STUDY SYNOPSIS

Study Title	A European, observational, three-year cohort comparative study on the safety of the fixed dose combination pravastatin 40 mg/ fenofibrate 160 mg (Pravafenix®) versus statin alone in real clinical practice. POSE: *Pravafenix® Observational Study in Europe*
Date and Version of the final study report	12 June 2023 - Version 1.0
EU PAS register number	EUPAS13661
Active substance	HMG CoA reductase inhibitors in combination with other lipid modifying agents Code ATC: C10BA03 Pravastatin/ Fenofibrate. HMG CoA reductase inhibitors Code ATC: C10AA Statins
Medicinal product	Pravafenix® (Fenofibrate 160 mg and Pravastatin 40 mg)
Product reference	Statins used in monotherapy at standard equipotent doses as defined by NCEP ATP III i.e., as the dose required to attain an approximate 30% to 40% reduction of LDL-C levels (atorvastatin 10 mg, lovastatin 40 mg, pravastatin 40 mg, simvastatin 20-40 mg, fluvastatin 40-80 mg and rosuvastatin 5-10 mg)
Marketing authorisation holder	Laboratoires SMB S.A. Rue de la Pastorale 26-28 1080 Brussels Belgium
Countries of study	Greece, Portugal, and Spain

1. Abstract

1.1. Title

A European, observational, three-year cohort comparative study on the safety of the fixed-dose combination (FDC) pravastatin 40 mg/fenofibrate 160 mg (Pravafenix®) versus statin alone, in real clinical practice.

1.2. Objectives

1.2.1. Primary Objective of the POSE Study

To compare the incidence rate of the main safety endpoints (see below Primary variable definition) between patients treated by Pravafenix® or by a statin in monotherapy in real clinical practice conditions, within a three-year follow-up period.

1.2.2. Secondary Objectives of the POSE Study

- To describe the patients' characteristics and treatment history.
- To describe the participating physicians' characteristics (for Greece and Portugal only).
- To compare the time to first occurrence of each component of the primary safety endpoint.
- To compare the incidence rate of cardiovascular events.
- To compare the time to first occurrence of a cardiovascular event.
- To compare the incidence rate of laboratory abnormalities during the follow-up period.
- To describe reported adverse events.
- To describe the patterns of use of Pravafenix® and to assess the routine risk minimisation.

1.3. Study Design

This was a multicentric, open-label, European, comparative, partly retrospective and partly prospective, observational cohort study with a three-year follow-up, in patients treated with Pravafenix® or with a statin at stable standard dose in monotherapy, conducted in real clinical practice. It included one interim analysis after one year of follow-up was completed for all patients, and one final analysis after three years of follow-up.

1.4. Setting

The study was performed according to two versions of the protocol, one for Greece and Portugal, and one for Spain due to a specific request from the Spanish Ethics Committee.

Prescribers could be general practitioners, cardiologists, internists, or endocrinologists, hospital-based or in private practice from Greece, Portugal, or Spain. A representative sample of physicians prescribing Pravafenix® was selected by the Contract Research Organization, independent of the MAH.

The selection of physicians was determined to ensure homogeneity and good representation of the study physician population at a national level. The representativeness of the participating physicians was checked regularly to allow sample size adjustments or new sampling if needed.

1.5. Patients and Study Size

1.5.1. Patients

Initially, each physician was allowed to recruit up to 20 patients overall (approximately 10 in the Pravafenix® arm and 10 in the statin arm). Ultimately, some sites were authorised to recruit more than 20 patients due to recruitment difficulties. The balance between Pravafenix® and the statin arm was maintained (ratio 1:1). All eligible patients were proposed the POSE study at the first clinic visit occurring after site initiation. All patients who agreed to participate had to sign an informed consent form (ICF).

Main inclusion criteria:

- Pravafenix® group (for Greece and Portugal): adult patients (≥18-years-old) currently treated with or intended to be treated at the time of inclusion with Pravafenix®. In case of ongoing therapy at enrolment, treatment with Pravafenix® must have started within 12 months prior to ICF signature date.
- Pravafenix® group (for Spain, upon request of the Ethics Committee): adult patients (≥18-years-old) treated with Pravafenix® for at least 6 months. Pravafenix® must have started within 12 months prior to ICF signature date.

OR

- Control (statin) group: adult patients (≥18-years-old) treated with a statin in monotherapy at stable standard dose for at least 3 months (dosage stability must have started within 12 months prior to ICF signature date). The standard dose of statin is defined by NCEP ATP III as the dose required to attain an approximate 30% to 40% reduction of LDL-C levels**Error! Bookmark not defined.**.

Exclusion criteria:

- Patients participating in other clinical studies.
- Concomitant lipid lowering therapies with fibrates.
- Patients for whom no medical records were available at study treatment initiation.

1.5.2. Sample Size (Including Dropouts)

A two-sided test of whether the hazard ratio is one with an overall sample size of 3000 patients (1500 in the control group and 1500 in the treatment group), achieved 80% power at a 0.050 significance level when the hazard ratio is 2. The total number of events qualifying for the primary endpoint, required to achieve this power, was 60. It was anticipated that proportions of subjects having the event during the study would be 0.020 for the control group and 0.040 (i.e., double) for the treatment group. These results assume that the hazard ratio was constant throughout the study and that Cox proportional hazards regression was used to analyse the data.

The one-year interim analysis revealed that most of the individual safety events (see Section 1.6.1: Primary variable) occurred with a rate of at least 0.002 and the proportion of patients experiencing at least one event was more similar between the two groups than initially predicted, with an observed absolute difference of 0.011 (instead of protocol assumption of 0.02). The sample size was then recalculated based on these results and the power of detecting at least one of the safety profile events, under the observed proportion of patients at one-year, was >99% in both arms.

Hence the PRAC confirmed the appropriateness of the initial sample size of 3000 patients.

1.6. Variables and Data Sources

1.6.1. Primary Variable ("Safety Profile")

The primary variable was defined as the incidence rate of the safety profile (composite endpoint defined as the proportion of patients with at least one occurrence of any of the key safety endpoints), between patients treated with Pravafenix® or with a statin in monotherapy in real clinical practice conditions during a three-year follow-up period.

Key safety endpoints were defined as follows:

- renal and urinary disorders, musculoskeletal and connective tissue disorders, hepatobiliary disorders, cholelithiasis, thromboembolic events (namely pulmonary embolism, deep vein thrombosis, thus venous events), pancreatitis, diabetes mellitus aggravated; all these events were classified as important identified risks according to the RMP, and
- blood homocysteine increase, interstitial pneumopathy and phototoxicity, all classified as important potential risks according to the RMP.

1.6.2. Secondary Variables

- Patients' characteristics at baseline (demographic data, lifestyle habits, CVD history, cardiovascular risk level assessment, comorbidities and target organ damage, lipid profile, safety lab results).
- Participating physician's characteristics at baseline (type of practice, country, percentage of physicians initiating the treatment) (for Greece and Portugal only, not permitted in Spain).
- Previous lipid lowering agent(s) at baseline.
- Concomitant medications (including all medications that a patient used at any stage during the study after First Study Treatment Administration up until Follow Up (Year 3) Visit date. Any medication started prior to First Study Treatment Administration and used during the study, or any medication started at any time after the First Study Treatment Administration are considered 'Concomitant'. Concomitant therapies are part of Concomitant Medications and included concomitant lipid lowering therapies, cardiovascular and diabetes therapies).
- Treatment changes after one, two, and three years of follow-up: percentage of patients switching from one treatment to another, percentage of patients discontinuing treatment, reasons for switching or stopping if applicable, over the whole study cohort, by country and (for Greece and Portugal) according to physicians' profile (assessed at end of documented treatment).
- Incidence rate of each main safety endpoint after one (interim analyse) and two years of follow-up.
- Time to first occurrence of each main safety endpoint.
- Incidence rate of fatal or nonfatal cardiovascular events after one, two, and three years of follow-up.
- Time to first occurrence of cardiovascular events.
- Incidence rate of laboratory abnormalities after one, two, and three years of follow-up.
- Incidence rate of Adverse events reported after one, two, and three years of follow-up.
- Percentage of patients following the recommended risk minimisation procedures after one year of follow-up (Pravafenix® group only).
- Patterns of use of Pravafenix® after one year of follow-up: percentage of patients taking Pravafenix® during a meal, percentage of patients following a diet, Pravafenix® posology taken (Pravafenix® group only).

1.6.3. Definitions Used for Statistical Analyses

The analyses sets were defined as follows:

- Safety Analysis Set (SAF): all patients who provided informed consent and who had a documented baseline visit. The SAF was used for all safety analyses.

- Full Analysis Set (FAS): all patients who provided informed consent, who had a documented baseline visit, with at least one visit of follow-up. The FAS was the primary analysis set of interest for all endpoints.
- Per-protocol Set (PP): all patients from the FAS who did not have any major protocol violations. were included in the PP. The PP was used to support primary endpoints analyses based on FAS Set.

Subgroup analyses (country, gender, physician's profile, SCORE cardiovascular risk) were prespecified.

Propensity score: the absence of randomisation did not assure the comparability of patients. A propensity analysis was this used to neutralise this imbalance, representing a valuable approach in the results. It allowed the modelling of time to event/incidences conditionally to the probability of having the treatment.

Recommended risk minimisation was defined using selected laboratory parameters and adverse events. It included the following investigations: creatine kinase monitoring, transaminase monitoring, creatinine renal clearance monitoring, cholelithiasis occurrence and interstitial lung disease occurrence.

Compliance to recommended biological recommendations was defined as the number of patients with abnormal laboratory values for whom the recommended risk minimisation was observed (biological monitoring), divided by the total number of patients with abnormal laboratory values from a laboratory exam.

1.6.4. Data Sources

The data were collected from patient medical records retrospectively for data obtained before patient inclusion in the study, and prospectively for data obtained after inclusion, over a study period of three years. Data were collected from treatment initiation with Pravafenix® or with a standard stable dose of statin monotherapy (baseline). The follow-up period ended after three years from baseline or at the end of the observed study treatment, whichever was earlier.

For each enrolled patient, an electronic questionnaire was completed by the prescribing physicians, including physician characteristics (for Greece and Portugal, only), patient characteristics, treatment taken and pattern of use, laboratory monitoring, and adverse events.

1.7. Results

1.7.1. Participants

A total of 3136 patients were enrolled in the study, 1562 in the Pravafenix® arm and 1542 in the statin arm. With 61 screening failures, a total of 3075 patients had a documented baseline visit and comprised the SAF (Pravafenix® arm, N=1546 patients, 50.0%; statin arm, N=1529 patients, 50.0%). At the end of the three-year follow-up period, 82.5% of all patients had completed the study, 80.2% patients in the Pravafenix® arm and 84.9% in the statin arm. The main reason for discontinuation was '*Lost to follow-up*' (5.2%), mostly in relation to COVID-19 constraints. The number of deaths was very low (N=12, 0.4%), and similarly distributed between groups.

The three European countries participating in the POSE study- were Greece, Spain and Portugal. The higher participation of patients from Greece (N=2612, 85%) was explained by a higher motivation of Greek sites and better market penetration. The Spanish sub-population accounted for 458 patients (15%), whereas the contribution of patients from Portugal was poor due to COVID-19 constraints (N=5 patients). As requested by the PRAC in its one-year interim Assessment Report, particular attention was paid to the comparison of populations recruited in Greece and Spain, due to the difference in inclusion criteria described above.

Based on data from Greece and Portugal, most prescribers (87%) were either internists or cardiologists, with the mode of practice being predominantly private (53.4%), or in a hospital (41.5%). This was in line with the target population defined as the Pravafenix® indication: high cardiovascular risk (or even very-high) patients, presenting with complex dyslipidaemia insufficiently controlled with statins alone (second-line therapy), often requiring specialized supervision.

1.7.2. Baseline Data

The two treatment arms were globally well-balanced regarding most patient and physician characteristics at baseline. The mean age for patients in the SAF was 61.4±12.1 years; nearly half of the patients (48.2 %) had a sedentary lifestyle, and 26.6% were chronic smokers. The most common medical history events were hypertension (56.1%) and diabetes mellitus (46.6%). The mean baseline values of key risk factors (lipids, blood pressure, glucose) were generally within therapeutic targets recommended at that time, and the prevalence of concomitant therapies accounted for 71.7% of patients), mainly representing cardiovascular and blood glucose control therapies (71.6%).

Overall, 23.9% of the patients had received previous lipid lowering agents. Most of the global population (N=2824, 91.9%) had treatment initiated by the participating physician, associated with dietary restrictions (97.4%), which was well-balanced between groups, in compliance with the indication labelling of Pravafenix® and that of statins. Overall, 10.7% of patients had a family history of premature CHD, and 13.9% had established CVD reflecting a secondary-prevention population (among the most fragile patients), with the two arms matching in terms of proportions. The most common CVD was CHD (60.7%), with similar incidence in the two treatment groups. When documented (N=2873, 93%), the level of risk based on the SCORE Chart was as follows: 19.5% of patients were classified as presenting with a "*very high"* cardiovascular risk, 50.2% with a "*high*" risk, 20.6% with a "*moderate*" risk and 7.1% with a "*low*" risk.

A few imbalances were observed regarding the baseline characteristics in the Pravafenix® group:

- This group was characterized by a higher prevalence of some major cardiovascular risk factors: men (59.4% vs. 50.1% in statin group), diabetes mellitus (52.8% vs. 44.4%), with these items reflecting mixed dyslipidaemia features. The combined "*very high/high*" risk categories were however similar (18.2% and 53.0% respectively, total 71.2%), to those of the statin arm (20.8% and 47.5% respectively, total 68.3%), reflecting the Pravafenix® target population: "*patients at high cardiovascular risk."*
- Almost twice as many patients in the Pravafenix® group than in the statin group (32.4% vs. 15.2%, respectively) had received a previous lipid lowering agent, in reference to Product labelling (second-line indication). However, most patients (99%) used Pravafenix® with no prior treatment of pravastatin 40 mg.

The comparison between patients recruited in Greece and patients recruited in Spain showed consistency in most items, suggesting internal validation, with the following exceptions:

- the Spanish sub-population was characterized by a lower CHD risk i.e., "*very high/high risk":*72.5% in Greece vs. 53.9% in Spain; and a lower presence of CHD: 63.3% vs. 41.3%, respectively.
- Better compliance to pre-treatment with a lipid lowering agent in the Pravafenix® arm was observed in Spain compared to Greece (57.9% vs. 28%), but always exceptionally with pravastatin 40 mg.

1.7.3. Primary Analyses (Safety Profile Over a Three-Year Follow-Up)

The absolute risks (AR) of safety profiles over the cumulative three-year follow-up period was 0.068% (n=101 events) in the Pravafenix® arm vs. 0.051% (n=76 events) in the statin arm, with the adjusted (accounting for propensity score) relative risk (RR) of safety profiles over the three-year period (**1.366**) with its 95% confidence interval spanning 1 (**0.967; 1.929**) in the FAS, and showing that there is no

significant difference between treatment arms. All sensitivity analyses confirmed this result, notably the PP analysis and subgroup analysis per country (Greece + Portugal vs. Spain).

With respect to initial sample size hypotheses and following sensitivity analyses (including country), the robustness of the primary result over three years is established, reflecting that using the above statistical approach, there is no clinically relevant difference between arms.

The incidence of each safety endpoint was very low (≤1%). Most of the events occurred during the first year of follow-up, then incidence regularly decreased over time in both arms. The results are fully consistent (even improved) with the one-year results assessed by the PRAC in 2021**,** i.e., adjusted RR: 1.377 (0.812; 2.337). In each treatment group, this result is driven by a higher incidence of "*Musculoskeletal and connective tissue disorders"* (overall N=80 events, 44 in the Pravafenix® group vs. 36 events in the statin group), *"Renal and urinary disorders"* (overall N=52 events, 28 vs. 24. respectively), and *"Diabetes mellitus aggravated"* (overall N=52 events, 31 vs. 21. respectively). Other components had a low global incidence (< 10 events), a single event ("*Blood homocysteine increase*") or even zero events ("*Interstitial pneumopathy*" and "*Phototoxicity*").

1.7.4. Secondary Analyses

Among secondary variables, the incidence of cardiovascular events is of special interest. The total number of cardiovascular events collected was low, the AR of fatal or non-fatal cardiovascular events over the cumulative three-year period was 0.0016% (N=24 events) in the Pravafenix® arm and 0.012% (N=18 events) in the statin arm. The adjusted RR over the three-year period (**1.209**) with its 95% confidence interval spanning 1 **(0.596; 2.453)** confirms there is no significant difference between the treatment arms.

With regards to lipid laboratory parameters, overall, in both treatment groups there was a steady reduction in the levels of total cholesterol, LDL-C, TG, apolipoprotein A-1, and apolipoprotein B100, and a concomitant rise in the levels of HDL-C from baseline to the three-year follow-up. Interim results at one-year were confirmed or even improved, notably:

- In the Pravafenix® group: mean TG levels decreased from 3.4±2.1 mmol/L at baseline (as expected, higher values than in the control group) to 1.7±0.9 mmol/L at three-years. In parallel, mean HDL-C level increased from 1.1±0.3 at baseline (as expected, lower values than in control group) to 1.2±0.3 mmol/L.
- In the statin group: mean TG level decreased from 1.6±0.8 to 1.3±0.4, and HDL-C increased from 1.3±0.3 to 1.3±0.3 mmol/L.

As far as other biological laboratory parameters were concerned, globally, there were no significant differences regarding the risk of developing biological laboratory abnormalities between treatment arms except for serum creatinine, alanine aminotransferase and homocysteine. The RR for these laboratory abnormalities were slightly increased in the Pravafenix® group compared to the statin group. These observations were however expected according to the Summary of Product Characteristics (SmPC) of Pravafenix®, where section 4.4 recommends regular monitoring of transaminases and creatinine levels during the first year of treatment, and special caution regarding patients with history of pulmonary embolism, for which the role of homocysteine is discussed.

The incidence of treatment-emergent adverse events (TEAEs) was low and similar for both arms (overall 10.9% for Pravafenix® group vs. 10.0% for statin group), and decreased over the course of the study (from 6.4% at one-year follow-up to 4.1% at three-year follow-up for Pravafenix®, vs. 5.2% at one-year follow-up to 4.3% at three-year follow-up for the statin arm). The majority of reported TEAEs were either mild or moderate in nature. The incidence of adverse drug reactions (ADRs) was overall 1.4% vs. 1.1% respectively, and less than 1% for both groups at three-years. The most frequently reported Preferred Terms (PTs) (incidence ≤0.3%) for TEAEs considered related to Pravafenix® were diabetes mellitus (0.3%), myalgia (0.2%), and renal impairment (0.2%). Likewise, the most frequently reported

PTs (incidence ≤0.4%) for TEAEs considered related to statin were diabetes mellitus (0.3%) and myalgia (0.2%).

During the three-year follow-up period, 0.01% of patients treated with Pravafenix® had a change in treatment compared to 0.05% treated with statins; 0.09% of patients in the Pravafenix® arm discontinued treatment vs. 0.06% in the statin arm.

Over the first-year follow-up period, the rate of compliance to the recommended biological recommendations was 33.3% for renal monitoring and more than 50% for creatinine kinase and transaminase monitoring. Over the three-year follow-up period, the lowest proportion of patients constantly monitored applied to the creatinine clearance monitoring. However, it should be noted that moderate to severe renal impairment is a contraindication of Pravafenix®, in relation to serum creatinine increase, whose clinical relevance is not established. The descriptive analysis of the patterns of use of Pravafenix® confirmed that in most cases Pravafenix® was taken during the evening meal as recommended by the SmPC and that the total daily dose was always respected.

1.8. Conclusion

Overall, a positive benefit / risk balance for Pravafenix® is confirmed.