Summary Table of Study Protocol

Title	RETrospective Observational Study of Evolocumab Use in Spanish Endocrinology Units (RETOSS-Endo)
Protocol version identifier	20160140
Date of last version of the protocol	21 April 2017
EU Post Authorisation Study (PAS) Register No	NA
Active Substance	Evolocumab
Medicinal Product	Repatha®
Product Reference	EU/1/15/1016
Procedure Number	EMA/H/C/3766
Marketing Authorisation Holder(s)	Amgen Europe B.V.
Joint PASS	NA
Research Question and Objectives	Research Question: What are the clinical characteristics of patients initiating evolocumab in Spanish Hospital Endocrinology Units, and how is their clinical management? Primary Objective: To describe the main clinical characteristics of patients with hyperlipidemia initiating evolocumab in Hospital Endocrinology Units Secondary Objective: To describe other clinical characteristics and management of patients with hyperlipidemia initiating evolocumab in Hospital Endocrinology Units
Countries of Study	Spain
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Marketing Authorisation Holder

Marketing authorisation holder(s)	Amgen Europe B.V.
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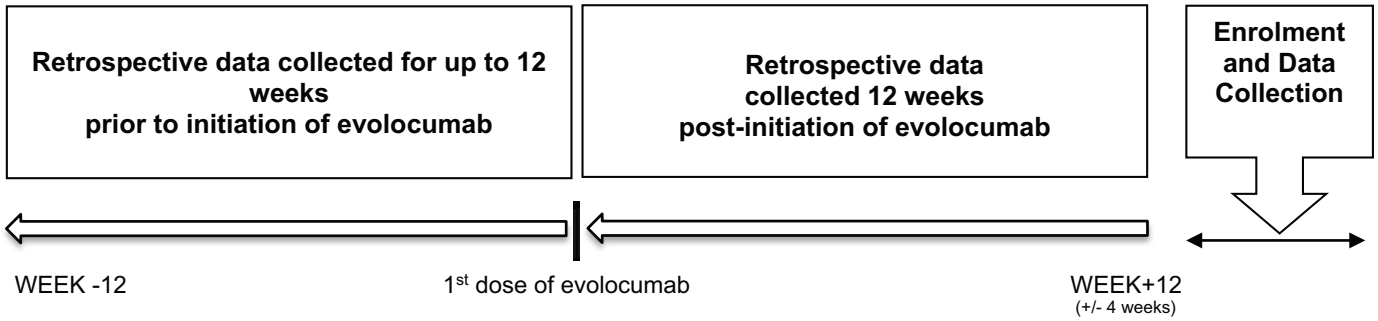
Investigator's Agreement

I have read the attached protocol entitled "Observational Research Study Title: RETrospective Observational Study of Evolocumab Use in Spanish Endocrinology Units (RETOSS-Endo)", dated 21s April 2017, and agree to abide by all provisions set forth therein.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Spain S.A.

Signature	
Name of Investigator	Date (DD Month YYYY)

Study Design Schema



- Enrolment occurs only if evolocumab has been initiated from February 1st 2016 to April 30 th of 2017 at physician discretion.
- Data of Follow-up period post-initiation of evolocumab will be fully retrospective.
- Estimated total Study Duration (retrospective follow-up) for an Individual Subject: 24 weeks (12 weeks pre-initiation of evolocumab and 12 weeks follow-up post-initiation of evolocumab).
- Retrospective Follow-up Period will comprise data up to 12 weeks pre-initiation of evolocumab and data up to 12 weeks after evolocumab initiation date.
- The closest LDL-C value prior to evolocumab initiation will be chosen.
- Planned Enrolment/Data Collection Period: 24 weeks

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2. List of Abbreviations

Abbreviation	Meaning
AEMPs	Spanish Agency of Medical Products
ASCVD	Atherosclerotic Cardiovascular Disease
CHD	Coronary Heart Disease
CV	Cardiovascular
CVD	Cardiovascular Disease
CRF	Case Report Form
EMA	European Medicines Authority
FH	Familial Hypercholesterolaemia
GFR	Glomerular Filtration Rate
HbA1c	Glycosylated Hemoglobin
HDL-C	High Density Lipoprotein-Cholesterol
ICH GCP	International Committee for Harmonisation Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
i.e.	*id est* (that is)
IgG2	Immunoglobulin G type 2
IPT	Therapeutic Positioning Report
IRB/IEC	Institutional Review Board/ Institutional Ethics Committee
LDL-C	Low Density Lipoprotein-Cholesterol
LDLR	Low Density Lipoprotein Receptor
LLT	Lipid Lowering Treatment
PCSK9	Protein Convertase Subtilisin/Kexin type9
SOP	Standard Operating Procedure
STEMI	Segment Elevation Myocardial Infarction
TIA	Transient ischaemic attack

3. Responsible Parties

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4. Abstract

- Study Title: RETrospective Observational Study of Evolocumab Use in Spanish Endocrinology Units (RETOSS-Endo)

- Study Background and Rationale:

  Type 2 diabetes is a major independent risk factor for coronary heart disease (CHD) and stroke, and concomitant dyslipidemia aggravates the cardiovascular (CV) risk (ADA 2016). In Spain, Hospital Endocrinology Units are responsible for the clinical care of patients with hypercholesterolemia, with special attention to two types of patients with high/very high CV risk profiles: atherogenic hyperlipidemia associated with diabetes mellitus and familial hypercholesterolemia (FH).

  Evolocumab (Repatha®) is a fully human monoclonal immunoglobulin G type 2 (IgG2) antibody directed against proprotein convertase subtilisin/kexin type 9 (PCSK9) which increases liver low density lipoprotein receptor (LDLR) levels resulting in associated reductions in serum low density lipoprotein-cholesterol (LDL-C). In Spain, evolocumab is reimbursed by the National Health System since 20th January 2016.

  Data from recent studies in the Spanish population show that, among diabetic patients with dyslipemia and FH patients, there is a high proportion of subjects that continue to experience high plasma LDL-C levels despite current medical care and treatment approaches (Martinez-Hervas *et al.* 2014; Perez de Isla *et al.* 2016). The present systematic, serial chart review study will allow to describe the clinical characteristics and management in the first weeks of subjects initiating evolocumab in Real World Life in Hospital Endocrinology Units in Spain. At present there is no information describing evolocumab use in real-world setting.

- Research Question and Objectives:

  - Primary Objective:
    - To describe the main clinical characteristics (LDL-C levels, Diabetes status, FH status prior to treatment initiation) of patients with hyperlipidemia initiating evolocumab in Hospital Endocrinology Units.
  - Secondary Objective:

  - To describe other clinical characteristics of patients with hyperlipidemia initiating evolocumab in Hospital Endocrinology Units.
  - To describe the clinical management of patients initiating evolocumab treatment in Hospital Endocrinology Units.
- Exploratory Objective:
  - To describe the referral process of patients initiating evolocumab treatment in Hospital Endocrinology Units.
- Hypothesis:
  - No formal hypothesis will be tested in this observational study.

- Study Design/Type:

  Retrospective, observational, serial chart review

- Study Population:

  The study population comprises patients with hypercholesterolemia, who initiated evolocumab as part of routine clinical management of their hyperlipidaemia, from February 1st 2016 to April 30th 2017, by an specialist in an Endocrinology Unit in Spain.

- Subject Eligibility Criteria:
  - Inclusion Criteria:
    - Adults (≥18 years) at the time of evolocumab initiation
    - Provided informed consent if applicable according to local requirements
    - Initiated on evolocumab at physician's discretion, independent of study protocol, from February 1st 2016 to April 30th 2017, by an specialist in a Hospital Endocrinology Unit in Spain
    - Received at least one dose of evolocumab at physician's discretion, by an specialist in a Hospital Endocrinology Unit in Spain
    - At least one LDL-C measurement within the 12 weeks prior to initiation of evolocumab (last value available in the previous 12 weeks)
  - Exclusion Criteria:
    - Enrolled in a study with a PCSK9 inhibitor within 12 weeks prior to initiation of evolocumab
    - Received a PCSK9 inhibitor within 12 weeks prior to initiation of evolocumab
    - Enrolled in a clinical study during the retrospective observational period ie, 12 weeks pre-initiation of evolocumab or up to 12 weeks after evolocumab initiation
- Follow-up:

  Individual (fully retrospective) follow-up is up to 24 weeks (up to 12 weeks pre-initiation of evolocumab and 12 weeks post-initiation of evolocumab). The baseline time-point will be the date of evolocumab initiation (index date).

The study is expected to capture data for subjects who initiated evolocumab between February 1 st 2016 and April 30th 2017.

- Variables:
  - Primary Outcome Measures
    - Clinical characteristics at baseline comprising:
      - LDL-C pre-initiation of evolocumab (last value available in the previous 12 weeks)
      - Diabetes status at evolocumab initiation (diagnosed/not diagnosed, year of diagnosis)
      - FH status at evolocumab initiation (diagnosed/not diagnosed, year of diagnosis)
  - Secondary Outcome Measures
    - Demographic and clinical variables at evolocumab initiation (age, race, gender, employment status, waist circumference, systolic blood pressure, diastolic blood pressure, heart rate, height, weight)
    - Family medical history (only first-degree relatives) at evolocumab initiation
    - Medical history at evolocumab initiation
    - Cardiovascular history at evolocumab initiation
    - Laboratory parameters over time
    - Clinical factor/s that determined evolocumab prescription at initiation
    - Use of evolocumab and other lipid-lowering therapies over time
    - Statin Intolerance (Y/N)
    - Foreseen frequency of routine visits after the first 12 weeks of evolocumab treatment
  - Exploratory Outcome Measures
    - Specialty of the physician that referred the patient to the Hospital Endocrinology Unit for initiating evolocumab treatment (if apply) and main reason for patient referral
    - Number of visits and type of other specialities consulted by the patients in the Hospital during the 24 weeks retrospective follow-up period
    - Hospital where evolocumab was initiated
    - Specialty of the physician that first diagnosed hypercholesterolemia
- Study Sample Size:

  The primary outcome measures for the study involve estimating the percentage of subjects with clinical characteristics of interest (FH, diabetes) and also estimating the baseline LDL-C levels. The planned sample size for the study is 150 subjects.

The sample size is expected to enable precise estimates of the outcome measures to be obtained.

- Data Analysis:

  All summaries of the data will be descriptive in nature. For categorical variables the frequency and percentage, with 95% confidence interval, will be given.

  Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum.

5. Amendments and Updates

None

6. Milestones

Milestone	Planned date
Start of data collection	15th September 2017
End of data collection	15th March 2018
Final report of study results	21stSeptember 2018

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Cardiovascular disease (CVD) represents the leading cause of death and disability in the world, comprising over 10% of the global total disease burden. Elevated cholesterol is among the leading risk factors for cardiovascular deaths, with an estimated prevalence of 39% globally among all adults (greater in high-income countries). It is estimated that up to 50% of the European population aged 35-64 years has a total cholesterol > 6.5 mmol/L (Tolonen *et al.* 2005) (equivalent to > 254 mg/dL). This high prevalence of dyslipidemia translates into significant cardiovascular morbidity and mortality.

Type 2 diabetes is a major independent risk factor for CVD-coronary heart disease (CHD) and stroke, and conditions such as hypertension and dyslipidemia frequently coexist with diabetes (ADA 2016). Data from the Emerging Risk Factor Collaboration, adjusted for age, sex, smoking status, and BMI, suggest that individuals with diabetes have double the risk of both myocardial infarction and stroke compared with those