Post-Authorisation Safety Study Abstract

Extrapyramidal symptoms in patients treated with Abilify Maintena®: Cohort study with a 2-year follow-up using European automated healthcare databases

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Sponsor   H. Lundbeck A/S
Ottiliavej 9, 2500 Valby, Denmark

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Abstract

Title	Extrapyramidal symptoms in patients treated with Abilify Maintena®: Cohort study with a 2-year follow-up using European automated healthcare databases
Rationale and background	Schizophrenia is a chronic remitting and relapsing mental disorder characterised by long duration, cognitive dysfunction, negative symptoms, delusions and other positive symptoms. Epidemiological data has estimated the lifetime prevalence of schizophrenia to be 0.3% to 0.7% and the incidence to be around 10 to 22 per 100,000 person-years.[1] The onset of schizophrenia is typically in late adolescence to early adulthood, where the average age of onset is 18 in men and 25 in women.
	The primary treatment for schizophrenia is the use of antipsychotic medications. While these antipsychotic medications are effective in reducing overall symptoms and risk of relapse in patients with schizophrenia, their efficacy depends upon compliance and patient adherence to therapy.[2] To improve patient adherence, long-acting injectable formulations of antipsychotics were developed. These "depot" treatments require patients to visit clinics to receive treatment every one to six weeks, eliminating the need for daily oral antipsychotic administration. Among these antipsychotics, the IM depot formulation of aripiprazole, Abilify Maintena®, has received a positive opinion from the CHMP on September 19, 2013. Aripiprazole is an organic compound discovered by Otsuka Pharmaceutical Company Ltd. Otsuka Pharmaceutical Company and H. Lundbeck A/S are jointly developing the IM depot formulation of aripiprazole.
	Pharmacological treatments for schizophrenia can be classified into first-generation typical antipsychotics and second-generation atypical antipsychotics which have fewer motor side-effects, but a higher incidence of metabolic side-effects. Extrapyramidal symptoms (EPS) are well known class-effects, that can be categorised as acute (e.g., dystonia, akathisia and parkinsonism) and tardive (e.g., tardive dyskinesia and tardive dystonia) syndromes.[3] They have a significant impact on subjective tolerability and adherence with antipsychotic therapy in addition to impacting global functioning. Unlike typical antipsychotics, atypical antipsychotics have a significantly decreased risk of inducing EPS at recommended dose ranges[3], and as a consequence, in general less frequent use of antiparkinsonian medications.[4]
	A recent meta-analysis of 13 clinical trials showed modest evidence of greater risk of developing extrapyramidal side-effects with second generation long-acting injectables than with their oral counterparts (RR=1.45, p=0.048).[5] A similar increased frequency has also been observed during the clinical development between aripiprazole oral formulation and aripiprazole IM depot formulation (11.7% *vs.* 18.4%, respectively), based on the results of the pivotal clinical trials 31-07-246 and 31-07-247. When considering historical oral aripiprazole data of EPS, incidence of EPS-related events for the oral formulation was of 8-32% (in short-term studies) and of 17-27% (in long-term studies). The low rate observed in Trial 31-07-247 may consequently be explained by the design of this specific trial: patients were stabilised on oral aripiprazole for a minimum of 8 weeks prior to randomisation, thereby lowering the incidence of AEs in this oral aripiprazole-treated patients cohort after start of the trial.
	"Extrapyramidal Symptoms, including Tardive Dyskinesia" has been listed as an

important identified risk in the Risk Management Plan (RMP) for aripiprazole. Continuous routine pharmacovigilance and additional pharmacovigilance activities to further assess the important identified risk of EPS-related events will be carried out to monitor the safety of Abilify Maintena® once on the market.

A post-authorisation safety study (PASS), regarded by the PRAC as an additional pharmacovigilance activity category 3, is proposed with this objective. This study will be performed using different automated healthcare databases in three European countries (Germany, Italy and Sweden). Indeed, automated healthcare databases can be appropriate tools for drug safety studies due to the recording of data independently of any study purpose, as highlighted in the Module VIII – Post-authorisation safety studies of the Guideline on Good PharmacoVigilance Practices (GVP) (19 April 2013 EMA/813938/2011 Rev 1). In addition, independent automatic continuous collection of data in such databases would limit the selection bias that would be inherent to any field observational study.

Research question and objective	The objective of the study is to further assess the risk of EPS-related events linked to the use of Abilify Maintena®, in routine clinical practice.
Study design	Historical cohort design using longitudinal Electronic Medical Records (EMR) or administrative claims databases (in primary and secondary care settings) in three European countries.
	In general, automated healthcare databases result from the automated collection of prescriptions, diagnoses and other patient characteristics from medical records or insurance claims. Based on a unique patient number, prescription/drug reimbursement claims or medical information are recorded in a longitudinal manner, as other variables that may include demographics, indications, hospitalisations and other types of care and procedures (according to databases).
Population	All new users of Abilify Maintena® (incident users) between country-specific market entry date and the end of the inclusion period will be included in the analysis.
	The first observed prescription of Abilify Maintena® for a patient after market entry is called the index prescription, and the index date relates to the date of this index prescription.
	Within the chosen European automated healthcare databases (see Section 9.4 *Data Sources*), this PASS will identify a cohort of patients that meet the following criteria for inclusion:

- at least one Abilify Maintena® prescription in EMR databases or one Abilify Maintena® reimbursement record in claims databases
- the index prescription for Abilify Maintena® occurs after the date of market entry and before the end of the inclusion period; the market entry date being country-specific, the dates of the inclusion period will vary across the three selected databases

Few exclusion criteria will be set in order to ensure exhaustivity of the sample and limit selection bias. Patients that meet the following criteria will be excluded:

- patients with a diagnosis of Parkinson's disease
- patients with a diagnosis of EPS in the last 45 days preceding the first prescription of Abilify Maintena®

Variables	To further assess the risk of EPS-related events (in terms of incidence, type of event, time to onset and known possible risk factors) linked to the use of Abilify Maintena® in routine clinical practice, the following variables will be analysed: • **Abilify Maintena® prescription**: index date, treatment duration • **EPS-related events:** during the treatment exposure period or up to 2-year after index date if the treatment duration is longer than 2 years • **Patients characteristics**: age at index date and gender • **Known possible risk factors for EPS**: previous episode(s) of EPS-related events (including type of EPS, date of occurrence), diabetes, concomitant diagnosis of depression[3,6-8] • **Previous antipsychotic use**: main type of antipsychotic drugs • **Concomitant other psychotropic medications**: drug name, dose, treatment duration
Data sources	A PASS using automated healthcare databases will ensure independent and automatic continuous collection of data from primary and secondary care settings without any selection bias by including all patients with at least one prescription of Abilify Maintena® during the study period. Based on a preliminary assessment, the following databases are proposed: • *in Germany*: The German Pharmacoepidemiological Research Database (GePaRD - BIPS database)[9] • *in Italy*: Lombardia regional healthcare database, accessed via the University of Milano-Bicocca[10] • *in Sweden*: National Prescription Register and National Patient Register[11] The selected countries will ensure a European « representativeness » with one database in Northern Europe, one in Central Europe, and one in Southern Europe. **In Germany**, the GePaRD is based on claims data of Statutory Health Insurance (SHI) providers. Data are registered in this database since January 2004 for all insurance members of the participating SHI providers, representing about 17% of the German general population and covering all geographical regions of the country. In preliminary analyses regarding the distribution of sex and age, the number of hospital admissions, and drug use, GePaRD was found to be representative for Germany. The frequency of database update might however be a limiting factor (as data is usually made available 1.5 to 2.0 years after collection). **In Italy,** the Lombardia regional healthcare database consists of information on health services provided by the Local Health Authority ("Azienda Sanitaria Locale" [ASL]) to approx. 9 Mio. inhabitants. Outpatient prescription information, hospital discharge diagnosis, and a demographic database are linked through a patient's unique identification number. Data is usually made available 1 year after collection.

	In Sweden, national prescriptions and patient registers compile and link exhaustive administrative information on all inhabitants (Swedish population size is of 9.3 million) through the unique social security identifier. Patients characteristics are available, as well as outpatient drug prescriptions (in primary and secondary care), and diagnoses (ICD-10 classification). Data is usually made available 1 year after collection. A commercial organisation that has the capability to perform data linkage across registers will be used.
	The choice of databases in the selected countries may be revisited if needed, based on modalities of collaboration with databases owners.
Study size	Analyses will be performed separately in each database, as it is not possible to pool the different datasets, the MAH having no direct access to the different databases.

The objective of the study is primarily descriptive. Consequently, sample size calculation relies on the precision estimation, using a normal approximation of the binomial distribution.

Based on post-authorisation exposure projections, the anticipated cumulative number of patients treated with Abilify Maintena® in the selected European countries is given in the Table 1 below for 2014, 2015, 2016 and 2017. The size of currently targeted databases is of around 9 million patients in Italy, 7.6 million in Germany and 9.3 million in Sweden. Based on a conservative hypothesis taking into account potential market access delays, it is expected that within two to three years from market entry, at least 500 exposed patients will be observable in each database.

Table 1 - Anticipated cumulative number of patients treated with Abilify Maintena® in the selected European countries for 2014, 2015, 2016 and 2017

	2014	**2015**	**2016**	**2017**
Germany	1500-2500	7500-9000	10000-16000	17000-21000
Italy	0	1800-2900	5000-7500	7500-12000
Sweden	180-220	700-1100	1200-1600	1900-2300

It is assumed an anticipated incidence rate of EPS-related events in the databases reflecting real-life clinical practice close to the one observed in Abilify Maintena® clinical program studies, in which it has been reported that the frequency of EPS events was 18.4% (based on the two pivotal studies 31-07-246 (52 weeks placebo-controlled) and 31-07-247 (38 weeks active-controlled)). With a minimum sample size of 500 patients per database, the expected absolute precision of the estimated incidence for EPS-related events with a 95% confidence will be 3.5% (half the confidence interval).

Data analysis	A statistical analysis plan will be prepared for each database in order to take into account specificities of each database. Indeed, datasets will not be pooled across countries, and analyses will be performed separately in each database as explained in the Section 9.5 *Study Size*.
	All variables will be summarised using descriptive statistics: N, mean, standard deviation, median, minimum and maximum values will be presented for continuous variables, and counts and percentages for categorical and binary variables. Missing values will be displayed, if any.
	To further assess the risk of EPS-related events linked to the use of Abilify Maintena® in clinical practice, crude incidence of EPS-related events and incidence per patient-month will be estimated, using the number of exposed patients with at least one EPS-related event (during treatment exposure period). In addition, an analysis on time to EPS onset will be performed using Kaplan-Meier estimator of survival function and Cox proportional hazards regression model.
	Kaplan-Meier survival curves will be drawn for all EPS-related events and with stratification on known possible risks factors. The log-rank test will be added for stratified analyses.
	In addition, a Cox proportional hazards regression model will be performed to measure the effect of known risk factors described in Section 9.3.3 *Other Variables* on the occurrence of EPS-related event in this population.
Milestones	For each selected database, the feasibility of the analysis will be assessed 24 months after Abilify Maintena® launch in Sweden and Italy and 36 months after launch in Germany, and then every 6 months (if the market uptake is adequate), to continuously monitor the number of patients available in each database. This delay takes into account the time lag for data availability in the different databases (from one and up to two years), meaning that 24 months after the launch date, data covering only up to the first year after this date will be available in the database.
	When the targeted sample size will be reached (at least 500 incident patients treated with Abilify Maintena®), the analysis will then be performed 2 years after in order to allow a minimum follow-up duration of 2 years. The database report would be available within 6 months after the start of the analysis. It is anticipated that reporting of study results for each database should be available between Q3 2019 and Q4 2020, according to the timelines reported in the table 2 below.

Table 2 - Anticipated timelines for study reports in each of the selected European countries*

	Launch date	Data availability time lag	Date of first feasibility check[+]	Expected date for targeted sample size	Duration of follow-up	Expected date of data reporting
Germany	June 2014	1.5 to 2 years	Q4 2017	Q2 2018	2 years	Q4 2020
Italy	November 2014	1 year	Q4 2017	Q4 2017	2 years	Q2 2020
Sweden	September 2014	1 year	Q3 2016	Q3 2017	2 years	Q1 2020

*These timelines are conditional to any market access issues and the number of patients treated with Abilify Maintena® over time
[+]The actual time point of first feasibility check is influenced by e.g. contracting and the time needed for study approval in the respective country

It is consequently anticipated to deliver the final study report (combining results from all three databases) in Q1 2021.