmark (aIRR 0.86, 95% CI 0.57; 1.31) or Sweden (aIRR 1.14, 95% CI 0.99; 1.31 [Table 25]).

Table 25. Analysis of association between desloratadine (DL) exposure and first seizure for the total population and stratified by country[a$] (Supplementary Analysis S4.1)

Country	Exposure status	Level	First seizures** (N)	Risk time***	p-value	Crude IRR	95% CI	p-value	aIRR*	95% CI
All	Currently DL exposed	Yes	454	1,168,897	<0.001	1.32	1.19; 1.46	0.001	1.20	1.08; 1.33
	Not currently DL exposed	No	1,961	6,651,608		1	Ref		1	Ref
Denmark	Currently DL exposed	Yes	25	134,392	0.83	0.95	0.63; 1.44	0.48	0.86	0.57; 1.31
	Not currently DL exposed	No	243	1,247,493		1	Ref		1	Ref
Finland	Currently DL exposed	Yes	103	326,088	0.005	1.37	1.11; 1.68	0.018	1.31	1.05; 1.63
	Not currently DL exposed	No	591	2,556,979		1	Ref		1	Ref
Norway	Currently DL exposed	Yes	57	173,685	0.001	1.85	1.29; 2.65	<0.001	2.28	1.57; 3.31
	Not currently DL exposed	No	61	343,630		1	Ref		1	Ref
Sweden	Currently DL exposed	Yes	269	534,731	0.016	1.18	1.03; 1.35	0.065	1.14	0.99; 1.31
	Not currently DL exposed	No	1,066	2,503,506		1	Ref		1	Ref

aIRR= adjusted incidence rate ratio; CI=confidence interval
$ For a complete list of codes, please see Annex 6 of the protocol
*All analyses adjusted for confounders in the minimum sufficient adjustment set: age (0-4, 5-19, 20-64, 65+), country (only for the analysis of the total population), sex, calendar year, seasonality, asthmatic status, severity of rhinitis, chronic urticaria status.
a Years 2001–2004 are combined due to too few observations to obtain convergence
**Data for seizures provided from Norway is ICD-10 R56 including both febrile and non-febrile seizure <5 years of age ; Seizure includes non-febrile seizure for Denmark, Finland and Sweden for ages <5 years of age.
*** Risk-time may not sum to total due to rounding

As in the main analyses, no association between the DL exposure definition and first SVT was seen in any one country [Table 26].

Table 26. Analysis of association between desloratadine (DL) exposure and supraventricular tachycardia (SVT) for the total population and stratified by country[a$] (Supplementary Analysis S4.2)

Country	Exposure status	Level	SVT (N)	Risk time	p-value	Crude IRR	95% CI	p-value	aIRR*	95% CI
All#	Currently DL exposed	Yes	416	1,334,015	0.45	0.96	0.87; 1.07	0.80	1.01	0.91; 1.13
	Not currently DL exposed	No	2,551	7,859,827		1	Ref		1	Ref
Denmark#	Currently DL exposed	Yes	100	170,734	0.85	1.02	0.83; 1.25	0.99	1.00	0.81; 1.23
	Not currently DL exposed	No	928	1,615,760		1	Ref		1	Ref
Finland#	Currently DL exposed	Yes	91	368,580	0.17	1.17	0.94; 1.46	0.43	1.10	0.87; 1.37
	Not currently DL exposed	No	632	2,999,235		1	Ref		1	Ref
Norway#	Currently DL exposed	Yes	35	191,279	0.64	0.91	0.61; 1.36	0.12	0.72	0.48; 1.09
	Not currently DL exposed	No	73	362,535		1	Ref		1	Ref
Sweden#	Currently DL exposed	Yes	190	603,422	0.89	0.99	0.85; 1.16	0.70	1.03	0.88; 1.21
	Not currently DL exposed	No	918	2,882,298		1	Ref		1	Ref

aIRR= adjusted incidence rate ratio; CI=confidence interval
$ For a complete list of codes, please see Annex 6 of the protocol
a Years 2001–2004 are combined due to too few observations to obtain convergence
All analyses adjusted for confounders in the minimum sufficient adjustment set: age (5-19, 20-64, 65+), country (only for the analysis of the total population), sex, calendar year, seasonality, asthmatic status, severity of rhinitis, chronic urticaria status.
#0-4 year age group not included due to privacy restrictions

An association in the incidence rate ratio of first A-fib/flu between exposed and unexposed follow-up time was not observed in any one country [Table 27]). As in the main analyses, no association between the DL exposure definition and first SVT in country-specific analysis.

Table 27. Analysis of association between desloratadine (DL) exposure and atrial fibrillation of flutter (A-fib/flu) for the total population and stratified by country[a$] (Supplementary Analysis S4.3)

Country	Exposure status	Level	A-fib/flu (N)	Risk time	p-value	Crude IRR	95% CI	p-value	aIRR*	95% CI
All#	Currently DL exposed	Yes	1,929	1,002,932	0.30	1.03	0.98; 1.08	0.003	1.08	1.03; 1.13
	Not currently DL exposed	No	10,859	5,794,115		1	Ref		1	Ref
Denmark#	Currently DL exposed	Yes	339	133,343	0.011	1.16	1.04; 1.30	0.12	1.10	0.98; 1.23
	Not currently DL exposed	No	2,846	1,300,241		1	Ref		1	Ref
Finland#	Currently DL exposed	Yes	468	289,903	0.41	1.04	0.95; 1.15	0.26	1.06	0.96; 1.17
	Not currently DL exposed	No	3,351	2,162,146		1	Ref		1	Ref
Norway#	Currently DL exposed	Yes	181	138,599	0.023	1.25	1.03; 1.51	0.059	1.21	0.99; 1.46
	Not currently DL exposed	No	257	245,816		1	Ref		1	Ref
Sweden#	Currently DL exposed	Yes	941	441,087	0.78	1.01	0.94; 1.08	0.10	1.06	0.99; 1.14
	Not currently DL exposed	No	4,405	2,085,912		1	Ref		1	Ref

aIRR= adjusted incidence rate ratio; CI=confidence interval
$ For a complete list of codes, please see Annex 6 of the protocol
*All analyses adjusted for confounders in the minimum sufficient adjustment set: age (20-24, …, 70-74, 95-79, ≥80) , country (only for the analysis of the total population), sex, calendar year, seasonality, asthmatic status, severity of rhinitis, chronic urticaria status.
a Years 2001–2006 are combined due to too few observations to obtain convergence
#0-4 and 5-19 year age groups not included due to privacy restrictions

The next set of supplementary analyses stratified the exposure follow-up time according to the number of prescription redemptions, when comparing exposed to unexposed follow-up time. An association between exposure status and first seizure was observed following the first-ever DL prescription redemption (aIRR 1.32, 95% CI 1.13; 1.54), and the second (aIRR 1.27, 95% CI 1.01; 1.61) , but not three or more redemptions (aIRR 1.09, 95% CI 0.94; 1.26,[Table 28]).

Table 28. Analysis of the association between desloratadine (DL) exposure and first seizure when using an alternative exposure categorization[$, a] (Supplementary Analysis S6.1)

Exposure status	First seizures (N)**	Risk time*	p-value	Crude IRR	95% CI	p-value	aIRR**	95% CI
Currently DL exposed following first prescription redemption	182	367,717	<0.001	1.68	1.44; 1.95	0.003	1.32	1.13; 1.54
Currently DL exposed following second prescription redemption	75	180,517		1.41	1.12; 1.77		1.27	1.01; 1.61
Currently DL exposed following third or more prescription redemption	197	620,663		1.08	0.93; 1.25		1.09	0.94; 1.26
Not currently DL exposed	1,961	6,651,608		1	Ref		1	Ref

aIRR=adjusted incidence rate ratio; CI=confidence interval
$ For a complete list of codes, please see Annex 6 of the protocol
*All analyses adjusted for confounders in the minimum sufficient adjustment set: age (0-4, 5-19, 20-64, 65+), country, sex, calendar year, seasonality, asthmatic status, severity of rhinitis, chronic urticaria status.
a Years 2001–2004 are combined due to too few observations to obtain convergence
* Risk-time may not sum to total due to rounding
**Data for seizures provided from Norway is ICD-10 R56 including all types of seizures for patients <5 years of age; Seizure includes non-febrile seizure ICD-10 R568 for Denmark, Finland and Sweden for ages <5 years of age.

No association between exposure status and first SVT was seen [Table 29].

Table 29. Analysis of the association between desloratadine (DL) exposure and SVT when using an alternative exposure categorization[$,a#] (Supplementary Analysis S6.2)

Exposure status	SVT (N)	Risk time*	p-value	Crude IRR	95% CI	p-value	aIRR**	95% CI
Currently DL exposed following first prescription redemption	106	363,206	0.026	0.90	0.74; 1.09	0.29	1.02	0.84; 1.25
Currently DL exposed following second prescription redemption	44	198,155		0.68	0.51; 0.92		0.78	0.58; 1.06
Currently DL exposed following third or more prescription redemption	266	772,655		1.06	0.93; 1.20		1.06	0.93; 1.20
Not currently DL exposed	2,551	7,859,827		1	Ref		1	Ref

IRR= incidence rate ratio; aIRR= adjusted incidence rate ratio; CI=confidence interval
$ For a complete list of codes, please see Annex 6 of the protocol
a Years 2001–2004 are combined due to too few observations to obtain convergence
#0-4 year age group not included due to privacy restrictions
*Risk-time may not sum to total due to rounding
**All analyses adjusted for confounders in the minimum sufficient adjustment set: age (5-19, 20-64, 65+), country, sex, calendar year, seasonality, asthmatic status, severity of rhinitis, chronic urticaria status.

Similarly, comparing exposed to unexposed follow-up time, an association between DL and first A-fib/flu was observed following the first-ever DL prescription redemption (aIRR 1.37, 95% CI 1.26; 1.49), but not the second (aIRR 1.10, 95% CI 0.97; 1.25) or the third or subsequent redemptions (aIRR 0.98, 95% CI 0.92; 1.04 [Table 30]).

Table 30. Analysis of the association between desloratadine (DL) exposure and A-fib/flu when using an alternative exposure categorization[$, a, #] (Supplementary Analysis S6.3)

Exposure status	A-fib/flu (N)	Risk time	p-value	Crude IRR	95% CI	p-value	aIRR*	95% CI
Currently DL exposed following first prescription redemption	563	265,033	0.012	1.13	1.04; 1.23	<0.001	1.37	1.26; 1.49
Currently DL exposed following second prescription redemption	244	144,019		0.90	0.80; 1.03		1.10	0.97; 1.25
Currently DL exposed following third or more prescription redemption	1,122	593,880		1.01	0.95; 1.07		0.98	0.92; 1.04
Not currently DL exposed	10,859	5,794,115		1	Ref		1	Ref

aIRR= adjusted incidence rate ratio; CI=confidence interval
$ For a complete list of codes, please see Annex 6 of the protocol
#0-4 and 5-19 year age groups not included due to privacy restrictions
*All analyses adjusted for confounders in the minimum sufficient adjustment set: age (20-24, …, 70-74, 95-79, ≥80) , country, sex, calendar year, seasonality, asthmatic status, severity of rhinitis, chronic urticaria status.
a Years 2001–2006 are combined due to too few observations to obtain convergence

In the final set of supplementary analyses, a sensitivity analysis was conducted using an alternative confounder adjustment set which is different than that which was controlled for in the primary analyses. For all exposure-outcome comparisons, the alternative confounder set included age, sex, country, calendar year, seasonality, asthma status, diabetes, hypo/hyperthyroidism, inflammatory disease, infections, and type 1 allergy and severe rhinitis combined. Antihypertensive treatment was also controlled for in the analyses of first SVT and A-fib/flu.

Using the alternative confounder adjustment set, the IRR of first seizure was 19% higher during exposed follow-up time compared to unexposed follow-up time (aIRR 1.19, 95% CI 1.07; 1.32 [Table 31]) compared to a 20% higher aIRR in the main analysis [Table 15].

Table 31. Analysis of association between desloratadine (DL) exposure and first seizure when adjusting for an alternative confounder adjustment set[a$b] (Supplementary Analysis S8.1)

Exposure status	Level	First seizures (N)	Risk time*	p-value	Crude IRR	95% CI	p-value	aIRR**	95% CI
Currently DL exposed	Yes	454	1,168,897	<0.001	1.32	1.19; 1.46	0.002	1.19	1.07; 1.32
Not currently DL exposed	No	1,961	6,651,608		1	Ref		1	Ref

aIRR= adjusted incidence rate ratio; CI=confidence interval
$ For a complete list of codes, please see Annex 6 of the protocol
a Years 2001–2004 are combined due to too few observations to obtain convergence
b Data for seizures provided from Norway is ICD-10 R56 including both febrile and non-febrile seizure <5 years of age ; Seizure includes non-febrile seizure (ICD-10 R568) for Denmark, Finland and Sweden for ages <5 years of age.
* Risk-time may not sum to total due to rounding
**All analyses adjusted for confounders in the minimum sufficient adjustment set: age (0-4, 5-19, 20-64, 65+), sex, country, calendar year, seasonality, severity of rhinitis, asthma status, diabetes, hypo/hyper-thyroidism, inflammatory disease, infections, and type 1 allergy

However, no association between exposure status was apparent in the analysis of first SVT (aIRR 0.96, 95% CI: 0.86, 1.07 [Table 32]).

Table 32. Analysis of association between desloratadine (DL) exposure and first supraventricular tachycardia (SVT) when adjusting for an alternative confounder adjustment set[a$#] (Supplementary Analysis S8.2)

Exposure status	Level	SVT (N)	Risk time*	p-value	Crude IRR	95% CI	p-value	aIRR**	95% CI
Currently DL exposed	Yes	416	1,334,015	0.45	0.96	0.87; 1.07	0.48	0.96	0.86; 1.07
Not currently DL exposed	No	2,551	7,859,827		1	Ref		1	Ref

IRR= incidence rate ratio; aIRR= adjusted incidence rate ratio; CI=confidence interval
$ For a complete list of codes, please see Annex 6 of the protocol
a Years 2001–2004 are combined due to too few observations to obtain convergence
* Risk-time may not sum to total due to rounding
#0-4 year age group not included due to privacy restrictions
**All analyses adjusted for confounders in the minimum sufficient adjustment set: age (0-4, 5-19, 20-64, 65+), sex, country, calendar year, seasonality, severity of rhinitis, asthma status, diabetes, hypo/hyper-thyroidism, inflammatory disease, infections, type 1 allergy, and antihypertensive treatment

The 8% higher IRR of first A-fib/flu seen in the main analysis [Table 21] is not seen in the supplementary analysis of first A-fib/flu using the alternative set of confounders (aIRR 1.04, 95% CI 0.99, 1.09 [Table 33]).

Table 33. Analysis of association between desloratadine (DL) exposure and first atrial fibrillation or flutter (A-fib/flu) when adjusting for an alternative confounder adjustment set[a$#] (Supplementary Analysis S8.3)

Exposure status	Level	A-fib/flu (N)	Risk time	p-value	Crude IRR	95% CI	p-value	aIRR*	95% CI
Currently DL exposed	Yes	1,929	1,002,932	0.30	1.03	0.98; 1.08	0.16	1.04	0.99; 1.09
Not currently DL exposed	No	10,859	5,794,115		1	Ref		1	Ref

IRR=incidence rate ratio; aIRR= adjusted incidence rate ratio; CI=confidence interval
$ For a complete list of codes, please see Annex 6 of the protocol
[a] Years 2001–2006 are combined due to too few observations to obtain convergence
#0-4 and 5-19 year age groups not included due to privacy restrictions
*All analyses adjusted for confounders in the minimum sufficient adjustment set: age ((0-4, 5-9, 10-14, …, 70-74, 95-79, ≥80) , sex, country, calendar year, seasonality, severity of rhinitis, asthma status, diabetes, hypo/hyper-thyroidism, inflammatory disease, infections, type 1 allergy, and antihypertensive treatment

10.5.2 Post-hoc analyses

In the final report for 4117-203 submitted to the EMA in 2019 and in the main analyses in this report, age was broken into four categories (0-4, 5-19, 20-64 and ≥65 years). In Post-hoc Analysis 1 [Table 16], age is adjusted in 5-year age categories within the age group, as in the updated results sent in the response to the Request for Supplementary Information (RSI). In this analysis, the aIRR for seizure 1.21 (95% CI 1.09; 1.35) is nearly identical to the aIRR presented in [Table 15] (aIRR 1. 20, 95% CI 1. 08; 1. 33). Adjustment for age within each age category, does not change the age-specific results in [Table 15].Thus, adjusting the seizure analysis for age in 5-year age groups does not alter the results from the main seizure analysis in any meaningful way.

In the final report for 4117-203 submitted to the EMA in 2019 and in [Table 18]in this report, age was grouped into four categories (0-4, 5-19, 20-64 and ≥65 years). In Post-hoc Analysis 2 [Table 19], age is adjusted in 5-year age categories within the age categories as in the updated results sent in the RSI response. In this analysis, the aIRR 0.98 (95% CI 0.88; 1.09) is similar to the aIRR presented in [Table 18] (aIRR 1.01, 95% CI 0.91; 1. 13). Thus, adjusting for age in 5-year age groups does not alter the results from the main SVT analysis in any meaningful way.

Post-hoc Analysis 3A [Table 34] shows the IR of first seizure using an alternate seizure definition, which includes febrile, non-febrile and other seizure across exposed and unexposed risk time (See [Annex 2] for seizure codes included for each country). For this analysis, the age cut-off for the youngest age group was modified from 4 to 5 years to correspond to the age when seizures with fever are considered febrile (by definition febrile seizures occur in children 5 years and younger) [Ref. 5.4: 05LTSX]. Similar to the main results of Substudy 2B [Table 14], the IR of first seizure per 100,000 PY during exposed follow-up time (i.e., among those currently exposed to DL, 64.4, 95% CI 60.0; 69.2) was higher than during unexposed follow-up time (i.e., among those currently not exposed to DL, 40.1, 95% CI 38.6; 41.7 [Table 34]). When analyzed within specific age categories, the IR was higher during exposed follow-up

time as compared to during unexposed follow-up time in all the age categories except the 20–64 years age group, where the IRs were similar. The IR of first seizure was the highest among those in the 0–5 years age group comparing DL exposed (356.7, 95% CI 324.8; 391.7) with DL unexposed (190.6, 95% CI 179.3; 202.6).

Table 34. Post-hoc Analysis 3A- Number of first seizure cases (febrile or non-febrile), risk time and incidence rate across persons currently and not currently exposed to desloratadine (DL)[$]

Age groups	Exposure status	Level	Persons included (N)	First seizures (N)	Risk time	Incidence rate	95% CI
All	Currently DL exposed	Yes	1,807,269	751	1,166,073	64.4	60.0; 69.2
	Not currently DL exposed	No		2,663	6,634,332	40.1	38.6; 41.7
0–5 years	Currently DL exposed	Yes	366,120	438	122798	356.7	324.8; 391.7
	Not currently DL exposed	No		1026	538373	190.6	179. 3; 202.6
6–19 years	Currently DL exposed	Yes	383,781	145	270247	53.7	45.6; 63.1
	Not currently DL exposed	No		667	1685511	39.6	36.7; 42.7
20–64 years	Currently DL exposed	Yes	920,235	125	669264	18.7	15.7; 22.3
	Not currently DL exposed	No		739	3782954	19.5	18.2; 21.0
≥65 years	Currently DL exposed	Yes	137,133	43	103762	41.4	30.7; 55.9
	Not currently DL exposed	No		231	627495	36.8	32.4; 41.9

IR=incidence rate; CI=confidence interval
$ For a complete list of codes, please see Annex 3 of the protocol

Post-hoc Analysis 3B [Table 35] presents the association of DL and first seizure using an alternate case definition which includes febrile, non-febrile or other seizure comparing exposed and unexposed person-time. An association between exposure status and first seizure was observed in the overall analysis (aIRR 1.50, 95% CI 1.38; 1.63), as well as the 0-5 year (aIRR 2.0, 95% CI 1.78; 2.24) and 6-19 year (aIRR 1.41, 95% CI 1.17; 1.70) age categories [Table 35].

Table 35. Post-hoc Analysis 3B- Analysis of association between desloratadine (DL) exposure and first seizure (febrile or non-febrile)[a$]

Age groups	Exposure status	Level	Crude model			Fully adjusted model*		
			IRR	95% CI	p-value	aIRR*	95% CI	p-value
All	Currently DL exposed	Yes	1.60	1.48; 1.74	<0.001	1.50	1.38; 1.63	<0.001
	Not currently DL exposed	No	1	Ref		1	Ref	
0–5 years	Currently DL exposed	Yes	1.87	1.67; 2.09	<0.001	2.00	1.78; 2.24	<0.001
	Not currently DL exposed	No	1	Ref		1	Ref	
6–19 years	Currently DL exposed	Yes	1.35	1.13; 1.62	0.001	1.41	1.17; 1.70	<0.001
	Not currently DL exposed	No	1	Ref		1	Ref	
20–64 years	Currently DL exposed	Yes	0.96	0.79; 1.16	0.64	0.92	0.76; 1.12	0.41
	Not currently DL exposed	No	1	Ref		1	Ref	
≥65 years	Currently DL exposed	Yes	1.13	0.81; 1.56	0.48	1.17	0.84; 1.63	0.36
	Not currently DL exposed	No	1	Ref		1	Ref	

IRR= Incidence rate ratio; aIRR= adjusted incidence rate ratio; CI=confidence interval
$ For a complete list of codes, please see Annex 6 of the protocol
a Years 2001–2004 are combined due to too few observations to obtain convergence
* Adjusted for confounders in the minimum sufficient adjustment set: age (0-4, 5-9, 10-14, …, 70-74, 75-79, 80+), country, sex, calendar year, seasonality, asthmatic status, severe rhinitis, chronic urticaria status. Due to too few individuals with severe rhinitis, no adjustment was performed in the analyses stratified by age group. Analysis adjusted for age categorized into 5-year age categories

Post-hoc Analysis 4 [Table 36] presents the IRR of first seizure stratified by country and age. Due to less than 10 events in the exposed or unexposed groups for each age category, data for Denmark was suppressed. An association between exposure status and first seizure was observed in the overall analysis in Finland (aIRR 1.34, 95% CI 1.08; 1.67) as well as the 5-19 year age category (aIRR 1.73, 95% CI 1.19; 2.50) ; in overall analysis including all age categories in Norway (aIRR 2.28, 95% CI 1.57; 3.31) as well as the 0-4 year age category (aIRR 2.26, 95% CI 1.45; 3.52); and in the overall analysis in Sweden (aIRR 1.17, 95% CI 1.02; 1.35), as well as the 0-4 year age category (aIRR 1.58, 95% CI 1.17; 2.14) [Table 36].

Table 36. Post-hoc Analysis 4- Analysis of association between desloratadine (DL) exposure and first seizure stratified by country[a**$]

Denmark

Age groups	Exposure status	Level	Crude model			Fully adjusted model*		
			IRR	95% CI	p-value	aIRR*	95% CI	p-value
All	Currently DL exposed	Yes	0.96	(0.63; 1.44)	0.83	0.86	(0.57; 1.31)	0.48
	Not currently DL exposed	No	1	Ref		1	Ref	
0–4 years	Currently DL exposed	Yes	-	-	-	-	-	-
	Not currently DL exposed	No	1	Ref		1	Ref	
5–19 years	Currently DL exposed	Yes	-	-	-		-	-
	Not currently DL exposed	No	1	Ref		1	Ref	
20–64 years	Currently DL exposed	Yes	-		-	-		-
	Not currently DL exposed	No	1	Ref		1	Ref	
≥65 years	Currently DL exposed	Yes	-		-	-		-
	Not currently DL exposed	No	1	Ref		1	Ref	

Finland

Age groups	Exposure status	Level	Crude model			Fully adjusted model*		
			IRR	95% CI	p-value	aIRR*	95% CI	p-value
All	Currently DL exposed	Yes	1.37	(1.11; 1.68)	0.005	1.34	(1.08; 1.67)	0.010
	Not currently DL exposed	No	1	Ref		1	Ref	
0–4 years	Currently DL exposed	Yes	1.21	(0.78; 1.87)	0.40	1.20	(0.76; 1.88)	0.45
	Not currently DL exposed	No	1	Ref		1	Ref	
5–19 years	Currently DL exposed	Yes	1.65	(1.15; 2.35)	0.010	1.73	(1.19; 2.50)	0.007
	Not currently DL exposed	No	1	Ref		1	Ref	
20–64 years	Currently DL exposed	Yes	1.10	(0.76; 1.61)	0.61	1.13	(0.77; 1.66)	0.53
	Not currently DL exposed	No	1	Ref		1	Ref	
≥65 years	Currently DL exposed	Yes	1.44	(0.76; 2.74)	0.28	1.51	(0.79; 2.90)	0.24
	Not currently DL exposed	No	1	Ref		1	Ref	

Norway

Age groups	Exposure status	Level	Crude model			Fully adjusted model*		
			IRR	95% CI	p-value	aIRR*	95% CI	p-value
All	Currently DL exposed	Yes	1.85	(1.29; 2.65)	0.001	2.28	(1.57; 3.31)	<0.001
	Not currently DL exposed	No	1	Ref		1	Ref	
0–4 years	Currently DL exposed	Yes	2.41	(1.57; 3.72)	<0.001	2.26	(1.45; 3.52)	<0.001
	Not currently DL exposed	No	1	Ref		1	Ref	

5–19 years	Currently DL exposed	Yes	-		-	-		-
	Not currently DL exposed	No	1	Ref		1	Ref	
20–64 years	Currently DL exposed	Yes	-		-	-		-
	Not currently DL exposed	No	1	Ref		1	Ref	

Sweden

Age groups	Exposure status	Level	Crude model			Fully adjusted model*		
			IRR	95% CI	p-value	aIRR*	95% CI	p-value
All	Currently DL exposed	Yes	1.18	(1.03; 1.35)	0.016	1.17	(1.02; 1.35)	0.025
	Not currently DL exposed	No	1	Ref		1	Ref	
0–4 years	Currently DL exposed	Yes	1.59	(1.19; 2.14)	0.003	1.58	(1.17; 2.14)	0.004
	Not currently DL exposed	No	1	Ref		1	Ref	
5–19 years	Currently DL exposed	Yes	1.22	(0.98; 1.52)	0.087	1.24	(0.99; 1.56)	0.069
	Not currently DL exposed	No	1	Ref		1	Ref	
20–64 years	Currently DL exposed	Yes	0.90	(0.71; 1.14)	0.38	0.94	(0.73; 1.20)	0.62
	Not currently DL exposed	No	1	Ref		1	Ref	
≥65 years	Currently DL exposed	Yes	1.09	(0.72; 1.65)	0.70	1.17	(0.76; 1.78)	0.48
	Not currently DL exposed	No	1	Ref		1	Ref	

IRR=incidence rate aIRR= adjusted incidence rate ratio; CI=confidence interval
a Years 2001–2005 and 2006-2008 are combined due to too few observations to obtain convergence
*Adjusted for confounders in the minimum sufficient adjustment set: age (5-year age groups) country, sex, calendar year, seasonality, asthmatic status, severe rhinitis, chronic urticaria status. Due to too few individuals with severe rhinitis, no adjustment was performed in the analyses stratified by age group.
**Data for seizures provided from Norway is ICD-10 R56 including both febrile and non-febrile seizure <5 years of age; Seizure includes non-febrile seizure for Denmark, Finland and Sweden for ages <5 years of age. For comparison with submitted PASS report (protocol P203), this table uses the 0-4 age breakdown of the original report.
$ For a complete list of codes, please see Annex 6 of the protocol

Post-hoc Analysis 5 [Table 37] shows the association between DL exposure and A-fib/flu overall and when stratified by age category when using an alternative exposure categorization and alternative confounder set overall and stratified by age category. The aIRR for the association between first-ever DL prescription redemption and first A-fib/flu was 1.37 (95% CI 1.26; 1.49) in Supplementary Analysis S6.3 [Table 30] using the main confounder set. Using the alternate confounder set, the aIRR between first-ever DL prescription redemption and A-fib/flu is 1.29 (95% CI 1.18 1.40). Evaluating the association stratified by categories, the aIRR is similar 1.28 (95% CI 1.10; 1.48) for the 20–64 year age category, and 1.29 (95% CI 1.16; 1.44) for the ≥65 year age category. The alternate confounder set may help adjust for residual confounding in supplemental analysis 6.3, but there does not appear to effect measure modification by age in the 20-64 and ≥65 year age categories.

Table 37. Post-hoc Analysis 5- Analysis of the association between desloratadine (DL) exposure and A-fib/flu when using an alternative exposure categorization and confounder set[$, a]

Exposure status	A-fib/flu (N)	Risk time	p-value	Crude IRR	95% CI	p-value	aIRR*	95% CI
Overall								
Currently DL exposed following first prescription redemption	563	265,033	*0.012*	*1.13*	*1.04; 1.23*	<0.001	1.29	(1.18; 1.40)
Currently DL exposed following second prescription redemption	244	144,019		*0.90*	*0.80; 1.03*		1.04	(0.92; 1.18)
Currently DL exposed following third or more prescription redemption	1,122	593,880		*1.01*	*0.95; 1.07*		0.95	(0.89; 1.01)
Not currently DL exposed	10,859	5,794,115		1	Ref		1	Ref
20-64 Age Group								
Exposure status	A-fib/flu (N)	Risk time	p-value	Crude IRR	95% CI	p-value	aIRR*	95% CI
Currently DL exposed following first prescription redemption	200	230168	0.025	1.22	(1.05; 1.40)	0.003	1.28	(1.10; 1.48)
Currently DL exposed following second prescription redemption	87	125535		0.97	(0.78; 1.20)		0.99	(0.80; 1.22)
Currently DL exposed following third or more prescription redemption	387	493654		1.10	(0.99; 1.22)		0.91	(0.82; 1.01)
Not currently DL exposed	3454	4834099		1	Ref		1	Ref
65+ Age Group								
Exposure status	A-fib/flu (N)	Risk time	p-value	Crude IRR	95% CI	p-value	aIRR*	95% CI
Currently DL exposed following first prescription redemption	363	34865	<0.001	1.35	(1.21; 1.50)	<0.001	1.29	(1.16; 1.44)
Currently DL exposed following second prescription redemption	157	18484		1.10	(0.94; 1.29)		1.07	(0.92; 1.26)

Currently DL exposed following third or more prescription redemption	735	100226		0.95	(0.88; 1.03)		0.96	(0.89; 1.04)
Not currently DL exposed	7405	960016		1	Ref		1	Ref

IRR=incidence rate ratio; aIRR= adjusted incidence rate ratio; CI=confidence interval
*All analyses adjusted for confounders in the minimum sufficient adjustment set: age (5-year age groups), sex, country, calendar year, seasonality, severity of rhinitis, asthma status, diabetes, hypo/hyper-thyroidism, inflammatory disease, infections, type 1 allergy, and antihypertensive treatment
a Years 2001–2006 are combined due to too few observations to obtain convergence

In post-hoc analysis 6 [Table 38], examines whether the time window prior to DL exposure to exclude prevalent disease for each country may result inclusion of prevalent disease. Since Norway has a shorter study time frame and shorter look-back period to determine prevalent disease, if the percent of prevalent disease excluded was lower for Norway than the other countries if the Norwegian analysis was capturing incident and prevalent seizure. In this analysis. The percent of people excluded for prevalent disease for the seizure outcome are similar across countries.

Table 38. Post-hoc Analysis 6- analysis of the time window for the prevalent disease exclusion criteria of more than two years prior to DL exposure by country for the seizure analysis.

	For children 0-4 years			For all ages ≥ 5 years		
Country	No. of people with events* more than 2 years prior to DL use (numerator)	Total no. of people with events* excluded in the study** prior to DL use (no-time constraint) (Denominator)	%	No. of people with Events* more than 2 years prior to DL use (numerator)	Total no. of people with events* excluded in the study prior to DL use (no-time constraint) (denominator)	%
Denmark	579	1,903	30.4	55,521	63,277	87.7
Finland	989	3,152	31.4	75,066	89,722	83.7
Norway	293	908	32.3	24,674	32,820	75.2
Sweden	1,492	4,384	34.0	83,358	116,391	71.6

*Most recent prevalent disease: previous seizure (ICD-10: R568, except for Norway using ICD-10: R56) and other diseases (epilepsy, malignant brain tumor, or head trauma or prescription of antiepileptic medicine) before inclusion

10.6 Adverse events/adverse reactions

This is a non-interventional database study based on secondary use of data collected for other purposes. No administration of any therapeutic or prophylactic agent is required in this protocol. No reporting of individual adverse events or product quality complaints to regulatory agencies is planned for this database study because there is no access to individual patient/subject records and it is not possible to assess the causality of individual cases. Study specific health outcomes of interest, including any that qualify as adverse events, will be summarized as part of any interim analysis (including safety analysis, if required) and in the final study report, which will be provided to regulatory agencies by the sponsor as required.

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Any relevant safety information will be summarized in the appropriate Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) and/or Development Safety Update Reports (DSUR) if required.

If an investigator elects to spontaneously report any suspected adverse reactions or product quality complaints, they should be reported via fax to Local Designated Point of Contact (DPOC) (Denmark: PPD; Finland: PPD Norway: PPD Sweden: PPD in English using an AE and PQC report form (Stand alone document available upon request) for reporting to worldwide regulatory agencies as appropriate.

11 DISCUSSION

11.1 Key results

This study aimed to describe use of DL during the study period in the general population and stratified by age, sex, calendar year, seasonality and comorbidity status. Overall there were 2.1 million incident users of DL during the study period and 281 million person-years at risk. Use of DL increased over the study period ranging from 7,277 incident users in 2001 to 268,662 incident users in 2015. The IR per 100,000 PY of DL use was greatest in the spring (IR 1,229.9, 95% CI 1,227.3; 1,232.5) and lowest in the winter (IR 419.3, 95% CI, 417.8; 420.8), consistent with the seasonality of allergic rhinitis.

The IR per 100,000 persons of DL use was slightly higher for females (IR 768.4, 95% CI 766.9; 769.8) than males (IR 740.9, 95% CI 739.5; 742.4). The IR per 100,000 PY of DL use decreased with increasing age, 0-4 year (IR 2,030.0, 95% CI 2,023.1; 2,036.9), 5-19 years (IR 925.9, 95% CI 923.3; 928.6), 20-64 years (IR 675.0, 95% CI 673.7; 676.2), and ≥65 years (IR 422.8, 95% CI 421.0; 424.7). The IR per 100,000 PY of use among patients with registrations: for asthma was 108.6, for severe rhinitis registrations was 4.1, and for chronic urticaria was 16.0.

Other key findings relating to the study objectives were that the IR per 100,000 PY of DL use was much higher in Finland (IR 839.7, 95% CI 837.7; 841.8), Norway (IR 942.1, 95% CI 938.7; 945.6) and Sweden (IR 956.6, 95% CI 954.6; 958.6) as compared with Denmark (IR 378.8, 95% CI 377.5; 380.1) and the mean number of defined daily doses was similar in Denmark (182.74 ± 492.96) and Finland (188.77 ± 363.63), but larger in Norway (241.29 ± 317.88) and Sweden (229.73 ± 423.90).

This study also aimed to describe the IR of the study outcomes in the general population. In the general population, the IR per 100,000 PY of: seizure was 37.6, SVT was 34.4, and A-fib/flu was 181.7. In this study, the observed patterns in the age-stratified IRs for seizure and A-fib/flu coincide with the known epidemiology of seizure and A-fib/flu, which are highest in the youngest and oldest age groups, respectively.

The prespecified study questions of this PASS set out to examine the association between current DL exposure and first seizure, first SVT and first A-fib/flu. This study found a higher rate of first seizure in DL exposed person-time compared with DL unexposed person-time. Across all age groups, the magnitude of the aIRR for seizure is small (aIRR 1.20, 95% CI 1.08; 1.33) when adjusted for confounders selected in the DAG analysis. Substudy 2 showed a higher IR of first seizure during exposed follow-up time (IR=38.8) as compared with unexposed follow-up time (IR=29.5). The overall finding of increased risk of first seizure is driven by increased IR of first seizure in the 0-4 (aIRR 1.65, 95% CI 1.34; 2.03) and in the 5-19 (aIRR 1.34, 95% CI 1.12; 1.61) year-old age categories. When comparing DL exposed and unexposed periods, exposure status was not associated with first seizure in patients ≥ 20 years. The association between DL and first seizure is consistent across sensitivity analyses that varied exposure definitions and adjusted for alternative sets of confounders.

This study found no association between DL exposure status and incident SVT. Substudy 3 showed no association between DL exposure and first SVT (aIRR 1.01, 95% CI 0.91; 1.13) adjusted for confounders selected in the DAG exercise. This finding was consistent across multiple subgroups, substudies and sensitivity analyses.

This PASS found a slightly higher rate of first A-fib/flu in DL exposed person-time compared with DL unexposed person-time. The main finding of Substudy 4 found an aIRR of first A-fib/flu of 1.08 (95% CI 1.03; 1.14) adjusted for confounders that were identified in the DAG exercise. The overall finding of increased IR of first A-fib/flu was driven by increased IR of first A-fib/flu in the ≥65 years age category (aIRR 1.10, 95% CI 1.03; 1.17) when comparing DL exposed and DL unexposed person-time. Due to Statistics Denmark privacy restrictions, there were too few events in patients <20 years of age to conduct the analysis, or include in the overall all age group analysis. There was no association between exposure status and first A-fib/flu in patients 20-64 years. The association between DL and first A-fib/flu was consistent across sensitivity analyses that varied exposure definitions but was substantially attenuated in an analysis that adjusted for an alternative set of confounders (aIRR 1.04, 95% CI 0.99; 1.09) than those used in the main analysis. This attenuation suggests that the association between DL and A-fib/flu found in the main analysis may be due to residual confounding.

11.1.1 Key Results in Comparison with P203 Results

Overall, the findings of this PASS (P205) are consistent with what was reported in P203. The results of the main analysis in P203 [Ref. 5.3.6: 05822K] found a higher rate of first seizure in DL exposed person-time compared with DL unexposed person-time. Across all age groups, the magnitude of the aIRR for seizure is small (aIRR 1.15, 95% CI 1.03; 1.29 (P203 Final Report- Table 2B2)) after adjustment for age, country, sex, calendar year, seasonality, asthmatic status, chronic urticaria status. The overall finding of increased risk of first seizure is driven by increased IR of first seizure in the 0-4 year-old (aIRR 1.47, 95% CI 1.16; 1.87) and in the 5-19 year-old (aIRR 1.32, 95% CI 1.09; 1.59) age categories when comparing DL exposed and DL unexposed person-time. DL exposure status was not associated with first seizure in patients 20 years old or older (P203 Final Report- Table 2B2). In this study, the overall aIRR is similar (aIRR 1.20, 95% CI 1.08; 1.33), as is that in the 0-4 year old (aIRR

1.65, 95% CI 1.34; 2.03) and the 5-19 year old (aIRR 1.34, 95% CI 1.12; 1.61) age groups [Table 15]. The slightly higher aIRR for seizure overall and in the 0-4 year old age group in particular is driven by the higher adjusted incidence rate ratio in Norway (aIRR 2.28, 95% CI 1.57; 3.31 [Table 25]). The overall aIRR in Norway is notably higher than in Denmark (aIRR 0.86, 95% CI 0.57; 1.31), Finland (aIRR 1.31, 95% CI 1.05; 1.63) and Sweden (aIRR 1.14, 95% CI 0.99; 1.31) [Table 25]. When broken out by age and country, the seizure findings from Norway appear to arise from the results in the youngest age group of 0-4 year olds (aIRR 2.26, 95% CI 1.45; 3.52) [Table 36]. Results of the older age groups in Norway are suppressed due to less than 10 events in the exposed or unexposed strata.

There are several reasons for the different seizure results in Norway. First, the definition of seizure is more inclusive in Norway, as Norway does not distinguish between types of seizure. The ICD-10 code R56 used to define seizure events includes all types of seizure (febrile, non-febrile and other seizures) in Norway, whereas for the main analyses the other Nordic countries use a more specific definition of seizure (ICD-10 R56.8), which only includes non-febrile seizure. The Norway main analysis results are closer in magnitude to the P203 results of the combined supplementary analysis for first febrile and non-febrile seizure among children age 0-4 years (aIRR 1.88, 95% CI 1.66; 2.13, (P203 Final Report Table S2.1)), suggesting that the inclusion of febrile seizure may increase the incidence rate ratio. Second, the period to assess whether a seizure event is an incident event or occurred prior to taking DL is shorter in Norway (a minimum of 2 years) than it is for the other countries. The shorter time to ascertain events occurring prior to initiating DL means that some recurrent events may be mis-categorized as incident events. However, post-hoc analysis 6 did not show country notable country variation in the percent of exclusions between countries when examining percent of exclusions that were more than 2 years prior to DL initiation, suggesting that mis-categorization of recurrent events in Norway would be small. Third, Norway has a much smaller population of individuals included and study period is much shorter—6 years, as compared to 15 years for Denmark and Finland, and 11 years for Sweden. Therefore, the overall person-time contributed by Norway is smaller. Due to the shorter study, there is also less time at risk and less opportunity to contribute unexposed person-time. Incidence rate ratios estimated for Norway have larger standard errors and are less robust than the other three countries.

The P203 PASS found no association between DL exposure status and incident SVT in the adjusted main analysis (aIRR 1.03, 95% CI 0.92; 1.15 (P203 Final Report Table 3B2 [Ref. 5.3.6: 05822K])) or in supplementary analyses. Similarly, this PASS (P205) also found no association between DL exposure status and incident SVT in the adjusted main (aIRR 1.01, 95% CI 0.91; 1.13 [Table 18]) or supplementary analyses. Results mentioned above do not adjust for 5 year age within the age category. Adjusting for 5-year age within the age groups does not alter the conclusion regarding no association between DL use and first SVT (Post-Hoc Analysis 2 [Table 19]).

In the updated results of the main analysis in P203 study [Ref. Responses: response-ema-pass-ws1655-final], a slightly higher rate was found of first A-fib/flu in DL exposed compared with DL unexposed person-time (aIRR 1.06, 95% CI 1.01; 1.12 (Updated Table 4B2)) adjusted for 5-year age (within age category), country, sex, calendar year, seasonality, asthmatic status, chronic urticaria status and severe rhinitis. The overall finding of increased rate of first A-

fib/flu is driven by increased IR of first A-fib/flu in the ≥ 65 years age category (aIRR 1.08, 95% CI 1.02; 1.15 (Updated Table 4B2)) when comparing DL exposed and DL unexposed person-time. The aIRR of first Afib/flu was consistent across sensitivity analyses that varied the exposure definition but was substantially attenuated in an analysis that adjusted for an alternative set of confounders (aIRR 1.01, 95% CI 0.96; 1.06 (P203 Final Report Table S8.3)). The results for A-fib/flu for this PASS (P205) also found a slightly higher rate of first A-fib/flu in DL exposed compared with DL unexposed person-time (aIRR 1.08, 95% CI 1.03; 1.14 [Table 21]) adjusted for 5-year age (within age category), country, sex, calendar year, seasonality, asthmatic status, chronic urticaria status and severe rhinitis. The overall finding of increased rate of first A-fib/flu is driven by increased IR of first A-fib/flu in the ≥65 years age category (aIRR 1.10, 95% CI 1.03; 1.17 [Table 21]) when comparing DL exposed and DL unexposed person-time. The aIRR of first A-fib/flu was consistent across sensitivity analyses that varied the exposure definition but was substantially attenuated in an analysis that adjusted for an alternative set of confounders (aIRR 1.04, 95% CI 0.99; 1.09 [Table 33]). The small difference in results between the updated results from P203 and P205 may be the result of the exclusion of the younger age groups due Statistics Denmark privacy restrictions the require omission of subgroups with less than 10 events. The omitted age groups have lower background rates of A-fib/flu than the older age groups, as such these exclusion could slightly increase the IRR.

Because DL is used on an as needed basis and it is difficult to capture when DL was taken, numerous sensitivity analyses were conducted. For A-fib/flu, most sensitivity analyses showed results that were consistent with the main analysis findings. In P203 supplementary analysis S6.3 showed an increased risk of A-fib/flu following the first prescription redemption (aIRR 1.29, 95% CI 1.18; 1.42 (P203 Final Report Table S6.3)). In this PASS (P205) including data from Norway, Supplementary Analysis 6.3 showed an increased risk of A-fib/flu following the first prescription redemption (aIRR 1.37, 95% CI 1.26; 1.49) [Table 30]. This is finding is attenuated when adjusting for the alternative confounder set (aIRR 1.29, 95% CI 1.18; 1.40 [Table 37]), indicating that there may be residual confounding. The small differences in results from P203 and P205 may because of the exclusion of the younger age groups due Statistics Denmark privacy restrictions and less than 10 events occurring in the exposed and/or unexposed groups.

11.2 Limitations

Variables used for inclusion and exclusion criteria

In Substudies 2B, seizure outcomes for which a drug overdose was also registered at the same hospitalization are excluded. In general, drug overdoses are likely to be underreported in the registers, as the registers often do not have sufficient detail to differentiate between overdoses from different types of drugs. Therefore, it was not possible to distinguish between overdoses from DL and overdoses from other drugs. Because overdoses of DL are rare compared to other drug overdoses, persons with any drug overdose registered during the same hospitalization as the seizure were excluded from analyses 2B. As a result, this study cannot determine whether the seizure outcomes were specifically associated with DL overdoses.

Sample size

Due to new privacy restrictions put forth by Statistics Denmark, counts less than 10 are required to be suppressed and overall calculations can no longer contain these subgroups. Therefore, the 0-4 and 5-19 age categories are not included in the analysis of the association between DL use and A-fib/flu and the 0-4 year age group is not included in the analysis of the association between DL use and SVT. Therefore, for P203 and P205 the overall results the combines age groups for A-fib and SVT analyses include different age groups and the overall combined results are not directly comparable for these outcomes.

As noted in the protocol and final report for P203, based on the assumptions made, the sample size was not adequate in the youngest age group for the assessment of the potential association between DL use and A-fib/flu. Also, for the 0-4 year-old age group only relatively strong associations (IRR=8.2) could be detected for the association between DL use and SVT.

Data from Norway

The study period is shorter for Norway (2008-2015) than for the other 3 countries (2001-2015) for Denmark and Finland and (2006-2015) for Sweden. Because of the date of establishment of each of the registries in Norway, the period to assess whether an event occurred prior to taking DL is shorter (a minimum of 2 years) than the other countries (11 years for Sweden and 6 years for Denmark and Finland). Further, the assessment period for measuring first DL use is 6 months in Norway. The shorter time to ascertain events occurring prior to initiating DL means that some recurrent events may be miscategorized as incident events. However, post-hoc analysis 6 indicates that if there was mis-categorization of recurrent events in Norway, it was likely small and would not have a large impact on the results. The shorter time period for Norway also means that there is a shorter time period for assessing prior DL use. It could be a patient took DL at a time period longer than 6 months prior. If a patient took a prescription more than 6 months previously in Norway, this would lead to misclassification of Supplemental Analysis 6 [Table 28], [Table 29], [Table 30] which categorizes current exposure with respect to first, second, third or more prescriptions.

Prescription redemption versus consumption

It is likely that in this study there was exposure misclassification. The prescription registers contain information about redeemed prescriptions, but no information about actual use of the drug. It is difficult to ascertain when patients were actually taking DL because it is a medication taken on an as needed basis. Therefore, lack of information about actual date of use of the drug is considered a major limitation. To address this limitation, multiple sensitivity analyses were conducted under the assumption that the closer to the date of the prescription redemption the more likely a patient is to be taking the drug. Further, sensitivity analyses also examined associations with the study outcomes stratified by repeated prescription redemption, as repeated prescription redemption likely indicates medication use. Overall, the sensitivity analyses with alternative definitions of exposure status supported the results obtained in the main analyses. The robustness of the findings to alternative definitions of exposure is reassuring.

Seizure diagnoses

The incidence rate of seizure in the general population in Sweden was nearly double the size as compared to Denmark and Finland. The same pattern was seen in the incidence rate of seizure in the currently DL unexposed periods. In Denmark, Finland, and Sweden, seizure in the present study was defined using ICD-10 system with codes R560 and R568 for febrile and non-febrile seizures, respectively. Most analyses in this PASS focused on non-febrile seizures. Due to privacy concerns, the Norwegian Health Authority did not allow release of ICD-10 codes that differentiated between febrile and non-febrile seizure. Instead, the Norwegian Health Authority provided a less specific code (R56) that aggregated more specific R56 subcodes including febrile, nonfebrile, post-traumatic and unspecified seizures. It is not possible to further delineate these subgroups of seizures. As febrile seizures only occur in children 5 years and younger (seizures with fever occurring in children 6 years and older are considered clinically distinct and worked up differently), a post-hoc sensitivity analysis using alternate age cut points (0-5 and 6-19 year old age category) was conducted in order to group the children that may have experienced febrile seizure together in one age category. For Norway, the 0-5 year age category will include febrile seizure, but it will also include other types of seizure.

ICD-10 R-codes are used for diagnosing symptoms. However, a seizure diagnosis can also be coded using G-codes, used for diagnosing neurological diseases. Seizure has not been defined in the present study based on G-codes. No information is available about how often the R- and G-codes are used in clinical practice and coding. However, there is no reason to believe that within a country, there would have been differential misclassification of seizure by exposure status.

Lack of migration history in Finland and Norway

Migration history for the Finnish or Norwegian populations was not available for the study. Therefore, individuals with a DL prescription redemption within the first 6 months after immigration could not be identified as potential prevalent users, who should have been excluded in the analysis. In Denmark and Sweden, the number of individuals excluded due to their migration history was small and the consequence of lacking migration history for Finland and Norway is also most likely small.

Lack of information on potential confounders

Potential confounders were identified using DAG methodology prior to initiating the analysis of data. Clinical experts were involved in DAG exercise. Two sets of potential confounders were identified for each outcome. One set was used for all main analyses; the second set was used in supplementary analyses.

For the cardiac outcomes, the cardiologist consultant on the project, believed that the second set of confounders (age (0-4, 5-19, 20-64, 65+), sex, country, calendar year, seasonality, severity of rhinitis, asthma status, diabetes, hypo/hyper-thyroidism, inflammatory disease, infections, and type 1 allergy) were the more clinically relevant and appropriate confounder set. Therefore, the adjusted results from this confounder set will be included in a future manuscript.

For the second confounder set, inflammatory diseases were defined as having had a diagnosis of inflammatory bowel disease, psoriasis, rheumatic diseases, vasculitis, or sarcoidosis or having redeemed at least two prescriptions of Calcipotriene (daivonex) in the five-year period before first DL prescription redemption. Other drugs used to treat inflammatory diseases including biologic treatments used to psoriatic arthritis, lupus, ankylosing spondylitis, systemic sclerosis are not included the confounder set, because these medications (i.e. biological treatments) are administered by the hospitals/outpatient clinics and not by prescriptions from pharmacies. These treatments are not well captured by the prescription drug registrars. Patients receiving biologic treatments but not coded as having inflammatory disease in the patient registrars would not be categorized as such.

After performing the analyses of this and the preceding study (P203), additional potential confounders have been considered. Concomitant medication use was not considered as a potential confounder when the DAG was derived. Data on concomitant medication use were not requested at the time of application for register data. The prespecified analysis only stipulated the extraction of specific medication use (DL, loratadine, non-sedating antihistamines, or anti-hypertensive medication) from the register data and therefore, other medication use could not be controlled for in the analysis. Potential confounders, such as, use of sympathomimetic decongestant drugs, which may be associated with A-fib/flu and may also be associated with initial symptomatic treatment of allergic rhinitis. For example, a published case report describes a patient with A-fib induced by use topical nasal decongestants (tramazoline) [Ref. 5.4: 057520]. A 2012 review of studies of drug induced atrial fibrillation identified other potential proarrhythmic drugs including, non-steroidal anti-inflammatory drugs (NSAIDS), corticosteroids, respiratory medications (oral steroids, oral beta-agonists, theophyllines), alendronate; these drugs had relative risks ranging from 1.3 for beta-agonists and 6.1 for high-dose pulse glucocorticoid therapy [Ref. 5.4: 05750T]. It is conceivable, then, that the observed association between DL and A-fib/flu could be confounded by unmeasured medication use, particularly decongestants.

11.3 Interpretation

This study found an association between DL exposure and two study outcomes: first seizure and first A-fib/flu. No association with DL exposure and SVT was found. Below, the evidence supporting a causal association is considered first for seizure and then for A-fib/flu. To help understand these findings, the results are described in the context of Hill's criteria for causation and pharmacovigilance data [Ref. 5.4: 05752B]. While Hill's criteria are not an exhaustive list by which a researcher can conclusively determine causation, they are a helpful framework for evaluating the results.

There are several components of Hill's criteria for causation: strength of association, consistency, temporality, biological gradient, plausibility/coherence, specificity, and experiment. Selected components are discussed, in turn, below.

Seizure

Strength of association: The results of this PASS indicated a small-to-modest strength of association between DL exposure and seizures. The results of the main analysis show 65% increase in first seizure in 0-4 year-olds and 34% increase in first seizure in 5-19 year-olds when comparing exposed with unexposed person-time, adjusting for the confounders selected in the DAG exercise.

Consistency: While there is variation in the effect estimates for this association in these age categories across countries, the association persisted in multiple sensitivity analyses that varied the exposure definitions and confounders that were adjusted for in the analyses. The presence of the finding across multiple sensitivity analyses indicates a consistent effect.

Specificity: Specificity means that a specific cause results in a specific outcome and that a specific outcome results from a single cause. There is no evidence of specificity, as there are many causes of seizures.

Temporality: As patients with a prior history of seizure were excluded, the results of this PASS show a temporal relationship between DL exposure and seizures.

Biologic gradient: While this study did not specifically examine dose of DL, a higher aIRR was found in time periods (0-4 weeks since last prescription) compared with ≥27 weeks since last prescription. It is clinically reasonable to assume that the probability of actual exposure to an as-needed medication is higher in the first four weeks following its dispensing than times more remote from the dispensing.

Further, there was an association between DL exposure and seizure following the first DL prescription compared with non-exposed person-time. There was no association between DL and first seizure following the second or third prescriptions compared with non-exposed person-time. Two potential interpretations are consistent with this observation. One is that the time after first dispensing represents a period when an individual potentially had more days of actual exposure to the drug. This finding is also consistent with the concept of depletion of susceptibles; it is possible that patients who are prone to DL-associated seizure experience the symptoms early and then, stop taking the drug.

Plausibility/coherence: While a mechanism for action has not been established to determine plausibility/coherence, existing literature and post-marketing reports indicate that some patients with a history of pre-existing seizures had seizures that worsened when DL was introduced and did not recur when DL was discontinued [Ref. 5.4: 045VR5]. This scenario indicates a positive challenge–de-challenge test and lends credence to plausibility.

Experiment: A company-sponsored unpublished meta-analysis of randomized double-blind DL trial data was conducted and described in a Health Authority response in 2012 [Ref. 5.3.6: 00V5KT]. This meta-analysis, which was based on 47 randomized, double-blind studies identified in the medical literature, included 8,640 patients exposed to DL monotherapy and 1,717 treated with DL combination therapy. Industry and non-industry sponsored trials, and adult, adolescent and pediatric patients were included. The meta-analysis identified no

adverse events of seizure among patients exposed to DL in these DL trials. The duration of exposure within the studies ranged from a minimum of 2 days to a maximum of 85 days. Of the 8,640 patients, 8,394 were adults or adolescents age 12 years and older, and 246 were children less than 12 years of age [Ref. 5.3.6: 00V5KT]. Thus, there were no seizure adverse events in data generated under experimental conditions. However, exposure time and the number of exposed in these trials was limited. That no seizures were observed in 246 children exposed to DL in trials provides only limited reassurance given the background rate of seizure in the 0-4 (IR 130.6, 95% CI 128.9; 132.4) and 5-19 (IR 36.8, 95% CI 36.3; 37.3) year age groups.

Pharmacovigilance and prior literature

In 2006, based on information from spontaneous reports, the MAH added seizure to the list of adverse reactions in the company core data sheet [Ref. 5.3.6: 04NFN0].

In 2013, a publication [Ref. 5.4: 045VR5] describing 4 case reports of seizures in children with a family history of seizures or other relevant medical history indicated that some patients with a history of pre-existing seizures had seizures that worsened when DL was introduced and did not recur when DL was discontinued. This scenario indicates a positive challenge–de-challenge test. Subsequent to this publication, but prior to the completion of this PASS, an update to the Special Warnings and Precautions Section of the DL label for convulsions was added in 2017 [Ref. 5.3.6: 04NFN0] [Ref. 5.4: 045VR5]. The company core data sheet states: "Desloratadine should be administered with caution in patients with medical or familial history of seizures, and mainly young children, being more susceptible to develop new seizures under desloratadine treatment. Healthcare providers may consider discontinuing desloratadine in patients who experience a seizure while on treatment."

Summary

This PASS indicates a small-to-modest association between DL exposure and seizures, particularly in children 0-4 years of age. This association is largely consistent across substudies and sensitivity analyses that varied the DL exposure definition and confounder set considered in the analysis. Pharmacovigilance data and results from this PASS suggest that seizures should be considered an adverse reaction to DL.

Public Health Implications

Based on the magnitude of association observed in this study, the safety risk posed by DL exposure on a population basis would be expected to be small. More specifically, among children 0-4 years of age, the adjusted absolute increase in incidence rate of first seizure in currently DL exposed person-time compared to not currently exposed person-time was 55.9 per 100,000 PY. Based on this rate difference, assuming a causal relationship and no residual confounding, one would expect 1 additional incident seizure for every 1,789 children aged 0-4 years using DL for one year. Among children and teenagers 5-19 years of age, the adjusted absolute increase in incidence rate of first seizure in currently DL exposed person-time compared to not currently exposed person-time was 10.2 per 100,000 PY. Based on this rate difference, assuming causal relationship and no residual confounding, one would expect 1 additional incident seizure for every 9,804 children or teenagers aged 5-19 years receiving DL

for one year. The foregoing statements are true assuming continual use. While patients using DL may have more severe allergy symptoms than patients using over-the-counter medications, DL is used for symptomatic treatment and is seldom used as continual year-round therapy.

A-fib/flu

Strength of association: This PASS found a small association between DL exposure and A-fib/flu. The results of the main analysis show 8% increase in first A-fib/flu overall and 10% increase in first A-fib/flu in ≥65 years when comparing exposed with unexposed person-time and adjusting for confounders selected in the DAG exercise, and adjusting for age in 5-year age groups in each age category.

Consistency: While the results of this study consistently show an association between DL exposed person-time and A-fib/flu in the ≥65 year age group in both the main analysis and sensitivity analyses that vary the exposure definition, this association is not seen in the 20-64year age category. In the general population, overall rate of A-fib/flu is highest in the ≥ 65 year age category and the age category that is presumably most vulnerable to A-fib/flu., The overall attenuation of effect and lack of association between DL exposed person-time and A-fib/flu when adjusting for an alternative confounder set suggests residual confounding may be driving the results observed in the main analysis. The lack of association with adjustment for an alternative confounder set, does not support a causal interpretation.

Specificity: Specificity means that a specific cause results in a specific outcome and that a specific outcome results from a single cause. In this instance, specificity does not apply, as A-fib/flu may result from multiple risk factors and causes.

Temporality: As patients with a recorded prior history of A-fib/flu were excluded, the results of this PASS indicate a temporal relationship between DL exposure and A-fib/flu. DL use occurs prior to the outcome.

Biologic gradient: While dose was not specifically examined to assess the presence of a biological gradient, there was a higher magnitude of association after first DL prescription compared with the main analysis. This association is not seen following the second or third DL prescription, A separate sensitivity analysis shows that the association between DL and A-fib/flu wanes after time since last prescription redemption increases from 0-8 weeks to ≥ 9 weeks.

Plausibility/coherence: While no specific mechanistic studies were undertaken, review of preclinical data evaluating the electrophysiological properties of the drug did not find a pro-arrhythmic mechanism suggested by pharmacology [Ref. 5.3.6: 03XD75]. Thus, there is no known mechanism of action that supports the plausibility/coherence of this association.

Experiment: In this PASS, an association between DL exposure and A-fib/flu was only seen in the ≥65 year age group. No signal for A-fib/flu was observed in DL clinical trial data [Ref. 5.3.6: 00LZQ9, 03XD75].

Pharmacovigilance and prior literature

The Merck Adverse Event Reporting and Review System database was searched through 01-Aug 2020, for reports related to DL and DL + pseudoephedrine. There were 19 cases containing 20 events listed as A-fib (13) or flutter (7) listed with DL and no events for DL + pseudoephedrine. Sixteen of the 19 cases were considered as having insufficient information to determine the possible causal association between DL and the reported adverse events. The missing information included medical history, concomitant medications, desloratadine therapy dates, the onset date of the adverse event, laboratories or tests performed to diagnose the adverse event, evaluation of predisposing risk factors, action taken with desloratadine, or outcome of the event.

In the remaining 3 cases, the assessments were confounded by either cardiovascular risk factors in the patients' medical histories, such as being overweight, renal insufficiency, type 2 diabetes mellitus, atherosclerosis, angina pectoris, COPD, hypertension, hypertrophic cardiomyopathies, among others, or by concomitant medications known to be associated with these adverse events.

The spontaneous reports included no instances of positive rechallenges for A-fib/flu.

The review of the literature search results did not identify any published clinical articles reporting a clinically significant association between DL and A-fib/flu.

Review of post-marketing cases and the available evidence in the published literature does not support an association between DL and A-fib/flu.

Summary

This PASS found a small association between DL exposure and A-fib/flu. Evidence is insufficient to conclude that the association between current DL use and A-fib/flu is causal. Several factors argue against a causal interpretation for the association between DL and A-fib/flu, including the strength of association and lack of consistency in the findings in subgroup and sensitivity analyses. The lack of association when adjusting for an alternative confounder set indicates that residual confounding may influence results.

Alternative explanations

Given that interpretation of the A-fib/flu findings through the lens of Hill's criteria are inconclusive, it is helpful to consider alternative explanations that may help explain A-fib/flu findings.

As noted in the limitations section, this study lacked information on some potential confounders. Several factors that could confound the relationship between DL and A-fib/flu were not controlled for in the analysis. First, concomitant medication use was not captured. In particular, use of sympathomimetic drugs or other stimulants, which may be associated with A-fib/flu and may also be associated with initial symptomatic treatment of allergic rhinitis. This confounder was considered post-hoc, when conducting the analysis of the study, and therefore, no data are available to include concomitant medication use as a confounder.

Second, clinically relevant comorbidities and risk factors for A-fib/flu were not adjusted for in the main analysis. For example, in supplementary analysis 8, an alternate confounder set was considered, which included seasonality, asthma status, diabetes, hypo/hyper-thyroidism, inflammatory disease, infections, type 1 allergy and severe rhinitis combined and anti-hypertensive treatment. After adjustment for this alternate confounder set, DL was no longer associated with A-fib/flu (aIRR 1.04, 95% CI 0.99, 1.09 [Table 33]). This attenuation suggests that residual confounding may affect the A-fib/flu results from the main analysis, and the alternative confounder set may be more clinically relevant with respect to A-fib/flu.

Public health implications

This PASS found a weak association between DL exposed person-time and A-fib/flu patients in ≥65 year age group. Given the small magnitude of association and no association in older age groups where the background risk is greatest, it is difficult to conclude that the association is causal. The possibility of residual confounding is also a plausible explanation for the results as an alternative confounder set attenuates these results. However, if one were to assume that the observed association is causal, the absolute risk difference is modest, which means that the risk of A-fib/flu attributable to DL exposure would be small. Among individuals ≥65years of age currently exposed to DL, the absolute overall increase in first A-fib/flu compared to individuals currently not exposed was 45.1 per 100,000 PY.

Study Strengths

The main strength of this study is that it includes nationwide population register data covering the entire population from four Nordic countries, and includes more than 2.1 million DL users. In addition to the large sample size, these data have minimal patients lost-to-follow-up and limited selection bias, as these data cover the entire country. This has relatively long follow-up time especially for the Danish and Finnish populations. Further, by using patients who were all initially exposed to DL, the study design minimizes confounding by patient factors that do not vary over time. Data include individual-level information on potential confounders for all individuals included. The quality of the registers is high due to the completeness and validity of the registered data [Ref. 5.4: 045TYK, 045TZL, 00W4G3].

11.4 Generalisability

The study outcomes have been previously validated. Previous studies validated the definition used for febrile seizure in Danish National Patient Register and reported a positive predictive value of 93%. Additionally, the A-fib/flu definition was validated in Danish National Patient Register and had a positive predictive value of 93%.

In this study, nation-wide Nordic registers were used with information on prescription drugs and hospital discharges. Since all registers have high completeness and high validity and all DL users and all individuals with seizure, SVT or A-fib/flu were included, the results have high external validity with generalizable results to Nordic and other European populations.

12 OTHER INFORMATION

None

13 CONCLUSION

This study was undertaken to evaluate the potential associations between DL and four outcomes, seizure, SVT, A-fib/flu and first recurrent seizure using Nordic national register data from Denmark, Finland, Norway, and Sweden. Using a register-based cohort design, the study enrolled new users of DL and compared periods of presumed current use with periods of presumed non-use, based on time since last dispensing. The study identified a small association with incident seizure overall (aIRR 1.20, 95% CI 1.08; 1.33), adjusted for age-, sex, country-calendar year, seasonality, asthma status, severe rhinitis status, and chronic urticaria. This finding was largely driven by associations in the younger (0-4 and 5-19-year old) age groups. For first seizure, aIRR is about 1.7 for 0-4 year-olds and 1.3 for 5-19 year-old age groups comparing exposed to unexposed PY. The associations were largely consistent across sensitivity analyses. Taken together with prior pharmacovigilance data, it is reasonable to conclude that seizures should be considered an adverse reaction to DL. Even if causality is assumed, however, the absolute rate difference is 56 per 100,000 PY in the 0-4 and 10 per 100,000 PY in the 5-19 year age groups, indicating absolute increases in risk are small.

The study found no association between current use of DL and risk of first SVT.

The study also found an association between current use of DL and risk of first A-fib/flu that persisted after adjustment for preselected confounders (aIRR 1.08, 95% CI 1.03; 1.14). In analyses stratified by age, the association was strongest for patients aged ≥65 years (aIRR 1.10, 95% CI 1.03; 1.17) and was not seen in the elderly, in whom the baseline risk of this outcome is known to be highest. Several factors argue against a causal interpretation for the association between DL and A-fib/flu. This association was not observed in the 20-64 year age group, was small in magnitude, and could be plausibly explained by residual confounding as evidenced by the attenuation with sensitivity analysis adjusting for alternative confounders. Evidence is insufficient to conclude that the association between current DL use and A-fib/flu is causal.

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Annex 1 Study Protocol

Product: MK-4117 1
Protocol/Amendment No.: 205-00 version 1
VEAP ID NO: 9149
EPIDEMIOLOGY NO.(PE STUDIES ONLY): EP07044.004

PASS INFORMATION

Title	Association between use of desloratadine and risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter: A Nordic register-based study
Protocol Version identifier	205-00 version 1
Date of last version of protocol	23-Jun-2020
EU PAS Register No:	Study not registered
Active substance	Desloratadine, ATC code R06AX27; Pharmacotherapeutic group: Antihistamines – H1 antagonist
Medicinal products:	AERIUS, AZOMYR, and NEOCLARITYN
Product reference:	EU/1/00/160, AERIUS EU/1/00/157, AZOMYR EU/1/00/161, NEOCLARITYN
Procedure number:	Not applicable
Marketing authorisation holder(s) (MAH)	Merck Sharp & Dohme B.V. Waarderweg 39 2031 BN Haarlem The Netherlands
Joint PASS	No
Research question and objectives	To describe the use of desloratadine in the general population; to describe the incidence rates of first seizure, supraventricular tachycardia, and atrial fibrillation or flutter; and to examine the associations between desloratadine exposure and risk of first seizure, supraventricular tachycardia, and atrial fibrillation or flutter.
Country(-ies) of study	Denmark, Finland, Norway, Sweden
Author	Annette Kjær Ersbøll National Institute of Public Health University of Southern Denmark Studiestræde 6 DK-1455 Copenhagen K Denmark Phone: PPD E-mail: PPD

Marketing authorisation holder(s) including MAH Contact Person	PPD Center Merck Sharp & Dohme (Europe), Inc. Lynx Binnenhof 5 1200 Brussels, Belgium Phone: PPD Fax: PPD E-mail: PPD
Merck Final Repository (RCAM) Date	25-Jun-2020
Date of Health Authority Approval of Protocol	Not applicable

Product: MK-4117 3
Protocol/Amendment No.: 205-00 version 1
VEAP ID NO: 9149
EPIDEMIOLOGY NO.(PE STUDIES ONLY): EP07044.004

SUMMARY OF CHANGES

Protocol Section	Change
N/A	N/A

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LIST OF ABBREVATIONS

AE	Adverse event
A-fib	Atrial fibrillation
A-flu	Atrial flutter
A-fib/flu	Atrial fibrillation or atrial flutter
aIRR	Adjusted incidence rate ratio
ApEHR	Institute of Applied Economics and Health Research
ATC	Anatomical Therapeutic Chemical Classification System
CHF	Chronic heart failure
CHMP	Committee for Medicinal Products for Human Use
COPD	Chronic obstructive pulmonary disease
DAG	Directed acyclic graph
DDD	Defined daily dose
DL	Desloratadine
DSUR	Development safety update report
EMA	European Medicines Agency
EU	European Union
ICD	International Classification of Diseases
IR	Incidence rate
IRR	Incidence rate ratio
MAH	Marketing authorization holder
MSD	Merck Sharp & Dohme, a subsidiary of Merck & Co., Inc.
NIPH	National Institute of Public Health, University of Southern Denmark
NSAE	Non-serious adverse event
PASS	Post-authorisation safety studies
PIC	Personal identification code
PPV	Positive predictive value
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
PV	Pharmacovigilance
PY	Person-years
OTC	Over-the-counter
QBA	Quantitative Bias Analysis
SAE	Serious adverse event
SAP	Statistical analysis plan
SCRID	Self-controlled risk interval design
SD	Standard deviation
SVT	Supraventricular tachycardia

1 RESPONSIBLE PARTIES

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2 ABSTRACT

Title	Association between use of desloratadine and risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter: A Nordic register-based study
Protocol Number / Version	205-00 version 1
Date	29-May-2020
Author	Annette Kjær Ersbøll, Professor, NIPH, University of Southern Denmark, Copenhagen, Denmark
Rationale & Background	A post-authorization safety study was needed to assess the potential risk of desloratadine exposure on seizures, supraventricular tachycardia, and atrial fibrillation or flutter. PASS (P203) was submitted and the regulatory commitment was accepted as complete using data from Denmark, Finland, and Sweden in January 2020. The original commitment and its associated protocol (P203) included analyses on four countries, but due to delay in receipt of the data from Norway, the EMA allowed MSD to provide a final report without these data. This protocol (P205) is a voluntary PASS including analyses as intended in the original study protocol (P203) of the Norway data both alone and in combination with the original three countries.
Research Question(s) & Objective(s)	To explore the use of desloratadine in the general population (Substudy 1); to describe the incidence rate of first seizure (Substudy 2A); to examine the associations between desloratadine exposure and risk of first seizure (Substudy 2B); to describe the incidence rate of supraventricular tachycardia (Substudy 3A); to examine the association between desloratadine exposure and supraventricular tachycardia (Substudy 3B); to describe the incidence rate of atrial fibrillation or flutter (Substudy 4A); and to examine the associations between desloratadine exposure and atrial fibrillation or flutter (Substudy 4B).

Study Design	Observational, nationwide, register-based study using person-specific linkage of data from the national population registers from Denmark, Finland, Norway, and Sweden ("Nordic countries") including all individuals who redeemed a prescription of desloratadine and all individuals with a registered diagnosis of seizure, supraventricular tachycardia, or atrial fibrillation or flutter.
Population	The population consists of a cohort of desloratadine users, a cohort of individuals with seizures, a cohort of individuals with supraventricular tachycardia, and a cohort of individuals with atrial fibrillation or flutter. The general population of the four Nordic countries will be used to derive estimates of the risk time by age, year, and country.
Variables	The exposure variable of interest is desloratadine for which current use (i.e., exposed period) will be defined as the period after each redeemed prescription equal to the number of days' supply plus a 4 week grace period to account for intermittent use and a possible wash-out effect. To minimize exposure misclassification, we propose to use person time at least 26 weeks beyond the dispensing date of the last prescription as the "unexposed" reference period. The outcome variables are first seizure, first supraventricular tachycardia diagnosis, and first atrial fibrillation or flutter diagnosis. Directed acyclic graphs (DAGs) were developed to identify the minimum sufficient adjustment set of confounders to include in the association analysis of each outcome.
Data Sources	Data will be obtained from nationwide population registers, including the national patient registers, the civil registration systems, and the prescription registers.
Study Size	The sample size is fixed, as it will consist of all individuals in four Nordic countries (Denmark, Finland, Norway, and Sweden) who have redeemed at least one prescription for desloratadine or who have received a diagnosis of seizure, supraventricular tachycardia, or atrial fibrillation or flutter.

Data Analysis	A descriptive analysis of desloratadine use in the general population will be performed. Furthermore, the incidence rates of seizure, supraventricular tachycardia, and atrial fibrillation or atrial flutter will be calculated. Among persons ever dispensed desloratadine, the associations between desloratadine exposure and first seizure, supraventricular tachycardia, and atrial fibrillation or flutter will be evaluated using Poisson regression of incidence rates accounting for confounding factors. Additional supplementary analyses will be performed.
Milestones	
Start of data collection:	31-July-2020
End of data collection:	15-August-2020
Final report of study results:	30-December-2020

3 AMENDMENTS AND UPDATES

None

4 MILESTONES

Milestone	**Planned Date**
Start of data collection	31-July-2020
End of data collection	15-August-2020
Registration in the EU PAS register	15-July-2020
Final report of study results	30-December-2020

5 RATIONALE AND BACKGROUND

Since market authorization, there have been a small number of adverse event reports of seizures and supraventricular arrhythmias in patients taking desloratadine (DL), but the case reports do not permit evaluation of the association. Denmark, Finland, Norway, and Sweden (hereafter also referred to as 'Nordic countries') offer unique opportunities for such a study by means of the existence of centralized registration of activities in the healthcare sector, covering complete populations over many years.

The European Medicines Agency (EMA) had previously requested that Merck Sharp and Dohme (MSD) consider options for a post-authorization safety study (PASS; Category 3 PV activity) to investigate whether there is an association between desloratadine (DL) use and seizures, supraventricular tachycardia, and atrial fibrillation or flutter in the general population. This PASS (P203) was submitted and the regulatory commitment was accepted as complete using data from Denmark, Finland, and Sweden in January 2020. Although the original commitment and its associated protocol (P203) included analyses on four countries, the data for Norway were very delayed and the EMA subsequently allowed MSD to provide a final report without these data.

This protocol (P205) is a voluntary PASS including analyses as intended in the original study protocol (P203) of the Norway data both alone and in combination with the original three countries. The findings for the analyses for all four countries (P205) will be submitted to the EU health authorities with the next PSUR. The only change from the original protocol's (P203) study methods/design is the removal of the secondary analyses. The subsequent final report for this protocol (P205) will build upon the report with the three countries to be inclusive of all four as was the intent of the original PASS.

DL is a prescription oral antihistamine approved in the European Union (EU) for the relief of symptoms associated with allergic rhinitis and urticaria in both adults and children (Annex 5. Data from the Danish National Prescription Register (www.medstat.dk/en; accessed 28 May 2014) suggest that about 270,000 Danish citizens (about 5% of the population) purchase antihistamines with a prescription at least once annually. This figure has been rather stable since the year 2000. The number of Danish citizens who purchase DL by a prescription at least once annually has increased from 7,317 in 2001 to 51,564 in 2012. The number of Danish children aged 0–4 years who purchased DL with a prescription at least once annually has increased from 8 in 2001 to 6,815 in 2012. The number of Danish children aged 5–19 years who purchased DL with a prescription at least once annually has increased from 935 in 2001 to 11,447 in 2012. In 2012, children aged 0–4 years accounted for 37% of all children (0–19 years) who purchased DL at least once. The background incidence of unprovoked seizures is rare; approximately 0.4-0.6 per 1,000 population per year [Hauser, W. A. and Beghi, E. 2008]. Patients with epilepsy experience seizures; however, not all individuals with seizures have epilepsy and not all seizures evolve into epilepsy [Hauser, W. A. and Beghi, E.

2008]. A previous study described clinical observations of seizures induced by DL in four children [Cerminara, C., et al 2013].

Supraventricular arrhythmias include supraventricular tachycardia (SVT), atrial fibrillation (A-fib), and atrial flutter (A-flu). Through review of cardiac events reported since marketing authorization, the MAH determined that SVT and A-fib constituted a potential risk and that the reported cases were distributed across all age groups, not just children. In the present study, new onset SVT and a composite of new onset atrial fibrillation or flutter (A-fib/flu) will be examined as two separate outcomes. The incidence rate (IR) of SVT is reported to be 13/100,000 person-years for persons aged 19 years or younger, 27/100,000 person-years for persons aged 20–64 years, and 122/100,000 person-years for persons aged 65 years or older [Orejarena, L. A., et al 1998]. Wilke et al. (2013) [Wilke, T., et al 2013] reported the incidence of A-fib to increase markedly by age with 0.0016 cases/1,000 person-years in children (<15 years) and approximately 30 cases/1,000 person-years for persons aged 80 years or older. No data on the epidemiology of A-flu were available.

The present protocol proposes a study using registers from the four Nordic countries to describe the association between DL use and seizures, SVT, and A-fib/flu.

6 RESEARCH QUESTION AND OBJECTIVES

The research question is to examine the associations between DL use and seizures, SVT, and A-fib/ flu in the general population.

Primary hypotheses (stated as null-hypotheses)

- There is no association between current DL use and first seizure.
- There is no association between current DL use and SVT.
- There is no association between current DL use and A-fib/flu.

Primary objectives

- Describe the use of DL during the study period in the general population overall and stratified by country, age, gender, calendar year, seasonality, severity of rhinitis, asthmatic status, and chronic urticaria status.
- Describe the IRs of the following outcomes in the general population:
    - Incident diagnosis of seizure;
    - Incident diagnosis of SVT; and

- Incident diagnosis of A-fib/flu.

- Compare the risk of incident seizure among persons while currently exposed to DL to the risk among the same persons while unexposed to DL for the total DL population and stratified by age, while adjusting for relevant confounding factors.

- Compare the risk of incident SVT among persons while currently exposed to DL to the risk among the same persons while unexposed to DL for the total DL population and stratified by age, while adjusting for relevant confounding factors.

- Compare the risk of incident A-fib/flu among persons while currently exposed to DL to the risk among the same persons while unexposed to DL for the total DL population and stratified by age, while adjusting for relevant confounding factors.

7 RESEARCH METHODS

7.1 Study Design

The proposed study will be an observational (non-experimental), nationwide, register-based study using data from the Nordic national population registers. The associations between current DL use and seizures, current DL use and SVT, and current DL use and A-fib/flu will be assessed in analyses using person-specific linkage of data (Table 1). The cohort of all DL users will be used for describing DL use (Substudy 1). The cohorts of individuals who have had first seizure, SVT, or A-fib/flu will be used to examine the IRs of first seizure, SVT, and A-fib/ flu in the general population (Substudies 2A, 3A, and 4A, respectively). A cohort study design among all DL users (i.e. a risk interval design including the DL-only cohort [Glanz, J. M., et al 2006]) will be used for the association between current DL exposure and first seizure, SVT, and A-fib/flu (Substudies 2B, 3B, and 4B, respectively).

Table 1 Overview of Substudies.

Primary objectives	
Substudy	**Aim**
1	Descriptive analysis of DL use in the general population
2A	Descriptive analysis of IR of first seizure in the general population
2B	Association between DL exposure and risk of first seizure
3A	Descriptive analysis of IR of first SVT in the general population
3B	Association between DL exposure and risk of first SVT
4A	Descriptive analysis of IR of first A-fib/flu in general population
4B	Association between DL exposure and risk of A-fib/flu

Pharmacoepidemiological studies typically use dispensed days' supply as a surrogate for current drug exposure, assuming they are used every day. However, in contrast to medications for many chronic diseases, antihistamines may be used intermittently, as needed for symptoms. For the main analyses in the present study of the association between current DL use and outcomes of interest (Substudies 2B, 3B, and 4B), person time exposed to DL will be determined from dispensing records. "Current use" (i.e., "exposed" period) will be defined for each prescription as the sum of days' supply plus a 4 week grace period to account for intermittent use and a possible wash-out effect. If a new DL prescription redemption occurs during an exposed period (either during the period equal to the sum of the days' supply or the 4 week grace period), the exposure period extends from that date with a period equal to the sum of days' supply in the newly redeemed prescription plus a 4 week grace period. Note: Days' supply will be calculated from the quantity of tablets or amount of solution dispensed and the standard daily dose based on the age of the patient (i.e., 6-11 months: 1 mg/day; 12 months-5 years: 1.25 mg/day; 6-11 years: 2.5 mg/day; ≥12 years: 5 mg/day). Because the drug is used "as needed", it is quite possible that there may still be exposed days in the period after the latest exposed period (i.e., after the exposed period that includes the sum of the days' supply plus a 4 week grace period). To minimize exposure misclassification, we propose to use person time at least 26 weeks beyond the dispensing date of the prior prescription as the "unexposed" reference period. The "unexposed" period is actually a period with remote exposure to DL because dispensing of DL is a condition of entering the study population. We will refer to the "remote exposure" period as "unexposed" (For more details, see section 7.3.1 and Figure 1). The time between the exposed period and the unexposed period is considered neither exposed nor unexposed.

The advantage of using this design restricted to DL users, in which the same persons may have both exposed and unexposed periods, is that we reduce confounding due to time-independent factors associated with DL use.

The study is divided into six parts described below (For more details, see section 7.7).

1. Substudy 1

A descriptive analysis of DL use in the general population. To describe DL use in the general population, we will identify both prevalent and incident users of DL and describe the distribution of the number of redeemed DL prescriptions for the total population and stratified by country, age, sex, calendar year, seasonality, severity of rhinitis, asthmatic status, and chronic urticaria status.

2. Substudies 2A and 2B

A descriptive analysis of the IR of first seizure overall in the general population and stratified by country, sex, and age will be conducted (2A).

Among persons ever dispensed DL, the association between exposure to DL use and first seizure will be evaluated using Poisson regression of the IR of first seizure for the total population and stratified by age when accounting for confounding factors (2B).

3. Substudies 3A and 3B

Descriptive analysis of the IR of SVT overall in the general population and stratified by country, sex, and age will be conducted (3A).

Among persons ever dispensed DL, the association between exposure to DL use and first SVT will be evaluated using Poisson regression of the IR of first SVT for the total population and stratified by age when accounting for confounding factors (3B).

4. Substudies 4A and 4B

Descriptive analysis of the IR of A-fib/flu overall in the general population and stratified by country, sex, and age will be conducted (4A).

Among persons ever dispensed DL, the association between exposure to DL use and first A-fib/flu will be evaluated using Poisson regression of the IR of first A-fib/flu for the total population and stratified by age when accounting for confounding factors (4B).

5. Supplementary analyses

In total, 10 supplementary analyses will be performed to examine the robustness of the results. These are described in further details in section 7.7.6 of the protocol as well as in the SAP.

7.2 Setting

The cohort of individuals with redeemed DL prescriptions will be identified from the four Nordic national prescription registers. Similarly, the cohort of all individuals with seizures (first seizure), the cohort of individuals with SVT, and the cohort of individuals with A-fib/flu will be identified from the four Nordic national patient registers. The population is comprised of all individuals with DL prescriptions and of all individuals with seizures, SVT, or A-fib/flu in the four Nordic countries in the period 2001–2015 in Denmark and Finland, 2008–2015 in Norway, and July 2005–2015 in Sweden (Table 5). Individuals for Substudies 2B, 3B, and 4B become eligible for the study cohort upon first dispensing of DL (See sections 7.2.1 and 7.2.2). Data will be available until and including 2015 for all countries.

7.2.1 Inclusion criteria

Substudy 1

- Individuals who have redeemed at least one prescription of DL during the study period (DL cohort) and have residential location in Denmark, Finland, Norway, or Sweden.
- General population living in Denmark, Finland, Norway, and Sweden on 01 January of each year.

Substudy 2A

- Individuals who have experienced a seizure during the study period (seizure cohort) and have residential location in Denmark, Finland, Norway, or Sweden.
- General population living in Denmark, Finland, Norway, and Sweden on 01 January of each year.

Substudy 2B

- Individuals who have redeemed at least one prescription of DL during the study period (DL cohort) and have residential location in Denmark, Finland, Norway, or Sweden.

Substudy 3A

- Individuals who have experienced a SVT during the study period (SVT cohort) and have residential location in Denmark, Finland, Norway, or Sweden.
- General population living in Denmark, Finland, Norway, and Sweden on 01 January of each year.

Substudy 3B

- Individuals who have redeemed at least one prescription of DL during the study period (DL cohort) and have residential location in Denmark, Finland, Norway, or Sweden.

Substudy 4A

- Individuals who have had an A-fib/flu diagnosis during the study period (A-fib/flu cohort) and have residential location in Denmark, Finland, Norway, or Sweden.

- General population living in Denmark, Finland, Norway, and Sweden on 01 January of each year.

Substudy 4B

- Individuals who have redeemed at least one prescription of DL during the study period (DL cohort) and have residential location in Denmark, Finland, Norway, or Sweden.

7.2.2 Exclusion criteria

Substudy 2A

- Individuals with a diagnosis of seizure, epilepsy, or prescriptions of antiepileptic medicine before entering the study period, as they have prevalent disease.

- Individuals with a diagnosis of malignant brain tumor or head trauma before the first seizure, as they are at high risk of seizures due to causes other than DL use.

Substudy 2B

- Individuals with a diagnosis of seizures, epilepsy, prescriptions of antiepileptic medicine, malignant brain tumor, or head trauma before redemption of first DL prescription, as they have prevalent disease or are at high risk of seizures due to causes other than DL use.

- Individuals with a brain tumor (benign and malignant), initiation of treatment with antiepileptic medicine, or head trauma occurring after beginning of DL use will be censored at date of first occurrence, as they are at high risk of seizures due to causes other than DL use.

Substudies 3A and 4A

- Individuals with a diagnosis of SVT or A-fib/flu before entering the study period, as they have prevalent disease.

- Individuals with a diagnosis of congenital pre-excitation syndrome (e.g., Wolff Parkinson White) before entering the study period, as they are at high risk of cardiac SVT or A-fib/flu due to causes other than DL use.

Substudies 3B and 4B

- Individuals with a diagnosis of SVT or A-fib/flu before use of DL, as they have prevalent disease.

- Individuals with a diagnosis of congenital pre-excitation syndrome (e.g., Wolff Parkinson White) before use of DL, as they are at high risk of SVT or A-fib/flu due to causes other than DL.

7.3 Variables

7.3.1 Exposure

The main exposure of interest in the present study is DL use identified in the national prescription registers by use of Anatomical Therapeutic Chemical Classification System (ATC) code R06AX27. The exploratory analysis will describe DL use based on data about persons who have redeemed at least one DL prescription (Substudy 1). In the association studies (Substudies 2B, 3B, and 4B), DL use is considered a time-varying variable, as the same person can be both exposed and unexposed during the study period depending on the time period from last redeemed DL prescription and the amount of days' supply redeemed at the last DL prescription redemption.

For the association analyses, person time exposed to DL will be determined from dispensing records and period of current use will be defined for each prescription as days' supply starting from the date of redemption plus a 4 week grace period to account for intermittent use and a possible wash-out effect. To minimize exposure misclassification, we propose to use person time at least 26 weeks beyond the dispensing date of the prior prescription as the "unexposed" reference period (in supplementary analysis 7, an alternative period of 52 weeks beyond the prior prescription is used to define the unexposed reference period). If a new DL prescription redemption occurs during an exposed period (either during the period equal to the sum of the days' supply or the 4 week grace period), the exposure period extends from that date with a period equal to the sum of days' supply in the newly redeemed prescription plus a 4 week grace period. In addition, a prescription redemption before 26 weeks after previous prescription redemption would mark the start of a new exposed period (and would not result in an unexposed period). Figure 1 below provides an example of how persons included in the association analyses enter and exit exposure periods during the study period.

Days' supply will be calculated from the quantity of tablets or amount of solution dispensed and the standard daily dose based on the age of the patient (i.e., 6-11 months: 1 mg/day; 12 months-5 years: 1.25 mg/day; 6-11 years: 2.5 mg/day; ≥12 years: 5 mg/day).

Figure 1 Example of current exposed periods versus unexposed periods for study subjects included in the association analyses (Substudies 2B, 3B, and 4B).

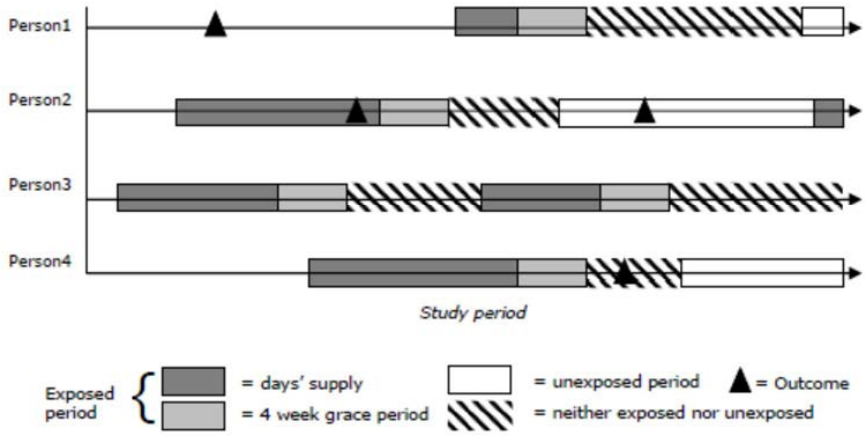

Figure 1 illustrates how subjects in the study population (i.e., restricted to persons with at least one *redeemed prescription of DL) enter and exit exposed and unexposed periods. An exposed period is a period starting from the day of redemption of a DL prescription and includes the following period equal to the number of days' supply in the drug packages purchased (illustrated with dark grey boxes) and a 4-week grace period (illustrated with the light grey boxes). Unexposed periods, which start 26 weeks after the dispensing date of the last DL prescription, are depicted with white boxes. The time between the end of the exposed period and the unexposed period is considered neither exposed nor unexposed; these periods are illustrated with shaded boxes. Moreover, the date at which an outcome (i.e., seizure, SVT, or A-fib/flu) occurs (if occurring) is marked with a black triangle. For example, person 1 experienced the outcome before redeeming DL for the first time (date of entering the study); and therefore, this person will be excluded. Person 2 experienced the first outcome while in an exposed period and a recurrent outcome occurred in an unexposed period. Person 3 was exposed to DL twice, but did not experience an outcome. Finally, person 4 was exposed to DL once and experienced the outcome in a period where the person was neither exposed nor unexposed; therefore, this outcome will not count toward the analysis of the association.*

In a supplementary analysis, an individual's exposure status is categorized according to time since last DL dispensing (periods 0–4, 5–8, 9–16, and 17–26 weeks each compared with >26 week since last DL dispensing), and individuals are considered unexposed in the period beyond 26 weeks after a DL prescription redemption until next DL prescription redemption, the end of the study period, death, emigration, or occurrence of the outcome, whichever comes first.

Loratadine, the parent compound of DL, is also available via prescription and over–the-counter in the Nordic countries. We think it is somewhat unlikely that patients would switch between DL and loratadine; however, it is possible that some of the time counted as unexposed in the analyses could actually be time exposed to loratadine. Moreover, other non-sedating prescription antihistamines are available in the Nordic countries, and if the effect on the outcomes is driven by use of non-sedating antihistamines in general rather than the specific effect of DL exposure, these drugs should be examined to elucidate potential misclassification of exposure. To explore exposure misclassification (i.e., the influence of loratadine and other non-sedating prescription antihistamines), on the associations under study), we will conduct supplementary analyses, which will be specified in the statistical analysis plan.

Regarding missing values in variables from the prescription registers, normally no registration is interpreted as the person does not use the drug (e.g., no registration of DL use is interpreted as the person has not used DL)). Prescription drugs are not available from sources other than the pharmacies, and all drugs purchased at pharmacies are included in the prescription register (the only exception are drugs supplied from hospitals, however less than 1% of DL is supplied by the hospitals). We do not expect missing information for data in the prescription registry that will be used to determine DL exposure (e.g., number of packs per redemption). However, we will examine data to see whether missing information occurs. Missing data handling will be determined after review of the data, but before data from different registers are linked together (e.g. handling of missing values for exposure data is blinded to outcome status and vice versa) and will be described in a data control report, which will be submitted with the study report.

7.3.2 Outcomes

Three outcome variables will be used in the present study: first seizure (Substudy 2B), first SVT (Substudy 3B), and first A-fib/flu (Substudy 4B). Except where noted, the case definition of seizure excludes febrile seizure, a condition in infancy and early childhood attributed to fever. However, supplementary analysis 2 will evaluate the outcomes of febrile and non-febrile seizures in children. (The diagnosis of febrile seizure is generally not used in adults.) Information on outcome variables will be obtained from the Nordic national patient registers, including diagnostic and treatment information for patients treated at the secondary and tertiary hospital level in all four Nordic countries using International Classification of Diseases (ICD)- 10 codes. We will exclude seizure cases if they are registered with brain tumor (benign and malignant), stroke, or acute drug intoxication or overdose of drugs during the same hospitalization as the seizure. Table 2 gives an overview of the outcome variables in the study. For all outcome variables, we will include the primary diagnoses from the emergency room or inpatient settings registered in the Nordic national patient registers.

The National Patient Registers are used for reimbursement of services to the hospitals. It is mandatory to enter specific information (such as name, date, main diagnosis) for the record to be established. Due to the requirements of the national registries, we do not expect missing data on the outcome variables. In Denmark and Finland, it is only possible to register hospitalizations into the Nordic national patient registers if complete information on the primary diagnosis, date, and hospital department is entered into the registration system. Therefore, no missing values should occur for these variables. This procedure is most likely the same for Sweden and Norway. Data in the Danish National Patient Register is automatically checked for missing codes, inconsistencies between diagnosis and gender, incorrect digits and errors in the personal identification code (PIC). If an error is detected, the record is returned to the source hospital for correction [Schmidt, M., et al 2015] .No studies have examined the validity of seizures in the total population, but Vestergaard et al (2006) examined the validity of the discharge diagnosis of febrile seizure in children the National Patient Register (ICD-10 code R56.0) [Vestergaard, M., et al 2006]. The positive predictive value (PPV) was 92.8% (95%CI: 88.8-95.7%). The sensitivity (defined as completeness by the authors) is 71.5% (95% CI: 66.3-76.4%) [Vestergaard, M., et al 2006]. The diagnosis of atrial fibrillation and atrial flutter has been validated in the Danish National Patient Register [Rix, T. A., et al 2012]. The PPV for the combined diagnosis of atrial fibrillation and atrial flutter (I48) was 92.6%. Other studies have found even higher PPVs [Frost, L., et al 2007] [Frost, L. 2004]. No studies have validated the diagnosis for supraventricular tachycardia (I47); however, we find it likely that this diagnosis has approximately the same validity in the National Patient Register as seen for atrial fibrillation and atrial flutter.

Table 2 Overview of the Outcome Variables in the Study

Substudy	Aim
Substudy 2B	First seizure: An incident case of seizure is a person with the first diagnosis of seizure
Substudy 3B	Supraventricular tachycardia (SVT): An incident case of SVT is a person with first diagnosis of SVT
Substudy 4B	Atrial fibrillation or atrial flutter (A-fib/flu): An incident case of A-fib/flu is a person with first diagnosis of A-fib or first diagnosis of A-flu. These two diagnoses will be combined into a composite endpoint

ICD-10 codes are listed in Annex 6. Note that the case definition of seizure in these substudies excludes febrile seizures.

7.3.3 Covariates

In the present study, we have used directed acyclic graphs (DAGs), also called causal diagrams, for confounder selection. DAGs are a well-accepted methodology for using causal knowledge and a set of formal mathematical principles for selecting which variables to adjust for when performing association analyses [Greenland, S., et al 1999]. They provide a systematic way to explore the relationships between the exposures, outcomes, and covariates (unidirectional, bidirectional, causal) and facilitate dealing with a large number of potential confounders. DAGs help make the assumptions underlying an analysis explicit. The selection of variables needed for confounder adjustment to obtain an unbiased estimate of the association under study is called the minimum sufficient adjustment set of confounders. We used the open source and freely available software DAGitty for the development of the DAGs [Textor, J., et al 2011]. DAGitty helps the researcher visualize the structure of relevant variables for the association under study included in the DAG, as well as to identify the minimum sufficient adjustment sets available for confounder adjustment. In the following paragraphs, we present a brief description of the DAG process; however, the full DAG process is described in Annex 8.

The factors listed in the left-hand column of Table 3 were considered potential confounders (i.e., candidate variables) for the association between DL use and seizures, SVT, and/or A-fib/flu based on the literature, as well as consultation with a group of clinical experts. The potential confounders were reviewed during a DAG meeting held on January 6, 2015. At this meeting, the relationships among the different factors were discussed, and DAGitty was used to help identify the minimum sufficient adjustment set of confounders to include in the association analysis of each outcome. Three DAGs including potential confounders of the association between DL use and seizures, SVT, and A-fib/flu, respectively, were developed by the Danish national investigators, MSD, ApEHR, and two clinical experts. After the DAG meeting, we consulted a dermatologist to confirm the correctness of the developed DAGs, especially regarding the relationships between urticaria and the other potential confounders. The DAGs helped clarify whether the potential confounders listed were confounders, colliders, or intermediate variables and which of the potential confounders constituted a minimum sufficient adjustment set. We selected the final minimum sufficient adjustment set, which will be used to adjust for confounding factors in the association studies based on whether we found that a given combination of confounders would be obtainable from the registers. The final minimum sufficient adjustment set for the association studies (i.e., 2B, 3B, and 4B) are seen in the right-hand columns of Table 3.

Table 3 Information on whether potential confounding factors are included in the DAGs and the minimum sufficient adjustment sets, which will be used for confounder adjustment in the association studies.

Potential confounding factors	Potential confounder included in the DAG			Confounders included in the selected minimum sufficient adjustment set for each association study		
	Seizures	SVT	A-fib/flu	Seizures	SVT	A-fib/flu
Age (age will be derived as a categorical and a continuous variable: Age groups [0–4 years, 5–19 years, 20–64 years, ≥65 years] and years)	Yes	Yes	Yes	Yes	Yes	Yes
Sex (male versus female)	Yes	Yes	Yes	Yes	Yes	Yes
Country of residence (Denmark, Finland, Norway, Sweden)	Yes	Yes	Yes	Yes	Yes	Yes
Calendar year (years ranging from 2001–2015)	Yes	Yes	Yes	Yes	Yes	Yes
Drug overdose (other than desloratadine)	Yes	Yes	Yes	No	No	No
Drug and alcohol abuse	Yes	Yes	Yes	No	No	No
Diabetes (both type 1 and type 2)	Yes	Yes	Yes	No	No	No
Use of hypoglycemic agents (oral anti-diabetics, insulin)	Yes	No	No	No	No	No
Hypertension	No	Yes	Yes	No	No	No
Thyroidism (both hypo- and hyperthyroidism, e.g., Grave's disease, thyrotoxicosis)	No	Yes	Yes	No	No	No
Structural heart disease: Left ventricular hypertrophy, left ventricular systolic dysfunction, chronic heart failure (CHF)	No	Yes	Yes	No	No	No
Seasonality (i.e., winter [December-February], spring [March – May], summer [June-August], and autumn [September-November])	Yes	Yes	Yes	Yes	Yes	Yes

Potential confounding factors	Potential confounder included in the DAG			Confounders included in the selected minimum sufficient adjustment set for each association study		
	Seizures	SVT	A-fib/flu	Seizures	SVT	A-fib/flu
Asthmatic status	Yes	Yes	Yes	Yes	Yes	Yes
Disease severity of rhinitis	Yes	Yes	Yes	Yes	Yes	Yes
Chronic obstructive pulmonary disease (COPD)	Yes	Yes	Yes	No	No	No
Smoking	Yes	Yes	Yes	No	No	No
Inflammatory disease	No	Yes	Yes	No	No	No
Metastatic disease	Yes	No	No	No	No	No
Infections	No	Yes	Yes	No	No	No
Stroke	Yes	Yes	Yes	No	No	No
Chronic urticaria	Yes	Yes	Yes	Yes	Yes	Yes
Unspecific autoimmune disease	Yes	Yes	Yes	No	No	No
Type 1 allergy	Yes	Yes	Yes	No	No	No
Antihypertensive treatment	No	Yes	Yes	No	No	No

Table 4 below shows the variables included in the minimum sufficient adjustment sets in all four association analyses. In addition to being confounders included in the association analyses, the variables in the minimum sufficient adjustment sets will be used to characterize the population using DL in the descriptive study of DL use (Substudy 1). The table describes how each of the variables will be operationalized. ICD-10 codes and ATC codes that will be used for the definition of the variables can be found in Annex 6.

Table 4 Definition of confounders included in the minimum sufficient adjustment sets that will be used for confounder adjustment in the association studies.

Confounders included in the minimum sufficient adjustment sets	Definition	Data source
Age	For the descriptive analyses of DL use, age will be defined as the age of the purchaser at the date of prescription redemption and stratified into age groups (0–4 years, 5–19 years, 20–64 years, ≥65 years). In the association studies, age is a time varying confounder; and therefore, risk time will be split up in years of age. We will evaluate whether age can be included as a continuous variable by examining the assumption of linearity. Alternatively, age will be included as a categorical variable.	Civil registration system
Sex	Sex is a time-independent confounder and will be included as males versus females in both the descriptive and association analyses.	Civil registration system
Country	Country of residence is a time-independent confounder, as persons will be excluded if emigrating the country. Country of residence will be included with four categories, i.e. Denmark, Finland, Norway, or Sweden in both the descriptive and association analyses.	Civil registration system
Calendar year	For the descriptive analyses of DL use, calendar year is defined as the year of prescription redemption. In the association studies, calendar year is a time varying confounder; and therefore, risk time will be split up in calendar years.	Prescription register
Seasonality	For the descriptive analyses of DL use, seasonality is defined as the season (i.e., winter [December-February], spring [March – May], summer [June-August], and autumn [September-November]) when the DL prescriptions are redeemed. In the association studies, seasonality is a time varying confounder; and therefore, risk time will be split up in seasons defined as winter (December–February), spring (March–May), summer (June–August), and autumn (September–November).	Prescription register
Asthma status	Both for the descriptive and association analyses, asthmatic status is defined as a binary variable indicating whether or not a person has redeemed treatment for asthma defined as at least two prescriptions of inhalant steroids within a six-month period and/or contacts hospitals with a diagnosis of asthma (including both primary and secondary diagnoses) during a five-year period before first DL exposure. To distinguish persons treated for chronic obstructive pulmonary disease from those treated for asthma, first registered asthma treatment has to be redeemed when the purchaser was 45 years or younger.	National patient register and prescription register

Confounders included in the minimum sufficient adjustment sets	Definition	Data source
Disease severity of rhinitis	Both for the descriptive and association analyses, severity of rhinitis will be defined as binary variable indicating whether or not a person has received treatment for severe rhinitis. Persons with severe rhinitis will be identified from the prescription register as persons who have redeemed immunotherapy at least once during a five-year period before first DL exposure.	Prescription register
Chronic urticaria	Both for the descriptive and association analyses, chronic urticaria status is defined as a binary variable indicating whether or not a person has a registered diagnosis of chronic urticaria in the five-year period before first DL exposure.	National patient register

7.3.4 Other variables

We will also obtain information on immigration and emigration, as well as date of birth and death status from the civil registration systems to be able to calculate the IRs in Substudies 2B, 3B, and 4B.

The interpretation of register-based variables with regard to missing information was discussed in section 7.3.1 and 7.3.2. For a few of the included register-based variables (e.g., sex and date of birth), all included persons should have information. We do not expect missing information on these variables; however, we will examine data to see whether missing information occurs. Missing data handling will be determined after review of the data, but before data from different registers are linked together (blinded to exposure to DL and outcome status) and will be described in a data control report, which will be submitted along with the study report.

7.4 Data Sources

The DL study will include register information from four Nordic countries – Denmark, Finland, Norway, and Sweden. In addition to a long history of collecting high quality information on births, deaths, immigration and emigration, disease incidence, and activities in the healthcare sector [Thygesen, L., et al 2011], exceptional opportunities to perform register-based research are driven by the unique PIC introduced in the Nordic countries in the 1960's and available to all persons with permanent residence in the Nordic countries [Pedersen, C. B. 2011]. The PIC makes it possible to link information at the individual level from several registers for scientific research purposes. The national prescription registers and national patient registers within each of the Nordic countries capture all the individual encounters of purchasing prescribed DL and allow sufficient longitudinal data to differentiate between first and recurrent seizures, as only first seizure will be analyzed, and to identify incident SVT and A-fib/flu cases. Person-specific use of DL will be elucidated from the

national prescription registers by obtaining information on redemption of DL prescription for each person [Furu, K., et al 2009]. Person-specific information on seizures, SVT, and A-fib/flu will be derived from the Nordic national patient registers.

Table 5 presents key information on the population-based health registers in the Nordic countries of relevance for the present study. Data will be available until and including 2015 for all countries. The data extraction period refers to the longest period for which data on exclusion variables (e.g., seizures, SVT, or A-fib/flu before baseline) can be obtained for.

Table 5 Overview of national health registers in the Nordic countries of relevance for the present study.

Register	Country			
	Denmark	Finland	Norway	Sweden
National prescription register	1995–2015	1994–2015	2004–2015	2005–2015
National patient register	1977–2015 (1)	1967–2015 (2)	2008–2015	1987–2015 (3)
Civil registration system	1968–2015	1967–2015	1964–2015	1965–2015
Study period	2001–2015 (15 years)	2001–2015 (15 years)	2008–2015 (8 years)	July 2005–2015 (11 years)
Data extraction period	1977–2015	1967–2015	2008–2015	1987–2015

(1) Contacts with outpatient clinics (incl. emergency departments) since 1995.
(2) Contacts with outpatient clinics (incl. emergency departments) since 1998.
(3) Contacts with outpatient clinics (incl. emergency departments) since 2001.

The national prescription registers include information on the date of prescription redemption, information on the purchaser, and information on the drug redeemed (e.g., ATC code, number of pills, daily dose, pack size, and number of packs purchased) [Kildemoes, H. W., et al 2011]. The Nordic national patient registers include diagnostic and treatment information for patients treated at the secondary and tertiary hospital level [Lynge, E., et al 2011] [Pukkala, E. 2011]. Clinical experts have been consulted on how to include information from the prescription and patient registers. Information on date of birth, immigration, emigration, and death will be obtained from the civil registration systems [Pedersen, C. B. 2011] [Pukkala, E. 2011].

7.4.1 Study Procedures

This is an observational, register-based study and pre-existing health-related national register data will be the sole data source. According to Danish, Finnish, Norwegian, and Swedish law, register-based studies can be carried out without consent from the individual subjects where the processing takes place for the sole purpose of carrying out statistical or scientific studies of significant public importance and where such processing is necessary in order to

carry out these studies. It is an absolute requirement that the publication of statistical or scientific results may never reveal the identity of individuals or otherwise compromise data subjects. We will obtain approval by the data agencies in the four countries before data management and data analyses will be performed.

7.5 Study Size

The proposed study will be performed in the framework of an observational design with the use of register-based data. The primary interest is to assess the association between current DL exposure in the general population and the outcomes (i.e., first seizure [Substudy 2B], first SVT [Substudy 3B], and first A-fib/flu [Substudy 4B]). For Substudies 2B, 3B, and 4B, a cohort study design among DL users will be used. The sample size in the present study will be fixed, as the study population for the association studies 2B, 3B, and 4B consists of all individuals in the four Nordic countries who have redeemed a DL prescription at least once. Hence, the aim of this section is to calculate the minimum detectable incidence rate ratio (IRR). Calculations concern Substudy 2B evaluating the association between DL use and first seizure, Substudy 3B evaluating the association between DL use and first SVT event, and Substudy 4B evaluating the association between DL use and first A-fib/flu. The actual annual IR of seizures, SVT, and A-fib/flu among current DL users is unknown and will be determined in the current study. Minimal detectable IRR were calculated based on a rearranged formula for sample size calculations developed by Bryant & Morganstein [Bryant, E. 1987] (Formula provided in Annex 7). The following are the parameters needed to calculate the minimum detectable IRR: the number of DL users in each age group (i.e., the fixed sample size); the proportion of exposed time (current exposure) and unexposed time (non-current/remote exposure) for DL users; the background event rates of seizures, SVT, and A-fib/flu; and the number of years included in the study along with statistical parameters and assumptions included in the equation (i.e., the significance level, power, and 1-sided versus 2-sided tests).

7.5.1 Fixed sample size

The number of DL users from each country has been estimated based on national drug sale statistics (Annex 1A). The annual unique number of DL users in Denmark, Finland, and Sweden for age groups 0–4, 5–19, 20–64, and ≥65 years is estimated to be 20,000, 86,000, 215,000, and 44,500, respectively. Data for Norway on DL prescriptions and seizures/SVT/A-fib/flu are available for a shorter time period; and therefore, Norway is not included in the calculations of the minimum detectable IRR. The number of annual unique DL users in the four countries is thereby slightly underestimated.

7.5.2 Proportion of current and non-current exposure time among DL users for the purpose of calculation of minimum detectable IRR

DL exposure (i.e., current DL use) is time-varying, and each person might have one or more periods as exposed and one or more periods as unexposed. Individuals in the study population (i.e., individuals who have redeemed at least one prescription of DL) are assumed to be exposed in a period following the date of DL purchase (i.e., current users). An estimate of the number of DL prescriptions redeemed per year in each age group was obtained from the feasibility study performed prior to developing the synopsis and the present protocol. For the minimum detectable IRR calculations, the mean number of prescriptions in each age group per year from the Danish data is used as an estimate of the average annual number of redemptions. The exposure period is then calculated as follows: (mean annual number of prescriptions in each age group*4 weeks (standard days' supply)) + 4 weeks grace period to account for intermittent use and a possible wash-out effect. Beyond this period, individuals are assumed to be unexposed (i.e., non-current users). The average number of prescriptions per year was estimated to be 1.50, 1.62, 1.78, and 2.30 for age groups 0–4, 5–19, 20–64, and ≥65 years, respectively[1].

Exposure periods for age groups 0–4, 5–19, 20–64, and ≥65 years were then calculated to be 10.00, 10.48, 11.12, 13.20 weeks, respectively. The proportion of exposed time in each age group is calculated as number of weeks exposed divided by number of weeks in a year (i.e., 52 weeks). For example, for age group 0–4 years, the proportion of exposed time is 10 weeks/52 weeks = 19%, and thus, the proportion of non-exposed or neither exposed nor unexposed time is 81%. Note: A simplified method was used to calculate exposed and unexposed person time for each age group for the purpose of estimating the minimum detectable IRR. The method for calculating exposed, unexposed, and neither exposed nor unexposed time for individuals for the study analysis is outlined in section 7.3.1.

7.5.3 Background event rate

The background incidence rate (i.e., IR) of seizures, SVT, and A-fib/flu was obtained from published studies [Hauser, W. A. and Beghi, E. 2008] [Orejarena, L. A., et al 1998] [Wilke, T., et al 2013]. IRs of seizure among unexposed individuals for age groups 0–4, 5–19, 20–64, and ≥65 years were estimated to be 65, 50, 40, and 40 per 100,000 person-years, respectively [Hauser, W. A. and Beghi, E. 2008]. The IR of SVT is reported to be 13/100,000 person-years for persons aged 19 years or younger, 27/100,000 person-years for persons aged 20–64

[1] By using Danish figures we might get conservative estimates of the minimal detectable IRR as mean number of prescriptions calculated for the feasibility study showed slightly lower means for Denmark compared to Sweden (figures from Finland and Norway were not available for these calculations). The average number of prescriptions per age group for the 20-64 and ≥65 year's age groups was calculated as the mean number of annual prescriptions (2001-2012) per age group using data from Denmark for ages ≥16 years. For the 5-19 year age group, the calculation was based on data from Denmark for ages 16-19. For the 0-4 year age group, the calculation was based on Swedish data from the feasibility study, which showed a tendency for a lower number of prescriptions in this age group compared to the older age groups.

years, and 122/100,000 person-years for persons aged 65 years or older [Orejarena, L. A., et al 1998]. Wilke et al. (2013) [Wilke, T., et al 2013] reported the incidence of A-fib to increase markedly with age with 0.0016 cases/1000 person-years in children (<15 years) and approximately 30 cases/1000 person-years for persons aged 80 years or older. No data on the epidemiology of flutter were available.

7.5.4 Number of years in the study

The maximum number of years (*t*) that an individual can be included in the study is 5 years for the age group 0–4 years and 12 years for the remaining age groups (≥5 years). The period of 15 years corresponds to the period where DL has been on the market. For the calculations of the minimum detectable IRR, we assume that individuals, on average, will be included in the study for a shorter period; and therefore, the maximum number of years included has been set to 2 years for ages 0–4 years and 6 years for ages ≥5 years.

7.5.5 Statistical parameters and assumptions

The minimum incidence rate ratio, IRR>1, that can be detected is calculated using the following parameter values and assumptions:

Significance level, α: 0.05

Power, 1-β: 0.80

1-sided test

7.5.6 Example of calculating the minimum detectable IRR

The mean number of DL prescriptions in the age group 0–4 years is 1.50 prescriptions. This gives an exposure period of (1.50*4 weeks) + 4 weeks = 10 weeks. In this age group, 20,000 children have redeemed DL (i.e., the fixed sample size for this age group). Due to the exposure period of 10 weeks in this group, the proportion of the time exposed to DL is 10 weeks/52 weeks per year = 19%. The background annual rate of seizures is 65/100,000 in this age group. It is assumed that individuals in this age group will be included in the study for an average of 2 years. When using a 1-sided test, significance level of 5% and power of 80%, the minimum detectable IRR will be 3.0.

Table 6 The minimum detectable incidence rate ratio (IRR>1) was calculated based on the Nordic population of SL users with at least one prescription of DL per year. Incidence rate (IR) of seizures is based on Hauser & Beghi (2008) [Hauser, W. A. and Beghi, E. 2008]. A 1-sided test, significance level of 5% and power of 80% have been used.

Age group (years)	Annual IR of seizures among unexposed individuals per 100,000 person-years	Mean number of individuals with at least one annual DL prescription in the Nordic countries	Estimated number of weeks exposed based on mean number of DL prescriptions per person	Minimum detectable IRR t=2 and 6 years (for age 0-4 years and age ≥5 years)
0–4	65	20,000	10.00	3.0
5–19	50	86,000	10.48	1.5
20–64	40	215,000	11.12	1.3
≥65	40	44,500	13.20	1.7

Table 7 The minimum detectable incidence rate ratio (IRR>1) was calculated based on the Nordic population of DL users with at least one prescription of DL per year. Incidence rate (IR) of SVT is based on Orejarena et al. (1998) [Orejarena, L. A., et al 1998]. A 1-sided test, significance level of 5% and power of 80% have been used.

Age group (years)	Annual IR of SVT among unexposed individuals per 100,000 person-years	Mean number of individuals with at least one annual DL prescription in the Nordic countries	Estimated number of weeks exposed based on mean number of DL prescriptions per person	Minimum detectable IRR t=2 and 6 years (for age 0-4 years and age ≥5 years)
0–4	13	20,000	10.00	8.2
5–19	13	86,000	10.48	2.1
20–64	27	215,000	11.12	1.4
≥65	122	44,500	13.20	1.4

Table 8 The minimum detectable incidence rate ratio (IRR>1) was calculated based on the Nordic population of DL users with at least one prescription of DL per year. Incidence rates (IR) for atrial flutter were not available; therefore, we base the calculations only on IR of A-fib obtained from Wilke et al. (2013) [Wilke, T., et al 2013]. A 1-sided test, significance level of 5% and power of 80% have been used.

Age group (years)	Annual IR of A-fib among unexposed individuals per 100,000 person-years	Mean number of individuals with at least one annual DL prescription in the Nordic countries	Estimated number of weeks exposed based on mean number of DL prescriptions per person	Minimum detectable IRR t=2 and 6 years (for age 0-4 years and age ≥5 years)
0–4	1.6	20,000	10.00	54.0
5–19	3.8	86,000	10.48	3.4
20–64	168.9	215,000	11.12	1.6
≥65	2154.3	44,500	13.20	1.1

7.6 Data Management

The handling of data in the DL study involves six steps and requires applications and approvals for access to data in each of the four Nordic countries. In addition to the acquisition and management of data, a primary scientific coordinator will be responsible for the overall study and establishment of a joint Nordic study dataset. Four national scientific coordinators will be responsible for steps 1–4 in each country, whereas the Danish scientific coordinator also will be responsible for steps 5–6.

The handling of data is categorized into the following six steps:

- All national scientific coordinators will apply to the relevant agencies for permission to perform the study and to get access to data.
- All national scientific coordinators will facilitate the construction of the study populations:
    - Study population consisting of all DL users during the study period.
    - Study population consisting of all individuals with seizure during the study period and the years prior to the study period.
    - Study population consisting of all individuals with SVT during the study period and years prior to the study period.
    - Study population consisting of all individuals with A-fib/flu during the study period and years prior to the study period.

- All national scientific coordinators are responsible for acquiring and validating the datasets and will explore how the data can be combined from the registers. Data quality control includes but is not restricted to check for legal values for each categorical variable, check of consistency between dates (at least date of birth before all other dates and date of death after all dates), and check and advise on the handling of missing data. All national scientific coordinators will produce a data control report describing the checks performed. All national scientific coordinators will derive the final dataset from the data obtained from the registers by combining the registers according to the study designs. All national scientific coordinators will produce a data control report describing the checks performed of the final dataset, including reasons for modifications and exclusions. In this process, all national coordinators have to agree on the reasons for exclusion (e.g., missing value on crucial variables, chronological errors in the relation between dates, non-legal values of categorical variables, and extreme values of continuous variables). The national scientific coordinators should send the final data set and the data control reports that describe the data and provide suggestions on how to handle missing values and invalid codes to the Danish scientific coordinator. A template for the data control report will be provided by the Danish scientific coordinator and will include the following requirements:

    1. Information on known misclassification of each variable (e.g., underreporting, low sensitivity or specificity, categorization with obvious invalid values, etc.).

    2. Check for legal values for each categorical variable. Check for reasonable distribution of variables. Include advice on how to handle unexpected observations.

    3. Check for reasonable minimum, maximum, and central tendency (median, mean) for each continuous variable. Check for outliers must be performed (e.g., exploratory plots, such as box-whiskers plot). Include advice on how to handle unexpected observations.

    4. Check of chronological relation between date variables: At least date of birth before all other dates and date of death after all dates, but also reasonable relation of dates of diagnoses and prescriptions. Unexpected patterns should be described and solutions for handling such observations should be included.

    5. Check of missing information on variables and include advice on how to handle such observations (e.g., delete observations with missing information, put missing observations into a specific category, etc.).

- The final datasets from Finland, Norway, and Sweden are transferred to Statistics Denmark where all subsequent data handling is done by the Danish scientific coordinator.

- The Danish scientific coordinator combines data as described by the document developed by all national scientific coordinators and the datasets from all countries will be joined into a combined analysis dataset. Relevant variables will be derived.

- The Danish scientific coordinator will assess the data validity of all countries by logical checks, examination of extreme values, and missing data. It is important that identification numbers are maintained to facilitate linkage back to the original datasets to be able to check the data and for the sake of transparency.

7.7 Data Analysis

Prior to conducting the data analyses, we will perform data management (as described in section 7.6) to ensure data quality and to correct inconsistencies and errors in the data. The data analysis will include the following five steps listed below. Note that specifications concerning all pre-defined supplementary analyses will be detailed in a separate statistical analysis plan before database lock and start of data analysis. The assumptions of the statistical models performed will be evaluated for each model in the analysis.

7.7.1 Substudy 1: Descriptive analysis of exposure of DL

A cohort study describing DL use in the general population will be performed. A person with prescription redemption of DL in Norway and Sweden within the first 6 months after establishment of the prescriptions registers will not be included in order to avoid left-truncation bias. In addition, to avoid analogous misclassification of prevalent with incident DL dispensings among immigrants, we exclude persons with DL prescription redemptions within 6 months after immigrating to Denmark, Finland, Norway, or Sweden. Prevalent users will be defined as persons who have at least one prescription of DL in the period of interest (e.g., the entire study period or each year). Incident users are first time users of DL in the period of interest. The following descriptive analyses will be performed:

- The distribution of prevalent and incident users in the total population and stratified by country, age, sex, calendar year, seasonality, severity of rhinitis, asthmatic status, and chronic urticaria status.

- Descriptive information on the mean, standard deviation, median, and maximum and minimum number of redeemed DL prescriptions in the total population and stratified by country, age, sex, calendar year, seasonality, severity of rhinitis, asthmatic status, and chronic urticaria status.

7.7.2 Substudy 2: First seizure

Substudy 2A

A cohort study estimating the incidence of first seizures in the general population will be conducted. The cohort of individuals with seizures and the distribution of the population by age, year , and country will be used to derive estimates for the general population. The number of individuals in the general population on 01 January of each year will be obtained from the NORDCAN database and used as an estimate of the number of person years at risk assuming each person in the population on 01 January of each year contributes one person year at risk [Association of Nordic Cancer Registries 2009]. The IRs of seizure will be shown for the total population and stratified by country, sex, and age. The 95% confidence interval for IRs will be calculated as:

$$.. \ /\exp(1.96/\sqrt{N_{new\ users}}) \text{ to } IR * \exp(1.96/\sqrt{N_{new\ users}})$$

where IR is the incidence rate, exp is the exponential function, and $N_{new\ users}$ is the number of new users [Kirkwood, B. R. 2003].

Substudy 2B

A cohort study among ever-DL users analyzing the association between exposed and unexposed time and first seizures will be performed for the total population and stratified by age. Current use (i.e., "exposed" period) will be defined for each prescription as days' supply plus a 4 week grace period to account for intermittent use and a possible wash-out effect. Unexposed time will be defined as the period starting 26 weeks from the dispensing date of the prior DL prescription until the next DL prescription redemption, if any. A person who has redeemed at least one prescription of DL is included in the cohort and enters the cohort at the date of first prescription redemption. Study individuals are followed until occurrence of a seizure; occurrence of one of the conditions described in section 7.2.2; 31 December 2015; emigration; or death, whichever comes first. The association between exposure to DL and first seizure will be evaluated using Poisson regression of the IR of first seizure, and the measure of effect is the IRR. A person with prescription redemption of DL in Norway and Sweden within the first 6 months after establishment of the prescriptions registers will not be included in order to account for truncation bias. In addition we exclude persons with DL prescription redemptions within 6 months after immigrating to Denmark, Finland, Norway, or Sweden. The analyses will be adjusted for confounders identified from the DAG (i.e., country, age, sex, calendar year, seasonality, severity of rhinitis, asthmatic status, and chronic urticaria status) (Table 4). We will evaluate whether age can be included as a continuous variable by examining the assumption of linearity. Alternatively, age will be included as a categorical variable.

7.7.3 Substudy 3: SVT

Substudy 3A

A cohort study estimating the incidence of SVT in the general population will be performed. The cohort of DL users, the cohort of individuals with SVT, and the distribution of the population by age, year, and country will be used to derive estimates in the general population. The number of individuals in the general population on 01 January of each year will be obtained from the NORDCAN database and used as an estimate of the number of person years at risk assuming each person in the population on 01 January of each year contributes one person year at risk [Association of Nordic Cancer Registries 2009]. The IRs of SVT will be shown for the total population and stratified by country, sex, and age. The confidence interval of IRs is calculated as outlined above under Substudy 2A.

Substudy 3B

A cohort study among ever-DL users analyzing the association between exposed and unexposed time (as defined in Substudy 2B) and first SVT will be performed for the total population and stratified by age. A person who has redeemed at least one prescription of DL is included in the cohort and enters the cohort at the date of first prescription redemption. Study individuals are followed until occurrence of a SVT; 31 December 2015; emigration; or death, whichever comes first. The association between exposure to DL use and first SVT will be evaluated using Poisson regression of the IR of first SVT, and the measure of effect is the IRR. A person with prescription redemption of DL in Norway and Sweden within the first 6 months after establishment of the prescriptions registers will not be included in order to account for truncation bias. In addition we exclude persons with DL prescription redemptions within 6 months after immigrating to Denmark, Finland, Norway, or Sweden. The analyses will be adjusted for confounders identified from the DAG (i.e., country, age, sex, calendar year, seasonality, severity of rhinitis, asthmatic status, and chronic urticaria status) (Table 4). We will evaluate whether age can be included as a continuous variable by examining the assumption of linearity. Alternatively, age will be included as a categorical variable.

7.7.4 Substudy 4: Atrial fibrillation/flutter

Substudy 4A

A cohort study estimating the incidence of A-fib/flu in the general population will be performed. The cohort of individuals with A-fib/flu and the distribution of the population by age, year, and country will be used to derive estimates in the general population. The number of individuals in the general population on 01 January of each year will be obtained from the NORDCAN database and used as an estimate of the number of person years at risk assuming each person in the population on 01 January of each year contributes one person year at risk [Association of Nordic Cancer Registries 2009]. The IRs of A-fib/flu will be shown for the

total population and for each country, sex, and age. The confidence interval of IRs is calculated as outlined above under Substudy 2A.

Substudy 4B

A cohort study among ever-DL users analyzing the association between exposed and unexposed time (as defined in Substudy 2B) and first A-fib/flu diagnosis will be performed for the total population and stratified by age. A person who has redeemed at least one prescription of DL is included in the cohort and enters the cohort at the date of first prescription redemption. Study individuals are followed until occurrence of A-fib/flu; 31 December 2015; emigration or death, whichever comes first. The association between exposure to DL use and first A-fib/flu will be evaluated using Poisson regression of the IR of first A-fib/flu, and the measure of effect is the IRR. A person with prescription redemption of DL in Norway and Sweden within the first 6 months after establishment of the prescriptions registers will not be included in order to account for truncation bias. In addition we exclude persons with DL prescription redemptions within 6 months after immigrating to Denmark, Finland, Norway, or Sweden. The analyses will be adjusted for confounders identified from the DAG (i.e., country, age, sex, calendar years, seasonality, severity of rhinitis, asthmatic status, and chronic urticaria status) (Table 4). We will evaluate whether age can be included as a continuous variable by examining the assumption of linearity. Alternatively, age will be included as a categorical variable.

7.7.5 Supplementary analyses

The following supplementary analyses will be conducted. Unless otherwise specified, supplementary analyses will be performed on the total population (i.e. not stratified by age) and using the primary exposure definition.

(1) alternative definitions of exposure based on time since last DL dispensing (periods 0-4, 5-8, 9-16, and 17-26 weeks each compared with >26 week since last DL dispensing) for Substudies 2B, 3B, and 4B. Because as-needed medications, such as antihistamines may not be taken daily, this approach reflects the clinical expectation that the probability of actual exposure on a given day is highest shortly after filling a prescription and diminishes with increasing time. Each time a DL prescription is refilled, the time since last dispensing will reset to 0.

(2) for Substudy 2B, differentiating between febrile and non-febrile seizures for children aged 0–4 years.

(3) for Substudies 2B, 3B, and 4B, analyses will exclude persons who have been diagnosed with chronic urticaria and/or have redeemed very high doses of DL (dose for chronic urticaria is typically 4 times the standard dose for allergic rhinitis). To operationalize the exclusion of persons with chronic urticaria and/or who redeems high doses of DL, we will exclude person time at risk for a person from the date of a diagnosis of chronic urticaria or

date of DL prescription redemption of an amount of pills equal to at least twice the days' supply of DL for the individual's age in the period before next DL prescription redemption.

(4) the association analyses in Substudies 2B, 3B, and 4B will be stratified by countries to examine potential differences across countries.

(5) additional supplementary analyses, which will be specified in the SAP, will evaluate the potential effect of exposure misclassification in Substudies 2B, 3B, and 4B (i.e. evaluate use of loratadine and other non-sedating prescription antihistamines).

(6) a supplementary analysis for Substudies 2B, 3B, and 4B will evaluate whether the potential risk of the outcomes is higher following the first ever-DL prescription redemption compared to the second, third prescription redemption etc.

(7) a supplementary analysis for Substudies 2B, 3B, and 4B for which non-exposed periods start 52 weeks following the last prescription redemption.

(8) a supplementary analysis using an alternative adjustment set to examine the robustness of the study results. This adjustment set consists of age, sex, country, calendar year, seasonality, severity of rhinitis, asthmatic status, diabetes, hypo-/hyperthyroidism, inflammatory disease, infections, type 1 allergy. For the outcomes supraventricular tachycardia and atrial fibrillation or flutter, antihypertensive treatment will also be added.

(9) a supplementary analysis restricted to calendar time where misclassification due to over-the counter (OTC) use does not exist.

7.8 Quality Control

By signing this protocol, all parties agree to following applicable standard operating procedures (SOPs). All parties also agree to ensuring all existing and new study personnel are appropriately trained to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Pharmacoepidemiology Practice (GPP), and all applicable federal, state, and local laws, rules and regulations. All parties should maintain transparency and open communication in order to effectively manage the study and proactively mitigate any risks.

The study is register-based. As a result, data quality is difficult to ascertain directly. However, previous studies have examined the validity and quality of information in the Nordic registers. The Danish National Prescription Registry contains data of high quality, including detailed information on dispensed drugs, and as the register covers all prescription dispensed in Danish pharmacies, loss to follow-up is unlikely for individuals with permanent residence in Denmark [Kildemoes, H. W., et al 2011]. The completeness of the Norwegian and Swedish prescription registers is characterized as good [Furu, K., et al 2009] [Wettermark, B., et al 2007]. Completeness of registration in the Norwegian prescription

register is ensured by law and quality checks are carried out monthly to identify possible errors or inconsistencies [Furu, K., et al 2009]. The patient identity data are only missing for approximately 0.3% of all items in the Swedish prescription register [Wettermark, B., et al 2007]. The Finnish prescription register has been described in detail and considered as excellent [Klaukka, T. 2001]. Data quality in the Danish National Patient Register is overall assumed to be of high quality; however validity of data depends on the diagnosis under consideration; the positive predictive values for diagnoses similar to those in this study are >90%. [Schmidt, M., et al 2015]. The Norwegian Patient Register has relatively good agreement with the Norwegian Cancer Register [Bakken, I. J., et al 2012] and the completeness and accuracy of the Finnish Patient Register has been evaluated as varying from satisfactory to very good for common diagnoses with positive predictive values ranging from 75%– 99% [Sund, R. 2012]. The validity of the Swedish Patient Register is high for many, but not all diagnoses. The positive predictive values of most diagnoses in the Swedish Patient Register compared to medical records ranges from 85–95% [Ludvigsson, J. F., et al 2011].

The statistical analyses will be performed on servers at Statistics Denmark. The programming will be performed by two researchers independently, limiting programming errors. The statistical programs will be stored on the servers at Statistics Denmark.

The Sponsor may conduct routine or for-cause audits to ensure oversight and conduct of the study are completed in accordance with the protocol, quality standards (e.g. GPP), and applicable laws and regulations. If a significant quality issue (SQI) is identified at any time during the conduct of the study, it must be escalated to the Sponsor immediately. A SQI is any issue with the potential to negatively impact, either directly or indirectly, the rights, safety and well-being of patients or study participants and/or the integrity of the data. In the event an audit or SQI results in corrective or preventive actions, all parties are expected to appropriately implement the action plan in a timely manner.

7.9 Limitations of the research methods

The present study utilizes observational data from nationwide population registers covering the entire population meaning the total population is included and that loss to follow-up is minimal, limiting the impact of selection bias on results. Furthermore, observational data are extracted from health registers which are established and operated for purposes not immediately related to the present study. This minimizes information bias related to the differential misclassification of outcomes, but introduces other types of limitations with respect to quantifying exposure, outcome, and confounders as outlined below:

Exposure: Use of DL

- The prescription registers capture information on purchasing of drugs from pharmacies. The actual adherence of prescribed drugs and consumption cannot be established in these databases. This is a major limitation because the drugs concerned are taken on an as needed basis to treat symptomatic disease. Thus, it is difficult to establish when persons are truly exposed to the drug. Therefore, supplementary analyses will be performed to characterize the relationship of prescribing and timing of events of interest by categorizing time since DL prescription to the outcomes of interest and by using 52 instead of 26 weeks beyond previous prescription redemption as start of an unexposed period.

- Left-truncation is a potential bias in the study meaning that we have no information on DL use before the start of registration of prescriptions in each country. Left-truncation bias in relation to DL use is only a relevant issue for Sweden and Norway since DL was available from 2001, but the prescription registers in Norway and Sweden were established in 2004 and 2005, respectively (Table 4). Therefore, we do not know whether a DL user in the first year of registration in Norway and Sweden is a long-term user (prevalent user) or a first-time user (incident user). To account for this potential bias, a person with prescription redemption of DL in Norway and Sweden within the first 6 months after establishment of the prescriptions registers will not be included. This is not a limitation in Denmark and Finland since DL was first approved in 2001 and the prescription registers in Denmark and Finland were established in 1995 and 1994, respectively. However, left-truncation bias might also occur when persons are immigrating into the study population. Therefore we also exclude persons with DL prescription redemptions within 6 months after immigrating to Denmark, Finland, Norway, or Sweden.

- There is a possibility that patients could purchase DL over-the-counter; however, because of reimbursement systems in the Nordic countries, it is actually less expensive to purchase prescription DL. In Norway and Sweden DL has only been allowed for prescription sale; However, in Denmark, DL has been available for over-the-counter sale since 2013, but over-the-counter sales only counted for less than 4 % of the total amount of DL purchased in 2013. A supplementary analysis will examine the associations under consideration restricting the time period to include only years where DL was not allowed for OTC sale.

- Loratadine, the parent compound of DL, is also available via prescription and over-the counter in the Nordic countries. We think it is somewhat unlikely that patients would switch between DL and loratadine. However, it is possible that some of the time counted as unexposed in the analyses could actually be time exposed to loratadine or over-the-counter DL. Moreover, other non-sedating prescription antihistamines are available in the Nordic countries, and if the effect on the outcomes

is driven by non-sedating prescription antihistamines in general, rather than the specific effect of desloratadine exposure only, these drugs should be examined to elucidate potential misclassification of exposure. To explore exposure misclassification (i.e., the influence of loratadine and other non-sedating prescription antihistamines on the associations under study), we will conduct supplementary analyses, which will be specified in the statistical analysis plan.

Outcome: Episodes of seizures, SVT, and A-fib/flu

- Seizures, SVT, or A-fib/flu not registered with a relevant diagnosis code in the national patient registers will not be included in the study. However, the completeness of registration is assumed high, since both a procedure for data control of information in the national patient registers is established, and hospitals have an incentive to register patients, as the financing of hospitals is based on the registration of patients treated and procedures performed. If under-recording exists, it would reduce the number of outcomes evaluated, but this under-recording is not likely to be differential (i.e. associated with periods of use or nonuse of DL) and introduce bias.

- The coverage of calendar years in the national patient registers differ between the Nordic countries and may be insufficient to capture the complete history of seizures, SVT, or A-fib/ flu at the individual level. Regarding seizures, recurrent seizures would be studied as primary seizures, if first seizure happened before start of registration.

- Truncation is a potential bias in the study meaning that we have no information on seizures, SVT, and A-fib/flu before the start of registration of each of these variables. For Denmark, Finland, and Sweden, information on seizures, SVT, and A-fib/flu is available from 1977, 1967, and 1987, respectively. Thus, the impact of truncation bias on results from these countries is limited. However, information on seizures, SVT, and A-fib/flu in Norway is only available from 2008, which limits the study period of the Norwegian data further and increases the risk of truncation bias.

- The present study aims at studying incident outcomes occurring in the community setting. To differentiate between incident and prevalent disease, we exclude persons with registered disease before baseline. In addition, we used surrogates of prevalence (i.e., redeemed prescriptions of antiepileptic medicine) to exclude persons with prevalent disease. To capture disease cases emerging in the community setting, we limit ascertainment to those sites of care where incident presentation would be present and use only primary diagnoses of hospitalization, as secondary diagnoses often represent conditions emerging during hospitalization.

Confounders

In the present study, we expect complete information on the central confounders of age, sex, calendar year, country, and seasonality, as these are measured as key variables in the registers and information on these variables has to be entered into the system to establish a record file.

Information on the three confounders of severity of rhinitis, asthmatic status, and chronic urticaria status is challenging to obtain from the nationwide registers for many reasons. First of all, these conditions in general emerge in the primary health care sector where patients normally seek care from their general practitioner for treatment of symptoms. Second, truncation bias may, as with regard to the measures of exposure and outcome, also occur in relation to these three confounders in Norway as the patient register was established in 2008, making the follow-up period rather short. Third, different issues regarding codes and use of drugs for the three conditions have to be realized and discussed to understand the potential impact of residual confounders in the present study. We have discussed these issues with clinical experts and the essence of the discussion is given below.

- Severity of rhinitis is measured as use of immunotherapy and the binary measure of severity of rhinitis will not capture different levels of disease severity. Therefore, we expect the sensitivity of the measure to be rather low and severity of rhinitis to be underreported in the present study. However, we do not expect misclassification of those persons who received immunotherapy, as it is assumed that persons receiving immunotherapy also have severe rhinitis. A quantitative bias analysis examining the impact of misclassification of severity of rhinitis on the results will be performed.

- Identifying persons with asthma by use of register data is challenging due to the fact that the drugs used for treatment of asthma overlap with the treatment of chronic obstructive pulmonary disease (COPD). In order not to misclassify persons with COPD into the group of persons with asthma, we identify persons with asthma as those initiating asthma treatment before the age of 45 years. However, this means that for the part of the population aged 45 years or older, we will only have information on asthmatic status from the patient register in which hospitalized cases are registered. These cases are more likely to have severe asthma than those identified through the prescription register meaning that residual confounders may be more likely to occur among the population older than 45 years than those younger. A quantitative bias analysis examining the impact of misclassification of asthma on the results will be performed.

- Chronic urticaria is a very rare diagnosis given at highly specialized hospital units. This means that we expect a delay from onset of symptoms of chronic urticaria and the diagnosis of chronic urticaria of approximately 2-5 years. In the period between onset of disease and diagnosis, persons may receive antihistamines, including DL prescribed by the general practitioner, for their symptoms. Therefore, chronic urticaria may be underreported in the hospital register and the sensitivity of the measure is expected to be somewhat low. To get an impression of how important this misclassification will be in the present study, we will look at how many of the persons with a diagnosis of chronic urticaria have redeemed prescriptions of DL during the five years prior to the date of diagnosis. A quantitative bias analysis examining the impact of misclassification of chronic urticaria on the results will be performed.

- As in any association study, there is always the possibility of unmeasured confounders or residual confounding resulting from roughly categorized confounders that could affect the results of the study.

Variables used for inclusion and exclusion criteria

In Substudy 2B, seizure outcomes for which a drug overdose is also registered at the same hospitalization are excluded. In general, drug overdoses are likely to be underreported in the registries, as the registries often do not have sufficient detail to differentiate between overdoses from different types of drugs. Therefore, it is not possible to distinguish between overdoses from DL and overdoses from other drugs. Because overdoses of DL are rare compared to other drug overdoses, persons with any drug overdose registered during the same hospitalization as the seizure are excluded from analysis 2B. As a result, this study cannot determine whether the seizure outcomes are specifically associated with DL overdoses.

Sample size

Based on the assumptions made, the sample size is not adequate in the youngest age group for the assessment of the potential association between DL use and A-fib. Also, in this age group only relatively strong associations (IRR=8.2) can be properly assessed for the association between DL use and SVT.

7.10 Other Aspects

N/A

8 PROTECTION OF HUMAN SUBJECTS

This is an observational study with no administration of any therapeutic or prophylactic agent. Subjects observed in this study will continue with the normal standard of care as provided by their personal physician. Pre-existing national register data will be the sole data source. According to Danish, Finnish, Norwegian, and Swedish law, register-based studies can be carried out without consent from the data subjects where the processing takes place for the sole purpose of carrying out statistical or scientific studies of significant public importance and where such processing is necessary in order to carry out these studies. It is an absolute requirement that the publication of statistical or scientific results may never reveal the identity of individuals or otherwise compromise data subjects. We will obtain approval by the data agencies in the four countries before data management and data analyses will be performed.

9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a non-interventional database study based on secondary use of data collected for other purposes. No administration of any therapeutic or prophylactic agent is required in this protocol. No reporting of individual adverse events or product quality complaints to regulatory agencies is planned for this database study because there is no access to individual patient/subject records and it is not possible to assess the causality of individual cases. Study-specific health outcomes of interest, including any that qualify as adverse events, will be summarized as part of any interim analysis (including safety analysis, if required) and in the final study report, which will be provided to regulatory agencies by the sponsor as required.

Any relevant safety information will be summarized in the appropriate Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) and/or Development Safety Update Reports (DSUR) if required.

If an investigator elects to spontaneously report any suspected adverse reactions or product quality complaints, they should be reported via fax to Local Designated Point of Contact (DPOC) (Denmark: PPD; Finland: PPD; Norway: PPD; Sweden: PPD in English using an AE and PQC report form (see section 12 for form) for reporting to worldwide regulatory agencies as appropriate.

10 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results will be disseminated in working reports. In addition, the results will be submitted for publication in international peer-reviewed journals.

The Risk Management Subteam (RMST) Lead /Clinical Safety Risk Manager (CSRM) Physician will be notified if any safety data are generated in the final study report or any interim report. The safety and conclusion sections of the final study report or interim report must be reviewed by the RMST Lead/CSRM Physician prior to finalization of the report. The review by the CSRM Physician must occur prior to any release of results to the public domain in the form of abstracts, posters, presentations or manuscripts.

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12 APPENDICIES

12.1 Annex 1 List of Stand-Alone Documents

No.	Document Reference No	Date	Title
1A.	N/A	May 2014	Number of Desloratadine Users

Documents are available upon request.

12.2 Annex 2 ENCePP Checklist for Study Protocols (Revision 4)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EUROPEAN NETWORK OF CENTRES FOR PHARMACOEPIDEMIOLOGY AND PHARMACOVIGILANCE

Doc.Ref. EMA/540136/2009

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:
Association between use of desloratadine and risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter: A Nordic register-based study

EU PAS Register® number: Study not yet registered
Study reference number (if applicable): 205-00

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]	☒	☐	☐	2; 4
1.1.2 End of data collection[2]	☒	☐	☐	2; 4
1.1.3 Progress report(s)	☐	☐	☒	-
1.1.4 Interim report(s)	☐	☐	☒	-
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	2; 4
1.1.6 Final report of study results.	☒	☐	☐	2; 4

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	5
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)	☒	☐	☐	5
2.1.2 The objective(s) of the study?	☒	☐	☐	6
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	6
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	-

Comments:

[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.

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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)	☒	☐	☐	7.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	7.4.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	7.5.2; 7.5.6
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))	☒	☐	☐	7.5.2; 7.5.6
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)	☒	☐	☐	9

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	7.2 7.4
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	7.2; 7.4
4.2.2 Age and sex	☒	☐	☐	7.3.3
4.2.3 Country of origin	☒	☐	☐	7.3.3
4.2.4 Disease/indication	☒	☐	☐	7.3.2; 7.3.3
4.2.5 Duration of follow-up	☒	☐	☐	7.2; 7.5.1, 7.5.4
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	7.2

Comments:

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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)	☒	☐	☐	7.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	7.7.6; 7.8
5.3 Is exposure categorised according to time windows?	☒	☐	☐	7.3.1; 7.8
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	7.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	7.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	7.3.1; 7.5.3

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?	☒	☐	☐	7.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	7.3.2
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)	☒	☐	☐	7.8
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:

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Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	7.3.3
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	7.4; 7.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	7.3.1; 7.3.3; 7.7; 7.9

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)	☒	☐	☐	7.3.3; Table 4; 7.7

Comments:

Regarding 8.1: we stratify by age and in a sensitivity analysis by country.

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)	☒	☐	☐	7.3.1; 7.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	7.3.2; 7.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	7.3.3-7.3.4; 7.4
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)	☒	☐	☐	7.3.1; 7.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	7.3.2; 7.4

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Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	7.3.3-7.3.4; 7.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	7.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	7.3.2
9.3.3 Covariates and other characteristics?	☒	☐	☐	7.3.3-7.3.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	7.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	7.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	7.5.1; 7.5.5; 7.5.6
10.3 Are descriptive analyses included?	☒	☐	☐	7.7
10.4 Are stratified analyses included?	☒	☐	☐	7.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	7.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	7.7
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	7.6
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	7.7.6

Comments:

Effect modification will be evaluated using stratified analyses by age. Different methods for evaluating effect modification have not been discussed.

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EPIDEMIOLOGY NO.(PE STUDIES ONLY): EP07044.004

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)	☒	☐	☐	7.6
11.2 Are methods of quality assurance described?	☒	☐	☐	7.6
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	-

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?	☒	☐	☐	7.9
12.1.2 Information bias?	☒	☐	☐	7.9
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).	☒	☐	☐	7.9
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)	☒	☐	☐	7.5.2

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?	☒	☐	☐	8
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	-
13.3 Have data protection requirements been described?	☒	☐	☐	8

Comments:

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

Comments:

Summary of changes is located before The table of contents

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)?	☒	☐	☐	10
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	10

Comments:

Name of the main author of the protocol: PPD

Date:

Signature: PPD

12.3 Annex 3 Administrative and Regulatory Details

Confidentiality:

Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the Institutional Review Board, Ethics Review Committee or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- *name, address, telephone number and e-mail address;*
- *hospital or clinic address and telephone number;*
- *curriculum vitae or other summary of qualifications and credentials; and*
- *other professional documentation.*

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter study, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

Administrative:

Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice and all applicable federal, state and local laws, rules and regulations relating to the conduct of the study.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the study in accordance with their institution's records retention schedule which is compliant with all applicable regional and national laws and regulatory requirements. If an institution does not have a records retention schedule to manage its records long-term, the investigator must maintain all documentation and records relating to the conduct of the study for 5 years after final report or first publication of study results, whichever comes later, per GPP guidelines. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. All study documents shall be made available if required by relevant regulatory authorities. The investigator must consult with the Sponsor prior to discarding study and/or subject files.

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center study (including multinational). When more than one study site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different sites in that Member State, according to national regulations. For a single-center study, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the study report that summarizes the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study in the study's final report. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of study methods, appropriate enrollment of subject cohort, timely achievement of study milestones). The Protocol CI must be a participating study investigator.

Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to the Clinical Trials Data Bank, such as ENCePP. *Merck, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated studies. Information posted will allow subjects to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.*

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this study or its results to the Clinical Trials Data Bank.

12.4 Annex 4 Qualified Person for PharmacoVigilance (QPPV)

PPD

European Union Qualified Person for Risk Management and Pharmacovigilance
Office of the European Union Qualified Person for Pharmacovigilance (EU QPPV)
Merck Sharp & Dohme (Europe), Inc.
Siège d'exploitation : 5, Clos du Lynx 1200 Bruxelles
Exploitatiezetel : Lynx Binnenhof, 5 1200 Brussel
Tel: PPD GSM: PPD Fax: PPD
Email: PPD

Emergency/Out of Hours: GSM number above or via PPD

Dear Sir/Madam

Re: EU QPPV Signature Page for PASS

INN: Desloratadine
Product: AERIUS
AZOMYR
NEOCLARITYN
Protocol No.: 4117-205
Epidemiology No.: EP07044.004
Protocol Date: 23-Jun-2020
MAH: Merck Sharp & Dohme B.V.

In line with the Guideline on Good PharmacoVigilance Practice (GVP), Module VIII – Post-Authorisation Safety Studies (PASS) and according to MSD internal SOPs, this study has been reviewed and approved by the European Qualified Person for Pharmacovigilance.

Yours faithfully

PPD

Associate Vice President,
EU Qualified Person for Pharmacovigilance

12.5 Annex 5 About Desloratidine

Aerius, Azomyr, and NeoClarityn in the EU, and in the rest of the world as, Claramax, Clarinex, Larinex, Dazit, Deselex, and Delot. It is an active metabolite of Loratadine, which is also on the market.

DL is available as tablets (including orally disintegrating and extended release) and as syrup.

DL is a second-generation H1-antagonist. It is a tricyclic antihistamine, which has a selective and peripheral H1-antagonist action. It is an antagonist at histamine H1 receptors, and an antagonist at all subtypes of the muscarinic acetylcholine receptor. It has a long-lasting effect, and in moderate and low doses, does not cause drowsiness because it does not readily enter the central nervous system.

Unlike other antihistamines, DL is also effective in relieving nasal congestion, particularly in patients with allergic rhinitis.

Most common side-effects are fatigue, dry mouth, headache, and gastrointestinal disturbances.

In the EU, DL is a prescription drug approved for the relief of symptoms associated with allergic rhinitis and urticaria in both adults and children. The Anatomical Therapeutic Classification (ATC) code for DL is R06AX27.

Table 9 Overview of DL formulations in the Nordic countries. Dates of approval are identical for all EU countries.

Formulation	Date of approval
Film coated tablet, 5 mg	15 January 2001
Orodispersible tablet, 2.5 mg	23 April 2007
Orodispersible tablet, 5.0 mg	23 April 2007
Oral solution, 0.5 mg/ml	23 April 200

12.6 Annex 6 ICD-10 Codes and ATC Codes

Diagnosis/drugs to be identified in registers	Proposed classification system	Proposed codes by clinicians
Acute drug intoxication and overdose of drugs	ICD-10	T88.6 T88.7 T36 T50
Antiepileptic medicine	ATC	N03A N05BA
Asthma	ICD-10	J45
	ATC	R03A and R03B
Atrial fibrillation or flutter	ICD-10	I48
Brain Tumor (both malignant and benign)	ICD-10	C70 and C71 D33
Chronic urticaria	ICD-10	L50 (excluding acute urticaria: L50.8D) L56.3
Congenital pre-excitation syndrome	ICD-10	I45.6
Desloratadine	ATC	R06AX27
Epilepsy	ICD-10	G40
Head trauma	ICD-10	S06
Loratadine	ATC	R06AX13
Malignant brain tumor	ICD-10	C70 and C71
Seizure	ICD-10	R56
Severe rhinitis (immunotherapy)	ATC	V01AA (excluding V01AA07)
Stroke (all types)	ICD-10	I61 I62 I63 I64.9
Supraventricular arrhythmias	ICD-10	I47.1

12.7 Annex 7 Minimum Detectable Incidence Rate Ratio Calculation

The minimum detectable incidence rate ratio (λ) was calculated based on Bryant & Morganstein [Bryant, E. 1987] and algebraically re-arranged to estimate $\lambda = \frac{p_1}{p_2}$:

$$(p_1 - p_2)^2 = (Z_\alpha + Z_\beta)^2 \left[\frac{p_1 q_1}{En} + \frac{p_2 q_2}{(1-E)n}\right]$$

where $\lambda = \frac{p_1}{p_2}$ is the minimum detectable incidence rate ratio
p_1 is the incidence rate of seizures (or supraventricular tachycardia (SVT) or atrial fibrillation/atrial flutter (A-fib/flu)) among current desloratadine (DL) users
p_2 is the incidence rate of seizures (or SVT or A-fib/flu) among non-current DL users
$q_1 = 1 - p_1$ and $q_2 = 1 - p_2$
Z_α is the significance level (type I error)
Z_β is type II error
n is the sample size (number of DL-ever-users)
E is proportion of the sample exposed to DL (i.e., proportion of weeks exposed to DL)
1-E is the proportion of not exposed to DL

Patients are assumed to be followed for 2 years (ages 0-4 years) and 6 years (ages ≥5 years).
The incidence of seizures (or SVT or A-fib/flu) among non-current DL users during the follow-up period, t (t=2 years for children age 0-4 years, otherwise t=6 years) is calculated using the exponential model:

$$p_2 = 1 - \exp(-p_2' t)$$

Where p_2' is the annual incidence rate of seizures (or SVT or A-fib/flu) among non-current DL users (i.e., background event rate).

Based on the known size of the population in the specific age group (n) (e.g., number of children age 0-4 years who have redeemed at least one prescription of DL, n=20.000), the IR of seizures (or SVA) among non-current users ($p_2 = 1 - \exp(-65 \cdot 2/100000)$) and the proportion of the sample exposed to DL (E = ((1.5*4) + 4 weeks)) / 52 weeks = 0.19), the minimum detectable incidence rate ratio (λ) can be calculated.

Using an alternative sample size formula from Woodward, we obtained similar results .

12.8 Annex 8 Directed Acyclic Graphs (DAGs) for the study on Desloratadine and risk of first seizure, atrial fibrillation or flutter, and supraventricular tachycardia

Primary DAG meeting	
Date	06 January 2015
Organizer	ApEHR
Attendees	NIPH PPD ApEHR PPD MSD PPD Clinical experts PPD
Purpose	To choose which confounding factors should be included and adjusted for in the study on desloratadine (DL) and risk of seizures and supraventricular arrhythmias.
Supplementary DAG meeting	
Date	11 March 2015
Attendees	NIPH PPD ApEHR PPD Clinical expert PPD
Purpose	To further discuss and clarify the relationship between dermatological factors such as chronic urticaria and the other variables included in the DAGs developed at the primary DAG meeting.
Software	DAGitty (http://www.dagitty.net/)

In the present study, we have used directed acyclic graphs (DAGs), also called causal diagrams for confounder selection. DAGs are a well-accepted methodology for using causal knowledge and a set of formal mathematical principles for selecting which variables to adjust for when performing association analyses [Greenland, S., et al 1999]. They provide a systematic way to explore the relationships between the exposures, outcomes, and covariates (unidirectional, bidirectional, causal) and facilitate dealing with a large number of potential confounders. DAGs help make the assumptions underlying an analysis explicit. The selection of variables needed for confounder adjustment to obtain an unbiased estimate of the association under study is called the minimum sufficient adjustment set of confounders. We used the open source and freely available software DAGitty for the development of the DAGs [Textor, J., et al 2011]. DAGitty helps the researcher visualize the structure of relevant variables for the association under study included in the DAG, as well as to identify the minimum sufficient adjustment sets available for confounder adjustment.

This document outlines the process used to develop the DAGs for the current study.

The purpose of the DAG Workshop on 06 January 2015 was to choose which confounding factors should be included and adjusted for in the study on DL and risk of seizures and supraventricular arrhythmias. This was done by going through all proposed potential confounders; and furthermore, adding potential confounders proposed by the external experts during the meeting. When discussing the previously proposed supraventricular arrhythmias outcome, it was brought up by the clinical experts whether it is reasonable to analyze this as a combined outcome (i.e., combining the diagnoses of A-fib/flu and SVT). The clinical experts indicated that pooling the diagnoses together as one outcome would not be clinically optimal and that it would be more appropriate to separate the diagnoses into two outcomes (i.e., A-fib/flu as one outcome and SVT as another outcome). Due to this discussion, we have chosen to separate SVT and A-fib/flu; and therefore, we developed three DAGs: one for seizures, one for A-fib/flu, and one for SVT.

During the DAG development process, we discussed the relevant potential confounders in the left columns of Tables 10 and 12 in the order in which they are listed. Key issues discussed are described in the “Discussion” column. It should be noted that this may have influenced the discussion of the relation between two potential confounders meaning that an association between two potential confounders was discussed when the second potential confounder was added to the DAG (e.g., the association between chronic obstructive pulmonary disease (COPD) and smoking was not only discussed when COPD was included in the DAG, but also at the time when smoking was added). After the DAG meeting, the minutes of the meeting were circulated to all participants for further comments and/or suggestions. This may also have influenced the order in which the confounders were listed in Table 10 and Table 12. Furthermore, we arranged a meeting with a dermatologist to get his suggestions for the DAG. We were especially interested in how to include chronic urticaria (one of the indications for desloratadine), how chronic urticaria was related to other factors

already in the DAGs, and whether we needed to include additional factors or associations in the DAGs, which might be different than for the allergic rhinitis indication.

We used the open source and freely available software DAGitty for the development of the DAGs [Textor, J., et al 2011]. DAGitty helps the researcher visualize the structure of relevant factors for the association under study included in the DAG, as well as to identify the minimum sufficient adjustment sets available for confounder adjustment to provide an unbiased estimate of the association of interest.

After the DAG meeting and discussions, the final directed paths that were drawn from each factor to the other factors in the DAGs were listed in the right column. Furthermore, we listed the different minimum sufficient adjustment sets identified by use of DAGitty for the three DAGs developed. We selected the final minimum sufficient adjustment set that will be used to adjust for confounding factors in the association studies based on whether we found that a given combination of confounders would be obtainable from the registers. Since there is no information on smoking or type 1 allergy available in the population registers, minimum sufficient adjustment sets including these two potential confounders were not eligible for selection. In cases where multiple minimum sufficient adjustment sets were candidates for confounder adjustment, we chose the minimum sufficient adjustment set where we found that the combination of confounders had the highest possible validity and quality in the population registers. Operational definitions of the variables in the minimum sufficient adjustment set are provided in the study protocol.

Afterwards, the DAGs were updated according to the final confirmed DAG meeting minutes and the final results were added to the protocol.

DAG for the association between DL use and seizure.

Table 10, Figure 2, and Table 11 provide information on the results of the discussion of the DAG concerning the association between DL use and first seizure. Table 10 lists the potential confounders discussed during the development of the DAG, Figure 2 shows the final developed DAG, and Table 12 provides the results of the DAG in terms of the minimum sufficient adjustment sets of confounders to include in the association analyses to obtain a confounder adjusted estimate of the association between DL use and first seizure. Finally, the specific minimum sufficient adjustment set that will be used to adjust for confounding of the association between DL and seizures was identified and included the following confounders: age, sex, country, calendar year, disease severity of rhinitis, asthmatic status, and chronic urticaria.

Table 10 Discussion of potential confounders of the association between DL use and first seizure

Potential confounders	Discussion	List of directed paths (head-to-tail arrows)
Age	Age affects the use of DL.	There is a directed path from age to: Inflammatory disease Disease severity of rhinitis Infections Asthmatic status COPD DL Smoking Metastatic cancer Drug and alcohol abuse Drug overdose of drugs other than DL Seizures Stroke Thyroidism Diabetes
Sex	Sex is associated with disease severity of rhinitis, as the prevalence of rhinitis is higher in males than females. There are sex differences in the incidence of stroke and smoking. There are sex differences in use of DL.	There is a directed path from sex to: Smoking Drug and alcohol abuse Stroke Inflammatory disease Diabetes Thyroidism Chronic urticaria Disease severity of rhinitis DL
Country of residence (Denmark, Finland, Norway, Sweden	There are probably country differences in use of DL. Country differences in smoking.	There is a directed path from country of residence to: DL Smoking

Potential confounders	Discussion	List of directed paths (head-to-tail arrows)
Calendar year	Preliminary data from the prescription registers demonstrate that the number of unique patients treated with DL varies by calendar year in each country, initially increasing and then showing some variation. Some, but not all of the variation may be due to differences in seasonality/pollen. Year is also associated with seasonality in that the influence of pollen may differ from year to year. There is a temporal trend in smoking, diabetes, inflammatory disease, type 1 allergy, and stroke.	There is a directed path from calendar year to: Inflammatory disease Diabetes Chronic urticaria Type 1 allergy Seasonality DL Smoking Stroke
Seasonality	There is a seasonal trend in DL use. The effect of seasonality could change from year to year. It was suggested that pollen level could be used as a proxy for the effect of seasonality. One of the experts explained that this is not simple because pollen level may vary from area to area and day to day. Pollen may also have a different influence from year to year for the same individuals. Thus, information on pollen level will not be included. Seasonality will be used as a proxy measure. There is a seasonal trend in disease severity of rhinitis and asthmatic status.	There is a directed path from seasonality to: DL Infections Disease severity of rhinitis Type 1 allergy Asthmatic status
Disease severity of rhinitis	Disease severity of rhinitis affects the use of DL. Very strong association. DL is a prescription drug and if you have severe rhinitis and use antihistamines regularly, then you might choose a prescription drug as DL, as this drug is subsidized. The severity of rhinitis therefore influences whether you prefer DL over over-the-counter antihistamines. Disease severity of rhinitis affects asthmatic status.	There is a directed path from disease severity of rhinitis to: DL Asthmatic status

Potential confounders	Discussion	List of directed paths (head-to-tail arrows)
Asthmatic status	Asthmatic status affects DL use.	There is a directed path from asthmatic status to: DL Infections
Chronic obstructive pulmonary disease (COPD)	Age affects risk of COPD.	There is a directed path from COPD to: Inflections
Comorbidity	Could be measured as history of hospital admissions or as an index (e.g., the Charlson index). Comment (MSD): This is a non-specific indicator. Really a proxy for something else. Should be specified what part of comorbidity on top of the other indicators discussed should be included. Specific comorbidities are better. Comment (expert): Agree that Charlson should not be used. Conclusion: Do not include comorbidity index, number of admissions, or number of hospital contacts.	Not relevant
Smoking	Smoking has an effect on seizures, COPD, asthmatic status, stroke, and metastatic cancer.	There is a directed path from smoking to: Metastatic cancer Seizures Stroke Asthmatic status COPD
Metastatic cancer	Metastatic cancer can increase risk of seizures.	There is a directed path from metastatic cancer to: Seizures
Use of other drugs	Comment (MSD): Most drugs are not associated with seizures at normal doses. In addition, this would be extremely difficult to operationalize. Drug-drug interactions have been shown but these interactions are generally very small. It is more probable that high drug doses may influence high use of other drugs. Conclusion: Do not include use of other drugs.	Not relevant

Potential confounders	Discussion	List of directed paths (head-to-tail arrows)
Drug overdose (of drugs other than DL)	Overdose of drugs other than DL affects the risk of seizures. Comment (MSD): One of the most common reasons of new seizures is overdose of alcohol and cocaine. The coding of overdose and the reason for overdose is not easily found in register studies. May be too complicated to operationalize. Comment (expert): Not specific enough codes for what kind of drug overdoses. Suggests using all drug overdoses as one variable (binary). Comment (expert): Very unreliable information in the registers. Persons with code for overdose (alcohol, drug, others) will probably be reliable, but there will be underreporting and it is difficult to differentiate between different types of overdose. Comment (MSD): The problem gets very messy, because drug overdose due to DL is part of this group and we may not be able to separate this specific group. Conclusion: Combine any overdose as one binary variable.	There is a directed path from drug overdose of drugs other than DL to: Seizures
Drug and alcohol abuse	Drug and alcohol abuse affects risk of seizures and overdose of drugs other than DL.	There is a directed path from drug and alcohol abuse to: Seizures Drug over dose of other factors than DL
Diabetes	Diabetes affects use of hypoglycemic agents and the risk of stroke Both diabetes type 1 and type 2 should be included.	There is a directed path from diabetes to: Stroke Hypoglycemic agents
Hypoglycemic agents (oral anti-diabetics, insulin)	Use of hypoglycemic agents affects the risk of seizures.	There is a directed path from hypoglycemic agents to: Seizures

Potential confounders	Discussion	List of directed paths (head-to-tail arrows)
Stroke	Stroke affects the risk of seizures. We will not differentiate between hemorrhagic or ischemic stroke as both increase the risk of seizures.	There is a directed path from stroke to: Seizures Inflammatory disease
Chronic urticaria	Chronic urticaria is associated with use of very high doses (much higher than the usual dose) of DL (Guidelines recommend up to 4 times the standard dose). Associated with sex. Prevalence of urticaria/chronic urticaria is higher in females than males. There is a temporal trend in prevalence of diagnosed chronic urticaria (increases) (i.e., calendar year affects chronic urticaria).	There is a directed path from chronic urticaria to: DL
Thyroidism (Thyroidism includes both hypo- and hyperthyroidism).	Thyroidism is associated with risk of stroke. Age affects risk of thyroidism. There are sex differences in risk of thyroidism.	There is a directed path from thyroidism to: Stroke
Unspecific autoimmune disease	Unspecific autoimmune disease is associated with risk of chronic urticaria, thyroidism, and diabetes.	There is a directed path from unspecific autoimmune disease to: Diabetes Thyroidism Chronic urticaria
Inflammatory disease	Inflammatory disease is associated with risk of chronic urticaria. Stroke increases risk of inflammatory disease. Sex and age are associated with risk of inflammatory disease.	There is a directed path from inflammatory disease to: Chronic urticaria
Infections	Infections can affect risk of chronic urticaria. There are sex differences in infections. COPD, asthmatic disease, and seasonality are associated with risk of infections.	There is a directed path from infections to: Chronic urticaria
Type 1 allergy	Type 1 allergy can affect risk of chronic urticaria and rhinitis. Seasonality affects risk of type 1 allergy.	There is a directed path from type 1 allergy to: Disease severity of rhinitis Asthmatic status Chronic urticaria

Figure 2 DAG for the association between DL use and first seizure

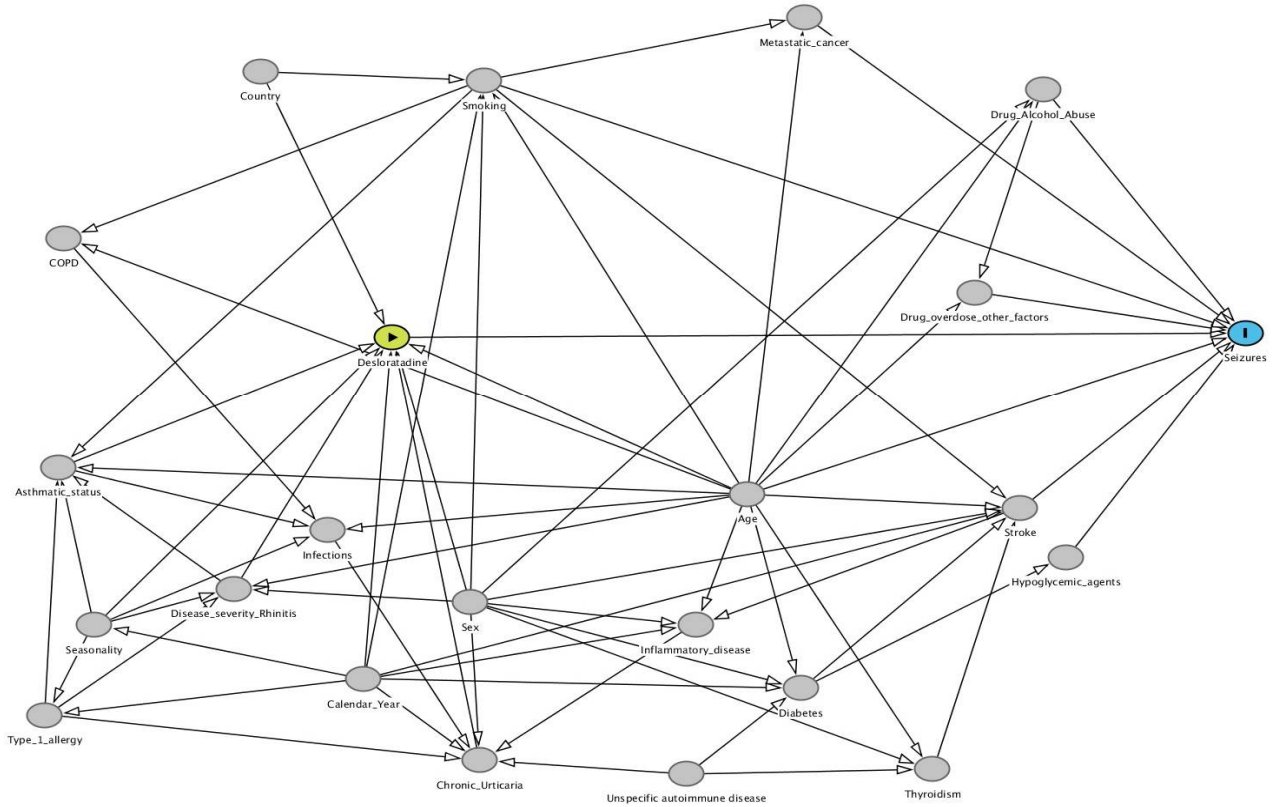

Table 11 Minimum sufficient adjustment sets for the DAG developed (Figure 2)

Potential confounders	Minimum sufficient adjustment sets																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Age	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sex	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X
Country	X	X	X	X	X			X	X	X	X								
Calendar year	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Seasonality	X	X	X	X	X	X	X	X	X	X	X								
Disease severity of rhinitis	X	X	X	X	X	X		X	X	X	X								
Asthmatic status	X	X	X	X	X	X	X	X	X	X	X								
COPD	X	X	X	X															
Smoking						X	X					X	X	X	X	X	X	X	X
Metastatic disease																			
Drug overdose																			
Drug and alcohol abuse																X		X	
Diabetes	X	X						X	X				X			X	X		
Hypoglycemic agents																		X	X
Stroke		X		X					X		X				X	X	X	X	X
Chronic urticaria					X	X	X					X							
Thyroidism (hypo-/hyperthyroidism)	X	X						X	X				X						
Unspecific autoimmune disease			X	X						X	X			X	X				
Inflammatory disease	X		X					X		X			X	X					
Infections								X	X	X	X	X							
Type 1 allergy	X	X	X	X			X	X	X	X	X	X							

Light grey background = confounder information not available in population registers (e.g., self-reported lifestyle factors).
Dark grey background = selected minimum sufficient adjustment set (number 5) and the alternative set (number 8).

The minimum sufficient adjustment set chosen for analysis

Table 11 shows the possible minimum sufficient sets available. The set used to adjust for confounding of the association between DL and seizures included the following confounders: age, sex, country, calendar year, disease severity of rhinitis, asthmatic status, and chronic urticaria. The selected set was chosen as it was the only one not including smoking and type 1 allergy.

Some rare diseases are treated with very high doses of desloratadine

It was brought up during the discussion that some rare diseases are treated with very high doses of DL (e.g., chronic urticaria). It is assumed that dermatologists prescribe DL in high doses for these rare diseases. A dermatologist was consulted on this matter to be sure we included the relevant diseases and relationships with other potential confounders in the DAG. We should consider how to take the high use of DL among patients with chronic urticaria into account when analyzing the data (e.g., in a supplementary analysis where we exclude persons who have redeemed high doses of DL or have a diagnosis of chronic urticaria).

In conclusion, it would complicate things to include other potential confounders also in light of the low number of outcomes in this setting.

DAG for the association between DL use and A-fib/flu

Table 12, Figure 3, and Table 13 provide information on the results of the discussion of the DAG concerning the association between DL use and A-fib/flu. Table 12 lists the potential confounders discussed during the development of the DAG, Figure 3 shows the final developed DAG, and Table 12 provides the results of the DAG in terms of the minimum sufficient adjustment sets of confounders to include in the association analyzes to obtain a confounder adjusted estimate of the association between DL use and first diagnosis of A-fib/flu. Finally, the specific minimum sufficient adjustment set that will be used to adjust for confounding of the association between DL and A-fib/flu was identified and included the following confounders: age, sex, country, calendar year, disease severity of rhinitis, asthmatic status, and chronic urticaria.

Table 12 Discussion of potential confounders of the association between DL use and A-fib/flu

Potential confounders	Discussion	List of directed paths (head-to-tail arrows)
Age	Age affects the use of DL.	There is a directed path from age to: Inflammatory disease Drug and alcohol abuse Hypertension A-fib/flu Pre-stroke Diabetes Structural heart disease Thyroidism Disease severity of rhinitis COPD DL Infections Smoking Asthmatic status Drug overdose of drugs other than DL
Sex	There are sex differences in risk of A-fib/flu. Sex is associated with disease severity of rhinitis, as prevalence of rhinitis is higher in males than females. There are sex differences in smoking and the incidence of stroke, inflammatory disease, hypertension, structural heart disease and thyroidism. There are sex differences in DL use.	There is a directed path from sex to: Smoking Inflammatory disease Hypertension A-fib/flu Pre-stroke Structural heart disease Thyroidism Chronic urticaria Disease severity of rhinitis DL Drug and alcohol abuse Diabetes
Country	There are probably country differences in use of DL. Country differences in smoking.	There is a directed path from country to: Smoking DL

Potential confounders	Discussion	List of directed paths (head-to-tail arrows)
Calendar year	Preliminary data from the prescription registries demonstrate that the number of unique patients treated with DL varies by calendar year in each country, initially increasing and then showing some variation. Some, but not all of the variation may be due to differences in seasonality/pollen. Year is also associated with seasonality in that the influence of pollen may differ from year to year. There is a temporal trend in A-fib/flu, smoking, diabetes, inflammatory disease, type 1 allergy, and stroke.	There is a directed path from calendar year to: Smoking Inflammatory disease A-fib/flu Pre-stroke Diabetes Chronic urticaria Type 1 allergy Seasonality DL
Seasonality	There is a seasonal trend in DL use. There are seasonal trends in A-fib/flu, disease severity of rhinitis, asthmatic status, infections, inflammatory disease, type 1 allergy, and stroke. The effect of seasonality could change from year to year. It was suggested that pollen level could be used as a proxy for the effect of seasonality. One of the experts explained that this is not simple in that pollen level may vary from area to area and day to day. Pollen may also have a different influence from year to year for the same individuals. Thus, information on pollen level will not be included. Seasonality will be used as a proxy measure.	There is a directed path from seasonality to: DL Infections A-fib/flu Disease severity of rhinitis Type 1 allergy Asthmatic status
Disease severity of rhinitis	Disease severity of rhinitis affects the use of DL. Very strong association. DL is a prescription drug and if you have severe rhinitis and use antihistamines regularly, then you might choose a prescription drug as DL, as this drug is subsidized. The severity of rhinitis therefore influences whether you prefer DL over over-the-counter antihistamines. Disease severity of rhinitis affects asthmatic status.	There is a directed path from disease severity of rhinitis to: DL Asthmatic status

Potential confounders	Discussion	List of directed paths (head-to-tail arrows)
Asthmatic status	Asthmatic status affects DL use.	There is a directed path from asthmatic status to: DL Infections
COPD	Age affects risk of COPD. COPD affects risk of A-fib/flu and infections.	There is a directed path from COPD to: A-fib/flu Infections
Comorbidity	Could be measured as history of hospital admissions or as an index (e.g., the Charlson index). Comment (MSD): A non-specific indicator. Really a proxy for something else. Should be specified what part of comorbidity on top of the other indicators discussed should be included. Specific comorbidities are better. Comment (expert): Agree that Charlson should not be used. Conclusion: Do not include comorbidity index, number of admissions, or number of hospital contacts.	Not relevant
Smoking	Smoking has an effect on COPD, asthmatic status, hypertension, stroke, and structural heart disease.	There is a directed path from smoking to: Hypertension Pre-stroke Structural heart disease Asthmatic status COPD
Inflammatory disease	Inflammatory disease is associated with risk of A-fib/flu, structural heart disease, and chronic urticaria. Stroke increases risk of inflammatory disease. Sex and age are associated with risk of inflammatory disease.	There is a directed path from inflammatory disease to: A-fib/flu Structural heart disease Chronic urticaria
Infections	Infections can affect risk of A-fib/flu and chronic urticaria. There are sex differences in infections. COPD, asthmatic disease, and seasonality can affect risk of infections.	There is a directed path from infections to: A-fib/flu Chronic urticaria

Potential confounders	Discussion	List of directed paths (head-to-tail arrows)
Hypertension	Hypertension affects risk of A-fib/flu and increases risk of structural heart disease and stroke.	There is a directed path from hypertension to: A-fib/flu Pre-stroke Structural heart disease Antihypertensive treatment
Drug overdose (of drugs other than DL)	Overdose of drugs other than DL may induce A-fib/flu. Conclusion: Include any overdose as one binary variable.	There is a directed path from drug overdose of drugs other than DL to: A-fib/flu
Drug and alcohol abuse	Drug and alcohol abuse affects risk of A-fib/flu and overdose of drugs other than DL.	There is a directed path from drug and alcohol abuse to: A-fib/flu Drug overdose of drugs other than DL
Thyroidism (hypo-/hyperthyroidism) and synonymous diagnoses (e.g., Grave's disease, thyrotoxicosis)	Thyroidism is associated with of A-fib/flu, stroke, and structural heart disease. Age affects risk of thyroidism. There are sex differences in risk of thyroidism.	There is a directed path from thyroidism to: A-fib/flu Pre-stroke Structural heart disease
Diabetes	Diabetes affects risk of A-fib/flu, hypertension, stroke, and structural heart disease. Both diabetes type 1 and type 2 should be included.	There is a directed path from diabetes to: Hypertension A-fib/flu Pre-stroke Structural heart disease
Structural heart disease: Left ventricular hypertrophy, left ventricular systolic dysfunction, CHF	Structural heart disease affects risk of A-fib/flu and stroke.	There is a directed path from structural heart disease to: A-fib/flu Pre-stroke
Stroke	Stroke does not increase the risk of any factors included in the DAG, but is the effect of factors included. Stroke is divided into two types: 1) pre-stroke that occurs independently of A-fib/flu and 2) post-stroke that is caused by A-fib/flu.	There is a directed path from pre-stroke to: Inflammatory disease OBS: A-fib/flu affects risk of post-stroke

Potential confounders	Discussion	List of directed paths (head-to-tail arrows)
Chronic urticaria	Chronic urticaria is associated with use of very high doses (much higher than the recommended dose) of DL. Associated with sex. Prevalence of urticaria/chronic urticaria is higher in females than males. There is a temporal trend in prevalence of diagnosed chronic urticaria (increases) (i.e., calendar year affects chronic urticaria). Inflammatory disease and infections can increase the risk of chronic urticaria.	There is a directed path from chronic urticaria to: DL
Unspecific autoimmune disease	Unspecific autoimmune disease is associated with risk of chronic urticaria, thyroidism, and diabetes.	There is a directed path from unspecific autoimmune disease to: Diabetes Thyroidism Chronic urticaria
Type 1 allergy	Type 1 allergy can increase the risk of chronic urticaria and rhinitis. Seasonality affects risk of type 1 allergy.	There is a directed path from type 1 allergy to: Disease severity of rhinitis Asthmatic status Chronic urticaria
Antihypertensive treatment	Hypertension affects the use of antihypertensive treatment. Use of antihypertensive treatment increases the risk of chronic urticaria.	There is a directed path from antihypertensive treatment to: Chronic urticaria

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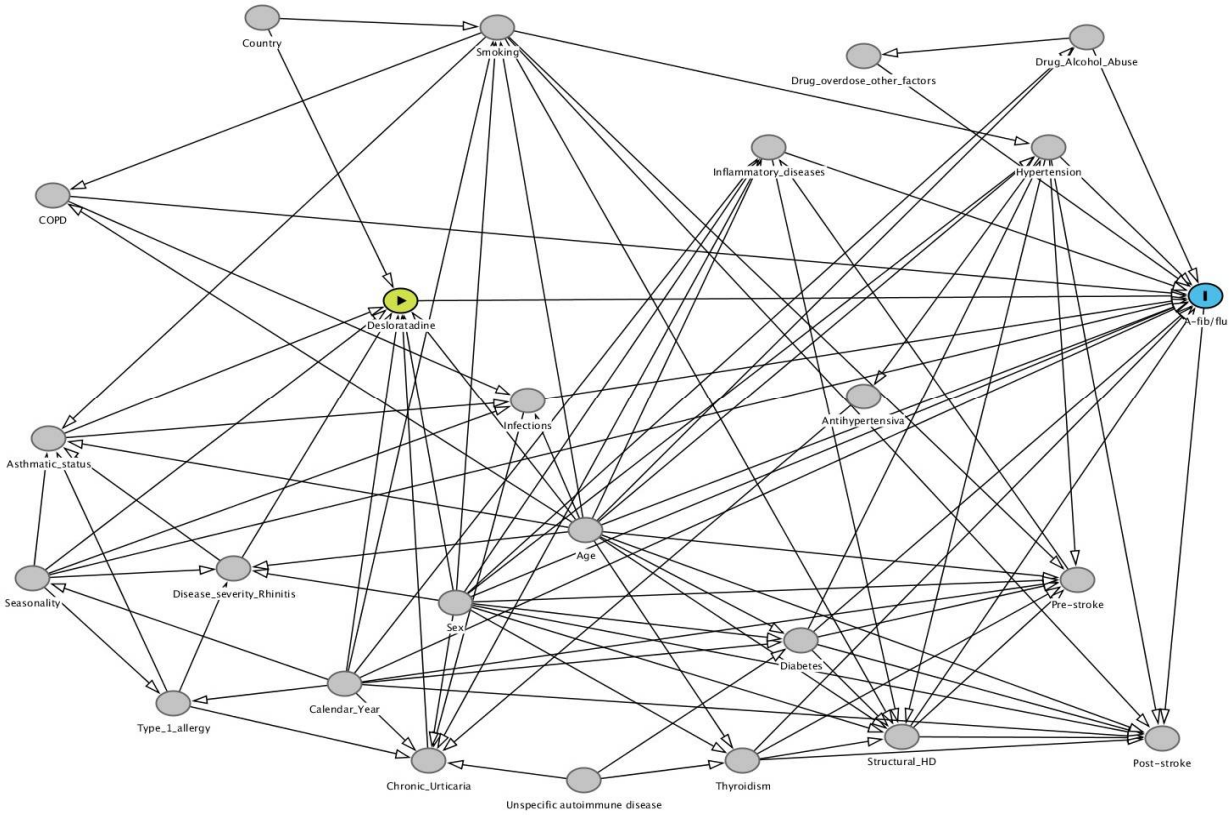
Figure 3 DAG for the association between DL use and A-fib/flu



05J9TR

Table 13 Minimum sufficient adjustment sets for the DAG developed (Figure 3)

Potential confounders	Minimum sufficient adjustment sets																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Age	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sex	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Country	X	X						X			X	X						
Calendar year	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Seasonality	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease severity of rhinitis	X	X						X	X		X	X						
Asthmatic status	X	X	X	X			X	X	X	X	X	X	X	X				
COPD					X	X	X								X	X	X	X
Smoking			X	X	X	X			X	X			X	X	X	X		X
Inflammatory disease	X	X	X	X	X	X	X				X	X	X	X		X	X	X
Infections	X	X	X	X	X	X					X	X	X	X	X	X	X	X
Hypertension							X				X	X	X	X		X	X	X
Drug overdose																		
Drug and alcohol abuse																		
Thyroidism (hypo-/hyperthyroidism)	X		X		X		X				X		X			X	X	
Diabetes	X		X		X		X				X		X			X	X	
Structural heart disease							X										X	
Stroke																		
Chronic urticaria							X	X	X	X					X			
Unspecific autoimmune disease		X		X		X						X		X				X
Type 1 allergy	X	X					X			X	X	X			X			
Antihypertensive treatment	X	X	X	X	X	X												

Light grey background = confounder information not available in population registers (e.g., self-reported lifestyle factors).
Dark grey background = selected minimum sufficient adjustment set (number 8) and the alternative set (number 1).

The minimum sufficient adjustment set chosen for analysis

Table 13 shows the possible minimum sufficient sets available. The set used to adjust for confounding of the association between DL and A-fib/flu included the following confounders: age, sex, country, calendar year, disease severity of rhinitis, asthmatic status, and chronic urticaria. The selection of which minimum sufficient adjustment set to use for confounder adjustment was based on our evaluation of the validity and quality of confounder information available from the registers. The combined set of confounders in the final selected minimum adjustment set was found to have the highest possible validity and quality.

DAG for the association between DL use and SVT

The DAG was almost similar for this outcome as for the A-fib/flu outcome. The following were the only changes:

No arrows from the following variables to SVT:

- Inflammatory diseases
- Hypertension
- COPD
- Calendar year
- Seasonality
- Diabetes

In this DAG, we do not differentiate between pre and post stroke, as this is not relevant for the SVT outcome and since the arrow points from stroke to SVT.

Figure 4 shows the final developed DAG and Table 12 provides the results of the DAG in terms of the minimum sufficient adjustment set of confounders to include in the association analyzes to obtain a confounder adjusted estimate of the association between DL use and first diagnosis of SVT. In Table 14, the minimum sufficient sets in the DAG of the association between DL use and SVT are listed. Finally, the specific minimum sufficient adjustment set that will be used to adjust for confounding of the association between DL and SVT was identified and included the following confounders: age, sex, country, calendar year, disease severity of rhinitis, asthmatic status, and chronic urticaria.

Figure 4 DAG for the association between DL use and SVT

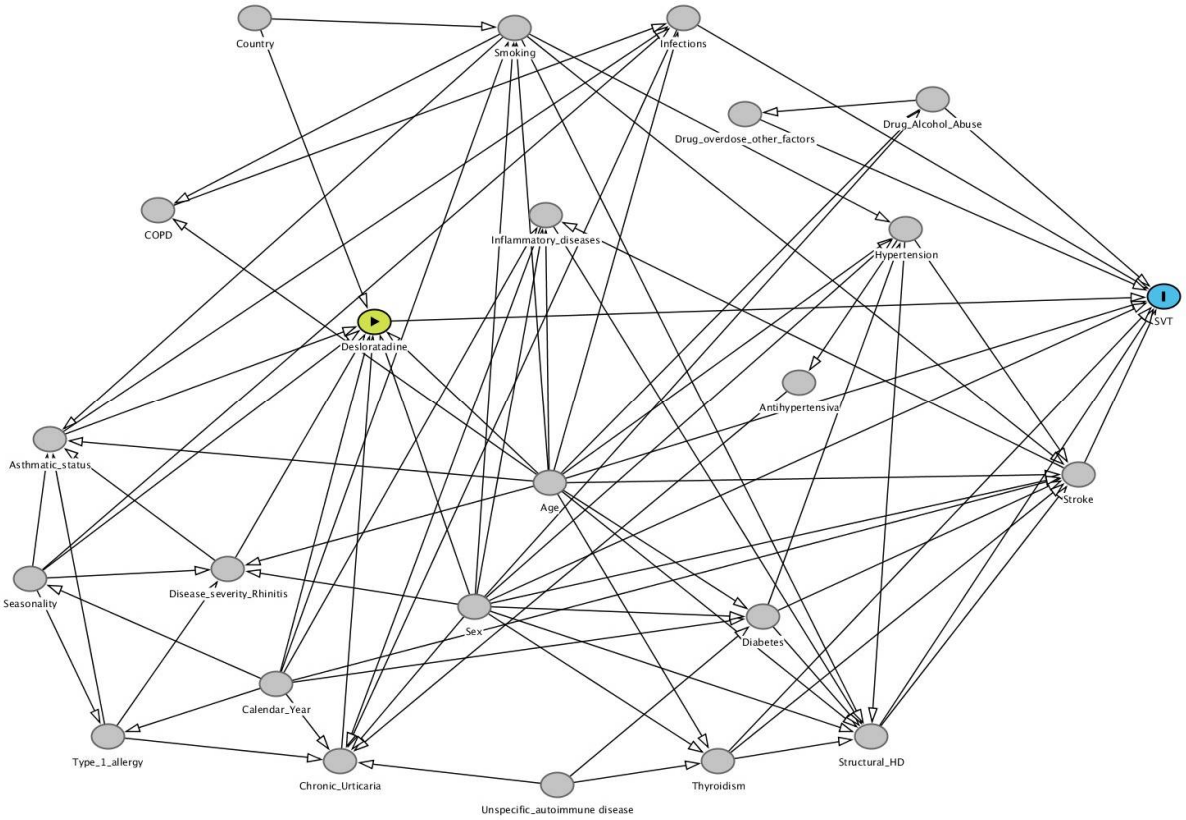


Table 14 Minimum sufficient adjustment sets for the DAG developed (Figure 4)

Potential confounders	Minimum sufficient adjustment sets																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Age	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sex	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Country			X	X					X			X	X				
Calendar year	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Seasonality	X	X	X	X			X	X	X	X	X	X	X				
Disease severity of rhinitis			X	X					X	X		X	X				
Asthmatic status	X	X	X	X			X	X	X	X	X	X	X				
COPD	X	X					X	X									
Smoking					X	X				X	X			X	X	X	
Inflammatory disease	X	X	X	X	X	X	X	X				X	X		X	X	
Infections			X	X	X	X						X	X	X	X	X	X
Hypertension							X	X				X	X		X	X	
Drug overdose																	
Drug and alcohol abuse																	
Thyroidism (hypo-/hyperthyroidism)	X	X	X		X		X	X				X			X		X
Diabetes	X		X		X		X					X			X		
Structural heart disease	X	X					X	X									X
Stroke	X	X					X	X									X
Chronic urticaria	X	X					X	X	X	X	X			X			
Unspecific autoimmune disease		X		X		X		X					X			X	
Type 1 allergy	X	X	X	X			X	X			X	X	X	X			
Antihypertensive treatment	X	X	X	X	X	X											

Light grey background = confounder information not available in population registers (e.g., self-reported lifestyle factors).
Dark grey background = selected minimum sufficient adjustment set (number 9) and the alternative set (number 3)

The minimum sufficient adjustment set chosen for analysis

Table 14 shows the possible minimum sufficient sets available. The set used to adjust for confounding of the association between DL and SVT included the following confounders: age, sex, country, calendar year, disease severity of rhinitis, asthmatic status, and chronic urticaria. The selection of which minimum sufficient adjustment set to use for confounder adjustment was based on our evaluation of the validity and quality of confounder information available from the registers. The combined set of confounders in the final selected minimum adjustment set was found to have the highest possible validity and quality.

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13 ATTACHMENTS

GLOBAL PHARMACOVIGILANCE - ADVERSE EVENT & PRODUCT QUALITY COMPLAINT REPORTING FORM

Case Details

Initial ☐ **F/U** ☐	**Sender/External Party Reference Number** (e.g. HA/BP/Vendor/Supplier Ref#):		**Aware Date** (DD-MM-YYYY):	
Sender (Business Partner, Investigator, Vendor, Supplier) Name and Address:			**Sender Reporting Date** (DD-MM-YYYY):	
MSD Internal Use Only:	**Local Ref #:**	**MARRS ID:**	**DPOC/PQC Ref#:**	**Central Receipt Date:**

Country of...	**Source Type:**	**Case Classification:**
Incidence "	Spontaneous ☐ Solicited ☒	NIS ☒ Market Research ☐
Patient "	Literature Study ☐ Literature Marketed ☐	PSP ☐ Social Media ☐
Reporter "		PSMP ☐ LCE ☐
		Non-Valid ☐

Program/ Study ID 4117-205 — Program/Study Name or Description: Association between use of desloratadine and risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter: A Nordic register-based study

This is a non-interventional study/program with no HCP assessment of seriousness or causality ☐

PATIENT ***(Complete in accordance with local privacy law(s))***

Patient

Patient Identifiers	Anonymized: ☐	Unknown: ☐
	First/Last Name:	Initials:
	Patient ID:	
Patient Demographics	Gender: Male ☐	Female ☐ Unknown ☐
	Date of Birth: / /	Age: - Age Group: -
	Weight: -	Height: -

REPORTER ***(Complete in accordance with local privacy law(s))***

Reporter

Reporter Contact Details	Anonymized: ☐ Unknown: ☐	Telephone:
	Name:	Fax:
	Address:	E-mail address:
Reporter Type	Company Rep ☐ Consumer ☐	Lawyer ☐ Other ☐
	Other Health Prof ☐ Pharmacist ☐	Physician ☐ Authority ☐

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GLOBAL PHARMACOVIGILANCE - ADVERSE EVENT & PRODUCT QUALITY COMPLAINT REPORTING FORM

ADVERSE EVENTS/PRODUCT QUALITY COMPLAINTS

Adverse Event(s) / PQCs

Reported Term	Onset Date	Stop Date	Outcome	Seriousness	Reporter Causality
	/ /	/ /	-	-	-
	/ /	/ /	-	-	-
	/ /	/ /	-	-	-
	/ /	/ /	-	-	-
	/ /	/ /	-	-	-
	/ /	/ /	-	-	-
	/ /	/ /	-	-	-
	/ /	/ /	-	-	-
	/ /	/ /	-	-	-
	/ /	/ /	-	-	-

PRODUCT(S)

Product(s)

Trade/generic name	S/C*	Formulation**	Indication	Start Date	Stop Date	Action Taken	Batch/Lot/UDI # / Expiry Date
	-			/ /	/ /	-	
	-			/ /	/ /	-	
	-			/ /	/ /	-	
	-			/ /	/ /	-	
	-			/ /	/ /	-	
	-			/ /	/ /	-	
	-			/ /	/ /	-	
	-			/ /	/ /	-	
	-			/ /	/ /	-	
	-			/ /	/ /	-	

* S = Suspect Product, C = Concomitant Product ** Include Dose + Frequency when available or specify in Description of Event(s) Section

CLASSIFICATION OF DEVICE EVENT/PRODUCT QUALITY COMPLAINT

Device (Component) Investigation

Check one or more of the criteria that the device event/product quality complaint **led to** or **might have led** to:

☐ Death of user, subject or another person
☐ Serious deterioration in state of health of the user, subject or other person: specified as: -
☐ Required intervention (to prevent permanent impairment/damage)
☐ Not Applicable

USAGE & OPERATOR

Usage of the Medical Device: -
Specify if Usage is "Other":
Was the Device used according to the leaflet?
Yes ☐ No ☐ Unknown:
If No, please specify:

Operator at time of event occurrence: -
Operator trained? Yes ☐ No ☐ Unk ☐ N/A ☐
Who trained the operator?

QA INVESTIGATION

Is the sample/device available for return?

☐ Yes, please provide contact details (name, phone#) of person responsible for sample:
☐ No, specify why the sample/device is not available for investigation:
☐ Specify the current location of the sample/device:

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MSD

GLOBAL PHARMACOVIGILANCE - ADVERSE EVENT & PRODUCT QUALITY COMPLAINT REPORTING FORM

DESCRIPTION OF EVENT(S), PRODUCT QUALITY COMPLAINTS (including relevant tests, history and observations and all other information not captured in data fields)
Follow-Up Comment: -

Form Completed By:	**Date Form Completed** (DD-MM-YYYY)**:**	**QC check Completed By:**	**QC Check Date** (DD-MM-YYYY)**:**

Annex 2 Variable Definitions

Annex 6 Variable Definitions

Variable	Definition	Data source	ATC	ICD-8	ICD-9	ICD-10
EXPOSURE						
Desloratadine	Exposure status	Prescription register	R06AX27			
Loratadine			R06AX13			
Non-sedating antihistamines			R06AE07, R06AE09, R06AX12, R06AX13, R06AX18, R06AX22, R06AX25, R06AX26, R06AX27, R06AX28, R06AX29			
OUTCOME VARIABLES						
Non-febrile seizure	A binary variable with categories yes and no	Patient register		-	-	R568*
Febrile seizure				-	-	R560*
Supraventricular tachycardia				42790	4270	I47*
Atrial fibrillation or flutter				42793, 42794	4273	I48*
Recurrent non-febrile seizure				-	-	R568*

Variable	Definition	Data source	ATC	ICD-8	ICD-9	ICD-10
VARIABLES USED FOR ADJUSTMENT						
Age	A time varying variable categorized as 0-4, 5-19, 20-64, ≥65 years	Civil registration system				
Sex	Male versus female	Civil registration system				
Country	Country of residence with categories Denmark, Finland, Norway, and Sweden	Civil registration system				
Calendar year	A time-varying variable Calendar years 2001, 2002, 2003, …, 2015 for prescriptions except for Tables 2A, 3A, 4A and 5B, where calendar year is defined for incident diagnoses (seizure, SVT, atrial fibrillation and recurrent seizure, respectively)	Prescription register; Patient register				
Seasonality	A time-varying variable Winter (December–February), spring (March–May), summer (June–August), and autumn (September–November).	Prescription register				
Asthma status	A binary variable with categories yes and no, based on prescriptions and/or contacts to the hospital					
	Redeemed treatment for asthma defined as at least two prescriptions of inhalant steroids within a six-month period during a five-year period before first DL exposure. First registered asthma prescription has to be redeemed when the purchaser was 45 years or younger	Prescription register	R03A* R03B*			

Variable	Definition	Data source	ATC	ICD-8	ICD-9	ICD-10
VARIABLES USED FOR ADJUSTMENT						
	Contacts to hospitals with a diagnosis of asthma (including both primary and secondary diagnoses) during a five-year period before first DL exposure	Patient register		-	-	J45*
Severe rhinitis	A binary variable with categories yes and no, based on prescriptions					
	Redeemed immunotherapy at least once during a five-year period before first DL exposure	Prescription register	V01AA* (excluding V01AA07)			
Chronic urticaria	A binary variable with categories yes and no, based on hospitals contacts					
	Registered diagnosis of chronic urticaria in the five-year period before first DL exposure.	Patient register				L50* (excluding L50.8D), L56.3
Diabetes	A binary variable with categories yes and no, based on prescriptions and/or contacts to the hospital					
	Redeemed at least two prescriptions of glucose-lowering drugs in the five-year period before first DL exposure	Prescription register	A10*			
	Registered diagnosis of diabetes in the five-year period before first DL exposure	Patient register				E10*-E14*
Hypo-/hyperthyroidism	A binary variable with categories yes and no, based on prescriptions and/or contacts to the hospital					
	Redeemed at least two prescriptions of drugs for treatment of hypo-/hyperthyroidism in the five-year period before first DL exposure	Prescription register	H03BB02 H03AA01			
	Registered diagnosis of hypo-/hyperthyroidism	Patient register				E00*-E07*

Variable	Definition	Data source	ATC	ICD-8	ICD-9	ICD-10
VARIABLES USED FOR ADJUSTMENT						
Inflammatory disease	A binary variable with categories yes and no, based on prescriptions and/or contacts to the hospital					
	Redeemed at least two prescriptions of Daivonex (drug against psoriasis) in the five-year period before first DL exposure	Prescription register	D05AX02			
	Registered diagnosis of inflammatory bowel disease, psoriasis, rheumatic diseases, vasculitis, or sarcoidosis in the five-year period before first DL exposure	Patient register				K50*-K52* L40* M05*-M08* L95* D86*
Infection	A binary variable with categories yes and no, based on hospitals contacts					
	Registered diagnosis of lung infection (pneumonia) or sinusitis in the five-year period before first DL exposure.	Patient register				J12*-J18*, J21*-J22* J01*, J32*
Type 1 allergy	A binary variable with categories yes and no, based on prescriptions and/or contacts to the hospital					
	Redeemed at least one prescription of immunotherapy drugs in the five-year period before first DL exposure	Prescription register	V01AA			
	Registered diagnosis of acute urticaria, anaphylaxis, quinckes oedema in the five-year period before first DL exposure	Patient register				L50.8D* T78*
	A binary variable with categories yes and no, based on hospitals contacts					

Variable	Definition	Data source	ATC	ICD-8	ICD-9	ICD-10
VARIABLES USED FOR ADJUSTMENT						
Antihypertensive treatment	Redeemed antihypertensive prescription (ACE inhibitor, angiotensin II receptor antagonist, calcium channel blocker, beta-blockers, alpha-blockers, thiazide (diuretic treatment), methyldopa, or moxonidine) at least twice during a five-year period before first DL exposure	Prescription register	C09A* C09C* C08CA* C07AB* C02CA* C03A*-C03E* C02AB* C02AC05			

* Subcodes

R56 CODES. The tables include seizure codes within the data.

R560: Febrile seizure

R568: Non-febrile seizure

DENMARK

ICD-10	Danish	English
R56	Konvulsioner IKA	Convulsions, not elsewhere classified
R560	Feberkramper	Febrile convulsions
R560A	Tetani ved feber	Tetani by fever
R568	Andre eller ikke specificeret	Other or unspecified
R568A	Convulsiones uraemicae	Convulsions uraemicae
R568B	Convulsiones universal	Convulsions universal
R568C	Affektkramper	Affect convulsions
R568D	Kramper UNS	Convulsions UNS
R568E	Førstegangs uprovokere	First time unprovoked
R568F	Oligoepilepsi	Oligoepilepsi
R568G	Non-epileptiske anfald	Non- epileptic seizure

FINLAND

ICD-10	Finnish	English
R56	Muualla luokittamattomat kouristukset	Convulsions, not elsewhere classified

R56.0	Kuumekouristukset	Febrile convulsions
R56.8	Muu tai määrittämätön kouristus / Tarkemmin määrittämätön kouristuskohtaus/ Kouristuskohtaus	Other and unspecified convulsions/ Fit NOS

SWEDEN

ICD-10	Swedish	English
R56	Convulsiones non alibi classificatae	Convulsions, not elsewhere classified
R560	Feberkramper	Febrile convulsions
R568	Andra och ospecificerade kramper	Other and unspecified convulsions
R5680	*	Code not valid
R568A	Affektkramper	Affect convulsions
R568U	*	Code not valid
R568X	Krampanfall, ospecificerade	Convulsions unspecified

* Kristian Bolin has September 29th 2020 talked to Socialstyrelsen. The reported codes (R5680 and R568U) are not valid and have been incorrectly stored in the register at Socialstyrelsen.
For the codes (R5680 and R568U) there are below 10 in each category.

NORWAY

ICD-10	Norwegian	English
R56	Kramper, ikke klassifisert annet sted	Convulsions, not elsewhere classified

Regarding Norwegian data the following subcodes are included in R56:
R56.0 (Feberkramper/ **ENG: Febrile convulsions**)
R56.8 (Andre og uspesifiserte kramper/ Anfall INA/ Krampeanfall INA/ **ENG: Other and unspecified convulsions**).