1. ABSTRACT

- **Title**

Observational Serial Chart Review of Repatha® Use in European Subjects With Hyperlipidaemia

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- **Keywords**

Evolocumab, hyperlipidaemia, familial hypercholesterolaemia, LDL-C, lipid-modifying therapy

- **Rationale and Background**

Globally, cardiovascular disease (CVD) is the leading contributor to total disease burden and the leading cause of death. In 2019, the global prevalence of CVD was 523 million cases, with an estimated 18.6 million deaths; of which the majority were due to ischemic heart disease (9.14 million) or stroke (6.55 million). Elevated cholesterol is among the leading risk factors for cardiovascular (CV) deaths (Roth et al, 2020).

The rationale for treatment of dyslipidaemia derives from extensive clinical trial data which demonstrate that the reduction in total cholesterol, non-high-density lipoprotein cholesterol (-HDL-C), and most importantly, low-density lipoprotein cholesterol (LDL-C) through pharmacological therapies lowers the risk of CVD events (Kannel et al, 1974; Kannel, 1995; Kannel et al, 1979). A Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis (CTT, 2010) which included 21 randomised controlled trials involving nearly 170,000 patients showed that every 1 mmol/L (equivalent to 39 mg/dL) reduction of LDL-C resulted in a 20% reduction in the risk of major vascular events (coronary death, non-fatal myocardial infarction, coronary revascularisation, or stroke).

The joint European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines, issued in 2016 (Catapano et al, 2016) and revised in 2019 (Mach et al, 2020), recommend statins as first-line pharmacotherapy to lower LDL-C and reduce CV risk. The guidelines recommend risk-based LDL-C goals and optimized LDL-C reduction by improving uptake of high-intensity statins. Recent observational studies, however, suggest that challenges remain in the implementation of the guidelines (Ray et al 2021a, Ray et al, 2021b). Some groups (Ray et al, 2021b) suggest that even with optimised statins, greater utilization of non-statin lipid-lowering therapy (LLT)/lipid-modifying therapy (LMT) may be needed to achieve goals in patients at highest risk.

Repatha® (evolocumab), a fully human monoclonal IgG2 antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9), inhibits circulating PCSK9 from binding to the low-density lipoprotein receptor (LDLR) in the liver, thus preventing PCSK9-mediated LDLR degradation. This in turn increases liver LDLR levels, resulting in reductions in serum LDL-C.

Repatha® is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet, in combination with a statin or statin with other LLTs in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. EMA approval (granted on 17th July 2015) was based on an extensive interventional clinical trial programme. More recently, the 27,564-patient FOURIER trial which evaluated LDL-C levels, reported a 20% relative risk reduction in major adverse cardiac events in subjects with established atherosclerotic disease given evolocumab compared

to those on optimised oral lipid lowering therapy. However, at present there is little information describing Repatha® use in a real-world setting.

Local health authorities across Europe require real-world evidence on product use in routine clinical practice for continuation and/or reassessment of access. Data from this study are intended to fulfil health authorities' requirements and to provide a robust source of published information for physicians. The study was conducted only in countries which require real-world data to be collected in the post-launch setting, and where local regulations allowed the study of use of a single treatment in clinical practice.

- **Research Question and Objectives**

Research Question

What are the clinical characteristics of patients prescribed Repatha® in the post-launch period, and how is their treatment managed?

Primary Objective

To describe the clinical characteristics of subjects at initiation of Repatha®

Secondary Objectives

- To describe LDL-C and other cholesterol concentrations over time
- To describe treatment patterns of use of Repatha® over time
- To describe treatment patterns of use of other lipid-modifying therapies over time
- To describe health resource utilisation components, including hospitalisations and physician visits

Exploratory Objective

To evaluate incidence of LDL-C below 55 mg/dL (below 1.4 mmol/L).

- **Study Design**

This non-interventional, observational cohort study used serial chart review of patients receiving Repatha® (as part of routine clinical management of their hyperlipidaemia) in 12 countries across Europe, to capture data on clinical parameters relevant to health authorities and physicians. The study did not alter the clinical management of patients.

Subject data were captured for up to 36 months (up to 6 months pre-initiation of Repatha® and up to 30 months follow-up post-initiation of Repatha®). The study period extended from February 2015 (which includes the 6-month period prior to the earliest possible prescription of commercial Repatha®) to June 2021.

The *baseline period* ran from the 6 months prior to the first dose of Repatha® through to the date of administration of the first dose of Repatha®. Therefore, the end of the baseline period coincided with the first dose of Repatha®.

The *study follow-up period* for each subject was 30 months after date of first administration of Repatha®, death, withdrawal of consent or loss to follow-up (whichever occurred earliest). Subjects were followed regardless of continuation/discontinuation of Repatha®, including for subjects who received only one dose of Repatha®.

- **Setting**

One hundred and seventy-nine specialist sites (i.e., which treated patients at high or very high risk of experiencing a CV event, including but not limited to familial hypercholesterolaemia [FH] patients), where patients were being treated with commercially-available Repatha®, were selected across 12 countries in Europe (Austria,

Belgium, Bulgaria, Czech Republic, Germany, Greece, Italy, Portugal, Slovakia, Spain, Sweden, and Switzerland).

- **Subjects and Study Size, Including Dropouts**

Inclusion Criteria

Subjects were required to meet all the following inclusion criteria:

- Adults (≥ 18 years)
- Provided informed consent if applicable according to local requirements
- Initiated on Repatha® at physician's discretion, after 01 August 2015
- Received at least one dose of Repatha®

Exclusion Criteria

If at least one of the following exclusion criteria was met, subjects were not eligible to participate in the study:

- Enrolled in an interventional study of PCSK9 inhibitor within 12 weeks prior to initiation of Repatha®
- Received commercially available PCSK9 inhibitor within 12 weeks prior to initiation of Repatha®

Sample size

No formal hypothesis was tested in this observational study, which aimed to estimate with sufficient precision the percentage of subjects with clinical characteristics of interest (FH, CV history, diabetes) and also estimate baseline LDL-C levels, with the intention of performing analyses by country. The planned sample size for the study was 2000 subjects across approximately 15 countries; an average of approximately 130 subjects per country. As the aim of the study was to capture use of Repatha® in clinical practice, this required the drug to be reimbursed; reimbursement criteria are variable from country to country and liable to change. As such, 3 of the originally planned countries were dropped due to lack of reimbursement or extremely narrow reimbursement criteria which meant the eligible population would have been too small to justify including them in the study.

- **Data Source(s) and Methods**

Data sources

Study site staff periodically (at a minimum, 3-monthly) abstracted data from subject medical notes into the electronic case report (eCRF) pages of the sponsor's electronic database. Data capture included the baseline and follow-up periods.

Variables

- *Exposure Assessment*
  - Exposure to Repatha® and other LMTs was assessed through medical chart review.
- *Primary Endpoints/Outcomes*

  Clinical characteristics at time of initiation of Repatha® as assessed in relation to:
  - FH status (diagnosed/not diagnosed)
  - CV history (see Appendix C of the statistical analysis plan [SAP] version 5.0 for a list of diagnoses/events)

- Diabetic status (diabetic/not diabetic; Type 1 or Type 2; glycosylated haemoglobin [HbA1c] measurement closest to initiation of Repatha®)
- Cholesterol values including total cholesterol, LDL-C, HDL-C, non-HDL-C, triglycerides (value[s] available in the 26-week baseline period)
- Demographics (age at initiation of Repatha®, gender, country)
- Cardiovascular risk factors (body mass index [BMI], smoking status, chronic kidney disease, history of hypertension, vascular bed involvement (see also Appendix C of the SAP [version 5.0])
- History of statin intolerance (y, n)
- Dose, dose frequency, commencement date of Repatha® administration
- Type, dose, dose frequency, commencement and discontinuation dates of other LMT administration including apheresis
- Dates and reason for hospital admittance/final diagnosis
- Dates of physician visits and reason for attendance

- *Secondary Endpoints/Outcomes*
  - Relevant laboratory measures including LDL-C, other test results of the lipid panel (over time; values available during the 30-month follow-up period)
  - Use of Repatha® (at initiation of Repatha® and during the 30-month follow-up period; type, dose, frequency, switching)
  - LMTs (over the full observation period [i.e., from baseline throughout the 30-month follow-up period]; type, dose, frequency, switching)
  - Incidence of hospitalisation (dates, including reason for admittance/final diagnosis)
  - Incidence of physician visits (dates, including reason for attendance)
- *Exploratory Endpoints/Outcome*
  - Subject incidence of LDL-C <55 mg/dL (<1.4 mmol/L)

All summaries were descriptive. Frequencies and percentages, with 95% confidence intervals (CIs), were provided for categorical variables and summary statistics for continuous variables

- **Results**

The majority (88.3%) of the 1951 subjects in the total full analysis set (FAS) population completed the study, and the majority (91.2%) remained on treatment with Repatha® at the end of the observation period. 1194 subjects (61.2%) enrolled ≤6 months after initiating Repatha® and 757 (38.8%) >6 months after initiating Repatha®.

Key primary outcomes

Demographics: The majority of subjects were male (62.5%), and the majority were <65 years (63.4%).

Statin intolerance: Most (60.2%) of the subjects had a history of intolerance to any statin; 53.3% with a history of muscle-related intolerance and 21.2% a history of non-muscle-related intolerance.

FH status: Of the total FAS population, 44.8% were diagnosed with FH. The proportion of subjects with FH varied widely across countries, ranging from 25.6% in Slovakia to 86.4% in Bulgaria.

CV history: Of the total FAS population, 84.6% had history of CV events at baseline. The most common CV events (>20%) were coronary artery disease, percutaneous coronary artery intervention, atherosclerosis, ischemic heart disease, acute coronary syndrome, carotid artery disease and ST-elevation myocardial infarction (STEMI). Across countries, the proportion of subjects with history of CV events ranged from 68.7% in Spain to 94.2% in Austria.

CV risk factors: Median systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 130.0 and 80.0 mmHg, respectively, for the total FAS population; 65.1% had hypertension and anti-hypertensives were used by the majority of these subjects. A small proportion of subjects (7.1%) had chronic kidney disease (CKD); mainly stage 2 or 3. Coronary, cerebrovascular, and peripheral vascular bed involvement was reported in 63.3%, 18.8% and 16.4% respectively. Never-smokers comprised 49.0% of the population. The majority of the population (70.7%) had a BMI ≥20 and <30 kg/m^2. The majority of the population (67.2%) were currently taking acetylsalicylic acid.

10-year CV risk estimate: Primary prevention subjects in the total FAS population had a median 10-year risk of CV event or death of 21.22% (ranging from 11.08% to 45.29% across countries) and secondary prevention subjects had a median risk of CV event of 26.36% (from 21.09% to 31.65% across countries), and a median risk of CV death of 9.01% (from 6.71% to 11.11% across countries).

Lipid parameters: Median lipid parameter values for the total FAS population were: LDL-C, 3.98 mmol/L; total cholesterol, 6.13 mmol/L; HDL-C, 1.27 mmol/L; triglycerides, 1.60 mmol/L and non-HDL-C, 4.63 mmol/L. Median values varied across countries.

LMT use: At the start of the baseline period (Month -6), 38.2% of the total FAS population used any statin; 27.0% used high-intensity statin; 23.5% used any statin with ezetimibe; 36.6% used ezetimibe at any dose or as part of any combination therapy; and 48.7% used neither ezetimibe nor statin. Small proportions (≤2.5%) used bile-sequestering resins, fibrates, fish oil and niacin at any dose or as part of any combination therapy. The only statins taken by >1% of the subjects were atorvastatin, rosuvastatin and simvastatin. A small proportion of the total FAS population (≤1.0%) received apheresis once a week or once in 2 weeks.

Secondary outcomes

LDL-C values over time: Median on-treatment values for the total FAS population dropped to 1.63 mmol/L at 1-3 months, and thereafter remained stable for the remainder of the study period (median percent change from baseline at Months 28 to 30: -58.23).

Repatha® use over time: Repatha® use remained very high through the study. Nearly all of the subjects still in the study at Month 12 and at Month 30 remained on treatment with Repatha® (92.7% and 92.2%, respectively). Throughout the study, most subjects received Repatha® at a dose of 140 mg every two weeks.

LMT use and apheresis over time: The proportion of subjects receiving each class of LMT, and the proportion receiving apheresis, stayed relatively constant through the study.

Hospitalisation over time: There was a small but steady decrease in the incidence of hospitalisation for a CV reason over time in the follow up period (from 2.6% at Month 1 to 3 to 1.2% at Month 28 to 30). The incidence of hospitalisation for a non-CV reason remained relatively steady over the study.

Exploratory outcome

Approximately 60% of the subjects achieved the post-baseline LDL-C target.

Other analyses

LDL-C assessments in pre- and post-Covid periods: There were a greater number of post-baseline LDL-C assessments in the pre-COVID-19 period (2.69 per subject-year) than in the post-COVID-19 period (1.61 per subject-year).

Safety outcomes

Median exposure to Repatha® was 25.76 months and median duration on study was 29.73 months.

Non-fatal treatment-emergent suspected adverse drug reactions (SADRs) were reported in 5.9% of the subjects, with 0.4% reporting serious SADRs; 0.3% reporting device-related SADRs and 3.2% reporting SADRs leading to Repatha® discontinuation (of whom 0.4% reported serious SADRs and 2.9% reported non-serious SADRs leading to discontinuation).

The system organ classes (SOCs) reported in >1% of the subjects were musculoskeletal and connective tissue disorders and general disorders and administration site conditions. The preferred terms (PTs) reported in >0.1% of the subjects were myalgia, arthralgia, headache, rhinitis, fatigue, nausea, back pain, influenza-like illness, nasopharyngitis, dizziness, rash, vertigo, abdominal pain upper, injection site hematoma, pain in extremity and hyperhidrosis.

Seven (0.4%) subjects reported serious non-fatal treatment-emergent SADRs. The only individual PTs that were reported in >1 subject were arthralgia, myalgia, and pain in extremity (n=2 each).

Five subjects (0.3%) reported device-related SADRs (injection site haematoma, flushing, muscle spasms and myalgia).

Eighteen subjects (0.9%) reported fatal treatment-emergent adverse events (AEs); no PT being reported in more than one subject.

More treatment-emergent SADRs were reported in the pre-COVID-19 period than in the post-COVID-19 period (0.066 per subject-year vs. 0.012 per subject-year, respectively).

- **Discussion**

In this real-world observational study on subjects with high or very high CV risk in 12 countries across Europe, most subjects (60.2% of the total FAS population) had a history of intolerance to any statin; 44.8% were diagnosed with FH; and 84.6% had history of CV events at baseline. Primary prevention subjects had a median 10-year risk of CV event or death of 21.22% and secondary prevention subjects a median risk of CV event of 26.36%, and a median risk of CV death of 9.01%. Median lipid parameter values at baseline were: LDL-C, 3.98 mmol/L; total cholesterol, 6.13 mmol/L; HDL-C, 1.27 mmol/L; triglycerides, 1.60 mmol/L and non-HDL-C, 4.63 mmol/L. At the start of the baseline period (Month -6), 38.2% of the total FAS population used any statin; 27.0% used high-intensity statin; 23.5% used any statin with ezetimibe; 36.6% used ezetimibe at any dose or as part of any combination therapy; and 48.7% used neither ezetimibe nor statin.

Repatha® was found to consistently lower LDL-C across the 30 month follow-up period (median change -58.23%, at Months 28 to 30), with approximately 60% of the subjects achieving the post-baseline LDL-C target (LDL-C <55 mg/dL). Treatment persistence was high and discontinuation from treatment infrequent, with nearly all subjects staying on Repatha® (92.7% at Month 12 and 92.2% at Month 30). Repatha® was well tolerated,

with comparable safety to that reported in clinical trials (Sabatine et al, 2015; Sabatine et al, 2017).

EAS/ESC guidelines state that patients at high CV risk who are unable to meet treatment goals for LDL-C despite maximally-tolerated statin treatment are recommended for treatment with a PCSK9 inhibitor (Mach et al, 2020). The high median LDL-C levels at Repatha® initiation in our subject population suggest that subjects at high or very high risk of CV events are starting treatment with Repatha® at much higher LDL-C levels than the guideline-recommended goals for treatment initiation or intensification (Mach et al, 2020). This may reflect the fact that reimbursement LDL-C thresholds in most countries in our study are higher than the treatment goals proposed in the guidelines (Ray et al, 2022). Median LDL-C levels at Repatha® initiation are variable across countries, possibly for the same reason. These results are in agreement with the cross-sectional observational DA VINCI study (Ray et al, 2021b).

In this study across 12 European countries, LDL-C levels at Repatha® initiation were three times higher than guideline recommendations for PCSK9i initiation, reflecting disparities between reimbursement criteria and guidelines.

- **Marketing Authorization Holder(s)**

Amgen Europe B.V.