4 ABSTRACT

Title	Association between use of desloratadine and risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter: A Nordic register-based study
Protocol Version	1.1
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Rationale and background	A post-authorization safety study is needed to assess the potential risk of desloratadine exposure on seizures, supraventricular tachycardia, and atrial fibrillation or flutter.
Research question and objectives	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); to examine the associations between desloratadine exposure and atrial fibrillation or flutter (Substudy 4B); to describe the incidence rate of first recurrent seizure (Substudy 5A); and to examine the association between desloratadine exposure and first recurrent seizure (Substudy 5B).
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, first atrial fibrillation or flutter diagnosis, and first recurrent seizure. 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, atrial fibrillation or atrial flutter, and first recurrent seizure will be calculated. Among persons ever dispensed desloratadine, the associations between desloratadine exposure and first seizure, supraventricular tachycardia, atrial fibrillation or flutter, and first recurrent seizure will be evaluated using Poisson regression of incidence rates accounting for confounding factors. Additional supplementary analyses will be performed.

Milestones	Approval of protocol by Committee for Medicinal Products for Human Use (CHMP)/Pharmacovigilance Risk Assessment Committee (PRAC): *TBD* Submission of application for permission to access national registries: 2 weeks after approval Start of data collection: 4 months after application submitted End of data collection: 12 months after start of data collection Data analysis: 6 months after end of data collection Submission of final report of study results (as a Type II variation): 6 months after completion of data analysis Preparation of manuscripts for scientific publication: First draft 2+ months after submission of the final study report The study milestones are dependent on the timelines for the applications for data access and the timelines for data collection from the registries. We have based the milestones on our best estimates of the time required; however, these timelines are not within control of the responsible parties and recently, the application and data collection processes have been taking longer due to new administrative procedures and requirements that are applicable for some studies many of which are due to additional requirements regarding data privacy. In particular, access to data in Finland requires sequential applications to the various individual registries, each of which has recently taken up to 12 months [Ref. 5.4: 046J05]. The current expectation is that the study report will be finalized 29 months after endorsement of protocol, while the MAH previously worked with an 18 months' period following protocol endorsement as included in the current version (number 1.1) of the EU Risk Management Plan. If there are further delays due to the application and data collection processes which affect the study timeline or the availability of data in one of the countries, we will inform the PRAC accordingly with a request for extension of the timelines.