1. ABSTRACT

- **Title**

Characterizing Repatha use among adult pregnant women, adult women of childbearing age and within the adult general population

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- **Keywords**

Repatha evolocumab; PCSK9i; cardiovascular; pregnancy

- **Rationale and Background**

Repatha® (evolocumab) is a proprotein convertase subtilisin kexin type 9 inhibitor (PCSK9i) antibody indicated to (1) reduce the risk of myocardial infarction (MI), stroke and coronary revascularization in adults with established cardiovascular disease (CVD) (2) as an adjunct to diet, alone or in combination with other lipid-lowering therapies for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol (LDL-C) and (3) as an adjunct to other LDL-C lowering therapies in patients with homozygous familial hypercholesterolemia to reduce LDL-C. As part of Repatha's regulatory postmarketing requirements to the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) two prospective observational research studies (pregnancy registries) were initiated to study the use of Repatha during pregnancy. Across both studies, only four exposures to PCSK9i's were identified within the first three years. To evaluate the futility these studies, a retrospective observational research study was conducted to examine the use of Repatha among adult (≥16 years of age) pregnant women, adult women of childbearing age (ages 16 - 54 years) and within the adult general population. The goal of these analyses was to better understand the real-world use of Repatha within the target populations of these prospective pregnancy registries.

- **Research Question and Objectives**

This objective of this study was to describe the use of Repatha (i.e. counts and proportions) within three cohorts: (1) among adult (≥16 years of age) pregnant women, (2) among adult women of childbearing age (ages 16-54 years) and (3) within the adult general population.

- **Study Design**

Retrospective cohort study

- **Setting**

We utilized data from two United States (US) based healthcare claims databases, IBM Watson Health MarketScan® Commercial Claims and Encounters with Medicare

Supplemental Research Database (i.e., MarketScan) and the UnitedHealth Group Optum Analytics (i.e., Optum). The MarketScan database included the Early View MarketScan data that allowed us to capture the most recent medication claims (including Repatha) and a preview of hospital claims (e.g., obstetrics to identify births). Additionally, we utilized multiple data sources from the European Union (EU) that cover countries including the United Kingdom (Clinical Practice Research Datalink or CPRD), Germany (IMS Germany Disease Analyzer Electronic Medical Records), Denmark (Danish Health Data Authority), Sweden (Swedish National Board of Health and Welfare) and Norway (Norwegian Institute of Public Health Prescription Database). In the US, data were available beginning August 27, 2015 (the date Repatha received US market approval) through June 30, 2018 in MarketScan and December 31, 2018 in Optum to assess study inclusion criteria and Repatha exposure(s). For Early View MarketScan, data were available from January 01, 2016 through April 30, 2019. Data were also available as early as January 01, 1996 (in MarketScan) and May 01, 2000 (in Optum) to allow for a subject assessment of history of ASCVD. In the EU, data were available as early as July 17, 2015 to accout for the earlier Repatha E.U. market approval.

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

Inclusion Criteria:

Pregnant Women Cohort*:

- Female
- 16 years of age or older (as of August 27, 2015)
- Have at least one birth (live or non-live) claim during the study period (August 27, 2015 until the end of available data)
- Have continuous medical and pharmacy health insurance coverage during the 480 days (includes up to 300 pregnancy days + 180 days prior to the last menstrual period) prior to the birth claim, with an allowable 45-day gap in coverage.

Women of Childbearing Age Cohort*:

- Female
- 16 to 54 years of age (as of August 27, 2015)

General Population Cohort**

- 16 years of age or older (as of July 17, 2015)

*US databases only

**EU databases only

During the study period, there were more than 13 million women of childbearing age identified both in the MarketScan and MarketScan EarlyView databases, and over 6 million women of childbearing age identified in the Optum database. During this same time period, 432,893 pregnant women with a live birth were identified in the MarketScan database, 273,077 in the MarketScan EarlyView database, and 250,356 in the Optum database. Among pregnant women who had a pregnancy that ended in a nonlive birth, a total of 122,118 women were identified in the MarketScan database, 102,813 in the MarketScan EarlyView database, and 63,234 women in the Optum database. In the EU, 16 individuals were identified as having ever been exposed to Repatha in the United Kingdom Clinical Practice Research Datalink, 279 in the IMS Germany Disease Analyzer Electronic Medical Records, 115 in a database from the Danish Health Data Authority, 1,267 in a database from the Swedish National Board of Health and Welfare and 1,063 in the Norwegian Institute of Public Health Prescription Database.

- **Variables and Data Sources**
  - Outcome: None
  - Exposure: Having at least one pharmacy dispense record (using all available national drug codes [NDC]) for Repatha within the 180 days prior to the start date of the last menstrual period (LMP) through the pregnancy end date (pregnant women cohort), between the ages of 16-54 years (women of childbearing age cohort) or at any time within the available data (general population cohort)
  - Other Covariates: Age, sex (general population cohort only), calendar year, history of ASCVD*, pregnancy trimester of exposure (pregnant women cohort only), and familial hypercholesterolemia (EU specific analyses).
    - *History of ASCVD was identified using ICD-9-CM, ICD-10-CM and CPT codes for acute myocardial infarction (AMI), unstable angina (UA), ischemic stroke (IS), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), cerebrovascular disease, transient ischemic attack (TIA), aneurysm, carotid endarterectomy, carotid / vertebral / basilar stenting, coronary atherosclerosis / angina / old AMI, endovascular stent graft, arterial bed atherosclerosis (not previously defined).
- **Results**

United States

Identification of Repatha claims for women of childbearing age between August 27, 2015 and June 30, 2018 for MarketScan, December 31, 2018 for Optum and April 30, 2019 for

MarketScan EarlyView is provided in Table 1. Between August 27, 2015 and June 30, 2018, there were more than 13 million women of childbearing age identified in the MarketScan database. Among these women, 1,866 (<0.001%) had at least 1 claim for Repatha. At the time of the woman's first Repatha claim, the majority (73.3%) were between 46 and 54 years of age, 15.4% were between 41 and 45 years of age, and 11.2% were between 16 and 40 years of age. Within Optum, over 6 million women of childbearing age were identified, of whom 204 (<0.001%) had a claim for Repatha. Comparable to what was seen in the MarketScan database, most of these women (73.0%) were between 46 and 54 years of age. Examining the MarketScan EarlyView database representing the most recent data available through April 30, 2019, a similar 13 million women of childbearing age were identified. Of these women, 2,434 (<0.001%) had a claim for Repatha and 74.9% of these claims were among women between 46 and 54 years of age.

Table 1. Repatha Claims For Women of Childbearing Age Between 27 August 2015 and 30 June 2018 (MarketScan), 31 December 2018 (Optum), and 30 April 2019 (MarketScan EarlyView)

	MarketScan		Optum		MarketScan EarlyView	
	N	Repatha Claim N (%)	N	Repatha Claim N (%)	N	Repatha Claim N (%)
Total	13,613,117	1,866 (100)	6,641,520	204 (100)	13,334,251	2,434 (100)
Age (years)						
16 – 19	1,043,908	5 (0.3)	426 600	1 (0.5)	702,127	5 (0.2)
20 – 24	1,900,654	9 (0.5)	800 410	1 (0.5)	1,880,041	8 (0.3)
25 – 30	1,900,661	19 (1.0)	1,069 496	1 (0.5)	1,983,313	27 (1.1)
31 – 40	3,341,821	176 (9.4)	1,820 305	20 (9.8)	3,372,761	230 (9.4)
41 – 45	1,843,899	288 (15.4)	899 234	32 (15.7)	1,798,144	341 (14.0)
46 – 54	3,582,174	1,369 (73.3)	1,625,475	149 (73.0)	3,597,865	1,823 (74.9)

Findings from pregnancies ending in live and nonlive births by Repatha claim status for women who were pregnant between August 27, 2015 and June 30, 2018 for MarketScan, December 31, 2018 for Optum, and April 30, 2019 for MarketScan Early View are provided in Table 2. Within the cohort of adult (≥16 years of age) woman who were pregnant during the study period, 432,893 women were identified in the MarketScan database with their pregnancy ending in a live birth. Of these pregnancies, 2,571 (0.6%) women had evidence of ASCVD before the start date of their last menstrual period (LMP). However, 0 women (with or without ASCVD) had a claim for Repatha during their pregnancy or within the 180 days prior to the start date of their

LMP. Similarly, there were 0 women exposed to Repatha during their pregnancy, or within the 180 days prior to the start date of their LMP, among the 273,077 pregnancies ending in a live birth in the MarketScan Early View database or the 250,356 pregnancies ending in a live birth in the Optum database. Although, 1,480 (0.6%) of the pregnant women identified in MarketScan EarlyView and the 1,538 (0.6%) pregnant women identified in Optum had a history of ASCVD.

Table 2. Pregnancies Ending in Live and Nonlive Births by Repatha Claim Status For Women Pregnant Between 27 August 2015 and 30 June 2018 (MarketScan), 31 December 2018 (Optum), and 30 April 2019 (MarketScan Early View)

	MarketScan		Optum		MarketScan EarlyView	
	Livebirth	Nonlive Birth	Livebirth	Nonlive Birth	Livebirth	Nonlive Birth
Total number of pregnancies	432,893	122,118	250,356	63,234	273,077	102,813
Repatha claim within the 180 days before last menstrual period	0	1[a]	0	0	0	1[a]
Repatha claim during pregnancy	0	0	0	0	0	0

[a]Represents the same patient. Repatha claim occurred 118 days prior to the last menstrual period.

In examining the cohort of pregnant women who had a pregnancy that ended in a nonlive birth, there was a total of 122,118 women identified in the MarketScan database. Of these women, 1,566 (1.3%) had a history of ASCVD prior to the start date of their LMP. However, 0 women had a claim for Repatha during their pregnancy and 1 patient was identified that had a claim for Repatha within the 180 days prior to the start date of her LMP, which occurred 118 days prior to the start date of her LMP with no subsequent claims for Repatha. In reviewing the more recent data from the MarketScan EarlyView database, a total of 102,813 pregnant women were identified that had a pregnancy ending in a nonlive birth, with 1,145 (1.1%) women having a history of ASCVD. Again, 0 women had a claim for Repatha during their pregnancy and the same woman, identified previously, was reidentified with Repatha exposure within the 180 days prior to the start date of her LMP. Lastly, there were 63,234 women identified in Optum who had a pregnancy ending in a nonlive birth as of December 31, 2018. No women had a claim for Repatha during their pregnancy or a claim for Repatha within the 180 days prior to the start date of their LMP, although 760 had a history ASCVD.

Europian Union

We analyzed data from two European Union healthcare databases, the Clinical Practice Research Datalink (herein after referred to as CPRD) based in the United Kingdom and sponsored by the Medicine and Healthcare products Regulatory Agency and the National Institute for Health Research and IMS Germany Disease Analyzer Electronic Medical Records Database (herein after referred to as Germany EMR) distributed by IQVIA. In addition, data from three public and government open-source databases from Denmark (the Danish Health Data Authority), Sweden (the Swedish National Board of Health and Welfare), and Norway (the Norwegian Prescription Database from the Norwegian Institute of Public Health) were reviewed.

In examining data from CRPD (United Kingdom), there were 16 individuals identified with Repatha exposure. None of these individuals were under 54 years of age. Of the women over 54 years of age who were exposed to Repatha (n=7), 3 were identified as having familial hypercholesterolemia (FH) through either a diagnosis code for FH or the Dutch Lipid Clinic Network Score / EUROASPIRE criteria. There were 0 pregnant women exposed to Repatha in the CPRD database. A similar analysis identified 279 patients exposed to Repatha in the German EMR with 0 women exposed to Repatha under 45 years of age. All women exposed to Repatha were over 45 years of age (n=95), but the current data do not allow for the identification of patients with FH and we did not have built in capabilities to identify pregnant women.

For the analyses of the government provided data from Denmark (the Danish Health Data Authority), 115 patients exposed to Repatha were identified, with the majority (57%) being men. All Repatha exposure in Denmark was in patients 45 years of age or older with limited exposure in women between 45 and 64 years of age (n=26). In addition, this database identified 168,123 deliveries that occurred between the years of 2015 and 2017 with 0 women exposed to Repatha during pregnancy. However, the data indicated that less than 5 women (privacy laws do not allow the reporting of information when there are less than 5 patients identified) were exposed to Repatha within the 12 months prior to becoming pregnant.

In Sweden, using the Swedish National Board of Health and Welfare database, 1,267 patients who were exposed to Repatha were identified with 40% of the exposure occurring among women. The majority of the 1,267 patients exposed to Repatha were over 45 years of age (n=1,171, 92%) and 93 (7%) were women between 16 and 54 years of age (child-bearing age). Data on pregnant women were unavailable.

From Norway, utilizing the Norwegian Prescription Database from the Norwegian Institute of Public Health database, there were 1,063 patients exposed to Repatha identified with 48% of these patients being women (n=507). Over 162 (the exact number cannot be calculated due to privacy in certain stratification combinations of age and sex) of the women receiving Repatha were between the ages of 16 and 54. Similar to that seen in the Swedish database, data on pregnant women were unavailable.

- **Discussion**

Utilizing data from two large and nationally-representative commercial claims healthcare databases representative of the working population in the United States, Repatha exposure was nearly nonexistent in pregnant women, including the time period within the 180 days prior to a woman becoming pregnant. More broadly, very few women of childbearing age (<0.001%) were exposed to Repatha. Most of the women identified in these analyses with Repatha exposure were at the upper end of the childbearing age range, during which pregnancy occurs infrequently. In addition, women commonly stop medication use prior to becoming pregnant (Illoh et al, 2017). This may explain why one woman was identified as being exposed to Repatha within 180 days before the start date of her LMP and not during pregnancy. Despite the large number of pregnant women who were included in these analyses and the substantial number who had a history of ASCVD, there were 0 women identified with Repatha exposure during pregnancy.

Across the five European Union databases there was no Repatha exposure identified among pregnant women and limited exposure among women of childbearing age. This is consistent with what has been seen in the prospective registry, where it is unlikely that pregnant women are using Repatha and thus the number enrolled in the registry who have FH and are pregnant is minimal.

- **Marketing Authorization Holder(s)**

Amgen, Inc.