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 PPD
Merck Final Repository (RCAM) Date	25-Jun-2020
Date of Health Authority Approval of Protocol	Not applicable

SUMMARY OF CHANGES

Protocol Section	Change
N/A	N/A

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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

Principal investigator	Annette Kjær Ersbøll, Professor National Institute of Public Health (NIPH) University of Southern Denmark Studiestræde 6 DK-1455 Copenhagen K Denmark PPD
Coordinating investigator for each country in which the study is to be performed	Denmark: Annette Kjær Ersbøll, Professor, NIPH, University of Southern Denmark, Denmark Finland: Eero Pukkala, Professor, School of Health Sciences, University of Tampere, Finland Sweden: Kristian Bolin, Professor, Department of Economics, Lund University, Sweden Norway: Kristian Bolin, Professor, Department of Economics, Lund University, Sweden
Sponsor contacts	PPD Pharmacoepidemiology Merck Sharp & Dohme, Corp., a subsidiary of Merck & Co., Inc. WP37A-250 770 Sumneytown Pike West Point, PA, United States 19486 PPD
Other contacts	Not applicable
Supplier/Collaborator	Institute of Applied Economics and Health Research (ApEHR) Ewaldsgade 3 DK-2200 Copenhagen Denmark Phone: PPD www.appliedeconomics.dk
Investigators	Kaushik Sengupta, Research assistant, NIPH, University of Southern Denmark, Denmark Thora Majlund Kjærulff, PhD Fellow, NIPH, University of Southern Denmark, Denmark

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).

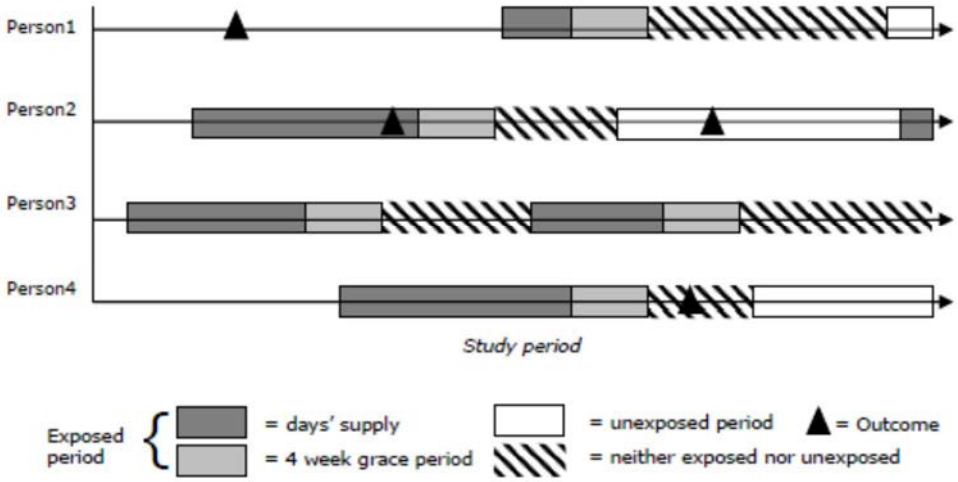

Figure 1 illustrates how subjects in the study population (i.e., restricted to persons with at least one *redeemed prescription of DL) enter and exit exposed and unexposed periods. An exposed period is a period starting from the day of redemption of a DL prescription and includes the following period 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.

11 REFERENCES

[Association of Nordic Cancer Registries 2009]	The NORDCAN project [Internet]. Copenhagen: Association of Nordic Cancer Registries; c2009 [updated 2014 Dec 17]. Available from: http://www-dep.iarc.fr/NORDCAN/english/frame.asp.	[045VPW]
[Bakken, I. J., et al 2012]	Bakken IJ, Gystad SO, Christensen OO, Huse UE, Laronningen S, Nygard J, et al. Comparison of data from the Norwegian Patient Register and the Cancer Registry of Norway. Tidsskr Nor Laegeforen. 2012 Jun 12;132(11):1336-40.	[0469WT]
[Bryant, E. 1987]	Bryant E, Morganstein DR. Sample size determination for longitudinal surveys. Survey Research Methods Section, American Statistical Association Meeting; 1987 Aug 17-20; San Francisco, CA: 1987.	[045WWJ]
[Cerminara, C., et al 2013]	Cerminara C, El-Malhany N, Roberto D, Lo Castro A, Curatolo P. Seizures induced by desloratadine, a second-generation antihistamine: clinical observations. Neuropediatrics. 2013 Aug;44(4):222-4.	[045VR5]
[Frost, L. 2004]	Frost L, Vestergaard P. Alcohol and risk of atrial fibrillation or flutter: a cohort study. Arch Intern Med. 2004 Oct 11;164(18):1993-8.	[04C0BQ]

[Frost, L., et al 2007]	Frost L, Andersen LV, Vestergaard P, Husted S, Mortensen LS. Trend in mortality after stroke with atrial fibrillation. Am J Med. 2007 Jan;120(1):47-53.	[04C0BS]
[Furu, K., et al 2009]	Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sorensen HT. The nordic countries as a cohort for pharmacoepidemiological research. Basic Clin Pharmacol 2009;106:86-94.	[00W4CX]
[Glanz, J. M., et al 2006]	Glanz JM, McClure DL, Xu S, Hambidge SJ, Lee M, Kolczak MS, et al. Four different study designs to evaluate vaccine safety were equally validated with contrasting limitations. J Clin Epidemiol 2006;59:808-18.	[03QPDQ]
[Greenland, S., et al 1999]	Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999 Jan;10(1):37-48.	[045RCQ]
[Hauser, W. A. and Beghi, E. 2008]	Hauser WA, Beghi E. First seizure definitions and worldwide incidence and mortality. Epilepsia 2008;49(Suppl 1):8-12.	[00W4CY]
[Kildemoes, H. W., et al 2011]	Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health. 2011 Jul;39(7 Suppl):38-41.	[045TYK]
[Kirkwood, B. R. 2003]	Kirkwood BR, Sterne JA. Essential Medical Statistics. 2nd ed. Malden (MA): Blackwell Publishing; 2003.	[045VXZ]
[Klaukka, T. 2001]	Klaukka T. The Finnish database on drug utilization. Nor Epidemiol. 2001;11(1):19-22.	[0469YG]
[Ludvigsson, J. F., et al 2011]	Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim J-L, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:1-16.	[03RSH6]

[Lynge, E., et al 2011]	Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health. 2011 Jul;39(7 Suppl):30-3.	[045TZL]
[Orejarena, L. A., et al 1998]	Orejarena LA, Vidaillet H Jr, DeStefano F, Nordstrom DL, Vierkant RA, Smith PN, et al. Paroxysmal supraventricular tachycardia in the general population. J Am Coll Cardiol 1998;31(1):150-7.	[03XNM4]
[Pedersen, C. B. 2011]	Pedersen CB. The Danish Civil Registration System. Scan J of Public Health 2011;39(7 suppl):22-5.	[00W4G3]
[Pukkala, E. 2011]	Pukkala E. Nordic biological specimen bank cohorts as basis for studies of cancer causes and control: quality control tools for study cohorts with more than two million sample donors and 130,000 prospective cancers. In: Dillner J, editor. Methods in biobanking. New York: Springer; 2011. p. 61-112.	[045W09]
[Rix, T. A., et al 2012]	Rix TA, Riahi S, Overvad K, Lundbye-Christensen S, Schmidt EB, Joensen AM. Validity of the diagnoses atrial fibrillation and atrial flutter in a Danish patient registry. Scand Cardiovasc J. 2012 Jun;46(3):149-53.	[04C0BZ]
[Schmidt, M., et al 2015]	Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015 Nov 17;7:449-90.	[04C0C2]
[Sund, R. 2012]	Sund R. Quality of the Finnish Hospital Discharge Register: a systematic review. Scand J Public Health. 2012 Aug;40(6):505-15.	[046B36]
[Textor, J., et al 2011]	Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams. Epidemiology. 2011 Sep;22(5):745.	[045WX9]

[Thygesen, L., et al 2011]	Thygesen L, Daasnes C, Thaulow I, Bronnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. Scan J Public Health 2011;39(Suppl 7):12-6.	[00W4D0]
[Vestergaard, M., et al 2006]	Vestergaard M, Obel C, Henriksen TB, Christensen J, Madsen KM, Ostergaard JR, et al. The Danish National Hospital Register is a valuable study base for epidemiologic research in febrile seizures. J Clin Epidemiol. 2006 Jan;59(1):61-6.	[04C0C7]
[Wettermark, B., et al 2007]	Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf. 2007 Jul;16(7):726-35.	[046B3C]
[Wilke, T., et al 2013]	Wilke T, Groth A, Mueller S, Pfannkuche M, Verheyen F, Linder R, et al. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. Europace 2013;15:486-93.	[03XNL7]

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.

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:

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:

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

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.

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:

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: 29/5/2020

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
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

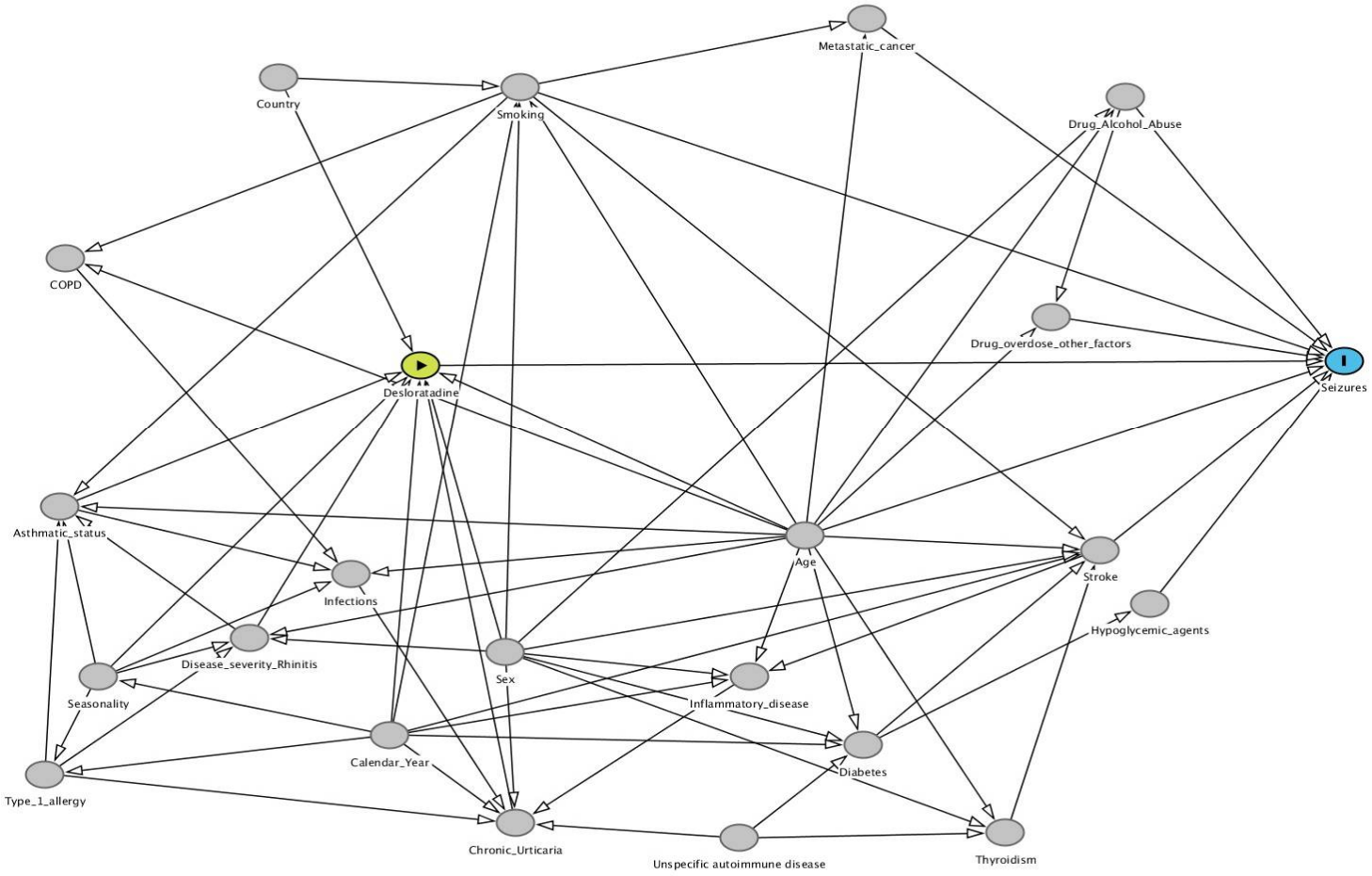

Table 11 Minimum sufficient adjustment sets for the DAG developed (Figure 2)

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

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

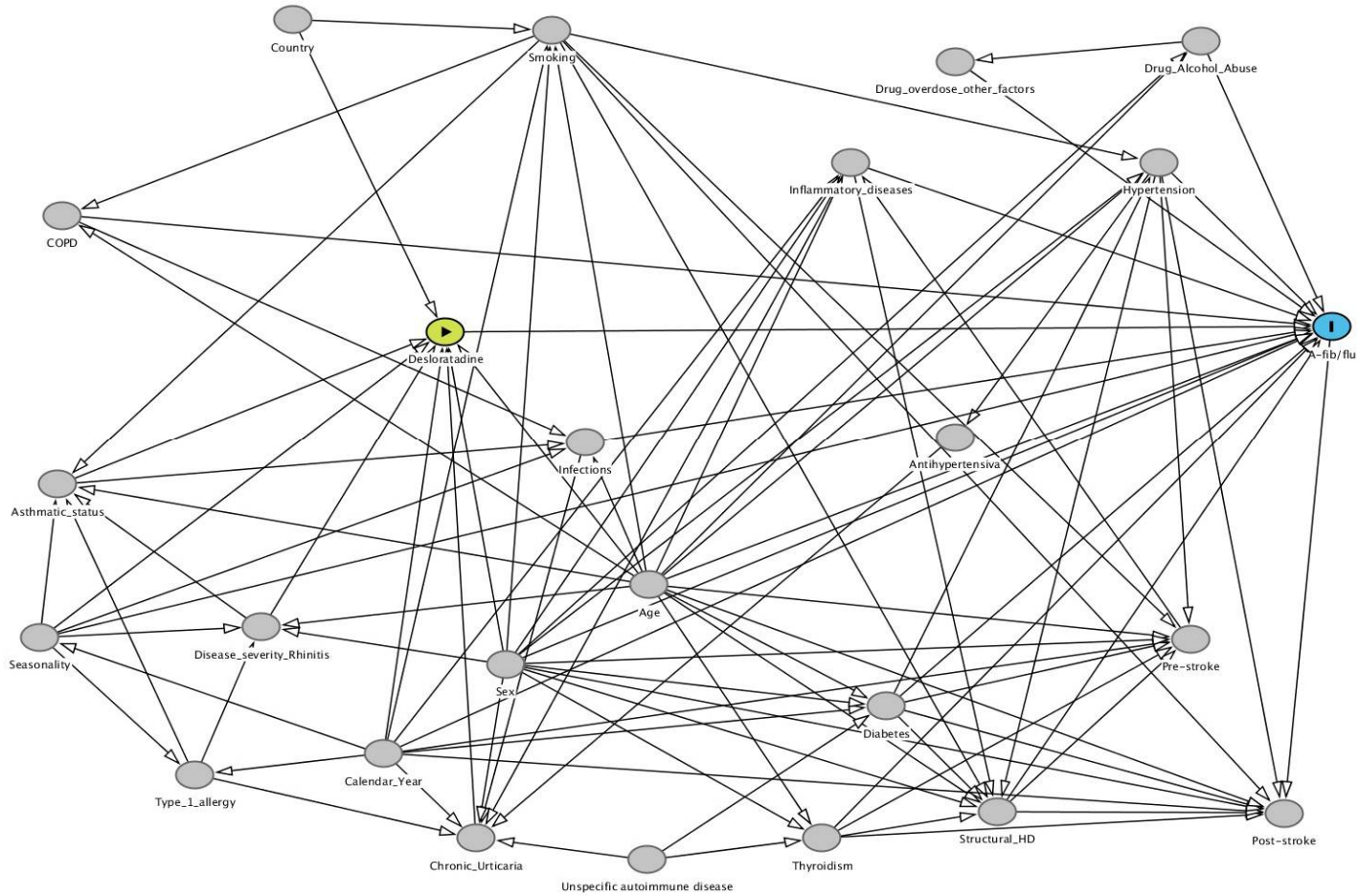

Table 13 Minimum sufficient adjustment sets for the DAG developed (Figure 3)

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

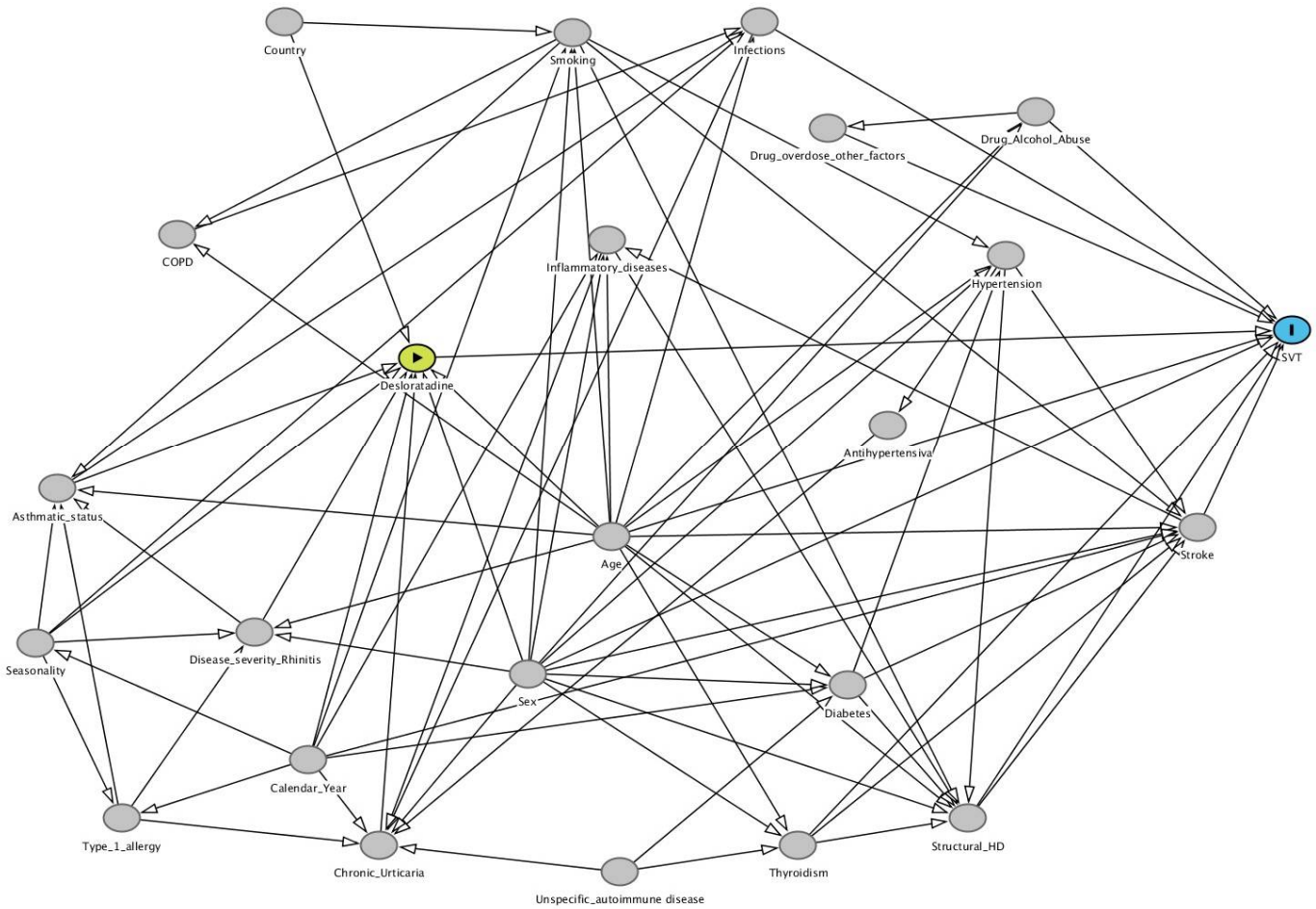

Table 14 Minimum sufficient adjustment sets for the DAG developed (Figure 4)

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.

13 ATTACHMENTS

MSD

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 " Patient " Reporter "	Spontaneous ☐ Solicited ☒ Literature Study ☐ Literature Marketed ☐		NIS ☒ Market Research ☐ PSP ☐ Social Media ☐ 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 ☐ Other Health Prof ☐ Pharmacist ☐		Lawyer ☐ Other ☐ Physician ☐ Authority ☐	

MSD

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:

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):