# Reducing Intracranial atheroSclErosiS with Repatha (RISER)

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# A. Background and Significance

## A.1. Intracranial Atherosclerotic Disease

Intracranial atherosclerotic disease (**ICAD**) is the cause of ischemic stroke in 40% of Asians, 29% of African-Americans, and 10% of Caucasians. These demographics make it the most common cause of stroke in the world.[1–5] A primary goal of stroke treatment is to prevent recurrence.[6,7] From 2000-2010, the average annual rate of recurrence for all causes of stroke was 5%.[8] For patients with treated carotid atherosclerosis, who have excellent medical and surgical options, the rate is below 5%.[9–12] In striking contrast, the WASID study (2005) reported that ICAD patients had a 22.9% annual recurrence. This was improved upon in the SAMMPRIS trial (2011), where aggressive medical management and a personal wellness coach achieved a 12.2% annual recurrence and surgical stenting led to a higher rate (20%).[13,14] Although the medical treatment that is effective for carotid stenosis reduces stroke risk for ICAD patients, there is significant opportunity for improvement.[15–18] Furthermore, many ICAD patients with stroke have minimal stenosis, yet large outwardly remodeling plaques.[19–21] This has led ICAD researchers to expand their focus beyond stenosis alone. High-resolution vessel wall MRI (**vwMRI**) is a powerful tool to study ICAD. Compared to luminal angiography (CTA, MRA, etc.), vwMRI protocols include imaging of both the lumen and, by suppressing blood on MRI, the vessel wall itself. vwMRI has unique potential to identify validated biomarkers of stroke risk that could be used for preliminary trials of novel therapeutic agents to reduce ICAD stroke risk.

## A.2. PCSK9 Inhibition for Patients with ICAD

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, by modifying LDL receptors, have been shown to dramatically lower LDL. There is robust evidence that lowering LDL cholesterol is beneficial in atherosclerotic disease, due to plaque-stabilizing effects. The FOURIER and ODYSSEY studies showed that patients randomized to PCSK9 inhibition had dramatic LDL reduction and a lower overall incidence of stroke (1.2 versus 1.6% of patients over three years). The GLAGOV study showed that, compared to placebo, evolocumab (Repatha) decreased coronary artery plaque volume. GLAGOV also demonstrated a linear relationship between LDL cholesterol reduction and plaque volume regression. However, these findings do not provide adequate evidence that Repatha reduces the risk of ICAD stroke. FOURIER and ODYSSEY did not adjudicate the etiology of stroke and, for the stroke outcome, they included cardioembolic and lacunar strokes, which typically account for up to 50% strokes. The risk reduction from a PCSK9 inhibitor like Repatha would primarily be for patients with large artery atherosclerosis, such as ICAD. As a result, the absolute risk reduction seen in those studies does not represent the potential of Repatha in a patient population at risk for stroke.

## A.3. Repatha

Repatha is an FDA-approved PCSK9 inhibitor shown to reduce the risk of cardiovascular events, including myocardial infarction, stroke, and coronary revascularization. Repatha is a patient-administered subcutaneous injection that is well tolerated. Common side effects include flu-like symptoms, cough, back pain, and dizziness. Further information can be obtained at: (https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/repatha/repatha_pi_hcp_english.pdf).

## A.4. Stenosis and Plaque Atheroma Volume Measured on vwMRI

We will measure both stenosis and atheroma volume to have two primary outcomes with validated biomarker potential. Stenosis is measured using WASID criteria.[13] Atheroma volume is either directly measured or inferred by measuring the area of entire vessel (the outer wall boundary area) on an axial slice and subtracting the lumen area. In a study of middle cerebral artery ICAD, the atheroma volume on vwMRI was larger in the 26 symptomatic patients compared to the 35 asymptomatic patients (12.9±3.1 $mm^2$ vs. 8.2±3.6 $mm^2$, $p<0.001$). A second study enrolled 139 patients with moderate to severe middle cerebral artery atherosclerosis, who contributed 112 culprit and 53 non-

culprit lesions.[22] The combination of stenosis + atheroma burden + luminal area produced an odds ratio of 3.99 (95% CI: 1.74-9.13, p=0.001) for culprit plaque. The GLAGOV study showed that PCKS9 inhibition reduced the percent atheroma volume of coronary arteries over a 78 week treatment period.[23] With atheroma volume now established as a viable biomarker, vwMRI is the optimal test to monitor it and stenosis, both for ICAD and in other locations of the cerebrovasculature, such as the carotid arteries, cervical vertebral arteries, and aortic arch.

### A.5. Impact

The result of this study will be a dataset that lays the foundation for a randomized controlled trial of Repatha in ICAD patients. The data collected in this study will allow us to optimize a future clinical trial designed to demonstrate a reduction in stroke risk, ultimately making more efficient and economical progress towards our ultimate research goal of preventing stroke with Repatha. While we are proposing future studies to reduce ICAD stroke risk, it should be noted that our study will also evaluate the potential for Repatha to decrease cerebrovasculature stenosis and plaque burden, which would be a compelling primary prevention indication.

## B. Approach

### B.1. Study Hypothesis

We hypothesize that inhibition of PCSK9 with Repatha in patients with moderate to severe intracranial atherosclerosis will reduce validated biomarkers of stroke risk (stenosis and percent atheroma volume). To answer our hypothesis, we propose a single arm study of Repatha in 150 patients with a prior history of ischemic stroke and ICAD causing at least 50% stenosis of a major intracranial artery in the Circle of Willis (**"**index artery**"**).

### B.2. Study Design

We will enroll 150 ICAD patients with a prior history of ischemic stroke. Patients will be enrolled at up to 8 medical centers in North America. All patients will receive Repatha for 78 weeks and will have an MRI before beginning study medication and a comparison MRI immediately after completing study medication.

### B.3. Investigational Treatment

The investigational treatment is Repatha 140 mg administered subcutaneously with a single-dose pre-filled pen syringe every 2 weeks for a total of 39 treatments. Dose modification is not allowed.

#### B.3.a. Inclusion Criteria

- Adult patients, ≥ 18 years of age
- History of ischemic stroke, defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction (American Heart Association definition).
- Large vessel atherosclerosis of an intracranial artery in the circle of Willis with 50-99% stenosis by WASID criteria (percent stenosis = (1-[diameter stenosis/diameter normal]) x 100%) on MRA, CTA or DSA
  - Eligible arteries: vertebral (V4), basilar, PCA (P1, P2), MCA (M1, M2), tICA, ACA (A1)
- Current statin use or contraindication to statin
- Fasting LDL-C ≥ 70 mg/dL or LDL-C ≥ 60 mg/dL if lipoprotein (a) > 30 mg/dL; within a year of randomization and on the current statin medication/dose

#### B.3.b. Exclusion Criteria

- Gadolinium or PCSK9 inhibitor allergy
- Acute or chronic kidney disease with eGFR<30 ml/min/1.73m$^2$
- Pacemaker or other MRI contraindications per American College of Radiology guidelines[24]
- Inability to return for 78 week follow-up clinic visit and vwMRI

- Pregnant at time of enrollment

### B.4. Investigational New Drug Status

We will not require an IND. Repatha is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease; and as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia to reduce low-density lipoprotein cholesterol (LDL-C). Our patient population meets these criteria given 1) history of ischemic stroke and 2) presence of moderate to severe ICAD.

### B.5. Patient Recruitment

Patients will be approached first by a member of their clinical care team in order to gain permission for a study member to approach to discuss the study in detail. Only co-investigators or study coordinators on this study will consent patients. Standard consenting procedures will be followed, including giving patients and family members adequate time to discuss the study with the study team and amongst themselves prior to consenting. A full, written, IRB- approved Informed Consent document will be provided to the patient (or representative) for signature after the patient or patient's representative has had time to read it and ask questions. A copy will be given to the patient for his/her records. Proxy consent by legally authorized representatives will be allowed in the case of post-stroke aphasia or other cognitive disability, in order to not bias study entry by stroke severity.

### B.6. Patient Withdrawal

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion. The investigator has the right to withdraw a patient from the study in the event of an intercurrent illness, adverse event, treatment failure, protocol violation, cure, and for administrative or other reasons. An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients will be avoided. Should a patient (or a patient's legally authorized guardian or representative) decide to withdraw, all efforts will be made to complete and report observations as thoroughly as possible. Early termination procedures will be followed.

### B.7. Patient Replacement

Patients prematurely withdrawn from the study can be replaced, if needed, to ensure an adequate number of evaluable patients. The investigator, (in cooperation with the study statistician, if applicable) will decide whether or not to replace withdrawn patients.

### B.8. Investigation Drug Management

At each study site, the drug management will be performed by their respective Investigational Drug Services (IDS). Study drug will be refrigerated at the site at a temperature of 2 to 8ºC; refrigerator temperature will be logged daily. At no time, will product be left unattended or outside the control of an individual knowledgeable with regard to product temperature requirements. Moreover, no one will administer product that has not been maintained according to temperature requirements. Study drug will be shipped at a temperature of 2 to 8°C to the investigator or designee at regular intervals or as needed during the study. During site close-out, and following drug reconciliation and documentation, all opened and unopened vials of study drug will be destroyed -or- returned to Amgen Inc. or designee. All drug accountability records will be kept current. The primary investigator will account for all opened and unopened vials of study drug. These records will contain the dates, quantity, and study medication:

a) dispensed to each patient,
b) returned from each patient (if applicable), and
c) disposed of at the site or returned to Amgen Inc. or designee

All accountability records will be made available for inspection by regulatory agency inspectors.

All drug compliance records will be kept current and will be made available for inspection by regulatory agency inspectors. Study drug will be given to patient at the baseline visit, and preferably at 6 month intervals thereafter. Instructions for shipping study drug to patients are provided in the appendix.

### B.9. Study Timeline

There are two in-person study visits (baseline and 78 week follow-up) when patients will undergo vwMRI, approximately 60 minutes long, with a simultaneous clinical evaluation by a study investigator physician and blood draw. Every 2-4 months, the study coordinator will determine medication adherence, adverse events, or patient-reported recurrent stroke (see **Figure 1**).

**Figure 1:** Schedule of Activities

| | Screen/ Baseline | Day 1 | Day 60 | Day 120 | Day 180 | Day 240 | Day 320 | Day 480 | Day 546 |
|---|---|---|---|---|---|---|---|---|---|
| **Informed Consent** | X | | | | | | | | |
| **Medical History/Current medications** | X | | X | X | X | X | X | X | X |
| **Vitals** | X | | | | | | | | X |
| **Review CTA or MRA[1]** | X | | | | | | | | |
| **Vessel wall MRI** | | X | | | | | | | X |
| **Pregnancy test** | X | | | | | | | | |
| **Creatinine** | X | | | | | | | | X |
| **Lipid panel** | X | | | | | | | | X |
| **Lipoprotein (a)** | X | | | | | | | | X |
| **Apolipoprotein B** | X | | | | | | | | X |
| **Physical exam** | X | | | | | | | | X |
| **Neurological exam** | X | | | | | | | | X |
| **NIHSS** | X | | | | | | | | X |
| **Modified Rankin Scale** | X | | | | | | | | X |
| **Stroke adjudication** | | | X | X | X | X | X | X | X |
| **Adverse event determination** | | | X | X | X | X | X | X | X |
| **Serious adverse events** | | | X | X | X | X | X | X | X |

1. To confirm ICAD of a major intracranial artery

### B.10. Study Duration

- Estimated duration of research (study start to final study deliverable): 2 Years / 6 Months
- Estimated duration of first patient enrolled to last patient out: 2 Year / 0 Months
- Estimated duration for Amgen to supply study drug: 2 Year / 0 Months

## C. Study Endpoints

## C.1. Primary Endpoints

The primary endpoints are nominal change in the stenosis and percent atheroma volume (PAV) of cerebrovasculture arteries from baseline to week 78. We will use measure stenosis and PAV on vessel wall MRI (vwMRI), which evaluates all arteries from the aortic arch to the distal intracranial vasculature in a single scan. The primary endpoints will be analyzed for both: 1) all intra- or extracranial arteries that have at least 25% stenosis, and 2) seperately for the intracranial arteries. Stenosis and PAV will be measured using standard methodology.

**C.1.a. Primary endpoint measurement:** All vwMRIs are on a 3T scanner with a 20- or 32-channel head coil and gadolinium. The field of view is from the aorta to the top of the skull. Sequences include the following for Siemens scanners and equivalents for Phillips and GE:

| **Sequence** | 3D ToF | DWI | 3D FLAIR | 3D MPRAGE | PD SPACE DANTE | 3D SWI | T1 SPACE DANTE | T2 SPACE DANTE |
|---|---|---|---|---|---|---|---|---|
| **Contrast (gadolinium)** | Pre | Pre | Pre | Pre | Pre | Pre | Pre/Post | Post |

*DANTE* = Delay Alternating with Nutation for Tailored Excitation (for blood suppression); *DWI* = Diffusion Weighted Imaging (Tensor technique); *GRE* = Gradient Recalled Echo; *MPRAGE* = Magnetization Prepared Rapid Acquisition Gradient recalled Echo; *PD* = proton density; *SPACE* = Sampling Perfection with Application optimized Contrasts using different flip angle Evolution; *SWI* = susceptibility weighted imaging (with quantitative susceptibility mapping); *ToF* = Time-of-Flight

At the completion of patient enrollment, two neuroradiologists will examine all vwMRIs in three separate viewing sessions to prevent viewer fatigue. They will be given a rater sheet directing them to record findings in the brain and all major vessels of the cerebrovasculature, including:

a) Stenosis: will be identified by the luminal imaging component of the vwMRI protocol (MR angiography of the head and neck). Stenosis will documented on the NIH Stroke CDE "Vessel Imaging Angiography"[25] for all cerebrovasculature vessels from the aorta to distal intracranial vessels. Any vessel with >25% stenosis qualifies for computation of this composite outcome.

b) Percent atheroma volume (**PAV**): We will use MRI-PlaqueView (VPDiagnostics, Seattle, WA) to measure PAV in the aortic arch, cervical carotid, cervical vertebral and all major intracranial arteries. MRI-PlaqueView is a powerful application that allows identification of (a) vessel lumen and outer wall (**OW**), (b) atheroma (both calcified and lipid rich). PAV is measured on the cross-sectional slice with the highest % stenosis. $PAV = \Sigma(OW_{area} - Lumen_{area})/\Sigma OW_{area} \times 1$

## C.2. Secondary endpoint 1

Secondary endpoint 1 is post-contrast plaque enhancement for intracranial arteries and intraplaque hemorrhage for the cartotid artery, which are determined by two experienced neuroradiologist raters. If there is disagreement, then a third rater serves as a tie-breaker. The signal intensity characteristics of both endpoints have been standardized in prior literature.

**C.2.a. Secondary endpoint 1 measurement:**

a) ICAD post-contrast plaque enhancement (**PPE**): is a dichotomous variable evaluated on the T1 pre- and post-gadolinium sequences, with multiplanar reconstruction so the ICAD can be seen in cross section.[26] PPE is defined by placing a region-of-interest over areas of gadolinium enhancement in ICAD to evaluate if it is equal to or exceeds the signal intensity of the pituitary infundibulum, as previously described.[27]

b) Carotid intraplaque hemorrhage (**IPH**): MPRAGE positive plaque is defined as voxels with at least 2-fold signal intensity compared to sternocleidomastoid muscle as previously described. MPRAGE positive plaques can be reliably identified. Kappa values for inter- and intra-rater reliability for detection of MPRAGE positive plaque were 0.806 and 0.818 respectively (very good agreement).[28,29]

c) MRA Flow Dynamics (**MFD**): We will measure MFD using accepted quantitative MRA methodology. The VERiTAS study provided prospective confirmation of the importance of MFD as a biomarker of stroke risk for patients with ICAD. Given that MFD can easily be measured in our vwMRI protocol, we will acquire the data required for its quantification.

### C.3. Secondary endpoint 2

To better understand the mechanism of Repatha's effect on intra- and extracranial atherosclerosis, we will measure the endpoint of change in cholesterol markers [LDL-C, HDL-C, lipoprotein (a), apolipoprotein B, and triglyceride level]. The change in cholesterol markers will be correlated with the primary and secondary study endpoints on vwMRI. Cholesterol values will be measured at the baseline and comparison MRIs, which are 78 weeks apart. If standard of care lab values are available within 30 days of the study visit, they can be used in place of the study lab value. An additional exploratory outcome that we will measure is the composite endpoint of "recurrent stroke," which encompasses new patient-reported symptomatic ischemic stroke, transient ischemic attack, or asymptomatic strokes that emerge between MRIs.

**C.3.a. Secondary endpoint 2 measurement:**

a) At both study MRIs, the study coordinator may collect two blood samples. Standard of care lab values can be used in place of these tests, if the values are from within 30 days of the study visit. If standard of care labs are not available, then the following samples will be tested. One sample may be tested with an i-STAT for creatinine levels prior to the MRI and, in women of child-bearing age who are not on birth control, a bHCG should be tested. The second sample may be sent for testing of LDL-C, HDL-C, triglycerides, apolipoprotein B, and lipoprotein (a), biomarkers of cardiovascular disease risk.

b) At both study visits (baseline vwMRI and follow-up vwMRI), a physician will assess patients and their medical records for stroke. The physician will also have access to the data from the neuroradiologist raters. The endpoint of stroke is defined for all arterial distributions in the cerebrovasculature.

### C.4. Data Collection and Management

Baseline and follow-up patient data are written on a case report form and then entered into a REDCap case report form (**eCRF**) based on the NIH Stroke Common Data Elements (CDE). We will also complete CRFs based on the "Demographics," "Health History," "Prior Health Status," and "Drugs" forms,[25] and utilize the SNOMED coding system for comorbidities.[30] All data analysis is conducted with Stata.

## D. Methodology

### D.1. Statistical methods

We will fit a mixed effects linear regression model, specifically a LOESS smoothing curve, to change in stenosis/PAV and on-treatment LDL-C, HDL-C, and lipoprotein(a). We will also use a multivariable linear regression model with the outcome of the primary endpoints, adjusted for covariates that could be confounders such as age, gender, smoking, statin use/dose and relevant medical comorbidities. The primary endpoints will also be compared to an assumed value of 0% change in stenosis and PAV that would correspond to optimal medical management without a PCSK9 inhibitor. Although, some studies have suggested statin therapy can reduce carotid atherosclerosis, no such effect is known for

ICAD. For this analysis, we will use linear mixed effects model to detect differences in the stenosis and PAV endpoints between patients taking Repatha or the presumed historical control values of 0% change. For the secondary endpoints, we will use logistic and linear regression depending on the nature of the variable and use the primary predictors of on-treatment LDL-C, HDL-C, and lipoprotein(a). For the exploratory endpoint of recurrent stroke, we will use the above mentioned methods as well as a Cox proportional hazards model for the endpoint of recurrent stroke with the observed rate in this study compared to controls matched according to degree to stenosis of the index artery. Due to differences in arterial structure and flow dynamics, there may be a more significant plaque reduction in certain intracranial vessels. We anticipate subgroup analyses, for example comparing change in stenosis or PAV in the middle cerebral artery versus the vertebral artery.

### D.2. Power Analysis

We power our study on the primary endpoint of change in stenosis and PAV. The GLAGOV trial showed 0.95% reduction in PAV for patients randomized to Repatha versus a 0.05% increase in PAV for patients in the placebo arm and was 78 weeks in length. Because the major intracranial arteries have a similar luminal diameter to coronary arteries, we may reasonably expect a 1% reduction in PAV for our 78 week study as documented in previous literature. Patients with intracranial atherosclerosis can be expected to have at least 3 additional sites of atherosclerosis, including extracranial arteries, that will be included in the series of PAV outcomes. Each subject will provide four sites of atherosclerosis and therefore, 4 PAV measurements. This cluster designed study will be modeled by a mixed effects linear regression to account for the cluster of arteries per patient. We obtain >80% power for our sample size of 150 patients, two-sided significance level 0.05, and a conservative assumed standard deviation of 4% from previous studies for the assumed 1% reduction in PAV against the documented control PAV of 0%.[23] With 150 patients, the minimum effect size possible to detect with 80% power is a 0.51% reduction. A 0.50% difference has been reported to be the cutoff to distinguish individuals that experience cardiovascular events versus those who do not.[23] Assuming a withdrawal rate of 25-30%, we would still reach >90% power for a 1% reduction with the above-listed conditions. We do not expect to show a significant reduction in recurrent stroke, but anticipate seeing a trend towards that outcome. This data could be used to accurately construct and power a subsequent trial with the primary outcome of recurrent stroke. Finally, in GLAGOV the linear relationship between change in stenosis, PAV and on-treatment LDL-C was very robust. We will be replicate this finding through means of a generalized linear mixed effects model. Our effective sample size may be sufficiently large enough to match the GLAGOV trial as each patient will be able to contribute an average of 4 arteries giving us an expected sample size between 800 and 1200 dependent on a conservative prediction of intra-class correlation. All reported p-values will be two-sided and deemed significant at the 0.05 level.

### D.3. Loss to Follow-up

Based on the SPRINT MIND trial, we anticipate that up to 25-30% will not complete the follow-up clinic visit or vwMRI, and have accounted for this in our sample size calculation.[31] If less patients than expected return for yearly follow-up MRI scans, we can enroll additional patients as needed, but do not expect this to be necessary or costly if necessary. If we have difficulty finding enough patients to enroll in the study, we will expand enrollment to the VA hospitals at our study sites, which would significantly increase potential patients.

## E. Safety Definitions, Reporting, and Monitoring

### E.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered the study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and

unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug. An AE also includes any worsening (i.e. any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug. The most commonly occurring adverse reactions reported from clinical studies with Repatha were injection site reactions (including erythema/redness, itching, swelling, pain, tenderness), upper respiratory tract signs and symptoms (mainly nasopharyngitis, sinusitis, influenza, and upper respiratory tract infection), back pain, urinary tract infection, and cough. For this study, investigators will record all potential AEs, but the following are always considered as AEs:

a) Increase in ALT: ALT >3 x ULN
b) Allergic events: allergic drug reactions and/or local injection site reactions deemed to be allergic by the Investigator (or have an allergic component), that require consultation with another physician for further evaluation of hypersensitivity/allergy as per the Investigator's medical judgment should be reported as an AE.
c) Overdose with Repatha: An overdose (accidental or intentional) is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic injection counts) and defined as at least five times the intended dose within the intended therapeutic interval (ie, 5 or more injections are administered in <14 calendar days), to be reported using the Term "OVERDOSE (accidental or intentional), indicating the circumstance in parentheses (eg, "overdose [accidental]" or "overdose [intentional]"). The patient should be monitored and appropriate treatment instituted. The circumstances of the overdose should be clearly specified in the verbatim and symptoms, if any, entered on separate AE/SAE forms.
d) Neurologic events: Neurologic events that require additional examinations/procedures and/or referral to a specialist should be reported as an AE. If the event does not require additional examinations/procedures and/or referral to a specialist, it should be reported as a standard AE.
e) Neurocognitive events: Neurocognitive events will be considered as AE.

### E.2. Serious Adverse Event (SAE)

A SAE is any untoward medical occurrence that at any dose:

a) Results in death,
b) Is life threatening, (Note: the term "life-threatening" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe),
c) Requires inpatient hospitalization or results in prolongation of existing hospitalization,
d) Results in persistent or significant disability/incapacity,
e) Is a congenital anomaly/birth defect, or
f) Is a medically important event or reaction. Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

### E.3. Recording and Reporting AEs and SAEs

All AEs and SAEs will be recorded on the REDCap electronic CRF ("eCRF") and in the patient's source documents. Laboratory, vital signs or ECG abnormalities will be recorded as AEs only if they are medically relevant. Unexpected and study drug-related SAEs will also be reported promptly to Amgen Inc. and the FDA under the voluntary MedWatch reporting system. The investigator will promptly report to the IRB all unanticipated problems involving risks to patients. This includes death and all SAEs related to the use of the study drug. To report an SAE, the FDA will be contacted within 24 hours and Amgen Inc. within 7 calendar days.

### E.4. Reporting AEs and SAEs Leading to Withdrawal from the Study

All SAEs and AEs that lead to a patient's withdrawal from the study will be reported to the IRB and to Amgen Inc. within 7 calendar days.

### E.5. Abnormal Laboratory, Vital Signs, or Other Results

The criteria for determining whether an abnormal objective test finding will be reported as an AE are as follows:

a) the test result is associated with accompanying symptoms, and/or
b) the test result requires additional diagnostic testing or medical/surgical intervention, and/or
c) the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the study, significant additional concomitant drug treatment, or other therapy.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Pregnancy occurring in a female patient during the study or within 14 days following the last dose of study drug will be reported to Amgen Inc. within 10 calendar days. After confirmation of pregnancy, patients will no longer be given study drug and will be instructed to refrain from taking additional doses. Follow-up of pregnancy outcomes will be mandatory during the study.

### E.6. Evaluation of Severity

The severity of an AE will be graded by the investigator using a 3–point scale (mild, moderate, or severe) and reported in detail as indicated on the CRF/eCRF and/or SAE form, as appropriate.

a) **Mild:** Does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.
b) **Moderate:** Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.
c) **Severe:** Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

If a laboratory value is considered an AE, its severity will be based on the degree of physiological impairment the value indicates.

### E.7. Evaluation of Causality

The relationship to treatment will be determined by the investigator and reported on the CRF/eCRF and/or SAE form, as appropriate. Events related to atherosclerosis such as primary atherosclerosis complications, will be considered anticipated unless they are fatal or present with unusual features in the context of the underlying condition. When determining causality of such events, the sponsor will consider them in the context of that individual patient's condition. Events that may be considered anticipated in a patient with advanced disease may not be considered anticipated in a patient with milder disease.

The following terms will be used:

a) **Not Related:** likely or clearly due to causes other than the study drug.
b) **Related:** possibly, probably, or definitely related to the study drug.

### E.8. Reasons for Permanent Discontinuation of Study Drug

When attributed to Repatha administration: hypersensitivity or angioedema reactions requiring hospitalization.

### E.9. Investigator Alert notification

UCLA or its designee will inform all investigators participating in this clinical trial, as well as any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the Investigator's Brochure, and has a reasonable suspected causal relationship to the study drug).

### E.10. Premature Termination

The investigator will notify UCLA of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision will be made by the investigator after consultation with UCLA. In all cases, the appropriate IRB and Health Authorities will be informed according to applicable regulatory requirements, and adequate consideration will be given to the protection of the patients' interests.

### E.11. Monitoring of Study Site

The study monitor and/or designee (e.g. contract research organization ("CRO") monitor) will visit the study site prior to enrollment of the first patient, and periodically during the study. In accordance with International Conference on Harmonisation ("ICH") guidelines, the monitor will compare the eCRF entries with the appropriate source documents. Additional review may include, but is not limited to, patient ICFs, documentation of patient recruitment and follow-up, AEs, SAEs, and concomitant therapy; as well as records of study drug dispensing, compliance, and accountability. A copy of the drug dispensing log will be provided to the study monitor upon request.

### E.11.a. Source Document Requirements

Investigator will prepare and maintain adequate and accurate patient records (source documents). The investigator will keep all source documents on file with the CRF. Case report forms and source documents will be available at all times for inspection by authorized representatives of the regulatory authorities.

### E.11.b. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on REDCap eCRFs by trained site personnel. An eCRF will be completed for each and every patient enrolled in the study. After review of the clinical data for each patient, the investigator will provide an electronic signature. A copy of each eCRF page will be retained by the investigator as part of the study record and will be available at all times for inspection by authorized representatives of the regulatory authorities. Corrections to the eCRF will be entered in the eCRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the system. For corrections made via data queries, a reason for any alteration will be provided.

### E.12. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the regulatory authorities. Should this occur, the investigator will be responsible for:

a) Informing UCLA of a planned inspection by the authorities as soon as notification is received
b) Providing access to all necessary facilities, study data, and documents for the inspection or audit
c) Communicating any information arising from inspection by the regulatory authorities to UCLA immediately
d) Taking all appropriate measures requested by the regulatory authorities to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs/eCRFs, medical records, correspondence, ICFs, IRB files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In all instances, the confidentiality of the data will be respected.

## E.13. Ethical and Regulatory Considerations

### E.13.a. Good Clinical Practice Statement

The investigator(s) will conduct the study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

### E.13.b. Informed Consent

The principles of informed consent are described in ICH Guidelines for GCP. UCLA shall have the right to review and comment on the informed consent form. It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each subject in accordance with 21 Code of Federal Regulations Part 50 (unless an exemption under such part has been approved by the IRB and documentation of same can be provided), prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the subject in language that he/she can understand. The ICF will be signed and dated by the subject and by the investigator or authorized designee who reviewed the ICF with the subject. Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF. Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given. The original ICF will be retained by the investigator as part of the patient's study record, and a copy of the signed ICF will be given to the patient. If new safety information results in significant changes in the risk/benefit assessment, the ICF will be reviewed and updated appropriately. All study patients will be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF will be maintained in the patient's study record and a copy will be given to the patient.

### E.13.c. Patients Confidentiality and Data Protection

The investigator will take all appropriate measures to ensure that the anonymity of each study patient will be maintained. The patient's and investigator's personal data will be treated in compliance with all applicable laws and regulations.

### E.13.d. Institutional Review Board /Ethics Committee

An appropriately constituted IRB, as described in ICH Guidelines for GCP, will review and approve:

a) The protocol, ICF, and any other materials to be provided to the patients (e.g. advertising) before any patient may be enrolled in the study
b) Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB will be informed as soon as possible

Ongoing studies will be reviewed by the IRB on an annual basis or at intervals appropriate to the degree of risk. In addition, the IRB will be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study. A copy of the IRB approval letter will be sent to UCLA prior to shipment of drug supplies to the investigator. The approval letter will include the study number and title, the documents reviewed, and the date of the review. Records of the IRB review and approval of all study documents (including approval of ongoing studies) will be kept on file by the investigator.

## E.14. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRFs will be signed by the investigator. This certification form accompanies each set of CRFs.

## E.15. Retention of Records

The investigator will retain all essential study documents, including ICFs, source documents, CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the

study, or longer if a longer period is required by relevant regulatory authorities. Records will be destroyed in a manner that ensures confidentiality.

### E.16. Publication Plan

Within 6 months of study termination, the primary investigator will submit an article detailing the study results for publication in the following medical journals, in order of submission: *New England Journal of Medicine, Stroke, Neurology, JAMA Neurology, Lancet Neurology.*

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# APPENDIX: Drug Shipment to Patients

1. When study medication is given to the coordinator, the hand packaging and labeling process will begin.
2. Study drugs need to be kept in a temperature range of 68°F to 77°F at all times, so to ship study medications we must prepare them with adequate ice packs and a Styrofoam box.
3. You can purchase the Styrofoam box and Ice Gel Pack on Amazon, which have the picture below and are very inexpensive.



4. Please ensure you keep the ice pack in a 68°F to 77°F temperature location at least 24 hours prior to shipment of drug.
5. Once the packaging is completed, prior to sending it to Fedex or UPS please ensure "UN3373 Biological Substance Category B" Labels/Stickers are attached on the box.
6. Once shipment is ready, you may contact UPS or Fedex via the internal mail office within institute. Please be sure that your shipment is by over-night shipping.
7. Once the study drugs are delivered to the participant, the study coordinator is required to contact participants to ensure study drugs were received and are not damaged.