Brand Name: Repatha

Generic Name: evolocumab

Manufacturer: Amgen®[3]

Drug Class: PCSK9 inhibitor[1,2,4]

Uses:

Labeled Uses[1,2,3,4]: As adjunct to diet and maximally tolerated statin therapy for adults with heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, or clinical ASCVD who require additional lowering of LDL-C.
Unlabeled Uses: N/A

Mechanism of Action[1,2,3,4]:

Human monoclonal IgG2 directed against human proprotein converstase subtilisin kexin 9 (PCSK9). Evolocumab binds to PCSK9 to inhibit PCSK9 binding to the low density lipoprotein receptor (LDLR), preventing degradation of LDLR via PCSK9. By inhibiting binding of PCSK9 and LDLR, evolocumab increases the number of LDLRs available to remove LDL cholesterol from the blood.

Pharmacokinetics[1,2,3,4]:

Absorption:

T_{max}	3-4 days
V_d	3.3L
$t_{½}$	11-17 days
Clearance	12 ml/hr (systemic)
Protein binding	Not reported
Bioavailability	72%

Metabolism & Elimination: At low concentrations, evolocumab is eliminated primarily through saturable binding to PCSK9, at higher concentrations the elimination is largely through a non-saturable proteolytic pathway.

Efficacy[5,6,7]:

Raal FJ et al. PCSK9 inhibition with evolocumab in heterozygous familial hypercholesterolemia (RUTHERFORD-2). Lancet. 2015; 385:331-340.

Study Design: Multicenter, randomized, double-blind, placebo-controlled, design study

Description of Study: *Methods*: Three-hundred-thirty one patients with heterozygous familial hypercholesterolemia from 39 study cites were enrolled. Coprimary endpoints in the study included percentage change in plasma LDL from baseline to week 12 and at the mean of weeks 10 and 12. Patients were eligible for the study if they were 18-80 years old, diagnosed with heterozygous hypercholesterolemia, and currently on stable lipid lowering therapy. Eligible patients were randomized in a 2:2:1:1 ratio to receive evolocumab subcutaneous 140mg every 2 weeks, evolocumab subcutaneous 420mg once monthly, placebo subcutaneous every 2 weeks, or placebo subcutaneous monthly for a total of 12 weeks. Of the patients enrolled in this study 87% of patients were taking statin therapy and 62% were also taking ezetimibe. Patients in the every 2 week group were assessed on day one and weeks 2, 8, 10, and 12 and those receiving monthly injections were assessed at weeks 0 and 8. *Outcome Results:* At 12 weeks the percent of LDL reduction for patients receiving evolocumab every 2 weeks versus placebo was 61.3% and 2.0% respectively ($p < 0.0001$). Those receiving evolocumab and placebo monthly demonstrated a LDL reduction of 55.7% and 5.5% respectively ($p < 0.0001$). The mean LDL reduction at weeks 10 and 12 was significantly decreased in both patient groups receiving evolocumab every 2 weeks or monthly when compared with placebo. A post-hoc analysis was done comparing percent change from baseline by genotype, LDL receptor class, or apolipoprotein B mutation status and LDL reduction remained similar to the primary outcome measure.

Limitations: This study was designed and sponsored by Amgen the manufactuer of evolocumab. The manufacturers' role in both the implementation and critique of this study introduces a large possibility for bias in the study and data presented. In addition, this study had a very extensive list of exclusion criteria which would limit the generalizability of results. Another limitation is the study duration, while 12 weeks is enough time to assess short term efficacy data this study does not provide information for efficacy or safety regarding sustained use of therapy.

Conclusion: The results of this study showed that in patients with heterozygous familial hypercholesterolemia, the addition of evolucumab, every two weeks or monthly, to standard lipid lowering therapy resulted in LDL reduction of approximately 60% in a 12 week time period. In this trial evolocumab was relatively well tolerated. Further studies need to be completed to determine long term efficacy and tolerability in populations represented in this study, as well as those excluded due to comorbid conditions.

Blorn DJ et al. A 52-Week Placebo Controlled Trial of Evolocumab in Hyperlipidemia. NEJM. 2014;370(19):1809-1819.

Study Design: Multicenter, double-blind, randomized, placebo-controlled, phase 3 trial

Description of Study: *Methods*: During a 4-12 week run in period, patients with hypercholesterolemia were assigned (based on recommendations from ATP III Guidelines) to receive one of four treatment options; diet modification, diet and atorvastatin 10mg daily, diet with atorvastatin 80mg daily, or diet with atorvastatin 80mg daily plus ezetimibe daily. Patients were eligible for inclusion in the study with a

measured LDL of 75 mg/dL or higher, or a LDL < 100mg/dL with a history of coronary heart disease were eligible for inclusion into the study. Nine hundred and one patients were randomized for inclusion in a 2:1 ratio to receive either 420mg evolocumab or placebo, administered subcutaneously every 4 weeks for 48 weeks. *Outcome Results:* The primary efficacy endpoint was the percent change from baseline in LDL cholesterol level at 52 weeks. At 52 weeks, the least squares regression mean reduction in LDL in the evolocumab group was 57.5% at 12 weeks and 57.0% at 52 weeks. Adverse events were similar among the two groups, with more events leading to discontinuation in the evolocumab group (2.2% vs 1.0%). The most common adverse effects reported during the study include nasopharyngitis, upper respiratory tract infections, influenza, and back pain.

Limitations: This study was designed and sponsored by Amgen the manufactuer of evolocumab. In addition, Amgen in collaboration with the authors of the trial were responsible for, data collection, drafting, and editing the report for publication. Demographic differences between the groups at baseline were recorded but the significance of these were not expressed making it difficult to determine appropriate demographic distribution. A large majority of patients enrolled in this study were white (approximately 70%), therefore we are unable to extrapolate the results across other races. Another limitation of this study, most specifically the run in period, is that initial run in therapies were chosen based on the goals of the ATP III Cholesterol Guidelines rather than the ACC/AHA Guidelines which are the new standard of practice.

Conclusion: The results of this study showed that evolocumab 420mg monthly when added to standard therapy significantly reduces LDL cholesterol levels when compared to placebo. Evolocumab was relatively well tolerated throughout this study. Incidence of myalgia was slightly higher in the evolocumab group 4% vs 3%, but not statistically significant. Based on these results, evolocumab can be used in conjunction with standard therapy to lower LDL cholesterol in patients whose cholesterol remains elevated after standard therapy. Further research should be done to extrapolate this data amongst all races, and outcomes data should be collected to determine evolocumabs role in reducing cardiovascular complications.

Nissen SE, Stroes E et al. Efficacy and Tolerability of Evolocumab vs. Ezetimibe in Patients With Muscle-Related Statin Intolerance (GAUSS-3). JAMA. Published online April 03, 2016. Doi:10.1001/jama.2016.3608

Study Design: double blind, placebo controlled crossover study with two phases

Description of Study: *Methods*: This was a two phase, crossover study where 491 patients with previous statin intolerance were randomized in phase A to receive Atorvastatin 10mg daily or placebo for 10 weeks. Equal numbers of men and women were enrolled in this study, a majority white, with a mean age of 60, and more than 80% had intolerance to 3 or more statins prior to randomization. After the first 10 weeks of treatment with atorvastatin or placebo, those who were unable to tolerate atorvastatin due to myalgias or those with a CK elevation of ten times the upper limit of normal were

considered for randomization into phase B. Patients eligible for phase B underwent a two week washout period between phase A and phase B. Two hundred eighteen patients were randomized 1:2 in phase B to receive ezetimibe + subcutaneous placebo or evolocumab + oral placebo for 24 weeks. *Outcome results:* The study pre-specified two coprimary endpoints: the mean of LDL levels at weeks 22 and 24, and the mean percent change in LDL from baseline at 24 weeks. The mean LDL level at 22 and 24 weeks for patients on evolocumab subcutaneous therapy 103 mg/dL with a 54.5% reduction, versus a mean LDL of 183 mg/dL and a 16.7% reduction with ezetimibe treatment. Percent change from baseline in LDL was 52.8% in the evolocumab versus 16.7% in the ezetimibe group. Safety and tolerability outcomes included incidence of any muscle-related adverse event (13.8% evolocumab vs 28.8% ezetimibe), muscle related event leading to drug discontinuation (7.6% evolocumab vs 6.8% ezetimibe), and other common adverse events. Other adverse events seen (frequency less than 10%) in the evolocumab group included nasopharyngitis, arthralgia, muscle spasms, fatigue, and headache.

Limitations: Amgen, the manufacturer of evolocumab was involved in the design, monitoring, and data collection for this trial. As in previous studies, the patient population represented in this study (>90% white) prevents us from extrapolating the success of evolocumab to other races/ethnicities. This study did not assess long term efficacy, or cardiovascular outcome data.

Conclusion: The results of this study show that in patients with documented statin intolerance, the use of evolocumab compared with ezetimibe resulted in greater reduction in LDL after 24 weeks. In addition, Evolocumab seems to be relatively well tolerated as patients reported fewer muscle related adverse events. Further studies should be completed to assess evolocumab's role in therapy for reducing cardiovascular outcomes such as myocardial infarction and stroke.

Contraindications[1,2,3,4]:

History of serious hypersensitivity reaction: Hypersensivity reactions including rash and urticaria have been reported. The needle cover of the prefilled syringe contains natural rubber, which may cause an allergic reaction in individuals with latex hypersensitivity.

Precautions[1,2,3,4]:

Allergic Reactions: Rash and urticaria have occurred. If signs or symptoms of serious allergic reactions occur, discontinue treatment with evolocumab, treat according to standardof care, and monitor until signs and symptoms resolve.

Adverse Effects[1,2,3,4]:

Occurring in >10% of patients

Respiratory

Naso-pharyngitis (4%-10.5%)

Occurring in >1% to <10% of patients

Cardiovascular

Hypertension (3%)

Central Nervous System

Dizziness (4%)

Fatigue (2%)

Dermatologic

Rash (1%)

Gastrointestinal

Gastroenteritis (3%-6%)

Nausea (2%)

Hematologic

Bruise (1%)

Infection

Influenza (8%-9%)

Local

Injection site reaction (6%)

Erythema at injection site (3%-6%)

Neuromuscular & Skeletal

Myalgia (4%)

Respiratory

Upper respiratory tract infection (9%)

Cough (1%-5%)

Sinusitis (4%)

Uncommon (<1%), postmarketing, and/or case reports

Antibody development

Decreased LDL < 25mg/dL

Hypersensitivity

Urticaria

Drug Interactions[1,2,3,4]

Belimumab: Monoclonal antibodies may enhance the adverse/toxic effect of Belimumab.

Dosing/Administration[1,2,3,4]

Adult Dosing

Heterozygous familial hypercholesterolemia or patients with primary hyperlipidemia with ASCVD:

140mg every 2 weeks OR 420mg once monthly

Homozygous familial hypercholesterolemia: 420mg once monthly

Pediatrics

Safety and efficacy have not been established

Elderly

Refer to adult dosing

Renal impairment

No dosage adjustment is needed for mild to moderate renal impairment. Specific guidelines for dose adjustments in sever renal failure are not available.

Hepatic impairment

No dosage adjustment is needed for mild to moderate hepatic impairment (Child-Pugh A or B). Specific guidelines for dosage adjustments in severe hepatic impairment are not available.

Special circumstances[1,2,3,4]:

Switching regimens: If switching dosing regimens, administer the first dose of the new regimen on the next scheduled date of previous regimen.

Missed dose: If a dose is missed, administer the next dose as soon as possible if there are more than 7 days until the next scheduled dose. If less than 7 days to next dose, omit the missed dose and administer the next dose according to the original schedule.

Conclusion:

Evolocumab, a novel PCSK9 inhibitor, appears to be efficacious in lowering LDL by 50-60% in patients with heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, and those with clinical cardiovascular disease who cannot tolerate and/or require further LDL reduction in addition to standard therapy. Studies have shown evolucumab is efficacious when used in combination with standard therapy and as single therapy for those who are unable to tolerate standard therapy (ie. statin, ezetimibe, and diet modification). As a subcutaneous injection, evolocumab appears to be relatively safe and well tolerated amongst patients when studied both in combination with standard therapy and when studied alone. Further studies need to be completed in conjunction with the new ACC/AHA Cholesterol guidelines to determine the role of evolocumab in reducing patients cardiovascular risk.

Recommended References:

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2. Evolocumab. Lexi-Drugs [database online]. Lexi-Comp, Inc; April 4, 2016.
3. Repatha® [package insert]. Thousand, Oaks: Amgen®: 2015.
4. Evolocumab. In: DRUGDEX® System [Internet Database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed: April 4, 2016.
5. Raal FJ et al. PCSK9 inhibition with evolocumab in heterozygous familial hypercholesterolemia (RUTHERFORD-2). Lancet. 2015; 385:331-340.
6. Blorn DJ et al. A 52-Week Placebo Controlled Trial of Evolocumab in Hyperlipidemia. NEJM. 2014;370(19):1809-1819.

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