Post Authorisation Safety Study Protocol Abstract

Study No.	15649A
Title	Use of Nalmefene (Selincro®) in European databases: Cohort design using longitudinal electronic medical records or claims databases
Protocol version identifier	3.0 (the version number in the footer is the system version number)
Date of last version of protocol	09 March 2015
EU PAS register number	Study to be registered before data analysis starts (planned Q3 2016)
Active Substance	ATC classification: N07BB05 Active substance: Nalmefene
Medicinal product	Selincro®, 18 mg, film-coated tablet
Product reference	EMEA/H/C/002583
Procedure number	Not yet assigned
Marketing authorisation holder	H. Lundbeck A/S
Joint PASS	No

1 Abstract

Title	Use of Nalmefene (Selincro®) in European databases: Cohort design using longitudinal electronic medical records or claims databases Protocol version 3.0 Date of last version of protocol: 09 March 2015
Rationale and background	Selincro® was granted a marketing authorisation by the European Commission on 25 February 2013 with the following indication: *"Selincro® is indicated for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level, without physical withdrawal symptoms and who do not require immediate detoxification. Selincro® should only be prescribed in conjunction with continuous psychosocial support focussed on treatment adherence and reducing alcohol consumption. Selincro® should be initiated only in patients who continue to have a high drinking risk level two weeks after initial assessment"*. Selincro® has been marketed in Europe since April 2013. Routine Pharmacovigilance will be carried out to monitor the safety of Selincro®. During the regulatory review process, it has been asked to propose additional pharmacovigilance activities to assess the following risks: • important identified risks "confusional state; hallucination, dissociation", "concurrent use with opioids", • important potential risk "off-label use", • important missing information "use in pregnant and lactating women", "use in children", "use in other ethnic groups than Caucasian", "overdose", "use in patients with increased (>3xULN) ALAT or ASAT", "use in patients with history of seizure disorder, including alcohol withdrawal seizures", "use in elderly", "use in patients with significant psychiatric comorbidity", "use in patients with significant somatic comorbidity, e.g. renal, hepatic, cardiac, neurological disorders", "long-term use over 1 year" and "use in patients with concurrent use of a Central Nervous System (CNS)-active medication (ATC N06A Antidepressants, N05A Antipsychotics, N05B Anxiolytics and N05C Hypnotics)". A Post-Authorization Safety Study (PASS) was proposed in the form of a non-interventional, prospective, cohort study to investigate patterns of use of Selincro® and frequency of selected adverse drug reactions in routine clinical practice. It has been recognized that the proposed prospective study carries some risks of bias that may be partly minimised at the study design stage or during data analysis, but cannot be fully eliminated due to the study's prospective and observational nature. The regulatory authorities requested the MAH to consider the available EU databases relevant to analysis of drug utilisation patterns. Indeed, automated databases can be appropriate tools for drug-use studies due to the recording of diagnosis and prescription data independently of any study purposes. However, some of the information identified in the RMP would not be available or only partly in such databases. Considering the limitations of such databases with regards to the collecting of all the necessary information, the decision to conduct the proposed prospective study together with the proposed database analyses was endorsed by the CHMP. After a review of possible EU databases that could be used for the proposed objectives, it was proposed to perform retrospective database analyses in three countries with complementary approaches, namely Germany, Sweden and the United Kingdom. Findings from both approaches (prospective collection and database extraction) such as common data collected during the same time period and in the same settings will be compared in order to enrich the discussions about the limitations of one study versus the

	other.
Research question and objectives	The primary objective of the database analysis is to describe: • The use of Selincro® in clinical practice, particularly in the following sub-populations: – elderly (aged 65 years and above), – pregnant women, – children (aged less than 18 years). and according to the availability of data in each selected database: – patients with increased (>3xULN) ALAT or ASAT, – patients with psychiatric comorbidity, – patients with somatic comorbidity, e.g. renal, hepatic, cardiac, neurological disorders, – patients with history of seizure disorder, including alcohol withdrawal seizures – patients with concurrent use of a Central Nervous System (CNS)-active medication (ATC N06A Antidepressants, N05A Antipsychotics, N05B Anxiolytics and N05C Hypnotics), – patients with concurrent use of opioids (N02A). The secondary objectives are to describe: • The use of Selincro® over more than one year and the occurrence of overdose. • The use of Selincro® in patients outside the indication defined in the section 4.1 of the SmPC (off-label use). The primary and secondary objectives will be adapted in each database protocol.
Study design	Cohort design using longitudinal electronic medical records or administrative claim databases.
Population	All new users of Selincro® (incident users) between country-specific market entry date and end of the inclusion period will be included in the analysis.
Variables	For the primary objectives: Selincro® prescription, age, gender, pregnancy status, psychiatric co-morbidities (list defined in the Annex 3), history of seizures disorders and/or alcohol withdrawal seizures, any renal, hepatic, cardiac or neurological co-morbidities (list defined in the Annex 3), CNS active co-medications and opioid drugs. If available: blood tests results (liver enzymes ALAT and ASAT). For the secondary objectives: Number of Selincro® prescriptions over time, diagnosis of alcohol, age.
Data sources	Germany: Statutory Health Insurance (SHI) claim databases. Sweden: national register of prescriptions and diagnosis. United Kingdom: Clinical Practice Research Datalink (CPRD), Electronic medical records (EMR) database held by a network of general practitioners (GPs).
Study size	The calculation of the minimal sample size is made for each database, and relies on the precision of the 95% confidence interval of the proportion of patients treated in the different sub-populations of interest, using the binomial distribution. Expected proportions span a large range, from an expected proportion of 6% of patients aged above 65 years (as observed in phase III clinical trials) to about 30% of patient with concurrent depression. In each database, a sample size of 2000 will ensure that the interval is no wider than 0.04 in sub-populations with a proportion of 30% (margin error ± 2% around the true proportion). For smaller proportions, that is 1% to 5%, the width of the confidence interval will be no wider than 0.02 (margin error ± 1% around the true proportion).

Data analysis	The purpose of the study is descriptive (no statistical testing will be performed) and analyses will be performed separately for each database. The primary study objective is to describe the proportion of sub-populations of interest in the overall population of patients initiating Selincro®. The secondary objectives are to describe the proportion of patients treated with Selincro® during more than one year, the percentage of patients with a number of Selincro® prescriptions exceeding the daily intake (overdose) and the percentage of women who are pregnant during the course of Selincro® treatment, the percentage of patients who are outside the licensed indication (off-label use) at the time of Selincro® initiation.
Milestones	For each selected database, the analysis related to the first and secondary objectives will be developed separately. The following timelines take into account the actual dates of launch and the number of patients treated available in the databases of interest as well as an alignment with the inclusion period of the prospective study: Final study protocol (PRAC approved) — Q4 2013 Start of the inclusion period — at country-specific launch Baseline Study Reports — Q4 2016 Final Study Reports — Q2 2018