EMA/569435/2024
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Pravafenix

International non-proprietary name: Fenofibrate / Pravastatin sodium

Procedure No. EMEA/H/C/001243/II/0037

Marketing authorisation holder (MAH) Laboratoires SMB s.a.

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Table of contents

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Laboratoires SMB s.a. submitted to the European Medicines Agency on 28 November 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of mixed hyperlipidaemia in adult patients while on a treatment with pravastatin 40 mg monotherapy or on another moderate-intensity statin regimen for PRAVAFENIX, based on final results from the non-interventional PASS: POSE (Pravafenix Observational Study in Europe); this is 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. As a consequence, sections 4.1 and 4.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted.

The requested variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) (EMEA-000501-PIP01-08) on the granting of a product-specific waiver.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jean-Michel Race Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	28 November 2023
Start of procedure	23 December 2023
CHMP Rapporteur Assessment Report	19 February 2024
PRAC Rapporteur Assessment Report	19 February 2024
PRAC members comments	28 February 2024
Updated PRAC Rapporteur Assessment Report	1 March 2024
PRAC Outcome	7 March 2024
CHMP members comments	11 March 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 March 2024
Request for supplementary information (RSI)	21 March 2024
CHMP Rapporteur Assessment Report	28 May 2024
PRAC Rapporteur Assessment Report	28 May 2024
PRAC members comments	5 June 2024
PRAC Outcome	13 June 2024
CHMP members comments	17 June 2024
Updated CHMP Rapporteur Assessment Report	21 June 2024
Request for supplementary information (RSI)	27 June 2024
CHMP Rapporteur Assessment Report	20 August 2024
PRAC Rapporteur Assessment Report	20 August 2024
PRAC members comments	28 August 2024
PRAC Outcome	5 September 2024
CHMP members comments	9 September 2024
Updated CHMP Rapporteur Assessment Report	12 September 2024
CHMP Opinion	19 September 2024

2. Scientific discussion

2.1. Introduction

The PASS study presented in this assessment report has already been assessed in the PASS/PSUSA (Procedure No. EMEA/H/C/001243/II/0034).

As part of the RMP, two Follow-Up Measures (FUMs) were addressed:

- FUM 006: to conduct a DUS to describe the real-life conditions of Pravafenix use, and consequently evaluate if routine risk minimisation (SmPC and PIL) adequately ensure the use of Pravafenix in the approved indications, as well as in the appropriate conditions, notably regarding the recommended biological monitoring during the first year of treatment.

- FUM 007: to conduct a Post-Authorization Safety Study (PASS) aiming to further evaluate potential and identified risks as outlined in the RMP, as well as CV endpoints.

Therefore, the FUMs were ultimately addressed in one cohort-comparative study, the POSE study, with a three-year follow-up. The results of the POSE study are the basis of this type II variation to broaden the Pravafenix indication, in accordance with Pravafenix use in real life and in the perspective of the fibrates referral.

The primary objective of the POSE study was to compare the incidence rate of main safety endpoints (composite endpoint, including all *Identified important risks* and some *Potential important risks* - RMP) between patients treated with Pravafenix or with a reference control group, in real clinical practice conditions. The control group was defined as statins used in monotherapy at standard equipotent doses as defined by 2004 NCEP ATP III i.e., as the dose required to attain an approximate 30% to 40% reduction of LDL-C levels (atorvastatin 10 mg, fluvastatin 40-80 mg, lovastatin 40 mg, rosuvastatin 5-10 mg, and simvastatin 20-40 mg,) (Grundy et al, 2004). Among various secondary endpoints, were the incidence rate of fatal/non-fatal CV events over time, and the time to first occurrence of CV events.

2.1.1. Problem statement

This variation aims to broaden the therapeutic indication of PRAVAFENIX, in accordance with PRAVAFENIX use in real life and in the perspective of the fibrates referral.

Of note, in February 2011 the CHMP granted a much broader class label to fibrates, based on the results of the ACCORD study together with fibrate trial meta-analyses in the context of an Article 31 Referral: *"In patients with mixed hyperlipidaemia at high cardiovascular risk when triglycerides and HDL-C are not adequately controlled with a statin alone"* (EMA/CHMP/580013/2012).

2.1.2. About the product

Pravafenix is a fixed dose combination (FDC) of the fibric acid derivative (fibrate) fenofibrate and the 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) pravastatin.

Laboratoires SMB SA, obtained a positive opinion from the Committee for Medicinal Products for Human Use (CHMP), with the granting of a Marketing Authorization (MA) for the fenofibrate 160 mg/pravastatin 40 mg FDC on April 14th, 2011 (European Decision).

The approved indication is: "*Pravafenix is indicated as an adjunct to diet and other non-pharmacological treatment (e.g. exercise, weight reduction) for the treatment of mixed hyperlipidaemia in adult patients*

at high cardiovascular risk to reduce triglycerides and increase HDL-C when LDL-C levels are adequately controlled while on a treatment with pravastatin 40 mg monotherapy."

The recommended dose is one capsule per day.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

No new ERA data have been submitted in this application, which is acceptable.

2.2.2. Discussion on non-clinical aspects

The applicant submitted a revised PEC calculation for this application to demonstrate that the PEC is not increasing. If the new PEC calculation were to show an increasing environmental impact, the applicant would have to submit an updated Phase II assessment.

Pravafenix use is already covered by a previous ERA (FUM in 2012) in which a Phase II tier A was performed for both products. This ERA was already assessed, and the conclusions reported that pravastatin and fenofibrate are not anticipated to pose a risk to environment. However, the Applicant included precautionary and safety measures for disposal and labelling in order to further lower the environmental risk of the use PRAVAFENIX in the Community. The conclusions of the already performed ERA are still valid and the statement in the SmPC section 6.6 *Special Precautions for disposal* is kept.

2.2.3. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, the extended indication does not lead to a significant increase in environmental exposure further to the use of fenofibrate / pravastatin sodium. There are no objections to the approval from a non-clinical perspective.

2.3. Clinical aspects

2.3.1. Clinical pharmacology

No new PK/PD clinical data have been submitted in this application, which is considered acceptable.

2.4. Clinical data

2.4.1. Dose response study(ies)

No new dose response clinical data have been submitted in this application, which is considered acceptable.

2.4.2. Main study(ies)

Title of Study

Non-interventional Post-Authorisation Safety Study (PASS): the POSE (Pravafenix Observational Study in Europe) study.

Methods

This was a multicentric, European, partly retrospective and prospective observational cohort study with a three-year follow-up, in patients treated with pravastatin 40 mg/fenofibrate 160 mg (Pravafenix) or with a statin used at standard stable dose in monotherapy followed by general practitioners (GPs), cardiologists, endocrinologists, internists in hospital-based or private practice in three European countries (Greece, Portugal and Spain).

This observational study did not induce any extra visits or specific exams for the patient, nor any specific treatments or interventions. Physicians were not required to change their usual practice in treating patients. Also, the study did not impose time windows between each visit, because this is a real-life post-marketing study.

This investigation took place in real clinical practice conditions. The recruitment started on December 2016 and ended in July 2019. The recruitment period was extended twice until the enrolment target of 3000 was reached. Information was collected retrospectively for data obtained before the patient inclusion and prospectively for data obtained after inclusion over a three-year follow-up period. The patient's allocation in a particular therapeutic strategy was not decided by the study protocol but it was determined by the medical routine practice. In addition, the decision to prescribe a particular medication was clearly dissociated of the decision to include that patient in the study. No intervention (diagnostic or follow up) which was not a routine clinical practice was performed to the patients, and epidemiologic methods for the analysis of collected data was applied.

This open label study included one interim analysis after one year of follow-up completed for all patients and one final analysis after three years of follow-up.

Physicians' population

Greece and Portugal

The selection of physicians was determined to ensure homogeneity and a good representation of the study physician population at the national level and took into account the following criteria: physician's profile (GP, cardiologist, internist, and endocrinologist), location (country), hospital-based or private practice.

The representativeness of the participating physicians was checked regularly in order to allow sample size adjustments or new sampling if needed.

An ongoing check of the participating physicians was foreseen to allow sample adjustments or new sampling, if needed. It should be noted that in case of physicians selected, who were located at big hospitals/private practices where several physicians with the same practices were likely to be involved in the study, one primary investigator and one or more sub-investigators were identified, but only the characteristics of the primary investigator were captured into electronic Case Report Form (eCRF) and all the patients were assigned to the primary investigator (only the primary investigator was considered a "participating physician" for the purpose of data collection and analysis).

Spain

In Spain, physicians were from primary healthcare, hospitals or public and private medicine.

A representative sample of physicians prescribing Pravafenix was selected by the CRO independently of the Marketing Authorization Holder (MAH) marketing information. These physicians are the most frequent prescribers of lipid lowering agents. In the observational, cross-sectional DYSIS study conducted in Europe and Canada to evaluate the prevalence of residual lipid abnormalities in patients receiving statin therapy, 60% of the physicians were GPs and 40% specialists. In the French DYSIS cohort, 4335 patients (61.6% high cardiovascular risk) were recruited by 740 centres including 69.5% of primary care centres / 30.5% specialists.

At first, physicians were initially contacted by phone by the CRO for presentation of the study. An invitation mail to participate in the selection process and complete a feasibility questionnaire was sent to each physician.

The distribution of the physicians depended on their willingness to participate in the study. In order to assure representativeness, up to maximum 20 patients were to be included by each physician. Therefore at least 150 physicians were to be selected to enrol the 3000 patients. A reminder was done to the non-responder physicians in order to collect the reasons for not responding and to detect an eventual selection bias.

Initiation of sites

This investigation took place in real clinical practice conditions. The study initiation tasks were performed by a local clinical research associate (CRA). As soon as the written agreement of participation and consistent financial contract were obtained from the physician, a study dossier was provided to each participating physician, including:

- the study protocol,

- the approval of Consultancy Committees of each country,

- the electronic patients' questionnaires,

- the patients' information sheet and ICF.

During the initiation visit, the physicians were given explanations concerning the study protocol, as well as the modalities for collecting data.

Plans for visits

This investigation took place in real clinical conditions of medical practice and care. Physicians were required not to change their typical practice in treating patients. Patients were to be treated according to the local prescribing information, and routine medical practice in terms of visit frequency and types of assessments performed. Baseline information was collected from the medical records at study treatment initiation and was added in the "inclusion questionnaire".

Baseline information included the status of the patient at start of Pravafenix treatment or at start of last stable standard dose of statin monotherapy before date of informed consent.

Baseline was not allowed to be more than 12 months before ICF signature date. Follow-up information to be collected over a period of three years was added in the "follow-up questionnaire" according to the visits performed by the physicians. End date for data collection was defined as the end of the 3-year follow-up after treatment initiation. If observed treatment needed to be changed (i.e. change of active substances) or if the patient died, follow-up was also stopped.

This open label study included one interim analysis after one year of follow-up had been completed for all patients and a final analysis after three years of follow-up, presented in this report. Due to COVID- 19 pandemic, the 1-year follow-up was delayed for many patients but the sponsor decided to perform the snapshot according to the planned date of 15th Jul 2020. Therefore, there was no impact on the planned dates for the interim analysis.

Patients

Inclusion and exclusion criteria

All eligible patients were invited to participate in the POSE study at the first clinic visit occurring after the site initiation. All the patients who agreed to participate signed an ICF.

Inclusion criteria (for Greece and Portugal):

- Adult patients (≥18 years old) currently treated or intended to be treated at 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.

OR

- Adult patients (≥18 years old) treated by a statin in monotherapy at stable standard dose for at least 3 months (dosage stability should 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; i.e. atorvastatin 10 mg, lovastatin 40 mg, pravastatin 40 mg, simvastatin 20-40 mg, fluvastatin 40-80 mg and rosuvastatin 5-10 mg.

Inclusion criteria (for Spain):

- Adult patients (≥18 years old) treated with Pravafenix for at least 6 months. Pravafenix should have started within 12 months prior to ICF signature date.

OR

- Adult patients (≥18 years old) treated by a statin in monotherapy at stable standard dose for at least 3 months (dosage stability should 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. The accepted statins are the following: atorvastatin 10 mg, lovastatin 40 mg, pravastatin 40 mg, simvastatin 20-40 mg, fluvastatin 40-80 mg and rosuvastatin 5-10 mg. Those patients are considered as the control group.

Exclusion criteria:

- The patients who were participating in other clinical studies concomitantly with this survey were not being included in this study.
- Concomitant lipid lowering therapies with fibrates.
- Patients for which no medical records were available at study treatment initiation.

Selection of patients

Starting from the site initiation visit, all the potentially eligible patients (i.e., fulfilling the inclusion criteria) were sequentially proposed to enter the POSE study when they attended a regular clinically scheduled visit. This rule allowed to avoid any selection bias, since all the patients were proposed the study in chronological order when they attended a regular clinic visit.

However, to ensure a 1:1 ratio between the two treatment arms at each site, the patient signed the ICF only if the difference between the number of patients in both arms was not greater than 2. If this difference was bigger, the patient was put on the waiting list until the balance between both study arms was achieved in the given site.

A few patient data were captured into eCRF regardless the fact that patients agreed to participate or not. Data collected allowed to prove that the characteristics of the patients who did not participate in the study were comparable to those of the patients who were enrolled (i.e., no selection bias).

After having given their participation agreement, the patients were subjected to data collection from an electronic questionnaire completed by the participation physician. Based on the calculation of the sample size, a cohort of 3000 patients was included in the study. It was not allowed to include a patient more than once in this observational study (e.g., a patient switching from statin to Pravafenix during the study could not be re-included in Pravafenix group).

Study populations

The following study populations were defined:

- Active Physicians: physicians who recruited at least one participating patient.
- Eligible patients not included: eligible patients who did not given informed consent, were not included into the study due to other reasons or did not provide baseline information.
- Participating patients: patients included in the study and having a documented baseline visit.
- Eligible patients: eligible patients not included + participating patients as defined above.

Characteristics of the eligible patients not included were to be compared to the patients who agreed to participate in the study to detect any participation bias.

Subgroup analyses per country, physician's profile (GPs/specialists) (for Greece and Portugal only), cardiovascular (CV) risk level or patient's gender were to be performed.

Variables

Exposure

The following patient exposures were compared:

- For Greece and Portugal: New user of Pravafenix: patients who had initiated Pravafenix over the last year intended to be treated at time of inclusion in the study.
- For Spain: User of Pravafenix: Patients treated with Pravafenix for at least 6 months. Pravafenix should have had started within 12 months prior to ICF signature date
- Prevalent user of statins at standard dose in monotherapy: patients who were treated by a statin in monotherapy at standard and stable dose for at least 3 months at time of inclusion in the study.

A standard dose of statin was defined by NCEP ATP III as the dose required to attain an approximate 30% to 40% reduction of LDL-C levels, i.e., atorvastatin 10 mg, lovastatin 40 mg, pravastatin 40 mg, simvastatin 20-40 mg, fluvastatin 40-80 mg and rosuvastatin 5-10 mg. For Spain, these were the only statins accepted.

Follow-up started at treatment initiation and continued until the last visit for data collecting after 3 years or end of respective treatment.

Variables for participating patients:

At baseline:

- Demography: age, gender, menopausal status, pregnancy, breastfeeding for women
- Clinical characteristics: height, weight, waist circumference, blood pressure, pulse rate.
- Lifestyle habits: smoking habits, alcohol consumption, sedentary lifestyle.
- CVD history.
- Medical history: hypertension, diabetes mellitus, liver disease, gallbladder disease, retinopathy, chronic or acute pancreatitis, myopathy and/or rhabdomyolysis, CPK elevation >5x ULN under previous statin treatment.
- Concomitant medications (concomitant medications at baseline include all medication started prior to first study treatment Administration and used during the study. Concomitant therapies are part of concomitant medications and include concomitant lipid lowering therapies, cardiovascular and diabetes medications).
- Lipid parameters: total cholesterol, LDL-C, HDL-C, TG, Apo A-I, Apo B.
- Other laboratory parameters: glucose, HbA1C, CPK, ASAT, ALAT, GGT, creatinine clearance, serum creatinine, homocysteine, CRP, amylase, lipase, total bilirubin, ALP.

Treatment for dyslipidaemia: name and daily dose of treatment, profile of prescriber who initiate the treatment, date of treatment initiation, Intake of treatment during a meal, dietary restrictions.

During follow up:

- Clinical characteristics: weight, waist circumference, blood pressure, pulse rate.
- Treatment for dyslipidaemia: date and reason of discontinuation, name of replacement medication if any.

Concomitant medications (concomitant medications during follow up include 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. Concomitant therapies are part of concomitant medications and include concomitant lipid lowering therapies, cardiovascular and diabetes medications).

- Lipid parameters: total cholesterol, LDL-C, HDL-C, TG, apolipoprotein A1 (Apo A-I), Apo B.
- Other laboratory parameters: glucose, glycated haemoglobin (HbA1c), CPK, aspartate aminotransferase (ASAT), ALAT, gamma-glutamyl transferase (GGT), creatinine clearance, serum creatinine, homocysteine, C-reactive protein (CRP), amylase, lipase, total bilirubin, alkaline phosphatase (ALP).
- Main safety endpoints since last visit:

o Renal and urinary disorders (blood creatine abnormal, blood creatinine abnormal, creatinine renal clearance abnormal, renal failure, renal disorder, blood urea abnormal, glomerular filtration rate abnormal, red blood cells urine positive, urine analysis abnormal).

o Musculoskeletal and connective tissue disorders (myopathy, myositis, myalgia, muscle disorder, blood creatine phosphokinase abnormal, muscle enzyme increased, rhabdomyolysis).

o Hepatobiliary disorders (transaminases increased, hepatic failure, hepatic pain hepatotoxicity, hepatitis, blood bilirubin abnormal, hepatic enzyme abnormal, gamma-glutamyl-transferase abnormal, transaminases abnormal, alanine amino-transferase increased, aspartate aminotransferase increased).

o Cholelithiasis (cholelithiasis, gallbladder disorder).

o Thromboembolic events (pulmonary embolism, deep vein thrombosis).

o Pancreatitis (pancreatitis, pancreatitis acute, pancreatic disorder, pancreatic enzymes abnormal, blood amylase increased).

o Diabetes mellitus aggravated (diabetes mellitus aggravated, diabetes mellitus exacerbated, worsening of diabetes, hyperglycaemia, blood glucose abnormal and new onset of diabetes).

o Blood homocysteine increase (blood homocysteine increased, blood homocysteine abnormal, hyperhomocysteinaemia)

o Interstitial pneumopathy (interstitial lung disease, pulmonary fibrosis).

o Phototoxicity (photosensitivity reaction, photosensitivity allergic reaction, retinal Phototoxicity).

- Fatal and non-fatal cardiovascular events (coronary heart disease, myocardial infarction, angina pectoris, heart failure), cerebrovascular disease (stroke, transient ischemic attack), peripheral arterial disease (intermittent claudication), aortic atherosclerosis and thoracic or abdominal aortic aneurysm since last visit.

Any other adverse events since last visit.

- Dates of all performed follow up clinical visits since baseline observation and laboratory assessments.

Other variables:

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

Compliance to the recommended biological recommendations was the number of patients with abnormal biological value and for whom the recommended risk minimisation was observed (biological monitoring), divided by the total number of patients with abnormal value of the laboratory exam.

Variables for eligible patients not included:

- Patient characteristics at baseline:
- Demography: age, gender (both protocols)
- Treatment for dyslipidaemia: name and daily dose of treatment, date of treatment initiation (only Greece and Portugal)
- Clinical characteristics: blood pressure (only Greece and Portugal)
- Lifestyle habits: smoking (yes/no) (only Greece and Portugal)
- Total cholesterol value (only Greece and Portugal)

Variables for active physicians (only Greece and Portugal):

- Profile (GP, cardiologist, endocrinologist, internist).
- Mode of practice (Private, Hospital-based).
- Country.

Risk window

The risk window began with the inclusion in the cohort and extended until the end of data collection.

Confounders

Demographic and lifestyle information (age, gender, waist circumference, blood pressure, alcohol consumption, concomitant treatments), history of diabetes and hypertension, cardiovascular disease history, CV risk, lipid profile and other covariates like history of liver disease, gallbladder disease, retinopathy, pancreatitis, myopathy and rhabdomyolysis were considered as potential confounders factors.

Data sources and measurement

The approach in this study was the collection of primary data specifically for the study. The data collection was partly retrospective and partly prospective. For each enrolled patient, an electronic questionnaire was completed by the participating physicians requesting the physician characteristics (for Greece and Portugal only), the patient's characteristics, the treatment taken and its pattern of use, the laboratory monitoring, and the description of adverse events. No patient's visit, laboratory analysis or exam other than those performed within the scope of the real clinical practice was imposed.

Patients' assessments were planned to be performed at the inclusion visit, then as recommended by the summary of product characteristics. The patient's data were collected from the source documents of the patient's medical file (original files, hospital reports, lab examinations, exchange of mails, etc.). If the participating physician was not the physician who initiated the treatment, he or she had to do his/her best effort to collect the data and laboratory test results performed at the time of initiation of treatment.

Each patient was allocated an identification number with the country code, the site number and the patient's number in the order of inclusion at the site. Electronic questionnaires were used for the data capture. The physician reported directly via a secure web-based application.

Bias

Starting from the site initiation visit, all the potentially eligible patients (i.e., fulfilling the inclusion criteria) were proposed to enter the POSE study when they attended a regular clinic visit. This rule allowed to avoid any selection bias, since all the patients were proposed the study in chronological order when they attended a regular clinic visit.

A few patient data applicable to Greece, Portugal and Spain were captured into eCRF regardless the fact that patients agreed to participate or not. Data collected purpose was to allow to prove that the characteristics of the patients who did not enter in the study were comparable to those of the patients who were enrolled (i.e., no selection bias). It should be noted that different information was collected in Greece and Portugal (vital signs, blood pressure, cholesterol and dyslipidaemia treatment i.e. Pravafenix or statin) whereas in Spain only data on age and gender were gathered. As an observational and open-label study no other forms of bias were required to be controlled for.

Study size

Initial hypotheses

The primary objective of this observational study was to estimate the hazard ratio for the main safety endpoints between patients treated by Pravafenix or by a statin in monotherapy in real clinical practice conditions of prescription within a 3-year follow up period.

The main important identified AEs related to Pravafenix according to the RMP included musculoskeletal and connective tissue disorders, renal and hepatobiliary disorders. According to a pooled analysis evaluating the safety of Pravafenix from the double blind and open phase III trials realized with 1526 patients, the percentage of patients presenting these adverse events ranged from 1% to 5%. No significant difference in intensity and/or frequency between Pravafenix and statin monotherapy groups were observed. The

emergent effects possibly related to Pravafenix were mainly those attributable to fenofibrate (especially an increase in creatinine levels, a decrease in creatinine clearance, and pancreatitis).

In the Assessment Report of Cholib (Fenofibrate/Simvastatin), the frequency of these specific adverse events (AEs) was evaluated in four double-blind studies which randomized 2,474 subjects with mixed dyslipidaemia [44]. For muscle effects, the standardized query showed a frequency of 2.2% in the co-administration group and 1.9% in the statin monotherapy group. Hepatic disorders showed a frequency of 5.4% in the co-administration group and 5.9% in the statin monotherapy group. A difference was noted between co-administration and monotherapy groups for renal effects with a frequency of 10.1% versus 4.6%, respectively.

In the ACCORD lipid study including 5,518 patients with type 2 diabetes mellitus with administration of fenofibrate and simvastatin or simvastatin monotherapy for an average 5-year follow-up, a significant different frequency of AEs was observed for renal effects only. Serum Creatinine >1.3 mg/dL was reported in men with a frequency of 36.7% in the fenofibrate/simvastatin group and 18.5% in the simvastatin monotherapy.

In a retrospective observational study comparing the rates of hospitalization for specific AE in a cohort of users of statins or fibrates, the adjusted incidence rate ratio for statin-fenofibrate combinations compared to statins alone was 3.75 for rhabdomyolysis, 1.47 for renal impairment and 2.87 for pancreatitis.

Based on these data, a sample size of 1500 subjects in each group were estimated for the present study.

Indeed, a two-sided test of whether the hazard ratio is one with an overall sample size of 3000 subjects (of which 1500 are in the control group and 1500 are in the treatment group) achieves 80% power at a

0.050 significance level when the hazard ratio is 2. The number of events required to achieve this power was overall 60. It was anticipated that proportions of subjects having the event during the study is 0.020 for the control group and 0.040 for the treatment group. These results assumed that the hazard ratio was constant throughout the study and that Cox proportional hazards regression was used to analyse the data.

Confirmed sample size (1-year interim Report)

The results at 1-year demonstrated the proportion of patients experiencing 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 therefore re-estimated based on the observations of the 1-year interim analysis. For a sample size of 1500, the probability of observing at least one event was 0.95 when the probability of an event was 0.002. The power of detecting at least one of the safety profile events, under the observed proportion of patients at 1-year, was >99% in both arms. Based on the number of events collected at one year follow up, The PRAC's Rapporteur agreed the statement of the MAH that "the analyses performed at 1 year follow up confirm that the study can continue with the current sample size as this provides a sufficient number of patients to detect rare events".

Analysis populations

Total Set

The Total Set consisted of all eligible patients. Eligible patients included both eligible patients not included and participating patients. Eligible patients not included were eligible patients who did not given informed consent, were not included into the study due to other reasons or did not provide baseline information. Participating patients were patients included in the study and having a documented baseline visit. For eligible patients not included the only information available was those recorded on "Preinclusion" eCRF page.

Total Set was used to describe patient disposition and protocol deviation.

Screening Failures

Screening Failures were defined as eligible patients not included into the study. Eligible patients not included were eligible patients who did not give informed consent, were not included into the study due to other reasons or did not provide baseline information.

Screening failures were used to evaluate potential participating bias by analysing patients' characteristics and participating physician's characteristics.

Safety Analysis Set (SAF)

All patients who provided informed consent and who had a documented baseline visit were included in the safety analysis Set.

The SAF Set was used for all safety analyses. The SAF Set was summarized and presented by Study Treatment received.

Full Analysis Set (FAS)

All patients who provided informed consent, who had documented baseline visit, with at least one visit of follow-up were included in the full analysis Set.

The FAS Set was the primary Analysis Set of interest for all endpoints. The FAS Set was summarized and presented by Study Treatment.

Per-protocol Set (PP)

All patients from the FAS Set who did not have any major protocol violations comprised the PP Set.

Prior to database lock at the end of the study, major protocol deviations were identified by Laboratoires SMB S.A. during a data review meeting (DRM). These major protocol deviations were considered while identifying the PP Set.

The PP Set was used to support the correspondent results of the primary endpoints based on FAS Set.

Subgroup definitions

The first subgroup was country. This study was conducted in three countries: Greece, Portugal and Spain. This factor was included to investigate potential country-specific effects on secondary endpoints, baseline characteristics and investigate for possible participating bias.

The second subgroup was gender. This factor was used to investigate potential epidemiological impact on some secondary variables and to investigate for potential participating bias.

The third subgroup was physician's profile. Physician could be a general practitioner, a cardiologist, an endocrinologist, an internist, or other physician. Physician could work in a private practice or in a hospital. This information was not available for Spain. This subgroup was included to evaluate potential physician's profile effects on secondary variables and baseline characteristics.

The fourth subgroup was cardiovascular risk level based on the SCORE Chart risk. This factor was used to investigate potential effects of cardiovascular risk level on secondary variables and baseline characteristics.

Statistical methods

The statistical results were displayed using tables, listings and/or graphs. The statistical analysis was performed using the software SAS. Statistical methods.

The statistical analysis was planned to be performed in two steps:

- One interim analysis after all patients had completed 1 year follow up (since start of treatment).

The aim of the interim analysis was a description of utilization of Pravafenix and presentation of safety data after 1 year of follow-up, which included also comparative analyses after 1 year of follow-up. As recruitment was completed at this stage, representativeness of participating physicians was analysed, and a description of study patients and duration of recruitment period was presented. These results were to be reviewed by an independent scientific committee.

- The final analysis, presenting all primary and secondary criteria of the study, including all comparative analyses was performed after the 3-year follow-up period.

Main summary measures

For continuous variables, the number of non-missing values, mean, standard deviation, minimum, median, maximum, and two-sided 95% confidence interval were presented. Unless otherwise specified minimum and maximum values were reported to the same number of decimal places as the recorded measurements, mean and median were reported to one more decimal place, and standard deviation and confidence interval one additional decimal place more than the mean.

For categorical variables, absolute (n) and relative frequencies (%) were reported. Relative frequencies were based on all observations and reported as percentages to one decimal place. Unless otherwise specified percentages were based on the number of patients with data in the population Analysis Set of each treatment and were not calculated for missing categories.

Adverse events and concomitant medications were reported on a patient basis. The percentages were calculated using the number of patients in the population Analysis Set of each treatment as the denominator.

All hypotheses were tested at a 5% level of significance using a two-sided test unless otherwise specified.

P-values were rounded to three decimal places. If a p-value was less than 0.001 it is reported as "<0.001". If a p-value was greater than 0.999 it is reported as ">0.999".

Main statistical methods

As this was an observational study, a propensity analysis was conducted to account for any imbalance in baseline characteristics in the treatment arms. The absence of randomisation did not allow assuring the comparability of patients. Propensity scoring allowed the modelling of time to event/incidences conditionally to the probability of having the treatment. The propensity score was calculated for each patient with the observed variables using a logistic regression model (model Pravafenix =covariables, with the variable Pravafenix taking value 0 or 1). The adequacy of the model was checked by standardized differences between groups. If the model was adequate no difference is expected between groups. Covariables were replaced by a unique variable which was the propensity score. Relative Risks were produced as "unadjusted" (not accounting for propensity score) and "adjusted" (accounting for propensity score). A Log-Binomial regression model was used to calculate the adjusted relative risk.

The primary analysis was conducted using absolute risk (incidence rate) and relative risk.

Incidence rate of the main safety endpoints between patients treated by Pravafenix or by a statin in monotherapy within three years of follow-up period are the primary endpoints. Main safety endpoints included:

- renal and urinary disorders,
- musculoskeletal and connective tissue disorders,
- hepatobiliary disorders,

- cholelithiasis,
- thromboembolic events (namely pulmonary embolism, deep vein thrombosis),
- pancreatitis,
- diabetes mellitus aggravated,
- blood homocysteine increase,
- interstitial pneumopathy,
- phototoxicity.

Additionally, based on these safety endpoints, safety profile was defined as the occurrence of at least one of them. Safety profile was a binary variable code as '1' if the patient had experienced at least one of the main safety endpoints, '0' otherwise.

Incidence rate (absolute risk) was defined as proportion of new patients with at least one occurrence of considered endpoint. If a patient had experienced more than once the same adverse event, the patient was counted only for the first time he/she had experienced that adverse event. Adjusted and unadjusted absolute and relative risks were provided based on incidence rates together with 95% confidence intervals.

The secondary analyses of the time to first occurrence of each safety endpoint, including safety profile, and cardiovascular events was analysed by time to event. Time to event was estimated by Cox proportional hazard model which is evaluated through survival analysis. Time to event was analysed in two steps. Univariate Cox proportional hazard models were performed using, one variable at a time, the following covariates: age, gender, country, waist circumference, systolic blood pressure, smoking status, high alcohol consumption, cardiovascular disease history, cardiovascular risk level, lipid profile variables (total cholesterol, HDL-C, LDL-C, TG) and concomitant treatments. Variables associated with a hazard ratio at $p<0.20$ were introduced in a multivariate Cox proportional hazard model with forward stepwise selection. In the multivariate Cox proportional hazard model quintiles of propensity score were used as strata and the treatment group was added as covariate. Kaplan-Meier estimates of cumulative survival probabilities were only plotted for each primary endpoint and cardiovascular risk.

Missing values

In the derivation of endpoints there was no replacement of missing data except for imputation of adverse event dates and concomitant medication dates.

Sensitivity analyses

To support the interpretation of the primary variables, further supportive and sensitivity analyses were conducted separately both on patients without any treatment change or treatment discontinuation during the entire treatment period and patients with treatment change or at least one treatment discontinuation for the FAS Set.

Results

Participants

Disposition of patients

A total of 3136 patients were eligible to the study, out of which 1562 were in the Pravafenix arm and 1542 were in the statin arm (control group) (sum 3104 patients). There were 61 screening failures. A total of

3075 patients with documented baseline visit constituted the SAF Set, out of which 1546 were treated with Pravafenix and 1529 were treated with a statin.

For clarification, these final samples sizes slightly differ from those presented in the interim 1-year analysis because some values, not filled in into the CRF at interim analysis time point, were completed at the end and therefore added in the appropriate set of patients for the final analysis.

At the end of the 3-year follow-up period, 82.5% of the overall patients completed the study; 80.2% patients from the Pravafenix arm and 84.9% from the statin arm. Overall, 9.6% of the patients discontinued the study; 11.0% patients from the Pravafenix and 8.1% from the statin arm, respectively.

The main reason for discontinuation was 'Lost to follow-up' (5.2%) mostly in relation with coronavirus constraints, slightly higher in the Pravafenix recipient. Low sample sizes were observed for all other reasons, limiting interpretation. The number of deaths was equal (n=6, 0.4%) from both arms.

Of note, the rate of study completion (82.5%) over the 3-yr follow up was consistent with the interim 1- yr analysis, which reported: *"4.5% of the overall patients discontinued the study; 4.8% patients from the Pravafenix and 4.1% from the statin arm. The main reasons for discontinuation were 'Lost to follow-up' (1.4%) and 'Other' (1.4%)".*

Analyses populations

The data collected for the 61 cases of screening failures allowed to establish that the characteristics of the patients who did not participate in the study were comparable to those of the patients who were enrolled (i.e., no selection bias). A total of 3075 patients comprised the SAF Set.

The Full Analysis Set (FAS) consisted of a total of 2983 (97.0%) patients, out of which, 1491 (96.4%) were treated with Pravafenix and 1492 (97.6%) were treated with a statin (control group). Likewise, the Per-protocol Set (PP) consisted of a total of 2954 (96.1%) patients, out of which 95.8% were treated with Pravafenix and 96.3% were treated with a statin.

Country distribution

Out of the 3075 patients in the SAF Set, the majority (N=2612, 85%) were from Greece whereas 458 (15%) were from Spain; only 5 patients were from Portugal

Physician' s profile

Out of the 2617 patients from Greece and Portugal from the SAF Set, most of them (2282, 87%) were followed by an internist (61.0%) or by a cardiologist (27.0%). The mode of practice was predominantly private (53.4%), or in an hospital (41.5%), or both (5.1%).

This is in line with the target population defined in the Pravafenix indication: high CV (or even very-high risk) patients, presenting with complex dyslipidaemia insufficiently controlled with statin alone (second-line therapy), often requiring a specialized supervision.

Descriptive baseline characteristics

Demography

The mean age for the participants in the SAF Set was 61.4+12.1 years; 60.1+12.2 years for the Pravafenix arm and 62.7+12 years for the statin arm.

Of note, the elderly patients with age > 75 years and satisfactory renal function accounted for 404 patients (169 in the Pravafenix arm and 235 in the statin arm).

The mean weight was 84.2+16.4 kg, higher in the Pravafenix group (87.6+17.0 kg) vs. 80.0+15.0 (statin group), in relation with abdominal adiposity (waist circumference: 102.5+13.3 cm vs. 98.2+12.8 cm, respectively).

They were overall 1684 (54.8%) men predominantly from the Pravafenix arm (59.4%), and 1391 (45.2%) women predominantly from the statin arm (49.9%)

Among women, most of them (83.2%) were postmenopausal, equally distributed in both arms.

Lifestyle characteristics

Out of the 3075 patients in the SAF Set, 48.2 % had a sedentary lifestyle, 26.6% were chronic smokers; but only 2.8% were high-alcohol consumers.

Medical history

Out of the 3075 patients in the SAF Set, there were 2209 (71.8%) with any medical history: 75.2% for the Pravafenix arm and 68.5% for the statin arm. Medical history can be split as follows:

Major cardiovascular risk factors

- Hypertension was the most frequently reported (56.1%) major risk factor, with similar prevalence (57.8%) from the Pravafenix arm vs. 54.4% from the statin arm;

- 46.6% of the patients suffered from diabetes mellitus; 52.8% from the Pravafenix arm vs. 44.4% from the statin arm. The higher percentage in the Pravafenix group was expected due to the specificities of mixed dyslipidaemia, one of the major risk factors for CVD in people with type 2 diabetes.

Baseline values were within an acceptable range of therapeutic goals, considering the prevalence of the diabetic population in both treatment arms:

- Mean systolic blood pressure: 132.3+13.4 mmHg, diastolic blood pressure 78.7+8.7 mmHg.

- Mean glycaemia: 6.6+2.5 mmol/L, mean HbA1c 51.5+16.6 mmol/mol.

Other diseases

Each category classified as "other diseases" applied to less than 3% of the patients:

- the frequency of "liver disease" history was low, slightly higher in the Pravafenix arm (2.4%) in comparison with the statin one (1.3%). Again, this could be explained by the mixed dyslipidaemia characterized by elevated TG levels, often associated with moderate transaminases elevation (hepatic steatosis). For reminder, active liver disease including unexplained persistent elevations in liver function tests (including serum transaminase elevation) exceeding 3-fold the upper limit of normal (ULN), are classical contra-indications of both classes (fibrates and statins), therefore of Pravafenix.

- Considering that moderate to severe renal impairment (defined as an estimated creatinine clearance < 60 ml/min) is a contra-indication to Pravafenix, it is likely that the population with diabetes mellitus included in the Pravafenix arm did not present with a high rate of microvascular complications (nephropathy, retinopathy); the absolute rate of "retinopathy" history was thus low and similar in both groups (1.4% and 1.5%, respectively). The mean baseline value of creatinine clearance was 1.4+0.8 ml/.

- A similar pattern to "liver disease" was noted for "chronic or acute pancreatitis" and "gall-bladder disease" history, the very low frequency (0.5%) preventing any valid interpretation. For reminder, chronic or acute pancreatitis (except for acute pancreatitis due to severe hypertriglyceridemia), and gallbladder constitute contra-indications to fibrates prescription.

- Expectedly, the frequency of muscle disorders history was also very low (< 1%), because of special warning for both classes (statins and fibrates) regarding muscular risk; therefore, a personal history of

myopathy and/or rhabdomyolysis with statins and/or fibrates, or confirmed creatine phosphokinase (CK) elevation above 5 times the ULN under previous statin treatment constitute contra-indications to Pravafenix.

Dyslipidaemia history

Most of the global population (91.9%) had treatment initiated by the participating physician, associated with dietary restrictions (97.4%) well-balanced between groups, in compliance with the indication labelling of Pravafenix and of statins.

Overall, 23.9% of the patients took a previous lipid lowering agent, with almost twice as many patients (32.4%) in the Pravafenix arm vs. 15.2% in the statin arm, see below MAH comment.

Most patients used Pravafenix with no prior treatment of pravastatin 40 mg monotherapy. Indeed, 19 patients only in the Pravafenix group (1%) were previously treated by pravastatin (9 patients previously treated by pravastatin 40 mg, 9 patients by pravastatin 20 mg and 1 by pravastatin 10 mg).

Cardiovascular disease history

Out of the 3075 patients in the SAF Set, there were 10.7% of patients with a family history of premature

CHD similarly reported in both groups, and 13.9% of patients with established CVD reflecting a secondary-prevention population, with similar rates in both arms. The most common CVD was CHD (60.7%), similarly described in both arms, followed with cerebrovascular location (30.6%), more frequently in the statin group (27% vs. 34%). This last consideration may refer to the cerebro-protective effects of statins, regarding ischaemic risk.

Concomitant medications

Out of the 3075 patients in the SAF Set, there were 2366 (76.9%) patients with any concomitant medication, and 2205 (71.7%) with any concomitant therapy**,** predominantly cardiovascular and antidiabetic therapy. The most frequent concomitant therapies were:

- Drugs acting on the Renin-Angiotensin-Aldosterone System: Angiotensin II Antagonists (overall 23.0%), ACE-Inhibitors (overall 10.2%), Aldosterone Antagonists (overall 1.8%);

- Drugs acting on blood glucose control: metformin (overall 29.2%), combinations of oral drugs (overall 9.7%), insulins and analogues (9.4%), Dipeptidyl Peptidase 4 (DPP-4) Inhibitors (overall 11.2%), Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors (overall 8.3%), Glucagon-Like Peptide-1 (Glp-1) Analogues (overall 5.8%), Sulfonylureas (4.5%);

- Beta-blocking agents (overall 18.1%);

- Platelet-aggregation inhibitors (overall 15.7%), antithrombotics (4.9%);

- Calcium-channel blockers (overall 14.3%);

- Diuretics thiazides (overall 7.3%), sulfonamides (4.8%°).

All medications were in general well-balanced between both treatment groups, except for management of diabetes mellitus, more frequent in the Pravafenix group due to a higher prevalence of this risk factors, as seen above.

Baseline other biological laboratory parameters

The baseline values concerning some key elements of monitoring (CK, hepatic enzymes, creatinine, homocysteine) were, except outliers, within normal range.

Summary of baseline data (SAF set)

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 to the indication label 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 monotherapy. The current restricted indication may have generated significant off-label use, as seen in this study, that the MAH is willing to correct with appropriate measures.

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 exceptionally with pravastatin 40 mg.

Main results

Primary variable (safety profile)

Propensity Score

The absolute risks (AR) and relative risk (RR) of each safety endpoint after one, two, and three years and over three years of follow-up were low, and no significant differences were observed between the treatment arms. Despite the baseline differences between them discussed above, the distribution of the propensity score confirmed that there were no significant differences between the two treatment groups.

Primary analysis (safety profile)

In the Pravafenix arm, the absolute risk (AR) of safety profile decreased from 0.035 (n = 52) at the Year 1 follow-up to 0.025 (n = 34) at the Year 2 follow-up to 0.012 (n = 15) at the Year 3 follow-up.

Similarly, in the statin arm, the AR of safety profile decreased from 0.023 (n = 35) at the Year 1 followup to 0.016 (n = 22) at the Year 2 follow-up to 0.014 (n = 19) at the Year 3 follow-up.
The AR of safety profiles over the cumulative three-year period was 0.068 (N= 101) in the Pravafenix arm and 0.051 (n = 76) in the statin arm. The adjusted (accounting for propensity score) RR of safety profiles over the three-year period (**1.366**) with its 95% confidence interval spanning 1 **(0.967; 1.929)** confirms there is no significant differences between both treatment arms.

Interpretation

- Of note, most of the events occurred during the first year of follow-up, then incidence regularly decreased over time in both arms. Primary result is thus consistent (although slightly different) with the 1-year results assessed by PRAC in 2021 i.e., unadjusted RR: 1.450 (0.496; 2.223), adjusted RR: 1.377 (0.812; 2.337). This can be explained by differences in the results of the propensity analysis, between the Interim CSR and the final one. This is due to the live data collection and additional baseline information being available at the time of the final CSR. The additional baseline information impacted propensity which in turn impacted the adjusted results.

- With respect to initial hypotheses, the total number of events required to achieve the predefined power (N=60) was largely exceeded (N=177); also, were the anticipated proportions (0.040 for Pravafenix vs. 0.020 for the control group) of subjects having the event during the study (0.068 vs.0.051, absolute difference of 0.017 instead of 0.02 protocol assumption, and 0.01 in the interim analysis). Hence robustness of the primary result within 3 years is established, reflecting that, above statistical approach, **there is no clinically relevant difference between both arms.**

- In each treatment group, this result is driven by a higher incidence of:

    - o "Musculoskeletal and connective tissue disorders" (overall N=80 events),
    - o "Renal and urinary disorders" (overall N=52 events), and
    - o "Diabetes mellitus aggravated" (overall N=52 events).

Given the specificities of Pravafenix (dual therapy exposing to increased muscular risk, high prevalence of diabetes mellitus in mixed dyslipidaemia, creatinine increases under fibrate therapy whose clinical significance is unproven), it was expected that the incidence was slightly higher in the Pravafenix group than in the control group. Other components had either a global low incidence (< 10 events) or had a single event in the Pravafenix group ("*Blood homocysteine increase*"), or even zero event ("*Interstitial pneumopathy*" and "*Phototoxicity*"). Interestingly these components are classified as important POTENTIAL risks in RMP, and not IDENTIFIED.

Key components of the primary variable (by decreasing frequency, RMP: important IDENTIFIED risks)

- Musculoskeletal and connective tissue disorders

In the Pravafenix arm, the AR of musculoskeletal and connective tissue disorders decreased from 0.017 (n = 26) at the Year 1 follow-up to 0.009 (n = 12) at the Year 2 follow-up and to 0.005 (n = 6) at the Year 3 follow-up. Similarly, in the statin arm, the AR of musculoskeletal and connective tissue disorders decreased from 0.013 (n = 19) at the Year 1 follow-up to 0.008 (n = 12) at the Year 2 follow-up and to 0.004 (n = 5) at the Year 3 follow-up.

The AR of musculoskeletal and connective tissue disorders over the cumulative three-year period was 0.030 (n = 44) in the Pravafenix arm and 0.024 (n = 36) in the statin arm. The adjusted RR of musculoskeletal and connective tissue disorder over the three-year period (**1.533**) with its 95% confidence interval

spanning 1 **(0.883; 2.663)** confirm there is neither significant nor clinically relevant differences between both treatment arms.

- Renal and urinary disorders

In the Pravafenix arm, the AR of renal and urinary disorders increased from 0.007 (n = 11) at the Year 1 follow-up to 0.008 (n = 11) at the Year 2 follow-up and decreased to 0.005 (n = 6) at the Year 3 follow-up.

Similarly, in the statin arm, the AR of renal and urinary disorders increased from 0.005 (n = 8) at the Year 1 follow-up to 0.009 (n = 13) at the Year 2 follow-up and decreased to 0.002 (n = 3) at the Year 3 follow-up.

The AR of renal and urinary disorders over the cumulative three-year period was 0.019 (n = 28) in the Pravafenix arm and 0.016 (n = 24) in the statin arm. The adjusted RR of renal and urinary disorders over the three-year period (**1.174**) with its 95% confidence interval spanning 1 (**0.629;2.188**) confirm there is neither significant nor clinically relevant difference between both treatment arms.

- Aggravated diabetes mellitus

In the Pravafenix arm, the AR of aggravated diabetes mellitus decreased from 0.009 (n = 14) at the Year 1 follow-up to 0.007 (n = 9) at the Year 2 follow-up and to 0.006 (n = 8) at the Year 3 follow-up.

In the statin arm, the AR of aggravated diabetes mellitus stayed constant from 0.004 (n = 6) at the Year 1 follow-up to 0.004 (n = 6) at the Year 2 follow-up and then increased to 0.007 (n = 9) at the Year 3 follow-up.

The AR of aggravated diabetes mellitus over the cumulative three-year period was 0.021 (n = 31) in the

Pravafenix arm and 0.014 (n = 21) in the statin arm. The adjusted RR of aggravated diabetes mellitus over the three-year period (**1.365**) with its confidence interval spanning 1 **(0.741; 2.516)** confirm there is no significant differences between both treatment arms.

- Thromboembolic events

In the Pravafenix arm, the AR of thromboembolic events increased from 0.001 (n = 1) at the Year 1 follow-up to 0.004 (n = 5) at the Year 2 follow-up and then decreased to 0.000 (n = 0) at the Year 3 follow-up. In the statin arm, the AR of thromboembolic events decreased from 0.001 (n = 2) at the Year 1 follow-up to 0.000 (n = 0) at the Year 2 follow-up and then stayed at 0.000 (n = 0) at the Year 3 follow-up.

The AR of thromboembolic events over the cumulative three-year period was 0.004 (n = 6) in the Pravafenix arm and 0.001 (n = 2) in the statin arm. The adjusted RR of thromboembolic events over the three-year period (**2.447**) with its 95% confidence interval spanning 1 (**0.461; 12.988**) confirms there is no significant differences between both treatment arms.

For further information concerning the Pravafenix group, all these events except one were reported in poly-medicated patients with multiple pathologies (including diabetes), in whom it is always difficult to assess the causal role of a single treatment. The causal role of Pravafenix was assessed (WHO) as "Possible" in all cases. Five out the six cases were serious (hospitalization), none was fatal. All except one (context of diabetic foot), recovered. These events were as follows:

- Three (3) venous events: deep venous thrombosis of one leg (N=2), one associated with pulmonary embolism; superficial thrombophlebitis (N=1). These events are described in the safety profile of Pravafenix.

- Three (3) arterial events, all reported in *very high* cardiovascular risk patients: thromboembolism of 1st, 2nd, 4th toes of one foot (N=1), in a context of aorto-iliac atherosclerotic disease with diabetic foot; acute

peripheral ischemia (N=1); transient ischemic stroke (N=1). Only veno-thromboembolic events are described in SmPC.

- Hepatobiliary disorders

In the Pravafenix arm, the AR of hepatobiliary disorders was very low; 0.001 (n = 1) at the Year 1 follow-up, 0.001 (n = 2) at the Year 2 follow-up and 0.000 (n = 0) at the Year 3 follow-up. In the statin arm, the AR of hepatobiliary disorders was also low; 0.001 (n = 1) at the Year 1 follow-up, 0.000 (n = 0) at the Year 2 follow-up and 0.002 (n = 3) at the Year 3 follow-up. The AR of hepatobiliary disorders over the cumulative three-year period was 0.002 (n = 3) in the Pravafenix arm and 0.003 (n = 4) in the statin arm. The adjusted RR of hepatobiliary disorders over the three-year period (0.716) with its confidence interval spanning 1 (0.157;3.260) confirm there is no significant differences between both treatment arms.

- Cholelithiasis (RMP: important IDENTIFIED risk)

In the Pravafenix arm, the AR of cholelithiasis was very low; 0.001 (n = 1) at the Year 1 follow-up, 0.001 (n = 1) at the Year 2 follow-up and 0.000 (n = 0) at the Year 3 follow-up. In the statin arm, the AR of cholelithiasis is also low; 0.001 (n = 1) at the Year 1 follow-up, 0.000 (n = 0) at the Year 2 follow-up and 0.001 (n = 1) at the Year 3 follow-up. The AR of cholelithiasis over the cumulative three-year period was 0.001 (n = 2) in both the Pravafenix and statin arms. The adjusted RR of cholelithiasis over the three-year period (1.679) with its 95% confidence interval spanning 1 (0.151; 18.635) confirm there is no significant differences between both treatment arms.

- Pancreatitis (RMP: important IDENTIFIED risk)

In the Pravafenix arm, the AR of pancreatitis was very low; 0.001 (n = 1) at the Year 1 follow-up, 0.001 (n = 1) at the Year 2 follow-up and 0.000 (n = 0) at the Year 3 follow-up. In the statin arm, the AR of pancreatitis was also low; 0.001 (n = 1) at the Year 1 follow-up, 0.000 (n = 0) at the Year 2 follow-up and, 0.001 (n = 1) at the Year 3 follow-up. The AR of pancreatitis over the cumulative three-year period was 0.001 (n = 2) in both the Pravafenix and statin arms. The adjusted RR of pancreatitis over the three-year period (0.533) with its confidence interval spanning 1 (0.0.34; 8.478) confirm there is no significant differences between both treatment arms.

Secondary variables

Fatal or non-fatal cardiovascular events

This endpoint is of special interest.

In the Pravafenix arm, the AR of fatal or non-fatal cardiovascular events decreased from 0.006 (n = 9) at the Year 1 follow-up to 0.007 (n = 10) at the Year 2 follow-up to 0.004 (n = 5) at the Year 3 follow-up.

In the statin arm, the AR of fatal and non-fatal cardiovascular events increased from 0.001 (n = 2) at the Year 1 follow-up to 0.007 (n = 10) at the Year 2 follow-up and then decreased to 0.005 (n = 6) at the Year 3 follow-up.

The AR of fatal or non-fatal cardiovascular events over the cumulative three-year period was 0.016 (n = 24) in the Pravafenix arm and 0.012 (n = 18) in the statin arm. The adjusted RR of fatal and non-fatal cardiovascular events over the three-year period (**1.209**) with its 95% confidence interval spanning 1 **(0.596; 2.453),** confirms that there are no significant differences between both treatment arms.

For information, all cardiovascular events reported during the study were already reported and analysed by the PRAC (2021Assessment Report), with these reassuring conclusions: *"All cases reports were submitted and analysed by PRAC as follows: among the serious cases of the POSE study, 24 cardiovascular events were retrieved in the Pravafenix group (reported for 22 patients) and 19 cardiovascular events were retrieved in the reference group (reported for 16 patients). The results did not show significant difference between the Pravafenix group and the reference group (OR: 1.34, 95% CI [0.70-2.57], p=0.37).*

The MAH detailed cases with cardiovascular events (serious and non-serious) retrieved during the reporting period. The cardiovascular events included atrioventricular block (1 case), cardiac arrest (1 case), cardiac artery disease/peripheral arterial disease without acute events (1 case), coronary disease (1 case), deep vein thrombosis/pulmonary embolism (1 case), hypertension (8 cases), intermittent claudication (1 case), myocardial infarction (2 cases), sinus tachycardia (2 cases), transient ischemic attack (1 case), arterial thrombosis limb (1 case) and vasovagal syncope (1 case).
Some effects are already listed in the SmPC (as pulmonary embolism, deep vein thrombosis). For some cases, there were confounded diseases or concomitant treatments. ***No new signal emerged from these data.*** *The MAH should continue to monitor the cardiovascular events."*

Lipid parameters
Overall, in both treatment arms, there was a steady reduction in the levels of total cholesterol, LDL cholesterol, triglycerides, apolipoprotein A-1, and apolipoprotein B100, and a concomitant rise in the levels of HDL cholesterol from baseline to the three-year follow-up in patients from both arms.

Other biological Laboratory Parameters
Globally, there was no significant differences regarding the evolution of the biological laboratory parameters between treatment arms except for alanine aminotransferase, gamma-glutamyl transpeptidase, serum creatinine, lipase, and alkaline phosphatase. In the Pravafenix arm, alanine Amino-transferase and alkaline phosphatase levels steadily decreased at each follow-up over three years, while in the statin arm it increased steadily over the same period. Otherwise, levels of gamma-glutamyl transpeptidase, serum creatinine, and lipase levels increased in the Pravafenix arm over three years and decreased in the statin arm.
Globally, there was no significant differences regarding the risk of developing biological laboratory abnormalities between treatment arms except for serum creatinine, alanine aminotransferase and homocysteine. The relative risks for these laboratory abnormalities were increased in the Pravafenix group compared to the statins group. These observations were expected in regard to the Summary of Product Characteristics of Pravafenix, where the precautions section recommends regular monitoring of transaminases and creatinine levels and to be cautious regarding patients with history of pulmonary embolism.

Recommended Risk Minimisation
Patients who had monitoring for CK, transaminases and renal measurement at all visits (Baseline, Follow-Up (Year 1), Follow-Up (Year 2) and Follow-Up (Year 3) that they attended until discontinuation were considered as "constantly monitored". No patient in either arm was discontinued because of any monitored risk factor. Over the 1-year follow-up period, the rate of compliance was of 33.3 % for renal monitoring and above 50% for CK and transaminase monitoring. Over the 3 years follow-up period, the lowest proportion of patients constantly monitored also applied to the creatinine clearance monitoring. However, it is reminded that moderate to severe renal is a contraindication of Pravafenix.

Pravafenix Usage Pattern
The descriptive analysis of the patterns of use confirms that Pravafenix was generally taken during the evening meal as recommended by SmPC and the total daily dose was respected.

Treatment Change and Treatment Discontinuation
During the 3-year follow-up period, 17 patients treated with Pravafenix had treatment change as compared to 75 patients treated with statins; 130 patients treated with Pravafenix had treatment discontinuation as compared to 94 patients treated with statins.

Although non-specified reasons accounted for the most treatment change or discontinuation, in the Pravafenix arm the most common specific reason was switching treatment while in the statin arm it was lack of efficacy.

Other analyses

Vital Signs
There was a small but noticeable decrease in weight, waist circumference, and blood pressure in both treatment arms.

Key POSE Safety Results

Given the positive PRAC evaluation, the most important safety results in the global population are presented, in the framework of this Type 2 Variation submission.

Primary analyses (Safety profile)

The absolute risks of safety profiles over the cumulative three-year follow-up period were 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) RR of safety profiles over the three-year period (1.366) with its 95% CI spanning 1 (0.967; 1.929) in the FAS and showing that there was no significant difference between treatment arms. All sensitivity analyses confirmed this result.

With respect to initial sample size hypotheses and following sensitivity analyses (including country), the robustness of the primary result over three years was established, reflecting that there was 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 were 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 was 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 "DM aggravated" (overall N=52 events, 31 vs. 21). Other components had a low global incidence (< 10 events), a single event ("Blood homocysteine increase) or even zero events ("Interstitial pneumopathy" and "Phototoxicity").

Interpretation

- Primary result is consistent with the results observed in the global population i.e.,
    - unadjusted RR 1.330 (0.996-1.775);
    - adjusted (accounting for propensity score) RR: 1.366 (0.967; 1.929).

- As for the global population, most of the events occurred during the first year of follow-up, then incidence regularly decreased over time in both arms.

- The primary result was driven by a higher incidence of:
    - "*Renal and urinary disorders*" in the Pravafenix group (N=12 events, among which 10 with Pravafenix).
    - "*Diabetes mellitus aggravated*" (N=11 events, predominantly [7 events] in the statin group vs. 4 events with Pravafenix).

- "*Musculoskeletal and connective tissue disorders*" (N=8 events, equally distributed between groups).

- Other components had either a very low incidence:

  - Two (2) "*thrombo-embolic (TE) events*" were reported (one in each group).
  - One (1) single event of "*hepatobiliary disorder*" (Pravafenix group) and one case of "*cholelithiasis"* (statin group) were observed.

The Pravafenix cases are summarized below (source CIOMS), or even no event ("*Pancreatitis*", "*Blood homocysteine increase*", "*Interstitial pneumopathy*" and "*Phototoxicity*").

Secondary Cardiovascular analysis

The incidence of CV events is of special interest. The total number of CV events collected was low, the AR of fatal or non-fatal CV 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% CI spanning 1 (0.596; 2.453) confirmed that there was no significant difference between the treatment arms.

Subgroup analysis (patients aged 75 years and above)

Participants

A total of 465 patients aged over or equal to 75 years were enrolled in the study, 191 in the Pravafenix arm and 269 in the statin arm. A total of 458 patients had a documented baseline visit and comprised the SAF (Pravafenix arm, N=189, 41.2%; statin arm, N=269, 58.8%). At the end of the three-year follow-up period, 81.2% of all patients had completed the study (77.8% and 83.6%, respectively). The main reason for discontinuation was 'Lost to follow-up' (5.9%), mostly in relation to Covid-19 constraints. The number of deaths was low (Pravafenix arm, n=1 patient from Covid-19 infection, 0.5%; statin arm, n=6, 2.2%).

Baseline characteristics

The two treatment arms were well-balanced regarding most patient characteristics at baseline.

The mean age for patients was 79.7+3.8 years; over half of the patients (57.4 %) had a sedentary lifestyle, and 7.2% were chronic smokers. The most common medical history events were arterial hypertension (79.3%) and DM (55.0%), more frequently reported than in the global population (56.1% and 46.6% respectively), due to age. The mean baseline values of key risk factors (lipids, blood pressure, glucose) were generally within therapeutic targets recommended at that time considering the very fragile subpopulation, and the prevalence of concomitant therapies (88.2% of patients), mainly CV and blood glucose control therapies, reflecting a well-treated subpopulation.

Overall, 31.0% of patients had established CVD reflecting a secondary-prevention population, nearly the double than the overall population (13.9%) due to age. Hence, this subpopulation was at much higher CV SCORE risk (approximately the double), than the overall population and 96.3% of the patients were classified as at very high/high CV risk level, compared to 69.7% in the overall population, similarly distributed between treatment groups.

The few imbalances between groups were:

- A slightly higher proportion of women (56.3%) predominantly from the Pravafenix arm (62.4%), whereas men (43.7%) were predominantly from the statin arm (48.0%).

Thus, the higher male prevalence observed in the overall POSE population (55.8%) in relation with mixed dyslipidaemia characteristics driven by the Pravafenix group (59.4% of men vs 50.1% statin group), was not found. It is likely that this feature was related to the advanced mean age (nearly 80 years) and the higher life expectancy for women.

- A higher prevalence of two major CV risk in the Pravafenix group, arterial hypertension (82.0% vs 77.3% statin arm) and DM (62.4% vs. 49.8%, respectively), consistent with mixed dyslipidaemia features and age impact in this subpopulation.

- The most common CVD history was cerebrovascular disease (overall 54.2%), slightly more frequently reported in the Pravafenix group (57.7% vs. 52.2%), followed with CHD (overall 45.1%), predominant in the statin group (52.2% vs. 32.7%).

Primary Analysis

The global incidence of safety endpoints was low: N=35 events, 20 in the Pravafenix arm and 15 in the statin arm. Most of them occurred during the first year of follow-up then incidence regularly decreased over time in both arms (except the four cases of "Musculoskeletal and connective Tissue Disorders" in the Pravafenix group, reported over the first two years). The AR of safety profiles over the cumulative three-year period was 0.093 (N= 17) in the Pravafenix arm and 0.049 (n = 13) in the statin arm. Within the limitations of sample size and low number of events, the unadjusted RR of safety profiles over the three-year period (1.879) with its 95% CI spanning 1 [0.936; 3.773] suggests that there was no significant difference between both treatment arms.

In each treatment group, the primary result was driven by a higher incidence of "Renal and urinary disorders" (10 events under Pravafenix therapy vs. 2 events in the statin group), "Diabetes mellitus aggravated" (4 vs. 7 events, respectively) and "Musculoskeletal and connective tissue disorders" (4 events in each arm).

Other components had either a very low incidence: one "thrombo-embolic event" per group (namely an "acute ischemia in low member") and one "hepatobiliary disorder" ("gallbladder polyp") in the Pravafenix arm, or no event ("Pancreatitis", "Blood homocysteine increase", "Interstitial pneumopathy" and "Phototoxicity").

Renal events

Except one case of End Stage Renal Disease assessed as "not related" (investigator) due to advanced DM, but "Possible" (WHO) as Pravafenix may have contributed to the event, not described in Pravafenix safety profile, other PTs i.e., glomerular filtration rate (GFR) decrease (2), renal impairment (1) or renal failure (1), are described.

Therefore, the slight numerical imbalance in the Pravafenix arm does not reflect any new signal in this subpopulation and Information about renal risk seems appropriately addressed in the SmPC, with adequate minimization measures, especially in the elderly/very elderly.

Muscular events

The very reassuring results regarding the muscular tolerability of the FDC were also consistent with results of the overall population: in the latest, the single case or rhabdomyolysis was reported in the statin arm and, among the most frequently reported Preferred Terms (PTs) (incidence ≤0.3%) for TEAEs considered related to Pravafenix, was myalgia (0.2%); likewise, among the most frequently reported PTs (incidence ≤ 0.4%) for TEAEs considered related to statin was also myalgia (0.2%).

Secondary CV Analyses

The global incidence of CV events collected was low (N= 8 events). The AR of fatal or nonfatal CV events over the cumulative three-year period was 0.022 (n=4 events) in the Pravafenix arm and 0.015 (n=4 events) in the statin arm. The unadjusted RR over the three year period (1.437) with its 95% CI spanning 1 [0.364; 5.673] suggests that there are no significant differences between both treatment arms, within the limitation of small number of events, in consistency with the overall population results.

Overall, in both treatment arms, there was a steady reduction in the levels of TC, LDL-C, TG, apoA1, and apolipoprotein B100, and a concomitant rise in the levels of HDL-C from baseline to the three-year follow-up in patients from both arms. The AR of abnormalities in Lipid parameters decreased over the follow-up period in both arms.

Discussion and Conclusion on this subgroup

The subgroup of the very elderly in POSE was sufficiently represented to allow a descriptive comparative approach between both therapeutic regimens (FDC and statin monotherapy).

The results of the analysis are considered sufficient to support the safety use of Pravafenix in patients 75-year-old aged or above. Along with the analysis of the main cohort, this 3-yearlong follow-up study supports the long-term safety use profile of the product. Of note, in most cases Pravafenix was taken during the evening meal as recommended by the SmPC and that the total daily dose was always respected.

Given that:

- on one side, this subpopulation was at much higher CV risk than the overall POSE population, likely due to the advanced mean age (nearly 80 years) and subsequent impact of comorbidities,

- on the other side, the analysis did not reveal any over-risk or new safety signal, the benefit / risk balance of Pravafenix appears positive in this subgroup.

Current risk minimization measures are adequate.

2.4.3. Discussion on clinical data

Context of Approval (as a reminder)
At the time of European approval (January 2011), Pravafenix was the first FDC registered for the treatment of mixed dyslipidaemia in high cardiovascular risk patients. The CHMP granted a restricted indication in cases when the LDL-C target threshold was met but with insufficient results for TG and HDL-C after pre-treatment with pravastatin 40 mg only, due to the following concerns about:
- a wider indication than that approved i.e., after pre-treatment with *any other equipotent statin* in terms of 30-40% LDL-C reduction (atorvastatin 10 mg, lovastatin 40 mg, simvastatin 20-40 mg, fluvastatin 40-80 mg and rosuvastatin 5-10 mg),
- the long-term safety of the FDC. Although the choice of fenofibrate was deemed reassuring, muscular tolerability (possible additive effects with the association of a statin and a fibrate), and cardiovascular risks (uncertainty of benefit with fibrates, as compared to a high level of evidence available with statins, in high cardiovascular risk populations), were specifically questioned.
Of note, in February 2011 the CHMP granted a much broader class label to fibrates, based on the results of the ACCORD study together with fibrate trial meta-analyses in the context of an Article 31 Referral:
"In patients with mixed hyperlipidaemia at high cardiovascular risk when triglycerides and HDL-C are not adequately controlled with a statin alone" (EMA/CHMP/580013/2012).
In the perspective of the RMP (important identified and potential risks) and of the routine risk minimization, notably the first year recommended biological monitoring of CK, transaminase levels and creatinine clearance (SmPC/Patient information Leaflet), the European health authorities decided that the single

observational POSE study conceived with adequate power, would address both the safety issues and the real-life conditions of use for Pravafenix.

Key Results

The POSE study positively fulfilled the following main objectives:

1. Primary objective: the study demonstrates with robustness in real clinical practice conditions, the similitude of the incidence rate (at least one) of the main safety endpoints (i.e., the safety profile) between patients treated by Pravafenix or by a statin monotherapy at equipotent doses, as defined above (control group), during a three-year follow-up period. The global incidence was low.

2. Among various secondary objectives:

- The study reveals a low and similar incidence rate of cardiovascular events in the Pravafenix group as in the statin group over the three-year follow-up.
- POSE also provides the PRAC/CHMP and the Sponsor with relevant information about the European population currently treated with Pravafenix, i.e., the patterns of Product use:
    - Respect of indication labelling for most items in the studied population, however with significant off-label use regarding the required pre-treatment with pravastatin 40 mg,
    - Routine risk minimization adequacy (correct first-year biological monitoring, adequacy of current Product Information),
    - Opportunity for RMP update regarding missing information (long-term safety data, specific populations).

3. The safety profile was defined as the incidence rate of a composite of the main safety endpoints (renal and urinary disorders, musculoskeletal and connective tissue disorders, hepatobiliary disorders, cholelithiasis, thromboembolic events, pancreatitis, diabetes mellitus aggravated, blood homocysteine increase, interstitial pneumopathy and phototoxicity).

Primary analysis and subsequent supportive analyses

The AR of the 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 the propensity score, due to some baseline imbalances between groups, see below) RR of safety profiles over the three-year period (1.366, 95% CI [0.967; 1.929] - FAS), 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).

The incidence of each safety endpoint was low (≤1%). Most of the events occurred during the first year of follow-up, and incidence decreased regularly over time thereafter in both arms.

The results are consistent (even improved) with the one-year results assessed by the PRAC in 2021.

In each treatment group, this result is driven by a slightly higher incidence of: *"Musculoskeletal and connective tissue disorders"* (80 events, 44 in the Pravafenix group vs. 36 events in the statin group), *"Renal and urinary disorders"* (52 events, 28 vs. 24. respectively), and *"Diabetes mellitus aggravated"* (52 events, 31 vs. 21. respectively). Other components had a low global incidence (< 10 events), a single event ("*Blood homocysteine increase*"), even zero events ("*Interstitial pneumopathy*" and "*Phototoxicity*").

Concerning secondary variables

- The total number of cardiovascular events collected was low, with the AR of fatal or non-fatal cardiovascular events over the cumulative three-year period of 0.0016% (24 events reported for 22 patients) in the Pravafenix arm and 0.012% (18 events reported for 16 patients) in the statin arm.

The adjusted RR over the three-year period (1.209, 95% CI [0.596; 2.453] - FAS) confirms there is no significant difference between the treatment arms. These events were already reported in the last PSUR

(covering the period 14/04/2019-14/04/2021) and not considered by the PRAC as reflecting any deleterious signal.
- A significant off-label use ("*important potential risk*" in the RMP issued at the approval time), was observed in terms of one non-respect of the indication labelling: the criteria of pre-treatment with pravastatin 40 mg was not met in most cases (99%), although pre-treatment with another lipid-lowering agent was documented in 32.4% of the Pravafenix recipients (mainly atorvastatin 10 mg, simvastatin 20-40 mg and rosuvastatin 5-10 mg). In most cases Pravafenix was taken during the evening meal as recommended by the SmPC and the total daily dose was always respected.
- Over the first-year follow-up period, the global 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 creatinine clearance monitoring.
- 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.
- With regards to lipid laboratory parameters, 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 TG reduction and HDL-C increase in the Pravafenix group (characterized as expected, by higher/lower baseline values, respectively).
- 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 was slightly increased in the Pravafenix group compared to the statin group.
- The incidence of 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 ADRs was overall 1.4% vs. 1.1% respectively, and less than 1% for both groups at three-years. The most frequently reported 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%). The number of deaths in total was very low (N=12, 0.4%), and similarly distributed between groups.

Limitations

Conducting a non-interventional study presupposes, according to the definition of a 'non-interventional study' in the EU guideline 2001/20/EC, that the documentation plan does not dictate or prescribe on diagnosis, therapeutic decision, and follow-up. The study only observes the individual use of a drug by the treating physician in the given indication. No interventional diagnostic or monitoring procedures are applied to the patients included in the study, only those which are applied in the course of current practice. Data are collected only from routine care of patients, and as such may be subject to underreporting. Nevertheless, a risk of underreporting applies to both treatment arms to the same extent, and thus do not affect comparative results. Thus, results must be discussed notably in terms of validity (internal and external), robustness of the primary results, and generalisability.

The generalisability of the study results may be limited to the countries where the study could be conducted (mainly Greece and Spain, Portugal accounting for only five patients), due to very limited penetration of the European market (pricing issues due to generics).

Although the two treatment arms were globally well balanced notably regarding the prescribers (overall,

87% internists or cardiologists, 53.4% private practice), and patients' characteristics at baseline (overall, mean age 61.4+12.1 years, 69% at *very high* or *high* cardiovascular SCORE risk, 13.9% in secondary prevention, correct LDL-C control and other risk factor control i.e., hypertension and diabetes), few imbalances were observed regarding the baseline characteristics of the Pravafenix arm: a higher prevalence of some major cardiovascular risk factors was reported i.e., men (59.4% vs. 50.1% in statin group), diabetes mellitus (52.8% vs. 44.4%, respectively), with these items reflecting mixed dyslipidaemia features. Also, almost twice as many patients in the Pravafenix group had received a previous lipid lowering agent compared to the statin group (global 32.4% vs. 15.2%, respectively), in reference to Product labelling (second-line indication reserved to Pravafenix).

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 in this final report, due to a difference in inclusion criteria (pre-treatment of 6-12 months with Pravafenix mandatory for Spain for this arm), that may have impacted results. The comparison between patients recruited in Greece and patients recruited in Spain showed consistency in most items, showing internal validation, with the following exceptions of the Spanish sub-population being 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 (but not pravastatin 40 mg) was observed in the Pravafenix arm compared to the statin arm (57.9% vs. 25.2%).

The number of safety endpoints (overall, 177 events) and fatal/non-fatal cardiovascular events (overall, 42 events) reported in the study can be considered as too low to draw any robust conclusion. Regarding the secondary endpoints, the Cox proportional hazard analysis and associated figures may have been impacted by the low incidence rates observed on-study.

Interpretation

In the Pravafenix subpopulation, conformity to the indication labelling can be considered acceptable regarding dietary restrictions (97.6%) and non-sedentary lifestyle (49.9%); mixed dyslipidaemia features (prevalence of men and associated diabetes, biological profile i.e., baseline high TG and low HDL-C values); cardiovascular risk level (*high* or even *very high* in 71.2% of cases) characterizing patients. Considering the mean baseline values of key risk factors (lipids, blood pressure, glucose) and the high prevalence (71.7% out of the patients were taking cardiovascular and blood glucose control therapies), together with the statin component of Pravafenix and the statin constituting the control group, the POSE population was deemed correctly treated.

To account for the above-noted slight imbalances between groups, propensity analyses based on all potential confounding factors were conducted including some baseline characteristics, and region (Greece plus Portugal vs. Spain as recruitment in Portugal too low for a meaningful comparison). Hence the comparability of the treatment arms was assured. Both unadjusted (not considering propensity analysis) and adjusted (considering propensity analysis) results showed numerical similarity. The change in inclusion criteria for Spain in comparison to Greece and Portugal was also not judged to have any impact on the findings. This statistical approach additionally supports the main study results.

With respect to sample size adequacy, the 1-year follow-up PRAC Assessment Report was based on the number of events qualifying the primary endpoint, and the table of probability provided by the MAH, i.e.:

- low total number of events (overall, 84 events at 1 year, 0.068%), but higher than expected (overall, 60 events over 3 years),
- greater similarity of proportion of patients experiencing at least one event more in both arms (0.036% for the Pravafenix group vs. 0.025% for the control group) than initially predicted (0.040 vs. 0.020, respectively).

The total initial sample size of 3000 patients was then confirmed by the PRAC. The power of detecting at least one of the safety profile events, was estimated to be superior to 99% in both arms.

Based on the final data (confirming the low global incidence of events, and the rate similarity in both groups), the primary analyses over three years including sensitivity analyses, confirm with robustness that with the above statistical approach, there is no clinically relevant difference between the two arms.
With respect to individual components of the primary endpoint, given the specificities of Pravafenix:
- dual therapy exposing patients to an increased muscular risk and a higher rate of aggravated diabetes due to baseline diabetes often associated to mixed dyslipidaemia,
- fibrate component exposing to creatinine increases, it is likely that this explains why these incidences were slightly higher in the Pravafenix group than in the control group. Nonetheless, their clinical acceptability is correct, with respect to benefits observed with the FDC, in high cardiovascular risk population.
The study was neither powered nor designed to compare cardiovascular effects of Pravafenix versus a statin alone and thus the results can only be descriptive. The total number of cardiovascular events collected during three years of treatment was low, as observed during the clinical development of Pravafenix. The low incidences of fatal and non-fatal cardiovascular events for both groups are consistent with the data from the pooled safety analysis performed for Pravafenix registration, where 14 non-fatal cardiovascular events (0.89%) were reported in the Pravafenix group after one year of follow up.
Overall, the low number of safety endpoints (including muscular endpoints) and fatal and non-fatal cardiovascular CV events reported in the POSE study is in line with the data coming from the pooled safety analysis performed for the Pravafenix registration and with the data coming from other observational studies from the literature with statins and fibrates. Overall, although the results of the presented analysis should be interpreted with caution implied by the nature of the observational study and the limitations as described above, they are reassuring and suggest similar long-term safety profile in both treatment regimens, as observed in routine clinical practice.
The global rate of compliance to the recommended biological recommendations (CK, renal, and transaminase monitoring) over the first-year follow-up period, as recommended in SmPC, is adequate.
Overall, the safety information of SmPC seems appropriate. More specifically:
- Muscular risk:
The greatest impediment in combining a fibrate with a statin is the potential risk of myopathy and rhabdomyolysis. The POSE data show the good muscular tolerability of the FDC, in line with the ESC 2019 guidelines considerations: "*there is no or very little increased risk for myopathy when combining statins with other fibrates, such as fenofibrate, bezafibrate, or ciprofibrate" Both fibrates and statins have been reported to cause myopathy and rhabdomyolysis. However, there are differences in myopathy risk between fibrates. In combination with a statin, rhabdomyolysis has been reported to be 15-fold and 33-fold higher with gemfibrozil than with fenofibrate, due to different pharmacokinetic interactions*.
The SmPC adequately addresses this risk as a personal history of myopathy and/or rhabdomyolysis with statins and/or fibrates or confirmed CK elevation above five times the ULN under previous statin treatment, constitute contra-indications to Pravafenix.
- Other risks (renal/hepatic/venous thromboembolic):
Globally, there was no significant differences regarding the risk of developing biological laboratory abnormalities between treatment arms except for creatinine, alanine aminotransferase and homocysteine. The relative risks RR for these laboratory abnormalities were slightly increased in the Pravafenix group compared to the statin group. These observations were expected according to the SmPC recommending (Section 4.4 in SmPC, Document 1 in Annex 2) regular monitoring of creatinine clearance and transaminases levels during the first year and beyond if necessary, and precaution in the event of a history of pulmonary embolism (although the link with increased homocystein levels under fibrates therapy and venous thrombotic events is not established).
The ESC/EAS guidelines state that as a class, fibrates have been reported to raise serum creatinine in both short- and long-term studies. *This increase seems to be fully reversible when the drug is stopped. Data from meta-analyses suggest that a reduction of calculated glomerular filtration rate does not reflect any adverse effects on kidney function*.

Moderate to severe renal impairment is a contraindication of Pravafenix, in relation to serum creatinine increase with fibrates.
With respect to hepatic tolerability, the impact of both classes (statins, fibrates) on moderate increase in transaminase levels is well known, with the majority returning to their baseline values without the need for treatment discontinuation.
Severe hepatic impairment including biliary cirrhosis or active liver disease including unexplained persistent elevations in liver function tests (including serum transaminase elevation) exceeding 3 x ULN, are also contraindications to Pravafenix.
Regarding the off-label use, the restricted indication granted in 2011 may have itself generated this outcome. The POSE study revealed that the "important potential" risk was indeed an "identified" one regarding the pre-treatment requirement. The most likely explanation is that therapeutic guidelines may recommend a more aggressive strategy to control LDL-C in (*very) high*-risk patients than pravastatin 40 mg. Pravastatin was one of the first statins available on the market with a huge post-marketing experience, and a high level of clinical evidence at 40 mg per day. It was thus chosen as the statin component during early clinical development but is less and less prescribed.
It is however important to note that despite this off-label use, no negative impact was observed in the Pravafenix group, with regards to:
- **the biological efficacy of Pravafenix on lipids**, including LDL-C control after one-year follow-up (mean 3.27+1.15 mmol/L Pravafenix group vs. 3.57+1.11 mmol/L control group) and over three years (mean 2.35+0.67 vs. 2.41+0.70 mmol/L, respectively). There was no loss of opportunity for patients switched to Pravafenix, irrespective of the equipotent statin prescribed before initiation,
- **the safety profile of Pravafenix,** as acknowledged by PRAC in 2021.

Generalisability
Special attention was paid by the CRO to the selection of sites, despite significant difficulties:
- Among the 922 sites contacted, 315 sites (34%) responded but 97 (31%) refused to participate. The response rate was lower than expected and the selection process was therefore extended to reach the needed number of sites. The feasibility questionnaire was translated in Spanish with the aim to facilitate the completion for the Spanish sites. The non-responding sites were contacted by e-mail and phone periodically (weekly/biweekly) for three consecutive months after the initial contact to maximize the possibility of responses being received. If after three months of contact attempts the site had neither completed a questionnaire nor formally declined, then attempts were ceased, and the site moved to the non-responder category permanently. Two years were ultimately needed to select the targeted number of sites (from June 2016 to May 2018).
- The Greek sites were proportionally more interested by participation than Spanish and Portuguese sites. The lack of experience in observational studies, the limited resources for administrative assistance of the sites and/or the competing studies made the patient recruitment challenging and 2.5 years were needed to recruit the targeted number of patients. For Greece and Portugal (more flexible as allowing new initiations of treatment with Pravafenix): patients who had initiated Pravafenix over the last year or were intended to be treated at the time of inclusion in the study were eligible for study participation. For Spain (more constraining): only patients treated with Pravafenix for at least 6 months and no more than 12 months were eligible for study participation.
With 61 screening failures, a total of 3075 patients had a documented baseline visit and comprised the SAF (1546 and 1529 patients, respectively). The data collected for these 61 cases established that the characteristics of the patients who did not participate in the study were comparable to those of the patients who were enrolled (i.e., no selection bias).
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. Given the observational methodology of the study, the rate of completion seems satisfactory.

In addition to long-term safety data, the study allowed the study of populations of interest, for whom information was missing at the time of approval: very elderly patients (> 75 years, 169 patients in the Pravafenix group), diabetic patients requiring insulin or analogues, patients with presence of established cardiovascular disease before the start of the trial.
Finally, as assessed by the PRAC in its one-year interim Assessment Report (2021) the comparisons between the POSE study cohorts and relevant cohorts from published studies could be considered as acceptable and the results suggested external validation of the POSE study population, notably:
- the POSE statin group had similar characteristics to those of the DYSIS Spain [47] and Portugal [48] cohorts: in the two latter studies, male patients were very slightly predominant (52.7% and 52.9% vs. 50% in POSE statin arm), type 2 diabetes accounted for 39% and 38% vs. 40.4% respectively, and a majority (71.2% and 66.7% vs. 68.6%) of high cardiovascular risk patients were studied.
- Also suggesting external validity for the Pravafenix group, were the characterization of a high proportion of patients with diabetes and/or metabolic syndrome, the POSE Pravafenix group had overall similar characteristics to those with type 2 diabetes and/or metabolic syndrome of the DYSIS cohorts [49], notably for age, male predominance, sedentary lifestyle, BMI, and the proportion of high cardiovascular risk.

clinical safety

Primary analysis and subsequent supportive analyses

The AR of the 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 the propensity score, due to some baseline imbalances between groups, see below) RR of safety profiles over the three-year period (1.366, 95% CI [0.967; 1.929] - FAS), showing that there is no significant difference between treatment arms. All sensitivity analyses confirmed this result.

The incidence of each safety endpoint was low (≤1%). Most of the events occurred during the first year of follow-up, and incidence decreased regularly over time thereafter in both arms.

The results are consistent (even improved) with the one-year results assessed by the PRAC in 2021.

In each treatment group, this result is driven by a slightly higher incidence of: *"Musculoskeletal and connective tissue disorders"* (80 events, 44 in the Pravafenix group vs. 36 events in the statin group), *"Renal and urinary disorders"* (52 events, 28 vs. 24. respectively), and *"Diabetes mellitus aggravated"* (52 events, 31 vs. 21. respectively). Other components had a low global incidence (< 10 events), a single event ("*Blood homocysteine increase*"), even zero events ("*Interstitial pneumopathy*" and "*Phototoxicity*").

Concerning secondary variables

- The total number of cardiovascular events collected was low, with the AR of fatal or non-fatal cardiovascular events over the cumulative three-year period of 0.0016% (24 events reported for 22 patients) in the Pravafenix arm and 0.012% (18 events reported for 16 patients) in the statin arm.
The adjusted RR over the three-year period (1.209, 95% CI [0.596; 2.453] - FAS) confirms there is no significant difference between the treatment arms. These events were already reported in a previous PSUR (covering the period 14/04/2019-14/04/2021) and not considered by the PRAC as reflecting any deleterious signal.

- A significant off-label use was observed in terms of one non-respect of the indication labelling: the criteria of pre-treatment with pravastatin 40 mg were not met in most cases (99%), although pre-treatment with another lipid-lowering agent was documented in 32.4% of the Pravafenix recipients (mainly atorvastatin 10 mg, simvastatin 20-40 mg and rosuvastatin 5-10 mg). In most cases Pravafenix was taken during the evening meal as recommended by the SmPC and the total daily dose was always respected.

- Over the first-year follow-up period, the global 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 creatinine clearance monitoring.

- 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.

- With regards to lipid laboratory parameters, 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 TG reduction and HDL-C increase in the Pravafenix group (characterized as expected, by higher/lower baseline values, respectively).

- 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 was slightly increased in the Pravafenix group compared to the statin group.

- The incidence of 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 ADRs was overall 1.4% vs. 1.1% respectively, and less than 1% for both groups at three-years. The most frequently reported 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%). The number of deaths in total was very low (N=12, 0.4%), and similarly distributed between groups.

The safety profile of Pravafenix does not change with the new proposed indication compared to the current indication. No changes to section 4.8 of the SmPC are required.

2.4.4. Conclusions on the clinical data

Whereas most indication criteria were met in the studied population, there was a significant off-label use regarding the required pre-treatment with pravastatin 40 mg, the POSE study revealed that the "Important potential" risk was an "identified" one regarding this requirement. It is likely that therapeutic guidelines may recommend a more aggressive strategy to control LDL-C in (very) high-risk patients than pravastatin 40 mg.
The subgroup of the very elderly in POSE was sufficiently represented to allow a descriptive comparative approach between both therapeutic regimens (Pravafenix and statin monotherapy).
The two treatment arms were well-balanced regarding most patient characteristics at baseline. The few exceptions in the Pravafenix group were a slightly higher proportion of women, of the major CV risk (HTA and DM), and of cerebrovascular disease history, whereas CHD history was predominant in the statin group. Overall, 31.0% of patients had established CVD reflecting a secondary-prevention population, nearly the double than the overall population (13.9%) due to age. Hence, this subpopulation was at much higher CV SCORE risk (approximately the double), than the overall population and 96.3% of the patients were classified as at very high/high CV risk level, compared to 69.7% in the overall population, similarly distributed between treatment groups. Overall, the new safety data from POSE allowing to propose an

amendment to the RMP for the subpopulation aged 75 years and above. The mention to the very elderly is proposed to be deleted in § Posology and Method of administration, §§ Special populations.

Overall, in both treatment arms, 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 in patients from both arms. The AR of abnormalities in lipid parameters decreased over the follow-up period in both arms.

Of note, although supportive, data from the FENOPRA-III-05-1 Phase 3 clinical study conceived in a more pragmatic approach, and from the POSE study bring valuable information to Pravafenix effects in various switch conditions, in a second-line perspective (add-on indication) in mixed dyslipidaemia insufficiently controlled with statin monotherapy, in accordance with the current therapeutic guidance.
After switching mostly from atorvastatin 10-20 mg or simvastatin 20-40 mg (FENOPRA III-05-1), the stability of LDL-C and the additional benefit of fenofibrate on non-HDL-C were shown over 24 weeks.
After predominant switching from atorvastatin 10-20 mg and simvastatin 20-40 mg to a less extent, from rosuvastatin 5-10 mg (POSE), there was a steady reduction in the levels of non-HDL, LDL-C, TG, and a concomitant rise in the levels of HDL-C from baseline to the three-year follow-up.

Despite the off-label use, no negative impact was observed in the Pravafenix group with regards to its biological efficacy on lipids. The evolution in the Pravafenix group paralleled that of the control group (mainly treated with atorvastatin 10 mg, to a less extent with rosuvastatin 5-10 mg, and simvastatin 20-40 mg), notably for mean LDL-C, without loss of opportunity in most patients. Individual variability in the response (outliers) can be managed by physicians (Pravafenix SmPC).

Overall, the low number of safety endpoints (including muscular endpoints) and fatal and nonfatal CV events reported in the POSE study is in line with the data coming from the pooled safety analysis performed for the Pravafenix registration and with the data coming from other observational studies from the literature with statins and fibrates. Although the POSE results should be interpreted with caution implied by the nature of the observational study and the limitations above, they are reassuring and suggest similar long-term safety profile in both treatment regimens (Pravafenix and control statin), as observed in routine clinical practice.

With respect to primary individual components, given Product specificities:

- the fibrate/statin dual therapy exposing to an increased muscular risk and to a higher rate of aggravated DM due to pre-existing DM often associated to mixed dyslipidaemia,

- the fibrate component exposing to a creatinine increase risk, it is likely that these incidences were slightly higher in the Pravafenix group than in the control group. Nonetheless, their clinical acceptability is satisfactory with respect to benefits observed with the FDC, in high CV risk population.

Regarding the muscular and renal risks, the 2019 ESC/EAS guidelines remind that:

- "There is no or very little increased risk for myopathy when combining statins with other fibrates, such as fenofibrate, bezafibrate, or ciprofibrate. Both fibrates and statins have been reported to cause myopathy and rhabdomyolysis. However, there are differences in myopathy risk between fibrates. In combination with a statin, rhabdomyolysis has been reported to be 15-fold and 33-fold higher with gemfibrozil than with fenofibrate, due to different pharmacokinetic interaction";

- the clinical relevance of crCL decrease under fibrate therapy is not established (Pravafenix SmPC, § 4.4).

The safety profile with the new indication confirms the profile from previous approved indication. No changes to section 4.8 of the SmPC are required.

2.4.5. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.5. Risk management plan

The MAH submitted an updated RMP version 4.1 in the first submission for this application (DLP by 12/07/23 and dated 27/11/2023) in order to incorporate the safety signals detected from the post authorization safety study (Pravafenix Observational Study in Europe, POSE study) and the results from PSURs from 2015 to 2023. The initial proposals from the MAH included the change of indication in line with the extension of indication, the compliance with the new GVP template (EMA/164014/2018 Rev.2.0.1), the addition of 2 important potential risks (*Muscle rupture* and *Bullous pemphigoid)* and 1 missing information (*Fertility, pregnancy, and lactation*), the removal of 3 safety concerns (*Off-label use, Patients above the age of 75 years, Long-term safety profile of the product*) and the incorporation of Increased risk of myopathy, Increased risk of hepatic events and Increased risk of pancreatic events into pre-existing safety concerns.

After the assessment, the lack of compliance of the proposed version of the RMP to the revised GVP template was acknowledged, considering that no additional Pharmacovigilance activity or additional risk minimization measure was undertaken and included in the RMP, the MAH provided a new version of the document by removing all the important potential or identified risks and the missing information form the list of safety concerns.

Therefore the latest version agreed upon is version 4.3, dated 1st July 2024 and with a DLP by 26 June 2024. The safety concerns were removed from the RMP as follows:

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

The whole RMP has been updated according to these changes and in line with the new template (EMA/164014/2018 Rev.2.0.1). The whole document clearly differentiates the previously existing safety concerns as well as the terminated additional pharmacovigilance activity (POSE study) and the new information on the absence of safety concerns and absence of additional pharmacovigilance or risk minimisation activity.

Following the initial assessment regarding the RMP, the MAH provided an updated version in line with the GVP V template and therefore without any important identified or potential risks and without missing information in the list of safety concerns. Considering the approvable responses of the MAH (please see Annex V):

☒The changes to the RMP are acceptable.

2.6. Update of the Product information

As a result of this variation, sections 4.1 and 4.2 of the SmPC are updated.

The Package Leaflet (PL) is updated accordingly.

2.6.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

"The change is to broad the indication to other statins and not only to pravastatin as previously authorised by EMA. So, the indication and population remain the same. The change has no major impact on the leaflet, it remains legible, clear and easy to use and so, new study was not conducted by the applicant".

3. Benefit-Risk Balance

As noted above, this variation aims to broaden the therapeutic indication of PRAVAFENIX, in accordance with PRAVAFENIX use in real life and in the perspective of the fibrates referral.

The clinical data that support the claimed extension and based on a non-interventional PASS: POSE (Pravafenix Observational Study in Europe) has already been subject of assessment and discussion in the PASS/PSUSA (Procedure No. EMEA/H/C/001243/II/0034) procedure. As a conclusion, a submission of a type II variation to broaden the Pravafenix indication, in accordance with Pravafenix use in real life and in the perspective of the fibrates referral has been requested. The current variation corresponds to the PSUSA request. Moreover, an update of the RMP, together with next PSUR submission (covering the period: 14/04/2021 to 14/04/2023) has also been requested. Current risk minimisation measures as recommended in SmPC seem appropriate.

3.1. Therapeutic Context

Pravafenix is a fixed dose combination (FDC) of the fibric acid derivative (fibrate) fenofibrate and the 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) pravastatin.

Based on several Phase I/III clinical studies and supportive published documentation regarding authorized active substances (Article 10(b) of 2001/83/EC-FDC application), the Marketing Authorization Holder (MAH), Laboratoires SMB SA, obtained a positive opinion from the Committee for Medicinal Products for Human Use (CHMP), with the granting of a Marketing Authorization (MA) for the fenofibrate 160 mg/pravastatin 40 mg FDC on April 14th, 2011 (European Decision). The recommended dose is one capsule per day during the evening meal.

Eligibility for initiating Pravafenix was part of the CHMP discussion, i.e., should LDL-C levels be adequately controlled using treatment with pravastatin 40 mg monotherapy, or an equivalent statin monotherapy regimen based on NCEP-ATP III guidelines (Grundy et al, 2004).

The approved restricted indication was based on discussions about equipotency between statins and long-term safety concerns with the FDC, notably regarding muscular and cardiovascular (CV) risks (EPAR-EMEA/H/C/001243).

Nevertheless, an off-label use, notably as second-line therapy to patients who have not responded adequately to treatment with other statins (not pravastatin 40 mg), was defined as an important potential risk of the European Risk Management Plan (RMP). This was to be addressed through routine pharmacovigilance and initially, through a Drug Utilization Study (DUS) requested in the RMP.

Consequently, the requested measures were addressed in one cohort-comparative study, the POSE study, with a three-year follow-up.

3.1.1. Main clinical studies

Non-interventional Post-Authorisation Safety Study (PASS): the POSE (Pravafenix Observational Study in Europe) study

This was a multicentric, European, partly retrospective and prospective observational cohort study with a three-year follow-up, in patients treated with pravastatin 40 mg/fenofibrate 160 mg (Pravafenix) or with a statin used at standard stable dose in monotherapy followed by general practitioners (GPs), cardiologists, endocrinologists, internists in hospital-based or private practice in three European countries (Greece, Portugal and Spain).

This observational study did not induce any extra visits or specific exams for the patient, nor any specific treatments or interventions. Physicians were not required to change their usual practice in treating patients. Also, the study did not impose time windows between each visit, because this is a real-life post-marketing study.

This investigation took place in real clinical practice conditions. The recruitment started on December 2016 and ended in July 2019. The recruitment period was extended twice until the enrolment target of 3000 was reached. Information was collected retrospectively for data obtained before the patient inclusion and prospectively for data obtained after inclusion over a three-year follow-up period. The patient's allocation in a particular therapeutic strategy was not decided by the study protocol but it was determined by the medical routine practice. In addition, the decision to prescribe a particular medication was clearly dissociated of the decision to include that patient in the study. No intervention (diagnostic or follow up) which was not a routine clinical practice was performed to the patients, and epidemiologic methods for the analysis of collected data was applied.

This open label study included one interim analysis after one year of follow-up completed for all patients and one final analysis after three years of follow-up.

3.2. Favourable effects

The primary objective of this observational study was to estimate the hazard ratio for the main safety endpoints between patients treated by Pravafenix or by a statin in monotherapy in real clinical practice conditions of prescription within a 3-year follow up period.

The POSE study positively fulfilled the following main objectives:

1. Primary objective: the study demonstrates with robustness in real clinical practice conditions, the similitude of the incidence rate (at least one) of the main safety endpoints (i.e., the safety profile3) between patients treated by Pravafenix or by a statin monotherapy at equipotent doses, as defined above (control group), during a three-year follow-up period. The global incidence was low.

2. Among various secondary objectives:

- The study reveals a low and similar incidence rate of cardiovascular events in the Pravafenix group as in the statin group over the three-year follow-up.

- POSE also provides the PRAC/CHMP and the Sponsor with relevant information about the European population currently treated with Pravafenix, i.e., the patterns of Product use.

The subgroup of the very elderly in POSE was sufficiently represented to allow a descriptive comparative approach between both therapeutic regimens (FDC and statin monotherapy).

The results of the analysis are considered sufficient to support the safety use of Pravafenix in patients 75-year-old aged or above. Along with the analysis of the main cohort, this 3-year long follow-up study supports the long-term safety use profile of the product. Of note, in most cases Pravafenix was taken during the evening meal as recommended by the SmPC and that the total daily dose was always respected.

With respect to initial hypotheses, the total number of events required to achieve the predefined power (N=60) was largely exceeded (N=177); also, were the anticipated proportions (0.040 for Pravafenix vs. 0.020 for the control group) of subjects having the event during the study (0.068 vs.0.051, absolute difference of 0.017 instead of 0.02 protocol assumption, and 0.01 in the interim analysis). Hence robustness of the primary result within 3 years is established, reflecting that, above statistical approach, there is no clinically relevant difference between both arms.

The AR of safety profiles over the cumulative three-year period was 0.068 (N= 101) in the Pravafenix arm and 0.051 (n = 76) in the statin arm. The adjusted (accounting for propensity score) RR of safety profiles over the three-year period (1.366) with its 95% confidence interval spanning 1 (0.967; 1.929) confirms there is no significant differences between both treatment arms.

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

The incidence of each safety endpoint was low (≤1%). Most of the events occurred during the first year of follow-up, and incidence decreased regularly over time thereafter in both arms. In the Pravafenix arm, the AR of renal and urinary disorders, musculoskeletal and connective tissue disorders, hepatobiliary disorders, cholelithiasis, thromboembolic events, pancreatitis, diabetes mellitus aggravated, blood homocysteine increase, interstitial pneumopathy and phototoxicity disorders were similar between both groups without negative tendency for the Pravafenix arm.

The total number of cardiovascular events collected was low, with the AR of fatal or non-fatal cardiovascular events over the cumulative three-year period of 0.0016% (24 events reported for 22 patients) in the Pravafenix arm and 0.012% (18 events reported for 16 patients) in the statin arm.

The adjusted RR over the three-year period (1.209, 95% CI [0.596; 2.453] - FAS) confirms there is no significant difference between the treatment arms. These events were already reported in the last PSUR (covering the period 14/04/2019-14/04/2021) and not considered by the PRAC as reflecting any deleterious signal.

A significant off-label use ("important potential risk" in the RMP issued at the approval time), was observed in terms of one non-respect of the indication labelling: the criteria of pre-treatment with pravastatin 40 mg was not met in most cases (99%), although pre-treatment with another lipid-lowering agent was documented in 32.4% of the Pravafenix recipients (mainly atorvastatin 10 mg, simvastatin 20-40 mg and rosuvastatin 5-10 mg). In most cases Pravafenix was taken during the evening meal as recommended by the SmPC and the total daily dose was always respected.

The rate of study completion (82.5%) over the 3-yr follow up was consistent with the interim 1- year analysis, which reported: "4.5% of the overall patients discontinued the study; 4.8% patients from the Pravafenix and 4.1% from the statin arm. The main reasons for discontinuation were 'Lost to follow-up' (1.4%) and 'Other' (1.4%)".

3.3. Uncertainties and limitations about favourable effects

Conducting a non-interventional study presupposes, according to the definition of a 'non-interventional study' in the EU guideline 2001/20/EC, that the documentation plan does not dictate or prescribe on diagnosis, therapeutic decision, and follow-up. The study only observes the individual use of a drug by the treating physician in the given indication. No interventional diagnostic or monitoring procedures are applied to the patients included in the study, only those which are applied in the course of current practice. Data are collected only from routine care of patients, and as such may be subject to underreporting. Nevertheless, a risk of underreporting applies to both treatment arms to the same extent, and thus do not affect comparative results. Thus, results must be discussed notably in terms of validity (internal and external), robustness of the primary results, and generalisability.

The generalisability of the study results may be limited to the countries where the study could be conducted (mainly Greece and Spain, Portugal accounting for only five patients), due to very limited penetration of the European market (pricing issues due to generics).

Although the two treatment arms were globally well balanced notably regarding the prescribers (overall, 87% internists or cardiologists, 53.4% private practice), and patients' characteristics at baseline (overall, mean age 61.4+12.1 years, 69% at very high or high cardiovascular SCORE risk, 13.9% in secondary prevention, correct LDL-C control and other risk factor control i.e., hypertension and diabetes), few imbalances were observed regarding the baseline characteristics of the Pravafenix arm: a higher prevalence of some major cardiovascular risk factors was reported i.e., men (59.4% vs. 50.1% in statin group), diabetes mellitus (52.8% vs. 44.4%, respectively), with these items reflecting mixed dyslipidaemia features. Also, almost twice as many patients in the Pravafenix group had received a previous lipid lowering agent compared to the statin group (global 32.4% vs. 15.2%, respectively), in reference to Product labelling (second-line indication reserved to Pravafenix).

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 in this final report, due to a difference in inclusion criteria (pre-treatment of 6-12 months with Pravafenix mandatory for Spain for this arm), that may have impacted results. The comparison between patients recruited in Greece and patients recruited in Spain showed consistency in most items, showing internal validation, with the following exceptions of the Spanish sub-population being 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 (but not pravastatin 40 mg) was observed in the Pravafenix arm compared to the statin arm (57.9% vs. 25.2%).

The number of safety endpoints (overall, 177 events) and fatal/non-fatal cardiovascular events (overall, 42 events) reported in the study can be considered as too low to draw any robust conclusion. Regarding the secondary endpoints, the Cox proportional hazard analysis and associated figures may have been impacted by the low incidence rates observed on-study.

3.4. Unfavourable effects

The global incidence of safety endpoints was low: N=35 events, 20 in the Pravafenix arm and 15 in the statin arm.

In each treatment group, the primary result was driven by a higher incidence of "Renal and urinary disorders" (10 events under Pravafenix therapy vs. 2 events in the statin group), "Diabetes mellitus

aggravated" (4 vs. 7 events, respectively) and "Musculoskeletal and connective tissue disorders" (4 events in each arm).

Other components had either a very low incidence: one "thrombo-embolic event" per group (namely an "acute ischemia in low member") and one "hepatobiliary disorder" ("gallbladder polyp") in the Pravafenix arm, or no event ("Pancreatitis", "Blood homocysteine increase", "Interstitial pneumopathy" and "Phototoxicity").

Except one case of End Stage Renal Disease assessed as "not related" (investigator) due to advanced DM, but "Possible" (WHO) as Pravafenix may have contributed to the event, not described in Pravafenix safety profile, other PTs i.e., glomerular filtration rate (GFR) decrease (2), renal impairment (1) or renal failure (1), are described.

3.5. Uncertainties and limitations about unfavourable effects

The slight numerical imbalance in the Pravafenix arm does not reflect any new signal in this subpopulation and Information about renal risk seems appropriately addressed in the SmPC, with adequate minimization measures, especially in the elderly/very elderly.

3.6. Benefit-risk assessment and discussion

The estimated hazard ratio for the main safety endpoints between patients treated by Pravafenix or by a statin in monotherapy in real clinical practice conditions of prescription within a 3-year follow up period has been positively fulfilled by the POSE study results. The study demonstrates with robustness in real clinical practice conditions, the similitude of the incidence rate (at least one) of the main safety endpoints (i.e., the safety profile) between patients treated by Pravafenix or by a statin monotherapy at equipotent doses, as defined above (control group), during a three-year follow-up period. The global incidence was low. Moreover, the study reveals a low and similar incidence rate of cardiovascular events in the Pravafenix group as in the statin group over the three-year follow-up. Indeed, the safety profile of Pravafenix does not change with the new proposed indication compared to the current indication. No changes to section 4.8 of the SmPC are required.

3.6.1. Additional considerations on the benefit-risk balance

The claimed extension is also supported by:

- the Referral decision regarding fenofibrate Indication labelling (based on the ACCORD-LIPID trial having used simvastatin 20-40 mg, considered equipotent to pravastatin 40 mg) and, to some extent, the Vazkepa regulatory precedent in a similar setting.

- the regulatory guidance: "Wording of therapeutic indication. A Guide for Assessors of Centralised Applications" (EMA/CHMP/483022/2019), stating: "The target population should be well defined and recognized in clinical practice;"

- the European therapeutic guidelines in force specifying the right place of fibrate/statin combinations in clinical practice and the classification of statin intensity (molecules and doses).

- the control group definition in the POSE study (assessing the conditions of use of Pravafenix in real life), approved by European health authorities: statin-dose regimens equivalent to pravastatin 40 mg based on Northern American guidelines.

3.7. Conclusions

Considering the POSE results showing switch conditions to Pravafenix at baseline (not limited to pravastatin 40 mg), with a significant off-label use pointed out by the PRAC, a positive CHMP opinion for a broader indication claim which was issued on 08/2023; the POSE results providing relevant long-term safety information, and the significant worldwide post-Authorization experience with Pravafenix shows a stable satisfactory safety profile.

The overall B/R of Pravafenix is considered positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of mixed hyperlipidaemia in adult patients while on a treatment with pravastatin 40 mg monotherapy or on another moderate-intensity statin regimen for PRAVAFENIX, based on final results from the non-interventional PASS: POSE (Pravafenix Observational Study in Europe); this is 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. As a consequence, sections 4.1 and 4.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.3 of the RMP has also been submitted.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.