NON-INTERVENTIONAL SAFETY STUDY

STUDY REPORT

Title	SPD489-825: Cohort Study of the Incidence of Major Cardiovascular Events in New Adult Users of Lisdexamfetamine and Remote Adult Users of Other ADHD Treatments
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Medicinal Product	Elvanse Adult
Product Reference	Sweden: 50796 – 8, Denmark: 53795 – 7
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Marketing Authorisation Holder(s)	Shire Pharmaceuticals Ireland Limited Takeda Pharma A/S Shire is now part of Takeda [redacted]
Joint PASS	No
Research Question and Objectives	The research question of interest was to evaluate the long-term cardiovascular safety of lisdexamfetamine (LDX) in adults. The primary objective of this study was to estimate, in real-world settings, the incidence rate and the adjusted incidence rate ratios of the composite major adverse cardiovascular events endpoint in a cohort of adult patients who are current new users of LDX (the LDX cohort) as compared with a cohort of remote users of other ADHD treatments.
Country(-ies) of Study	Denmark and Sweden

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1.0 ABSTRACT

Title

Cohort Study of the Incidence of Major Cardiovascular Events in New Adult Users of Lisdexamfetamine and Remote Adult Users of Other ADHD Treatments

Keywords

attention-deficit/hyperactivity disorder; lisdexamfetamine; major cardiovascular events.

Rationale and Background

Elvanse Adult (lisdexamfetamine dimesylate [LDX]) is a therapeutically inactive amphetamine prodrug which is indicated as part of a comprehensive treatment programme for attention-deficit/hyperactivity disorder (ADHD) in adult patients, including first-line pharmacotherapy treatment with LDX. Stimulant medications for the treatment of ADHD have been associated with elevated blood pressure and heart rate, and these, in turn, may increase the risk of cardiovascular endpoints. This potential association has been investigated in population-based non-interventional studies. Studies evaluating the effect of ADHD treatments on the risk of cardiovascular outcomes in adults showed inconclusive results, although some of the studies reported an association with an adverse cardiovascular outcome under evaluation. Uncontrolled confounding and selection bias were primary concerns in those studies. As part of the marketing authorisation approval for the treatment of ADHD in adults in Europe, Shire, now part of the Takeda group of companies, was asked to examine the long-term safety of LDX in adults using surrogate markers for the potential risks of cerebrovascular disorders and ischaemic cardiac events.

Research Question and Objectives

The primary objective of this study was to estimate, in real-world settings, the incidence rates (IRs) and the adjusted incidence rate ratios (IRRs) of the composite major adverse cardiovascular events (MACE) endpoint in a cohort of adult patients who are current new users of LDX ("LDX users" or "LDX cohort") as compared with a cohort of remote users of other ADHD treatments ("remote users"—use ending 181 days to 24 months before the index date). Secondary objectives included the evaluation of the potential long-term effects of LDX, the estimation of the IR and IRRs of secondary endpoints (extended MACE [EMACE], a composite coronary component of EMACE, a composite stroke component of EMACE, and a composite endpoint of sudden cardiac death [SCD] and serious ventricular arrhythmia [SVA]), and the estimation of the IR and IRR of MACE by subcategories of concomitant use of other ADHD medications during current LDX use, compared with remote use of other ADHD treatments.

Study Design

A non-interventional population-based cohort study was conducted using selected electronic health care data sources: the Danish National Registers and the Swedish National Registers. The study compared a cohort of adult patients who were new users of LDX with a cohort of patients with remote use of other ADHD medications, matched on age, sex, region, and cohort entry date.

The Clinical Practice Research Datalink (CPRD) database in the United Kingdom was initially planned to be used as a data source in the study. However, due to low uptake of LDX in the United Kingdom, this data source was removed, as documented in protocol version 3.0, which was endorsed by the Swedish Medical Products Agency on 20 September 2019.

Setting

The study was conducted following a common protocol in population-based health databases in Denmark and Sweden. The study period defined in each data source as the time between the date of first recorded dispensing of LDX among adults and the latest date of drug dispensing data availability was between March 2013 and December 2017 in Denmark; and between September 2013 and December 2018 in Sweden.

Subjects and Study Size, Including Dropouts

The study size was driven by the person-time at risk of LDX use that was available in the selected data sources during the defined study period.

The source population was all individuals aged 18 years or older registered in the study databases during the study period with at least 12 months of data available before cohort entry and meeting criteria to be included in either the LDX cohort or remote users cohort. The LDX cohort included adults with a first dispensing for LDX, for whom prescription data were available within at least 12 months preceding the first LDX dispensing date (index date), and no prior LDX dispensings were recorded. The remote users cohort was identified by selecting adults with at least one dispensing of medication indicated for ADHD treatment, other than LDX, ending within 24 months before the index date, and with no dispensings of these medications ending within at least 180 days before the index date. The members of the remote users cohort were matched with replacement to each LDX new user in a ratio of up to 5 to 1 by age, sex, region, and index date.

Variables and Data Sources

Use of LDX was identified during the study period using the Danish National Prescription Registry in Denmark and the Prescribed Drug Register in Sweden. The index date in the LDX cohort was the first LDX dispensing in the data source delineating entry into the LDX study cohort and initiation of patient follow-up. The index date of each patient in the remote users cohort was the index date of the matched LDX user, which was at least 181 days after the dispensing end date of the last ADHD medication. Patients could enter the remote users cohort more than once if they fulfilled the inclusion criteria. Each remote user could be matched to one or more LDX users, and thus have more than one index date (counted as patient/index dates).

Current use of LDX was considered the time at risk for main analysis (both primary and secondary outcomes) and comprised the sum of all episodes of current LDX use. Risk of MACE during post-LDX use time at risk was analysed as a sensitivity analysis. Post-LDX use was the sum of all periods of time starting after the end of an episode of current LDX use and ending at the earliest of the end of follow-up or the start of another episode of LDX use. In a sensitivity analysis, current and post-LDX use time at risk were split by single LDX use or multiple drug use (defined as concurrent treatment with other ADHD medications).

The primary endpoint of interest in this study was MACE, a composite cardiovascular outcome, which included the first occurrence of any of the following individual components during the follow-up: hospitalisation for acute myocardial infarction, fatal or non-fatal, hospitalisation for stroke, fatal or non-fatal, out-of-hospital coronary heart disease death, including SCD and out-of-hospital cerebrovascular death.

The secondary endpoints of interest were (1) EMACE endpoint comprising all MACE components and additionally the hospitalisation for either unstable angina or transient ischaemic attack, (2) the composite coronary components of EMACE, (3) the composite cerebrovascular

components of EMACE and (4) a composite endpoint consisting of SCD and SVA, including ventricular tachycardia, ventricular flutter, and ventricular fibrillation.

The potential confounders included demographic characteristics (sex, age, education), hospital outpatient and inpatient diagnosis of comorbidities (cardiovascular diseases, hypertension, dyslipidaemia, psychiatric medications diseases including ADHD), and pharmacy-dispensed comedications, and ADHD-related history.

Exposure propensity scores were utilised to adjust the analyses for potential confounding factors. The final propensity score model included the matching factors, characteristics with an IRR in the univariate model for MACE greater than 1.25 or lower than 0.80 and with a prevalence of 5% or higher among LDX users or remote users cohort, and clinically important outcome predictors regardless of their prevalence, including individual cardiovascular comorbidities, kidney disease, chronic obstructive pulmonary disease (COPD), malignancies, psychiatric comorbidities and associated medications. To estimate propensity scores, a multivariable logistic regression model was fitted. Propensity score distribution was assessed, and patients in both groups below the first percentile of the LDX cohort or above the 99th percentile of the remote users cohort were excluded from further analysis. Propensity scores were stratified by quintiles of the LDX propensity score distribution. Balance on the distribution of baseline variables was checked after trimming within each propensity score quintile.

Crude IRs, IRRs, and 95% confidence intervals (CIs) were estimated using Poisson regression with robust estimation of the variance (to take into account that remote users could be matched more than one LDX patient), with LDX initiation as the exposure of interest, MACE (or other study endpoints) as the outcome, the natural logarithm of the time at risk as the offset, and propensity score quintiles as a covariable.

Several exploratory analyses (stratification by age, sex, history of cardiovascular disease, diagnosis of ADHD, history of psychiatric disease, impact of long-term exposure, and impact of other ADHD medications) and sensitivity analysis (when the carryover period was extended, for post-LDX use, ie, the time at risk after current use ends, for the intention-to-treat analysis, when applying the same inclusion criteria, or when analysing the effect of prior exposure) and analysis were performed.

The analyses were conducted separately for Denmark and Sweden, and combined estimates of effects were obtained using meta-analytic techniques as appropriate.

Results

A total of 5,516 and 40,163 LDX users were included in the study in Denmark and Sweden, respectively. These LDX users were matched to 27,494 patients/index dates (16,697 unique patients) in the remote users cohort in Denmark and to 200,389 patients/index dates (44,516 unique patients) in the remote users cohort in Sweden.

After matching and trimming, approximately 50% of patients in each cohort were aged 18 through 29 years, and nearly 50% were female. The prevalence of cardiovascular comorbidities was similar between LDX users and remote users in both countries and was lower than 1% for many of the conditions. The prevalence of psychiatric comorbidities was high in both LDX and remote users. In Denmark and Sweden, mood disorders and anxiety disorders were the most frequent psychiatric comorbidities, and these together with eating disorders were more prevalent in LDX users than in remote users. The use of comedications was in general low and similar in both countries. Nearly all patients in the LDX cohort and all patients in the remote users cohort had a prior ADHD diagnosis or dispensing of ADHD medications. In both countries, the

distribution of the baseline characteristics after matching and trimming was similar to the distribution before trimming.

Overall, the utilisation of LDX in Denmark and Sweden was similar. The duration of current LDX use was shorter than 6 months for approximately 50% of the patients in Denmark and 40% in Sweden, and longer than 12 months for approximately 35% of the patients in Denmark and 40% in Sweden. Almost 60% of LDX users in Denmark and 50% of LDX users in Sweden had concomitant use of methylphenidate during the episodes of current LDX use. Approximately 70% of patients in both countries received LDX with a starting daily dose of 30 mg at the index date.

For the primary outcome (MACE), there were 9 events among LDX users and 76 events among remote users in Denmark. In Sweden, there were 63 MACE events among LDX users and 144 events among remote users. In Denmark, the crude IRs of MACE were similar among LDX users (IR, 1.63 per 1,000 person-years) and among remote users (IR, 1.61 per 1,000 person-years). In Sweden, IR of MACE among LDX users (IR, 1.40 per 1,000 person-years) was slightly higher than among remote user (IR, 1.17 per 1,000 person-years). The adjusted IRRs (95% CI) of MACE for LDX users versus remote users were 1.01 (0.48-2.13) in Denmark and 1.13 (0.75-1.71) in Sweden. For the secondary outcome EMACE, the adjusted IRRs (95% CI) for LDX users versus remote users were 0.92 (0.45-1.88) in Denmark and 0.98 (0.68-1.41) in Sweden. The adjusted IRRs (95% CI) for coronary heart disease were 1.11 (0.41-2.98) in Denmark and 1.37 (0.75-2.47) in Sweden, whereas the IRRs (95% CI) for cerebrovascular disease was 0.90 (0.35-2.30) in Denmark and 0.74 (0.46-1.19) in Sweden. The IRRs for hospitalisation for SCD and SVA were below 1 in both countries.

The exploratory analysis and the sensitivity analysis in both countries were in line with those observed for the primary analysis of MACE.

A total of 45,679 LDX users and 227,883 remote users were included in the pooled data set. The descriptive characteristics of the pooled data set after matching and trimming were similar to those observed in the individual countries. The pooled adjusted IRR (95% CI) for MACE for LDX users versus remote users was 1.10 (0.77-1.58). The pooled adjusted IRRs for all the secondary outcomes of interest were in line with those observed for the primary analysis.

The pooled adjusted IRR (95% CI) of MACE among LDX users compared with remote users for long-term use of LDX was 1.59 (0.86-2.95). When analysing the risk of MACE during current LDX use compared with remote users, the pooled adjusted IRR (95% CI) in patients with concomitant use of other ADHD medications was 1.26 (0.83-1.93) while the IRR for patients with current single use of LDX was 0.96 (0.60-1.54).

Results from exploratory analyses of the pooled data set when stratifying by age and sex were similar to those obtained in the main analysis. The pooled adjusted IRRs (95% CI) for LDX users with no history of cardiovascular disease was 1.53 (0.97-2.40), for LDX users with diagnosis of ADHD was 1.27 (0.82-1.96), and for LDX users with history of psychiatric disease was 1.18 (0.79-1.75).

Results from sensitivity analyses in the pooled data set when the carryover period was extended, for the intention-to-treat analysis, when applying the same inclusion criteria, or when analysing the effect of prior exposure were similar to those obtained in the main analysis. For post-LDX use with other ADHD treatment, there was an increased risk of MACE among LDX users compared with remote users (IRR, 1.65; 95% CI, 1.06-2.57).

Discussion

Results from this cohort study among adult new LDX users indicated that the use of LDX was not associated with a substantially increased risk of MACE compared with remote users of other ADHD medications in Denmark or Sweden. The pooled IRR of MACE comparing new LDX users with remote users of other ADHD medications in Denmark and Sweden was 1.10 (95% CI, 0.77-1.58). The upper limit of the 95% CI for this estimate was below the prespecified threshold of 3.00. The results were consistent across all secondary, exploratory, and sensitivity analyses, although some variations in the IRRs were observed, which was likely related to the small number of events.

In conclusion, the results of the present study did not show evidence of an increase above the prespecified threshold in risk of MACE in patients with ADHD initiating LDX compared with remote users of other ADHD medications

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