MEDICAL MUTUAL®

Drug Policy

Policy:	**201529**	**Initial Effective Date: 10/19/2015**
Code(s):	**HCPCS C9399, J3490 and J3590**	**Annual Review Date: 06/22/2023**
SUBJECT:	**Repatha (evolocumab) injection for subcutaneous use**	**Last Revised Date: 06/22/2023**

☐Subject to Site of Care

Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.

OVERVIEW

Repatha, a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor antibody, is indicated for the following uses:[1]

- **Established cardiovascular (CV) disease**, in adults to reduce the risk of myocardial infarction (MI), stroke, and coronary revascularization.
- **Primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH])**, in adults as an adjunct to diet, alone or in combination with other low-density lipoprotein cholesterol (LDL-C)-lowering therapies to reduce LDL-C.
- **HeFH, in pediatric patients ≥ 10 years of age**, as an adjunct to diet and other LDL-C lowering therapies.
- **Homozygous familial hypercholesterolemia (HoFH)**, as an adjunct to diet and other low-density lipoprotein (LDL)-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients ≥ 10 years of age and older, to reduce LDL-C.

The safety and effectiveness of Repatha have not been established in pediatric patients with HeFH or HoFH who are younger than 10 years of age.[1] Another PCSK9 inhibitor that is available is Praluent® (alirocumab subcutaneous injection).[2] Leqvio® (inclisiran subcutaneous injection), a small interfering ribonucleic acid (RNA) directed to PCSK9 messenger RNA, is a similar product.[3]

POLICY STATEMENT

This policy involves the use of Repatha. Prior authorization is recommended for pharmacy and medical benefit coverage of Repatha. Approval is recommended for those who meet the conditions of coverage in the **Criteria, Dosing, Initial/Extended Approval, Duration of Therapy**, and **Labs/Diagnostics** for the diagnosis provided. **Waste Management** applies for all covered conditions that are administered by a healthcare professional. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria and Waste Management section. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Repatha as well as the monitoring required for AEs and long-term efficacy, initial approval requires Repatha be prescribed by or in consultation

with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy unless otherwise noted below.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Repatha is recommended in those who meet the following criteria:

1. **Atherosclerotic Cardiovascular Disease.*** Approve for 1 year if the patient meets one of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets allow the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has had one of the following conditions or diagnoses (a, b, c, d, or e):
       - **a)** A previous myocardial infarction or a history of an acute coronary syndrome; OR
       - **b)** Angina (stable or unstable); OR
       - **c)** A past history of stroke or transient ischemic attack; OR
       - **d)** Peripheral arterial disease; OR
       - **e)** Patient has undergone a coronary or other arterial revascularization procedure in the past; AND
         Note: Examples include coronary artery bypass graft surgery, percutaneous coronary intervention, angioplasty, and coronary stent procedures.
     - **iii.** Patient meets one of the following (a or b):
       - ~~**a)**~~ Patient meets both of the following [(1) and (2)]:
         - **(1)** Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND
         - **(2)** Low-density lipoprotein cholesterol level after this treatment remains ≥ 70 mg/dL; OR
       - **b)** Patient has been determined to be statin intolerant by meeting one of the following criteria [(1) or (2)]:
         - **(1)** Patient experienced statin-related rhabdomyolysis; OR
           Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR
         - **(2)** Patient meets all of the following [(a), (b), and (c)]:
           - **(a)** Patient experienced skeletal-related muscle symptoms; AND
             Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
           - **(b)** The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND
           - **(c)** When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND
             Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

iv. Medication is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders; OR

B) Patient Currently Receiving Repatha. Approve if according to the prescribing physician, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Repatha for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Repatha, Initial Therapy criteria must be met.

2. Heterozygous Familial Hypercholesterolemia (HeFH).* Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, and iv):

i. Patient is ≥ 10 years of age; AND

ii. Patient meets one of the following (a, b, or c):

a. Patient has an untreated low-density lipoprotein cholesterol (LDL-C) ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR

b. Patient has genetic confirmation of heterozygous familial hypercholesterolemia by mutations in the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9, or low-density lipoprotein receptor adaptor protein 1 gene; OR

c. Patient has been diagnosed with heterozygous familial hypercholesterolemia by meeting one of the following diagnostic criteria thresholds [(1) or (2)]:

(1) Prescribing physician confirms that the Dutch Lipid Network criteria score was > 5; OR

(2) Prescribing physician confirms that Simone Broome criteria met the threshold for "definite" or "possible (or probable)" familial hypercholesterolemia; AND

iii. Patient meets one of the following (a or b):

a) Patient meets both of the following [(1) and (2)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND

(2) Low-density lipoprotein cholesterol (LDL-C) level after this treatment remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting one of the following [(1) or (2)]:

(1) Patient experienced statin-related rhabdomyolysis; OR

Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).

(2) Patient meets all of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND

Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND

(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

iv. Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders; OR

B) Patient Currently Receiving Repatha. Approve if according to the prescribing physician, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Repatha for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Repatha, Initial Therapy criteria must be met.

3. Homozygous Familial Hypercholesterolemia (HoFH).* Approve for 1 year if the patient meets one of the following (A or B):

A) Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, and iv):

i. Patient is ≥ 10 years of age; AND

ii. Patient meets one of the following (a, b, or c):

a) Patient has genetic confirmation of two mutant alleles at the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 gene locus; OR

b) Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level > 500 mg/dL AND meets one of the following [(1) or (2)]:

Note: Untreated refers to therapy with any antihyperlipidemic agent.

(1) Patient had clinical manifestations of homozygous familial hypercholesterolemia before 10 years of age; OR

Note: Clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma.

(2) Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia; OR

Note: An example of heterozygous familial hypercholesterolemia in both parents would be if both had an untreated LDL-C level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL.

c) Patient has a treated LDL-C level ≥ 300 mg/dL AND meets one of the following [(1) or (2)]:

Note: Treated refers to after therapy with at least one antihyperlipidemic agent. Some examples of antihyperlipidemic agents include statins (e.g., atorvastatin, rosuvastatin, lovastatin, simvastatin, pravastatin), ezetimibe, a PCSK9 inhibitor (e.g., Praluent [alirocumab subcutaneous injection]), Evkeeza (evinacumab-dgnb intravenous infusion), or Juxtapid (lomitapide capsules).

(1) Patient had clinical manifestations of homozygous familial hypercholesterolemia before 10 years of age; OR
Note: Examples of clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma.

(2) Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia; AND
Note: An example of heterozygous familial hypercholesterolemia in both parents would be if both had an untreated LDL-C ≥ 190 mg/dL and/or an untreated total cholesterol > 250 mg/dL.

iii. Patient meets one of the following (a or b):

a) Patient meets both of the following [(1) and (2)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND

(2) LDL-C level after this treatment remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting one of the following criteria [(1) or (2)]:

(1) Patient experienced statin-related rhabdomyolysis; OR
Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR

(2) Patient meets all of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND
Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND

(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND
Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

iv. Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders; OR

B) Patient Currently Receiving Repatha. Approve if according to the prescribing physician, the patient has experienced a response to therapy.
Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Repatha for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Repatha, Initial Therapy criteria must be met.

4. Primary Hyperlipidemia.* Approve for 1 year if the patient meets ONE of the following (A or B):

Note: This is not associated with atherosclerotic cardiovascular disease (ASCVD), heterozygous familial hypercholesterolemia (HeFH), or homozygous familial hypercholesterolemia (HoFH) and may be referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated low-density lipoprotein cholesterol (LDL-C) levels.

A) Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, and iv):

- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has a coronary artery calcium or calcification score ≥ 300 Agatston units; AND
- **iii.** Patient meets one of the following criteria (a or b):
  - **a)** Patient meets all of the following [(1), (2), and (3)]:
    - **(1)** Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]); AND
    - **(2)** Patient has tried one high-intensity statin therapy above along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND
    - **(3)** LDL-C level after this treatment regimen remains ≥ 100 mg/dL; OR
  - **b)** Patient has been determined to be statin intolerant by meeting one of the following [(1) or (2)]:
    - **(1)** Patient experienced statin-related rhabdomyolysis; OR
      Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR
    - **(2)** Patient meets all of the following [(a), (b), and (c)]:
      - **(a)** Patient experienced skeletal-related muscle symptoms; AND
        Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
      - **(b)** The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND
      - **(c)** When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND
        Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.
- **iv.** Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders; OR

B) Patient Currently Receiving Repatha. Approve if according to the prescribing physician, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Repatha for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Repatha, Initial Therapy criteria must be met.

Note:
* A patient may have diagnoses pertain to more than one FDA-approved indication, therefore, consider review under different approval conditions, if applicable (e.g., a patient with heterozygous familial hypercholesterolemia or homozygous familial hypercholesterolemia may have had a clinical ASCVD event, a patient with primary hyperlipidemia may have heterozygous familial hypercholesterolemia).

Dosing in Repatha (medical benefit only). *Dosing must meet the following:*

Heterozygous Familial Hypercholesterolemia [HeFH]
The recommended subcutaneous dosage of Repatha in patients with HeFH is either 140 mg every 2 weeks OR 420 mg once monthly. When switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen.

Homozygous Familial Hypercholesterolemia [HoFH]
The recommended subcutaneous dosage of Repatha in patients with HoFH is 420 mg once monthly. In patients with HoFH, measure LDL-C levels 4 to 8 weeks after starting Repatha, since response to therapy will depend on the degree of LDL-receptor function.

Initial Approval/ Extended Approval.
A) *Initial Approval:* 1 year
B) *Extended Approval:* 1 year

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Repatha has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

1. **Concurrent use of Repatha with Praluent (alirocumab subcutaneous injection) or Leqvio (inclisiran subcutaneous injection).** Praluent is another PCSK9 inhibitor and should not be used with Repatha.[2] Leqvio, a small interfering ribonucleic acid (RNA) directed to PCSK9 messenger RNA, is a similar product and should not be given with Repatha.[17]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

Documentation Requirements:
The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation

supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

REFERENCES

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Prior approval is required for HCPCS Codes J3490 and J3590 or J9999

†When *unclassified drugs* (J3490) or *unclassified biologics* (J3590) or *unclassified antineoplastics* (J9999) is determined to be Repatha

Edits and Denials:

Prior approval: Prior approval is required for Repatha **(HCPCS Codes J3490 , J3590, J9999)**. Requests for prior approval will be authorized by a nurse reviewer if submitted documentation meets criteria outlined within the Corporate Medical Policy.

Requests for prior approval will be forwarded to a qualified physician reviewer if submitted documentation does not meet criteria outlined within Corporate Medical Policy.

TOPPS: Claims received with **HCPCS Codes J3490, J3590, J9999** will pend with **Remark Code M3M or M4M** and will be adjudicated in accordance with the Corporate Medical Policy.

Liability: A participating provider will be required to write off charges denied as not medically necessary.

HCPCS Code(s):	
C9399	Unclassified drugs or biologics
J3490	Unclassified drugs
J3590	Unclassified biologics

APPENDIX A

Simon Broome Register Diagnostic Criteria.[16]

Definite Familial Hypercholesterolemia
Raised cholesterol
--Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult (aged > 16 years);
AND
--Tendon xanthomas in the patient or in a first (parent, sibling, or child) or second-degree relative (grandparent, aunt, or uncle);
OR
DNA-based evidence of LDL-receptor, familial defective APOB, or PCSK9 mutation.
Possible (or Probable) Familial Hypercholesterolemia
Raised cholesterol
--Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult (aged > 16 years);
AND
Family history of premature myocardial infarction younger than 50 years of age in second-degree relative or younger than 60 years of age in first-degree relative;
OR
Raised cholesterol
--Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult (aged > 16 years);
AND
Family history of raised cholesterol > 7.5 mmol (290 mg/dL) in adult first-degree or second-degree relative or > 6.7 mmol/L (260 mg/dL) in child or sibling aged < 16 years.

LDL-C – Low-density lipoprotein cholesterol; LDL – Low-density lipoprotein; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

APPENDIX B.

Dutch Lipid Network Criteria.[17]

Criteria	**Score**
Family History	
First-degree relative with known premature coronary and/or vascular disease (men < 55 years, women < 60 years)	1
First degree relative with known LDL-C > 95th percentile for age and sex	1
First-degree relative with tendon xanthomata and/or arcus cornealis, OR	2
Children aged < 18 years with LDL-C > 95th percentile for age and sex	2
Clinical History	
Patient with premature CAD (age as above)	2
Patient with premature cerebral or peripheral vascular disease (age as above)	1
Physical Examination	
Tendon xanthomas	6
Arcus cornealis at age < 45 years	4
LDL-C	
LDL-C ≥ 8.5 mmol/L (330 mg/dL)	8

LDL-C 6.5 to 8.4 mmol/L (250 to 329 mg/dL)	5
LDL-C 5.0 to 6.4 mmol/L (190 to 249 mg/dL)	3
LDL-C 4.0 to 4.9 mg/dL (155 to 189 mg/dL)	1
DNA analysis	
Functional mutation LDLR, APOB or PCSK9 gene	8
Stratification	**Total score**
Definite familial hypercholesterolemia	> 8
Probable familial hypercholesterolemia	6 to 8
Possible familial hypercholesterolemia	3 to 5
Unlikely familial hypercholesterolemia	< 3

LDL-C – Low-density lipoprotein cholesterol; CAD – Coronary artery disease; LDLR – Low-density lipoprotein receptor; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.