Title Page

Protocol Title:		A Phase 1b/2a Study to Evaluate the Safety and Efficacy of AMG 592 in Subjects With Active Rheumatoid Arthritis With Inadequate Response to Standard of Care Therapy
Short Protocol Title:		Safety and Efficacy of AMG 592 in Subjects with Active Rheumatoid Arthritis
Protocol Number:		20170149
Investigational Product:		AMG 592
Trade Name:		not applicable
Sponsor	**Name of Sponsor:**	Amgen Inc
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EudraCT Number:		2017-001944-36
NCT Number:		**NCT03410056**
Protocol Date:		**Document Version** / **Date** Original / 26 June 2017 Amendment 1 / 23 May 2018 Amendment 2 / 26 July 2018 **Amendment 3 / 06 June 2019**
Version/Date:		**Data Element Standards Version** 5.0

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Investigator's Agreement:

I have read the attached protocol entitled A Phase 1b/2a Study to Evaluate the Safety and Efficacy of AMG 592 in Subjects with Active Rheumatoid Arthritis With Inadequate Response to Standard of Care Therapy, dated **06 June 2019**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

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

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

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1. Protocol Synopsis

Protocol Title: A Phase 1b/2a Study to Evaluate the Safety and Efficacy of AMG 592 in Subjects with Active Rheumatoid Arthritis With Inadequate Response to Standard of Care Therapy

Short Protocol Title: Safety and Efficacy of AMG 592 in Subjects with Active Rheumatoid Arthritis

Study Phase: Phase 1b/2a

Indication: Rheumatoid Arthritis (RA)

Rationale

This is a double-blind, placebo-controlled, multicenter phase 1b/2a study to evaluate the safety and efficacy of AMG 592 in subjects with active RA. The phase 1b part of the study will evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of AMG 592 and will define the maximum tolerated dose. This information will be used to determine the recommended phase 2a dose (RP2D) for the phase 2a part of the study. The phase 2a part of the study will assess the efficacy and safety of AMG 592 in subjects with moderate to severe RA treated with the RP2D.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
Phase 1b • To evaluate the safety and tolerability of subcutaneous (SC) dose administrations of AMG 592 in subjects with active RA	**Phase 1b** • Treatment-emergent adverse events. • Clinically significant changes in vital signs, laboratory safety tests, and electrocardiograms (ECGs)
Phase 2a • To evaluate the efficacy of AMG 592 at week 12 as measured by the American College of Rheumatology 20% improvement criteria (ACR 20) in adult subjects with moderate to severe RA	**Phase 2a** • ACR 20 at week 12

Objectives	Endpoints
Secondary	
Phase 1b • To characterize the pharmacokinetic (PK) profile following treatment with AMG 592	Phase 1b • AMG 592 serum concentration and PK parameters including, but not limited to, maximum observed concentration (C_{max}), the time of maximum observed concentration (T_{max}), and area under the concentration-time curve (AUC_{tau}) after the first and last doses. Area under the concentration-time curve over the dosing interval will be calculated & reported for each dosing regimen
• To evaluate the incidence of anti-AMG 592 antibody formation and cross-reactivity to human IL-2.	• Anti-AMG 592 antibodies and cross-reactivity to IL-2. • Anti-AMG 592 and anti-IL 2 neutralizing antibodies
Phase 2a • To evaluate the effect of treatment with AMG 592 on other measures of disease activity at week 12	**Phase 2a** • ACR 50/70 at weeks 12 • Disease activity score (28 joint) calculated using the erythrocyte sedimentation rate formula (DAS28-ESR) score and change from baseline at week 12 • Disease activity score (28 joint) calculated using the C-reactive protein formula (DAS28-CRP) score and change from baseline at week 12
• To evaluate the safety of AMG 592	• Treatment-emergent adverse events. • Clinically significant changes in vital signs, laboratory safety tests
• To characterize the PK of AMG 592 in subjects with RA	• AMG 592 serum concentration and PK parameters

Hypotheses

Phase 1b:

AMG 592 will be safe and well tolerated in subjects with active RA.

[redacted]

Overall Design

Phase 1b

The phase 1b part of the study is a double-blind, placebo controlled, multiple ascending dose (MAD) study to evaluate the safety, PK, and PD of AMG 592 in subjects with active RA with inadequate response to standard of care therapy (ie, methotrexate and other standard of care therapies as defined below in the summary of eligibility criteria and Section 6.1 and 6.2). Subjects will be treated for a total of 12 weeks after which they will be followed for an additional 6 weeks for safety and additional PK/PD data collection.

The phase 1b will include 4 **planned** dosing-cohorts. Subjects within a dosing-cohort will be randomized in a 3:1 ratio to AMG 592 (n = 6) or placebo (n = 2) as follows: cohort 1 [redacted]; cohort 2 [redacted] cohort 3 [redacted] and cohort 4 [redacted] in addition to standard of care therapy. **Approximately 8 additional subjects (6 AMG 592; 2 placebo) may be enrolled into each of cohorts 2 and 3.** Dosing cohorts will enroll sequentially with the exception of cohorts 2 and 3, which will enroll concurrently. A Dose Level Review Meeting (DLRM) will convene after the last subject in each cohort completes the week 4 visit. The exception is for cohorts 2 and 3 where **an initial** DLRM will convene after the **first 16** enrolled **subjects (8** in **each cohort) complete** the week 4 visit **and a second DLRM will convene after the remaining 16 enrolled subjects (8 in each cohort) complete the week 4 visit**. The decision to dose the next cohort will be based on the aggregated review of safety data. After incidents of interest (including selected adverse events or intolerable PD levels) are observed, a Bayesian logistic regression model (BLRM) (Bailey et al, 2009; Neuenschwander et al, 2008) will be implemented to model these events to aid dosing decisions before each DLRM. DLRM members will be responsible for dosing recommendations (followed by an Amgen decision), which may include escalation to the next planned dose, escalation to an intermediate dose (a dose lower than the next planned dose), de-escalation to a lower dose; continuation, delay, or termination of dosing. Additional dosing cohorts may be added **and/or existing cohorts may be expanded** based on emerging data. [redacted]

[redacted] The phase 2a part of the study will commence after a RP2D is identified in the phase 1b part of the study. [redacted]

Number of Subjects

In the phase 1b part of the study**, sufficient subjects will be randomized to yield approximately 48 subjects** (**approximately 36 randomized** to AMG 592 and **12 randomized** to placebo**; see Section 5.2.1**). **The total sample size may be higher than 48 subjects if, following a DLRM recommendation additional dosing cohorts**

are added and/or existing cohorts are expanded, or subjects are replaced as per Section 5.2.1. Additional subjects may be enrolled in each cohort to enable all screened eligible subjects to participate in the study. Within each cohort subjects will be randomized to AMG 592 or placebo in a 3:1 ratio.

[redacted]

Summary of Subject Eligibility Criteria

Subjects must be adults with active RA and must be receiving treatment with methotrexate (oral or subcutaneous) for ≥ 12 weeks and on a stable dose ≥ 15 mg weekly for ≥ 8 weeks prior to day 1. For the phase 1b part of the study, subjects must have a DAS28-CRP > 2.6 at screening and the concurrent use of other non-biological disease modifying anti-rheumatic drugs (DMARD) is allowed. For the phase 2a part of the study, subjects must have ≥ 6 swollen joints (based on 66-joint count) and ≥ 6 tender joints (based on 68-joint count) at screening and baseline and a C-reactive protein (CRP) greater than the upper limit of normal at screening. Subjects must be free of infections and significant concurrent medical conditions and laboratory abnormalities. Subjects must have negative test for tuberculosis, hepatitis B and C, human immunodeficiency virus (phase 1b only), and urine drug and alcohol. Women of childbearing potential must have a negative pregnancy test at screening and baseline and must agree to use a highly effective method of birth control.

For a full list of eligibility criteria, please refer to Section 6.1 to 6.2.

Treatments

AMG 592 and placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. Both are liquid formulations presented in highly similar glass vials and stored in the same manner. Placebo will be presented in similar containers and stored in the same manner as AMG 592. AMG 592 or placebo will be administered by subcutaneous injection [redacted]

In the phase 1b part of the study, 4 dose cohorts are planned (cohort 1: [redacted] cohort 2: [redacted] cohort 3: [redacted] and cohort 4: [redacted]).

[redacted]

Procedures

Written informed consent must be obtained from all subjects before any study-specific screening procedures are performed. The following procedures will occur per the schedule of activities: medical and medication history, physical examination, physical measures, vital signs, electrocardiograms, concomitant medication assessment, tender and swollen joint assessment and count, clinical outcome assessments, tuberculosis testing, urinalysis, and blood draw for serum chemistry, hematology, hepatitis B and C testing, human immunodeficiency virus testing (phase 1b only), CRP, ESR, PK/PD, anti-AMG 592 antibodies, biomarker development and pharmacogenetics sample. Women of childbearing potential will have pregnancy tests performed at screening and during the study. Safety assessments including adverse events, serious adverse events, and disease related events assessments will be performed throughout the safety follow-up.

For a full list of study procedures, including the timing of each procedure, please refer to Section 9.2 and the Schedule of Activities in Table 2-1, Table 2-2 and Table 2-3.

Statistical Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, PD, and biomarker data. Descriptive statistics on continuous measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Data will be presented and summarized by treatment and also by time as appropriate.

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment emergent adverse events will also be provided.

The analyses of safety laboratory endpoints will include summary statistics at selected timepoints by treatment group. Shifts in grades of safety laboratory values between the baseline and the worst on-study value will be tabulated.

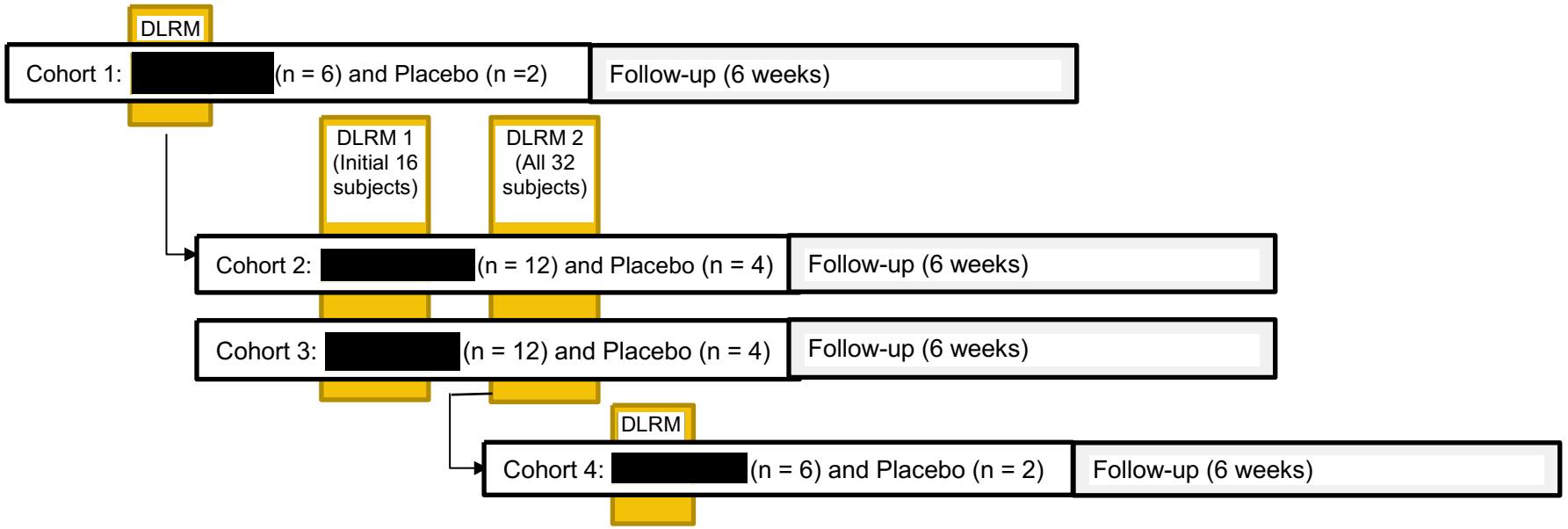
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor Name: Amgen Inc

2. Study Schema and Schedule of Activities

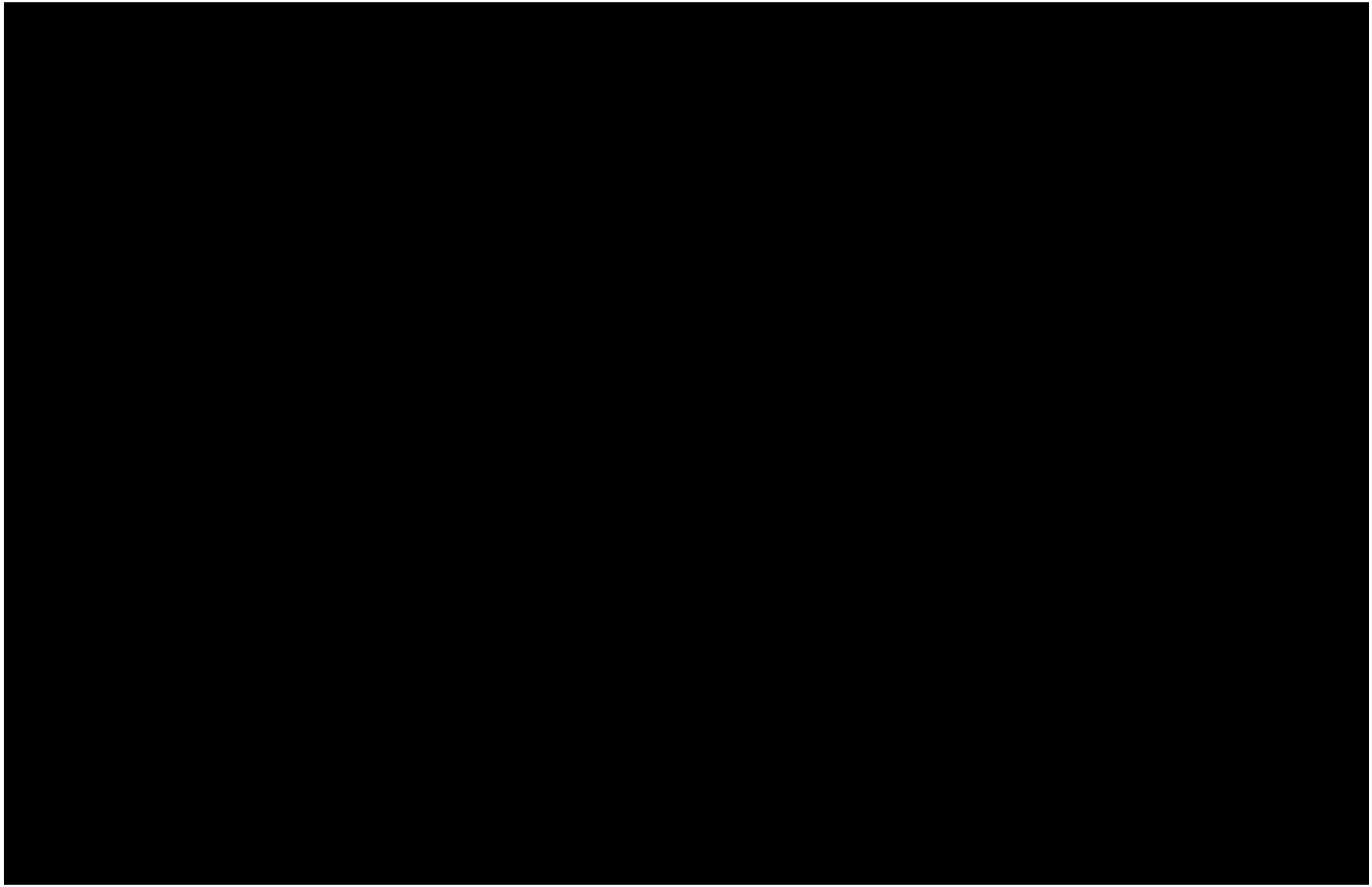
2.1 Study Schema

Figure 2-1. Study Schema Phase 1b



[redacted]
Doses and size of subsequent treatment cohorts may change as determined by safety, BLRM by logistic regression modeling, and pharmacokinetic/pharmacodynamic modeling:

- DLRM: 4 weeks after last subject in cohort enrolled except for cohorts 2 and 3 where an initial DLRM (DLRM 1) will convene after the first 16 enrolled subjects (8 in each cohort) completes the week 4 visit and a second DLRM (DLRM 2) will convene after the remaining 16 enrolled subjects (8 in each cohort) complete the week 4 visit.
- Treatment Period: 12 weeks
- Follow-up: 6 weeks after week 12 for collection of additional safety, pharmacokinetic, pharmacodynamics data. For subjects who complete the study at week 18, the visit includes all required safety follow-up collection. All subjects who terminate the study early (ie, prior to completing the week 18 visit) will complete an Early Termination visit consisting of all assessments included in the week 12, day 85 pre-dose visit. In addition, a safety follow-up visit will occur 6 weeks (± 3 days) after the last dose of investigational product to collect all required safety data including of adverse events, serious adverse events, disease related events, concomitant therapies, safety labs/assessments, anti-AMG 592 antibody, and urine pregnancy test.



2.2 Schedule of Activities

Table 2-1. Phase 1b Schedule of Activities Screening and Treatment Period

	Screening	BL	Treatment Period																												
Study week											1		2	3	4	5	6	7	8	9	10	11	12								
Study day	-28	-1	1				2	3	4	8	11	15	22	29	36	43	50	57	64	71	78	85					86	87	88		
Hours post dose			Predose	0	0.25-2.0	6	12	24	48													Predose	0	0.25-2.0	6	12	24	48	72		
GENERAL AND SAFETY ASSESSMENTS																															
Informed consent	X																														
Inclusion and exclusion criteria	X	X	X																												
Demographics	X																														
Physical examination	X																					X									
Height	X																														
Weight	X		X																			X									
Medical history	X	X																													
Substance use	X	X	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X	X	X		
Activity	X	X												X				X				X									
ECG triplicate [a]	X	X				X	X	X			X		X		X				X				X								
Vital signs	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest X-ray [b]	X																														
Adverse events [c]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Serious adverse events [c]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Disease-related events [c]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Prior therapies review	X	X	X																												
Concomitant therapies review [c]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X	X	X	
LABORATORY ASSESSMENTS																															
Serum and/or urine pregnancy test [c, d]	X	X													X			X				X									
Tuberculosis test [e]	X																														
Urine drug/alcohol screen	X	X																													
HIV, Hepatitis B and C [f]	X																														
CRP & ESR [c, f]	X	X												X				X				X									
Chemistry [c, f]	X	X						X			X		X		X				X			X									
Hematology [c, f]	X	X						X			X		X		X		X		X		X	X									
FSH [g]	X																														
Urinalysis	X																														
PBMC [c, f]			X								X				X				X			X									
RF & Anti-CCP antibody [f]	X																														

Footnotes defined on next page

Table 2-1. Phase 1b Schedule of Activities Screening and Treatment Period

	Screening	BL	Treatment Period																											
Study week											**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**							
Study day	**-28**	**-1**	**1**					**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**					**86**	**87**	**88**
Hours post dose			**Predose**	**0**	**0.25-2.0**	**6**	**12**	**24**	**48**														**Predose**	**0**	**0.25-2.0**	**6**	**12**	**24**	**48**	**72**
[redacted]																														
PHARMACOKINETICS AND ANTIBODIES																														
Pharmacokinetic samples [f]			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X
Anti-AMG 592 antibody [f]			X										X		X				X				X							
BIOMARKER AND PHARMACOGENETICS																														
Biomarker development sample [f]			X								X		X		X				X				X							
Pharmacogenetics sample [i]			X																											
[redacted]																														

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BL = baseline; ECG = electrocardiogram; HIV = human immunodeficiency virus; FSH = follicle stimulating hormone; [redacted] SFU = safety follow-up; RF = rheumatoid factor; anti-CCP = anti-cyclic citrullinated peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PBMC = peripheral blood mononuclear cell; [redacted] PK = pharmacokinetic.

[a] Three sets of triplicate ECGs will be collected at the Day -1 visit. At screening and after Day -1 triplicate ECGs will be collected. See Section 9.2.3.3.

[b] Only for subjects with a positive tuberculosis test (ie, positive purified protein derivative [PPD] or indeterminate Quantiferon)

[c] For subjects who complete the study at week 18, the visit includes all required safety follow-up data collection. All subjects who terminate the study early (ie, prior to completing the week 18 visit), will complete an Early Termination visit consisting of all assessments included in the week 12, day 85 pre-dose visit. In addition, a safety follow-up visit will occur 6 weeks (± 3 days) after the last dose of investigational product to collect all required safety data including adverse events, serious adverse events, disease related events, concomitant therapies, safety labs/assessments, anti-AMG 592 antibody, and urine pregnancy test.

[d] For women of childbearing potential, serum pregnancy test is required at screening. All other pregnancy tests are urine. Positive urine pregnancy test should be confirmed with serum pregnancy test.

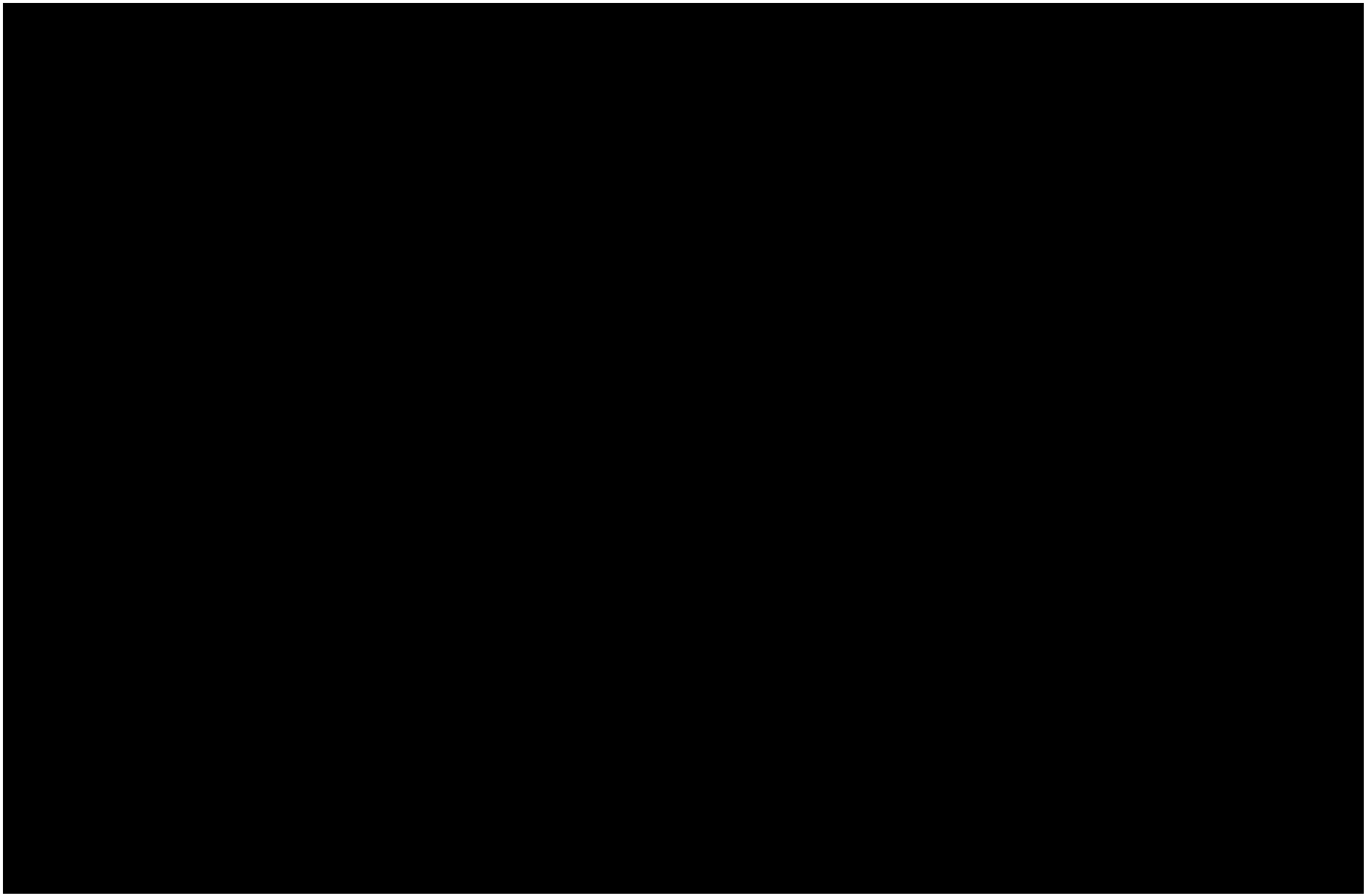
[e] Either a PPD or Quantiferon test will be done during screening.
[f] All clinical laboratory (ie, chemistry, hematology) and pre-dose blood samples must be collected prior to administration of investigational product. Pharmacokinetic (PK), pharmacodynamic and antibody blood samples may not be drawn through a central or peripheral line. PK samples should be collected at the exact nominal time point as noted. If unable to collect a PK sample at the specified nominal time point collect it as close as possible to the nominal time point and record the actual collection time. PK samples not collected at exact nominal time point will not be considered protocol deviations.
[g] Can be done as a part of the clinical chemistry.
[redacted]
[i] DNA will be extracted only in subjects who provide additional consent for pharmacogenetics testing.
[redacted]

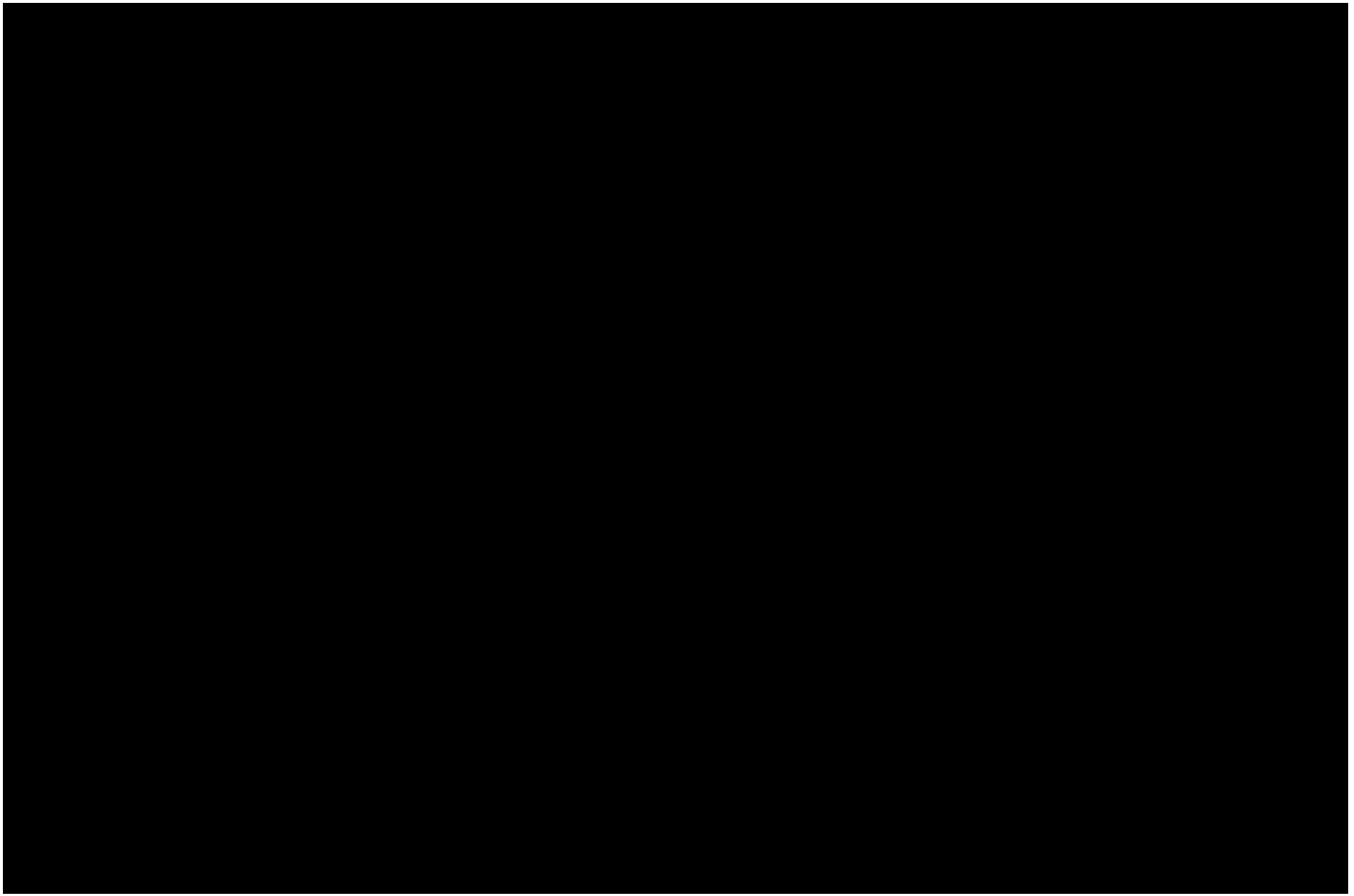
Table 2-2. Phase 1b Schedule of Activities Follow-up

	Follow-up			
Study week	**13**	**14**	**16**	**18/SFU[a]/EOS**
Study day	**92**	**99**	**113**	**127**
GENERAL AND SAFETY ASSESSMENTS				
Weight				X
Vital signs	X	X	X	X
Adverse events	X	X	X	X[a]
Serious adverse events	X	X	X	X[a]
Disease-related events	X	X	X	X[a]
Concomitant therapies review	X	X	X	X[a]
LABORATORY ASSESSMENTS				
Urine pregnancy test				X[a]
CRP and ESR				X[a]
Hematology		X	X	X[a]
Chemistry				X[a]
PBMC				X[a]
[redacted]				
PHARMACOKINETICS AND ANTIBODIES				
Pharmacokinetic samples	X	X	X	X
Anti-AMG 592 antibody				X
BIOMARKER				
Biomarker development sample				X

SFU = Safety follow-up; EOS = end of study for individual subject; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PBMC = peripheral blood mononuclear cell.

[a] For subjects who complete the study at week 18, the visit includes all required safety follow-up data collection. All subjects who terminate the study early (ie, prior to completing the week 18 visit), will complete an Early Termination visit consisting of all assessments included in the week 12 day 85 pre-dose visit. In addition, a safety follow-up visit will occur 6 weeks (± 3 days) after the last dose of investigational product to collect all required safety data including adverse events, serious adverse events, disease related events, concomitant therapies, safety labs/assessments, anti-AMG 592 antibody, and urine pregnancy test.





3. Introduction

3.1 Study Rationale

The phase 1b part of this study is a double-blind, placebo controlled, multiple ascending dose (MAD) study to evaluate the safety and tolerability of AMG 592 in subjects with active rheumatoid arthritis (RA) and to determine the recommended phase 2a dose (RP2D) for the phase 2a part of the study. The phase 2a part of this study is a proof of concept study to evaluate efficacy and safety of AMG 592 in subjects with moderate to severe RA. There are no data available yet demonstrating the use of AMG 592 in active rheumatoid arthritis patients who are inadequately responding to methotrexate. This study will help determine if AMG 592 could be a useful therapeutic agent in the current treatment landscape where subjects use methotrexate as a part of standard of care and have ongoing disease activity that requires additional treatment.

3.2 Background

3.2.1 Disease

Rheumatoid arthritis is an incurable, chronic, disabling autoimmune disease that affects 0.5% to 1% of the population and is 3 times more prevalent in women than in men. It is characterized by inflammation of the membrane lining in the joints, leading to joint damage and bone destruction and causing severe disability and increased morbidity and mortality. The current therapeutic approach is to start with disease modifying anti- rheumatic drugs (DMARDs) early in the illness to prevent joint damage, and conventional DMARDs such as methotrexate have been the mainstay of treatment for decades. A significant advance in the management of RA is the use of biological agents, including multiple tumor necrosis factor (TNF)-blockers, B-cell depletion (rituximab), anti-interleukin-6 receptor monoclonal antibody (tocilizumab), and agents which interfere with T-cell activation (abatacept). However, up to a third of patients do not adequately respond to treatment, and about 50% stop responding to any particular DMARD within 5 years, either owing to lack of efficacy or following the development of adverse events. Up to 50% of patients with RA are disabled within 10 years of the onset of disease and overall life expectancy is reduced (Emery, 2010; Weinblatt, 1996).

3.2.2 T regulatory Cells in Rheumatoid Arthritis

T regulatory cells (Tregs) are a subset of CD4 T cells that suppresses inflammation and whose numbers and function are maintained by interleukin 2 (IL-2). Many inflammatory conditions, including RA, are characterized by a loss in the homeostatic balance between Tregs and effector T cells or by defects in Treg function.

Several studies have demonstrated reduced Treg numbers in RA patients compared to healthy subjects or a lower ratio of Treg to pro-inflammatory T cells such as TH17 or Th1 T cells in RA blood or synovial tissue (Morita et al, 2016; Guggino et al, 2014; Samson et al, 2012; Behrens et al, 2007). RA is also associated with defects in Treg function such as impaired suppression of inflammatory cytokine production (Ehrenstein et al, 2004). Clinical improvement in response to RA therapies correlates with increased Treg numbers, suggesting that correction of this imbalance by increasing Tregs, may play a role in disease amelioration (Kikuchi et al, 2015; Samson et al, 2012; Nadkarni et al, 2007).

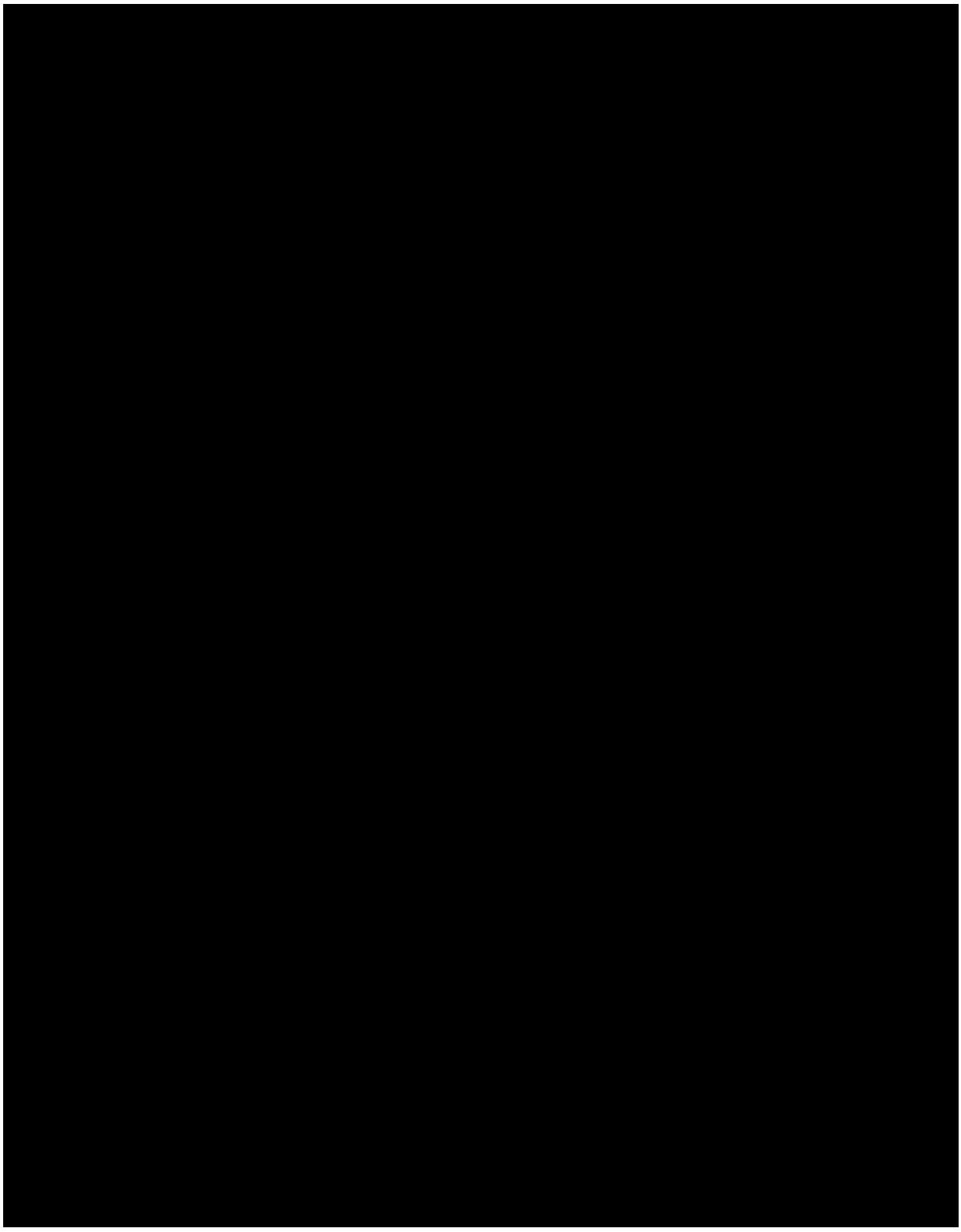
3.2.3 Low Dose Interleukin 2 in Inflammatory Disease

Low dose IL-2 (aldesleukin) has been shown to increase Treg numbers in multiple inflammatory diseases such as systemic lupus erythematosus ([SLE] Humrich et al, 2015), Type 1 Diabetes (Yu et al, 2015), chronic graft versus host disease ([GVHD] Koreth et al, 2011), hepatitis c virus induced vasculitis (Sadoun et al, 2011) and alopecia areata (Castela et al, 2014) as well as to correct defects in Treg function in SLE (von Spee-Mayer et al, 2015), Type 1 Diabetes (Long et al, 2010; Long et al, 2012) and GVHD (Matsuoka et al, 2013). Genetic variants of the IL-2 receptor have been associated with the severity of RA joint destruction and persistence (van Steenbergen et al, 2015).

The therapeutic efficacy of low dose IL-2 has been studied in chronic GVHD (Koreth et al, 2011; Koreth et al, 2016), hepatitis C induced vasculitis (Sadoun et al, 2011), SLE (Humrich et al, 2015), and alopecia areata (Castela et al, 2014). The clinical response to low dose IL-2 has been promising in these small early phase studies in multiple diverse inflammatory conditions. In all of these conditions the overall safety and tolerability profile of low-dose IL-2 has been acceptable with mild to moderate constitutional symptoms associated with higher levels of exposure. However, the therapeutic window between adequate Treg enrichment and stimulation of effector cells is narrow and may limit achievement of optimal Treg expansion. For instance, in a recent Phase 1b clinical trial of chronic GVHD (ClinicalTrials.gov NCT00529035), an IL-2 dose of 3 x 10^6 IU/m^2 daily induced persistent National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grade 1 constitutional symptoms (fever, malaise, and arthralgia) necessitating a 50% dose reduction (Koreth et al, 2011). In addition adesleukin can activate

pro-inflammatory/effector lymphocytes such as CD4+ T effector cells (Teff) and natural killer (NK) cells, which may compromise efficacy and safety.

These data suggest the potential for a therapeutic agent with greater Treg selectivity and a prolonged PD effect compared with IL-2.



[redacted]

3.2.5 Risk Assessment

As of 12 March 2019, approximately 100 subjects have received at least 1 dose of AMG 592. Repeated subcutaneous doses of up to [redacted] **have been studied for up to 3 months in subjects with RA and systemic lupus erythematosus.** The most common adverse event **experienced by subjects was** mild (grade 1) painless erythema at or near the injection site, sometimes accompanied by pruritus, that was self-resolving. **Two serious hypersensitivity reactions to AMG 592**

have been reported. In addition, worsening arthritis deemed related to AMG 592 has been reported in the ongoing 20170149 study. The majority of these events were reported by a single site. No clinically significant therapeutic related abnormalities in electrocardiograms, hematological or biochemical laboratory investigations, or vital signs have been reported. More detailed information about the known and expected risks and reasonably expected adverse events of AMG 592 may be found in the Investigator's Brochure.

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
Phase 1b • To evaluate the safety and tolerability of subcutaneous (SC) dose administrations of AMG 592 in subjects with active RA	**Phase 1b** • Treatment-emergent adverse events. • Clinically significant changes in vital signs, laboratory safety tests, and electrocardiograms (ECGs)
Phase 2a • To evaluate the efficacy of AMG 592 at week 12 as measured by the American College of Rheumatology 20% improvement criteria (ACR 20) in adult subjects with moderate to severe RA	**Phase 2a** • ACR 20 at week 12
Secondary	
Phase 1b • To characterize the pharmacokinetic (PK) profile following treatment with AMG 592	**Phase 1b** • AMG 592 serum concentration and PK parameters including, but not limited to, maximum observed concentration (C_{max}), the time of maximum observed concentration (T_{max}), and area under the concentration-time curve (AUC_{tau}) after the first and last doses. Area under the concentration-time curve over the dosing interval will be calculated & reported for each dosing regimen
• To evaluate the incidence of anti-AMG 592 antibody formation and cross-reactivity to human IL-2.	• Anti-AMG 592 antibodies and cross-reactivity to IL-2. • Anti-AMG 592 and anti-IL 2 neutralizing antibodies
Phase 2a • To evaluate the effect of treatment with AMG 592 on other measures of disease activity at week 12	**Phase 2a** • ACR 50/70 at weeks 12 • Disease activity score (28 joint) calculated using the erythrocyte sedimentation rate

Objectives	Endpoints
	formula (DAS28-ESR) score and change from baseline at week 12 • Disease activity score (28 joint) calculated using the C-reactive protein formula (DAS28-CRP) score and change from baseline at week 12
• To evaluate the safety of AMG 592	• Treatment-emergent adverse events. • Clinically significant changes in vital signs, laboratory safety tests
• To characterize the PK of AMG 592 in subjects with RA	• AMG 592 serum concentration and PK parameters

Exploratory
[redacted]

[redacted]

4.2 Hypotheses

Phase 1b:

AMG 592 will be safe and well tolerated in subjects with active RA.

[redacted]

5. Study Design

5.1 Overall Design

5.1.1 Phase 1b Study Design

The phase 1b part of the study is a double-blind, placebo controlled, MAD study to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of AMG 592 in subjects with active RA with inadequate response to standard of care therapy. Subjects within a dosing cohort will be randomized in a 3:1 ratio to AMG 592 or placebo in addition to standard of care therapy as shown in Table 5-1. AMG 592 or placebo will be administered [redacted] by subcutaneous (SC) injection. Dosing cohorts will enroll sequentially with the exception of cohorts 2 and 3, which will enroll concurrently and share dose level review **meetings (DLRMs**).

[redacted]

After the last subject enrolled in each cohort completes the week 4 visit, a DLRM will convene to determine the acceptability of dose escalation. The exception is for cohorts 2 and 3 where **an initial** DLRM will convene after the **first 16** enrolled **subjects (8** in **each cohort) complete the week 4 visit and a second DLRM will convene after the remaining 16 enrolled subjects (8 in each cohort) complete** the week 4 visit. The decision to dose the next cohort will be based on the aggregated review of safety data. After incidents of interest (including selected adverse events or intolerable PD levels) are observed, a Bayesian logistic regression model (BLRM) (Bailey et al, 2009; Neuenschwander et al, 2008) will be implemented to model these events before each DRLM to aid dosing decisions. DLRM members may also consider available aggregated summaries of emerging safety, PK and PD data.

Amgen DLRM members may consider safety, PK, PD data from other completed and ongoing phase 1b AMG 592 studies to aid in dosing decisions. Emerging safety, PK and PD data from ongoing AMG 592 studies may be used to support decisions to skip dosing cohorts, reduce dosing cohort size or change doses for a given cohort. If emerging safety data from other ongoing studies is used in support of dosing decisions, a dose will only be declared tolerable if it is supported by safety from at least 5 subjects at or above this dose level across all phase 1b studies. DLRM members will be responsible for dosing recommendations (followed by an Amgen decision), which may include escalation to the next planned dose, escalation to an intermediate dose (a dose lower than the next planned dose), de-escalation to a lower dose; continuation, delay, or termination of dosing.

Additional dosing cohorts may be added **and/**or **existing cohorts may be expanded** based on emerging data. These cohorts may be used to explore alternate dosing levels and/or dosing schedules or add additional subjects at previously given dose levels. A DLRM is required for escalation to higher doses but not for allocation of additional subjects to doses equivalent to or lower than previously given that have been deemed

tolerable. Additional dose levels will not exceed [redacted] For additional details on the DLRM see Appendix 3.

Subjects will be treated for a total of 12 weeks after which they will complete a 6-week follow-up until week 18 for collection of additional safety, PK and PD data as described in the Schedule of Activities (Table 2-2). For subjects who complete the study at week 18, the visit includes all required safety follow-up data collection. All subjects who terminate the study early (ie, prior to completing the week 18 visit), will complete an Early Termination visit consisting of all assessments included in the week 12 day 85 pre-dose visit. In addition, a safety follow-up visit will occur 6 weeks (± 3 days) after the last dose of investigational product to collect all required safety data including adverse events, serious adverse events, disease related events, concomitant therapies, safety labs/assessments, anti-AMG 592 antibody, and urine pregnancy test.

[redacted] The phase 2a part of the study will commence after a RP2D is identified in the phase 1b part of the study. [redacted]

[redacted]

[redacted]

The overall study designs for the phase 1b [redacted] parts of the study are described by the study schemas in Section 2.1. The endpoints are defined in Section 4.1.

5.2 Number of Subjects

In the phase 1b part of the study sufficient subjects will be randomized to yield approximately 48 evaluable subjects (approximately 36 randomized to AMG 592 and 12 randomized to placebo; see Section 5.2.1). The total sample size may be higher than 48 subjects if, following a DLRM recommendation, additional dosing cohorts are added and/or existing cohorts are expanded, or if subjects are replaced as per Section 5.2.1. Additional subjects may be enrolled in each cohort to enable all screened eligible subjects to participate in the study. Within each cohort subjects will be randomized to AMG 592 or placebo in a 3:1 ratio.

[redacted]

Subjects in this clinical investigation shall be referred to as "subjects". For the sample size justification, see Section 10.1.

5.2.1 Replacement of Subjects

In the phase 1b part of the study subjects who **are** randomized but **discontinue** investigational **medicinal** product **before completing the week 4 visit may** be replaced.

[redacted]

5.2.2 Number of Sites

Approximately **18** sites in North America and Europe will participate in the phase 1b part of the study [redacted] Sites that do not enroll subjects within 3 months of site initiation may be closed.

5.3 End of Study

5.3.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

[redacted]

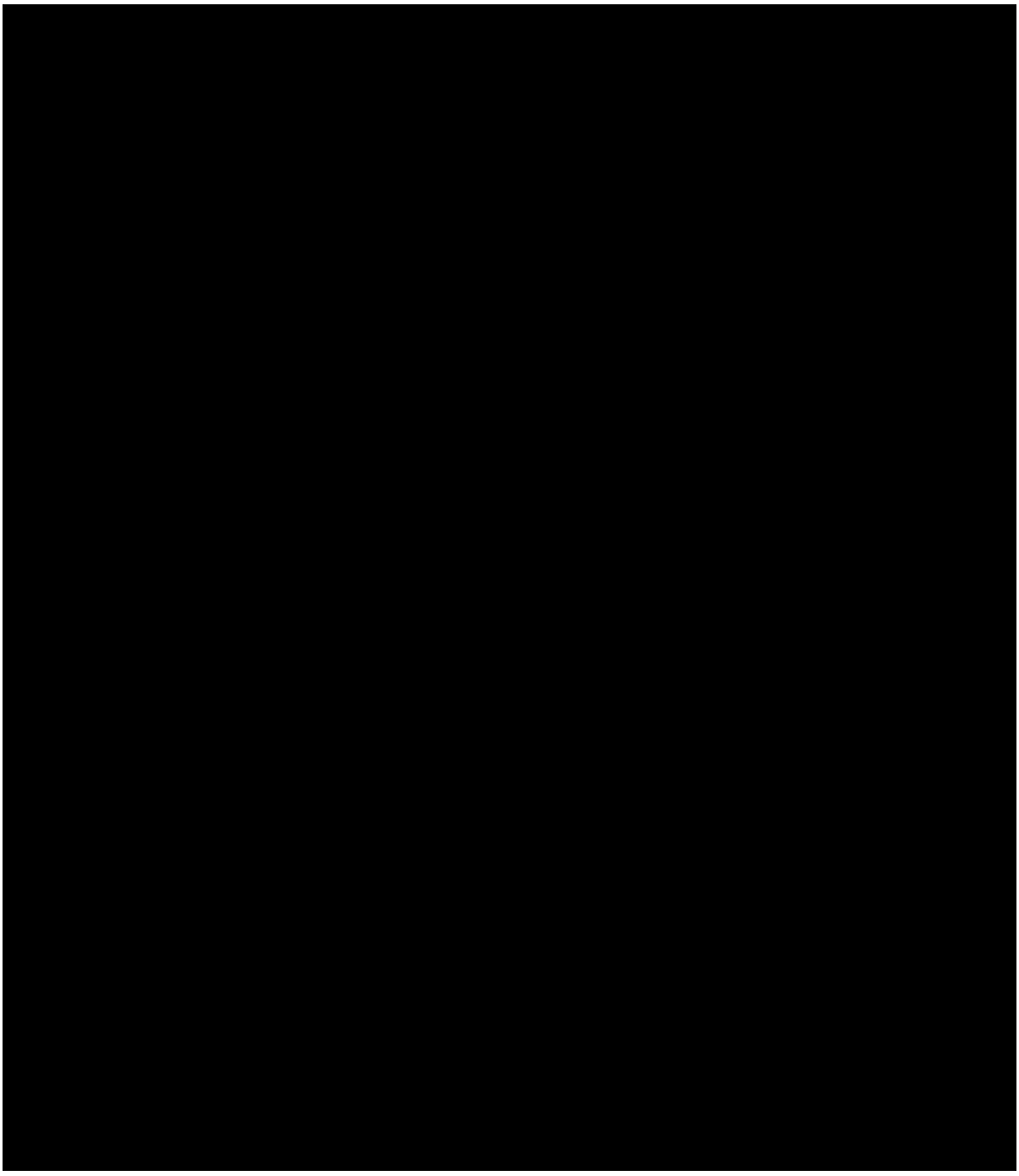
If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, safety follow-up), as applicable.

5.3.2 Study Duration for Subjects

The phase 1b part of the study will consist of up to a 28 day screening period, a 12 week treatment period and a 6 week follow up. The maximum duration of trial participation for an individual subject will be 22 weeks. [redacted]

[redacted]



6. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). This log may be completed and updated via an Interactive Voice Response System (IVRS).

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Appendix 3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

6.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

101 Subject has provided informed consent prior to initiation of any study specific activities/procedures.

102 Age ≥ 18 to ≤ 70 years of age at screening

103 A diagnosis of RA consistent with the 1987 or 2010 American College of Rheumatology (ACR)/European League Against Rheumatism classification criteria

104 Active RA defined as:

- Phase 1b: DAS28-CRP > 2.6 at screening. The 28-joint count consists of the finger joints excluding the distal interphalangeal joints, the wrists, elbows, shoulders, and knees.
- Phase 2a: ≥ 6 swollen joints (based on 66-joint count) and ≥ 6 tender joints (based on 68-joint count) at screening and baseline. The distal interphalangeal joint should be evaluated but not included in the total count to determine eligibility. Additionally, C-reactive protein (CRP) must be greater than the upper limit of normal (ULN) per the central laboratory at screening.

105 Receiving treatment with methotrexate for ≥ 12 weeks and on a stable dose ≥ 15 mg weekly for ≥ 8 weeks prior to day 1. A lower methotrexate dose is acceptable (but no lower than 10 mg weekly) if it is the highest tolerated dose and gastrointestinal or hematologic toxicity at doses ≥ 15 mg weekly is documented by the investigator.

106 Receiving treatment with folic or folinic acid per investigator judgment or according to local standard of care.

107 Phase 1b only: Subject may be receiving a stable dose of leflunomide, sulfasalazine, hydroxychloroquine, minocycline in combination with methotrexate and the dose must be stable for ≥ 8 weeks prior to day 1.

108 Subject may be receiving a stable dose of prednisone ≤ 10mg daily or other equivalent corticosteroid dose and the dose must be stable for ≥ 2 weeks prior to day 1.

109 Phase 1b only. Normal or clinically acceptable ECG values (12-lead reporting ventricular rate and PR, QRS, QT and QTc interval) at screening and baseline based on opinion of the investigator.

110 Immunizations (tetanus, diphtheria, pertussis, seasonal influenza [during flu season], and pneumococcal [polysaccharide] vaccinations) up to date per local standards as determined by the investigator.

6.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply.

Disease Related

201 Class IV RA according to ACR revised response criteria

202 Diagnosis of Felty's Syndrome (RA, splenomegaly and granulocytopenia)

Other Medical Conditions

203 Prosthetic joint infection within 3 years of screening or native joint infection within 1 year prior to screening.

204 Active infection (including chronic or localized infections) for which anti-infectives were indicated within 4 weeks prior to day 1 OR presence of serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to day 1.

205 Known history of active tuberculosis.

206 Positive test for tuberculosis during screening defined as either:

- positive purified protein derivative (PPD) (≥ 5 mm of induration at 48 to 72 hours after test is placed) OR positive Quantiferon test
- a positive PPD and a history of Bacillus Calmette-Guérin vaccination are allowed with a negative Quantiferon test and negative chest x ray
- a positive PPD test (without a history of Bacillus Calmette-Guérin vaccination) or a positive or indeterminate Quantiferon test are allowed if they have ALL of the following at screening:
  - no symptoms per tuberculosis worksheet provided by Amgen
  - document history of a completed course of adequate prophylaxis (completed treatment for latent tuberculosis per local standard of care prior to the start of investigational product)
  - no known exposure to a case of active tuberculosis after most recent prophylaxis
  - negative chest X-ray

207 Positive for hepatitis B surface antigen, hepatitis B core antibody (confirmed by hepatitis B DNA polymerase chain reaction [PCR] test) or detectable hepatitis C virus RNA by PCR (screening is generally done by hepatitis C antibody [HepCAb], followed by hepatitis C virus RNA by PCR if HepCAb is positive). A history of hepatitis B vaccination without history of hepatitis B is allowed.

208 Phase 1b only: Positive for Human Immunodeficiency Virus (HIV) at screening or known to be HIV positive. Phase 2a only: Known history of HIV

209 **Phase 1b only:** Positive drug or alcohol urine test **for illicit drugs** at screening. **Prescription medications detected by the drug test are allowed if they are being taken under the direction of a physician.**

210 Presence of one or more significant concurrent medical conditions per investigator judgment, including but not limited to the following:

- poorly controlled diabetes or hypertension
- chronic kidney disease stage IIIb, IV, or V
- symptomatic heart failure (New York Heart Association class II, III, or IV)
- myocardial infarction or unstable angina pectoris within the past 12 months prior to randomization
- severe chronic pulmonary disease (eg, requiring oxygen therapy)
- multiple sclerosis or any other demyelinating disease
- major chronic inflammatory disease or connective tissue disease other than RA (eg, systemic lupus erythematosus with the exception of secondary Sjögren's syndrome)

211 Malignancy except non-melanoma skin cancers, cervical or breast ductal carcinoma in situ within the last 5 years.

212 History of alcohol or substance abuse within 6 months of screening

213 Phase 1b only: Current smoker, and/or use of any nicotine or tobacco containing products within the last 6 months prior to day 1. These types of products include but are not limited to: snuff, chewing tobacco, cigars, electronic cigarettes, cigarettes, pipes, or nicotine patches.

214 Phase 1b only: Subject unwilling to limit alcohol consumption to ≤ 1 drink of alcohol per day and ≤ 3 drinks per week for the duration of the study, where a drink is equivalent to 12 ounces of regular beer, 8 to 9 ounces of malt liquor, 5 ounces of wine, or 1.5 ounces of 80 proof distilled spirits. Phase 1b only: Unwilling or unable to abstain from alcohol consumption within 48 hours prior to each visit (including screening).

Prior/Concomitant Therapy

215 Subjects who have received intra-articular or systemic corticosteroid injections for treatment of acute RA flare (not being part of a regular therapeutic regimen) within 4 weeks prior to screening.

216 Currently receiving or had treatment with cyclophosphamide, chlorambucil, nitrogen mustard, or any other alkylating agent ≤ 6 months prior to day 1.

217 Prior treatment with more than a total of 3 therapies that include biologic DMARDs or oral synthetic DMARDs (such as tofacinitib, baricitinib). Prior treatment consists of at least 4 doses of a given therapy where the doses were given solely for treatment of RA disease. Prior therapies must not have been used within the following time periods:

- ≤ 4 weeks prior to day 1 for etanercept and anakinra
- ≤ 6 months for rituximab
- ≤ 2 weeks for oral janus kinase inhibitors
- ≤ 9 weeks prior to day 1 for all therapies not listed above

218 Currently receiving or had treatment with any of the following ≤ 12 weeks prior to day 1:

- azathioprine
- cyclosporine
- gold
- mycophenolate mofetil
- Prosorba column
- Tacrolimus

219 Phase 2a only: Currently receiving or had treatment with leflunomide ≤ 12 weeks prior to day 1 unless an active washout with cholestyramine has been performed.

220 Phase 2a only: Currently receiving or had treatment with any of the following ≤ 4 weeks prior to day 1:

- hydroxychloroquine
- sulfasalazine
- minocycline
- intra-articular, intramuscular or intravenous corticosteroids, including adrenocorticotropic hormone
- intra-articular hyaluronic acid injections
- live vaccines

221 For Phase 2 only: Unstable dose of non-steroidal anti-inflammatory drugs (NSAID), acetaminophen, and/or analgesics which is taken on an unscheduled basis (ie, not daily or scheduled every certain number of hours) and/or initiated < 4 weeks prior to day 1.

222 Received the following within 12 hours prior to screening or day 1: acetaminophen, NSAIDs, tramadol, and/or any narcotic analgesics such as but not limited to hydrocodone, codeine, tramadol, propoxyphene and/or oxycodone (unless in the form of oxycontin). Subject has taken oxycontin within 24 hours prior to screening or day 1.

223 Phase 1b only: Received any herbal medicines (eg, St John's wort), or non-vitamin dietary supplements (eg, magnesium) with the exception of calcium within 4 weeks prior to day 1.

Prior/Concurrent Clinical Study Experience

224 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

Diagnostic Assessments

225 Presence of laboratory abnormalities at screening including the following:

- Aspartate aminotransferase (AST) or alanine amino transferase (ALT) at screening > 1.5X upper limit of normal (ULN)

- Serum total bilirubin (TBL) ≥ 1.5 mg/dL (≥ 26 µmol/L)
- Hemoglobin ≤ 10.5 g/dL(≤ 105 g/L)
- Platelet count < 100,000/mm^3 (< 100 x 10^9/L)
- White blood cell count < **2,500** cells/mm^3 (< **2.5** x 10^9/L)
- Absolute neutrophil count (ANC) < 1,**000**/mm^3 (< 1.**0** x 10^9/L)
- Calculated glomerular filtration rate of ≤ 50 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) formula

226 Any other laboratory abnormality, which, in the opinion of the investigator, poses a safety risk, will prevent the subject from completing the study, will interfere with the interpretation of the study results, or might cause the study to be detrimental to the subject.

Other Exclusions

227 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 6 weeks after the last dose of investigational product.

228 Females of child-bearing potential with a positive pregnancy test (assessed by a serum pregnancy test at screening and a urine pregnancy test at baseline).

229 Female subjects of childbearing potential unwilling to use 1 highly effective method of contraception during treatment and for an additional 6 weeks after the last dose of investigational product. Refer to Appendix 5 for additional contraceptive information.

230 Subject has known sensitivity to any of the products or components to be administered during dosing.

231 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments [COAs]) to the best of the subject and investigator's knowledge.

232 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

6.3 Lifestyle Restrictions

6.3.1 Alcohol and Tobacco

The following alcohol and tobacco restrictions apply to the phase 1b part of the study only.

At screening and throughout the duration of the study, subjects must not consume > 1 drink of alcohol per day and no more than 3 drinks per week, where a drink is equivalent to 12 ounces of regular beer, 8 to 9 ounces of malt liquor, 5 ounces of wine, or 1.5 ounces of 80 proof distilled spirits.

Subjects must abstain from alcohol consumption within 48 hours prior to each visit (including screening).

Subjects must not use of any nicotine or tobacco containing products throughout the study. These types of products include but are not limited to: snuff, chewing tobacco, cigars, cigarettes, pipes, electronic cigarettes, or nicotine patches.

6.3.2 Activity

In the phase 1b part of the study subjects will abstain from strenuous exercise for 72 hours (eg, running, weight lifting for greater than 1 hour) before each blood collection for clinical laboratory tests.

6.4 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Appendix 3).

The subject must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study defined as the point at which the subject signs the informed consent form receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by IVRS. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the study.

6.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure

information will be collected that includes demography, screen failure details, eligibility criteria, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened (Section 9.1.1).

7. Treatments

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of investigational product.

7.1 Treatment Procedures

7.1.1 Investigational Products

7.1.1.1 Amgen Investigational Product: AMG 592

AMG 592 and placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

Both are liquid formulations presented in highly similar glass vials and stored in the same manner. An investigational product instruction manual (IPIM) containing detailed information regarding the storage, preparation, and administration of investigational product will be provided separately.

7.1.1.1.1 Dosage Administration and Schedule

In the phase 1b part of the study, AMG 592 or placebo will be administered by SC injection [redacted] starting on day 1. The following dose cohorts are planned in the phase 1b portion of the study:

[redacted]

[redacted]

For both the phase 1b and phase 2a part of the study investigational product will be administered by SC injection in the abdomen, thigh or upper arm by authorized site personnel. A physician must be available at the time of investigational product administration.

In the phase 1b part of the study doses of investigational product through week 4 and during week 12, must be given within 1 hour after the specified time point for the day 1 pre-dose blood samples, and within 12 hours after the rest of scheduled pre-dose blood sampling time points. After week 4 (excluding week 12) doses of investigational product must be given within ± 1 day of the scheduled visit time point. If that window is missed, that dose will not be administered, and the next dose will be administered at the next scheduled dosing date.

[redacted]

In the phase 1b part of the study, study subjects must remain at the site at least 6 hours following the first dose and at least 1 hour following the second dose of investigational product. The site must contact the subject by phone 6, 12, and 24 hours after the second dose of study drug to ascertain safety. Thereafter study subjects must remain on site for at least 30 minutes following the third and all subsequent doses of investigational product. [redacted]

7.1.1.1.2 Accountability

The amount of investigational product used in preparation, total volume of preparation, quantity administered, start date, start time, and box number of AMG 592 are to be recorded on each subject's CRF.

7.1.2 Non-investigational Products

There are no therapies designated as non-investigational products in the study.

7.1.3 Medical Devices

There are no investigational medical device(s) used in this study.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

7.1.4 Other Protocol-required Therapies

There are no other protocol required therapies

7.1.5 Other Treatment Procedures

There are no other treatment procedures

7.1.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s), device(s) or combination product(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

Amgen will collect product complaints in this study for investigational product.

Any product complaint(s) associated with an investigational product(s), non-investigational product(s), device(s), or combination product(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

7.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

The following medications are not allowed at any time during the study:

- azathioprine
- gold
- mycophenolate mofetil
- Prosorba column
- Any other investigational agents or commercially available biologic DMARDs
- Cytotoxic agents including chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents
- oral janus kinase inhibitor (eg, tofacitinib, baricitinib)

- Live vaccines
- Tacrolimus
- Cyclosporine
- T cell depleting agents (eg, antithymocyte globulin, Campath)
- Recombinant IL-2 (eg, Proleukin)

During the phase 1b part of the study all herbal medicines (eg St John's wort), vitamins, and supplements are not allowed, with the exception of Vitamin D and calcium.

[redacted]

7.2 Method of Treatment Assignment

In the phase 1b part of the study subjects will be randomized to receive AMG 592 or placebo in a 3:1 ratio via IVRS.

[redacted]

Assignment to the treatment arms will be based on a computer-generated randomization schedule prepared by Amgen before the start of the study. Each randomized subject will receive a single, unique randomization number via IVRS at randomization. The randomization date is to be documented in the subject's medical record as registered in the IVRS.

7.3 Blinding

The phase 1b part of the study is double-blind. Treatment assignment will be blinded to all subjects and site personnel described below.

[redacted]

7.3.1 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment is to only be unblinded when knowledge of the treatment is essential for further clinical management of the subject on this study. Unblinding at the study site for any other reason will be considered a protocol deviation. The Amgen Trial Manager must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the subject's condition. In this case, the Amgen Trial Manager must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.

7.3.2 Access to Individual Subject Treatment Assignments by Amgen or Designees

Phase 1b

The Amgen early development lead will be unblinded and will monitor the study on an ongoing basis. Other Amgen staff and their designees involved in the study will not be blinded, but will be given access to the unblinding or potentially unblinding information only when there is a need to use the information for analysis, discussion and internal decision-making, in particular, when concerning safety issues. Access to treatment assignments and other restricted data are described in Amgen standard documents. Unblinded individuals will ensure the keeping of the blind. Unblinding and potentially unblinding information should not be distributed to the investigators or subjects prior to a study cohort being formally unblinded.

[redacted]

7.4 Dose Modification

7.4.1 Hepatotoxicity Stopping Rules

Refer to Appendix 7 for details regarding drug-induced liver injury (DILI) guidelines, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

7.4.2 Dose-cohort Study Escalation/De-escalation and Stopping Rules (Phase 1b)

7.4.2.1 Dose Level Review Meetings

After all evaluable subjects within a cohort have completed the week 4 visit, a DLRM will be held to review data and make dose escalation/de-escalation decisions (see Appendix 3). **The exception is for cohorts 2 and 3 where an initial DLRM will convene after the first 16 enrolled subjects (8 in each cohort) complete the week 4 visit and a second DLRM will convene after the remaining 16 enrolled subjects (8 in each cohort) complete the week 4 visit.**

7.4.2.2 Dose Cohort Stopping Rules

The following dose cohort stopping rules will be used in the phase 1b part of the study. Dosing will be stopped or modified as shown in Table 7-1.

Table 7-1. Dose Cohort Stopping Rules

Scenario	Action
Occurrence of a CTCAE version 4.0**3** Grade 3 adverse event deemed related to investigational product in 2 or more subjects within in a single dosing cohort	Stop dosing and convene DLRM (if event occurs outside the regularly scheduled DLRM) Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance Consider unblinding, as appropriate[a] Upon majority vote by the DLRM members, one of the following **recommendations** may be made • stop enrollment of the cohort (if applicable) • enrollment of the cohort may resume as planned • the cohort may be expanded at the same dose • enrollment of the study may continue at a lower dose OR Upon unanimous vote by the DLRM members, 1 of the following **recommendations** may be made: • escalation to an intermediate dose (a dose lower than the next planned dose) may take place • escalation to the next planned dose may occur
Any occurrence of a CTCAE version 4.0**3** ≥ Grade 4 adverse event	Stop dosing additional subjects in the cohort and convene DLRM (if the event occurs outside the regularly scheduled DLRM) Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance. Consider unblinding to determine relatedness to investigational product[a] If the adverse event is determined by majority vote of the DLRM members to be related to the investigational product and clinically or medically significant, no further doses should be administered at this dose and no dose escalation should proceed. Enrollment of the study may continue at a lower dose or a lower dose cohort may be added to the study. Otherwise, upon majority vote of the DLRM members, one of the following **recommendations** may be made: • enrollment of the cohort may resume as planned • the cohort may be expanded at the same dose • enrollment of the study may continue at a lower dose or a lower dose cohort may be added to the study

[a] subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject, or may impact the safety of subjects currently enrolled or of subjects in subsequent cohorts. A decision to stop dosing will not occur without unblinding of the subject's treatment assignment.

7.4.3 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

7.4.3.1 Amgen Investigational Product: AMG 592

No dosage adjustments are allowed in either the phase 1b or phase 2 parts of the study. The reason for dose change of investigational product is to be recorded on each subject's CRF.

7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product during the study are provided in the IPIM.

7.6 Treatment Compliance

Subjects will receive the SC doses of AMG 592 at the research facility administered by qualified study personnel for the duration of the study.

7.7 Treatment of Overdose

The effects of overdose of AMG 592 are not known.

7.8 Prior and Concomitant Treatment

7.8.1 Prior Treatment

Prior therapies that were being taken/used from 6 months prior to the first dose of investigational product will be collected. Collect complete prior therapy history for RA. For prior therapies collect therapy name, indication, dose, unit, frequency, route, start date and stop date.

7.8.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant therapies or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.1.7 and those mentioned below.

Concomitant therapies are to be collected from first dose of investigational product through the safety follow-up. Collect therapy name, indication, dose, unit, frequency, route, start date and stop date

7.8.2.1 Methotrexate

All subjects must maintain a stable dose and the same route of administration (ie, oral or subcutaneous) of methotrexate through the treatment period in both the phase 1b and phase 2a parts of the study. The doses of methotrexate should be taken on the same day of the week (± 2 days). After the treatment period the dose of methotrexate may be adjusted.

Subjects must also take folic acid or folinic acid supplementation during the study. The dose of folic acid or folinic acid will be as per investigator judgment or according to local standard of care. The dose of folic acid may be adjusted in response to methotrexate-related toxicity.

7.8.2.2 Analgesics and NSAIDs

If the study subject enters the study taking a stable dose of acetaminophen, analgesics, or NSAIDs on a scheduled basis (see exclusion criterion 221), the dose can be reduced or discontinued during the study if necessary for safety reasons or standard of care. No new analgesics or NSAIDs may be added during the treatment period.

During treatment period analgesics or NSAIDs must not be used within 12 hours before a scheduled study visit where efficacy is assessed, with the exception of oxycontin which may not be used within 24 hours of a scheduled study visit where efficacy is assessed. In both the phase 1b and phase 2a parts of the study, efficacy is assessed at baseline and at weeks 4, 8, and 12.

After the treatment period, analgesics and NSAIDs may be added as required or the dose adjusted per investigator judgment in both the phase 1b and phase 2a parts of the study.

7.8.2.3 Corticosteroids

Subjects entering the study while taking oral corticosteroids cannot change their dose during the treatment period. Addition of new corticosteroids regardless of route of administration is not allowed. After the treatment period new corticosteroids, administered by any route may be added or dose adjusted per investigator judgment. Investigators should make every effort to reduce the steroid dose for subjects responding to investigational product and to taper steroids after the resolution of disease flare.

7.8.2.4 DMARDS

In the phase 1b part of the study only, subjects entering the study taking sulfasalazine, hydroxychloroquine, minocycline or leflunomide cannot change their dose during the initial treatment period. After the treatment period, new non-biologic DMARDs may be added or dose adjusted per investigator judgment.

[redacted]

8. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 8.1, 8.2.1, and 8.2.2.

8.1 Discontinuation of Study Treatment

Subjects can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 2-1, Table 2-2 and Table 2-3) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, disease-related events and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Appendix 3.

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- Decision by Sponsor
- Lost to follow-up
- Death
- Ineligibility determined

- Protocol deviation
- Non-compliance
- Adverse event
- Subject request
- Requirement for alternative therapy
- Protocol-specified criteria; see Section 7.4.2
- Pregnancy

8.2 Discontinuation From the Study

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, **publicly** available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Appendix 6 for further details). Refer to the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.2.1 Reasons for Removal From Washout, Run-in or Invasive Procedures

Not applicable to this study

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent from study
- Death
- Lost to follow-up

8.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator can search **publicly** available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

9. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 2-1, Table 2-2, and Table 2-3).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

9.1 General Study Periods

9.1.1 Screening, Enrollment and Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the site will register the subject in the IVRS and screen the subject in order to assess eligibility for participation. The screening window is up to 28 days.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for rescreening 2 times.

Rescreen subjects must first be registered as screen failures in IVRS and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 28 day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. Subjects rescreening within the original 28-day screening period only need to repeat the assessment(s) that did not originally meet the eligibility criteria; all other initial screening assessments do not need to be repeated. Subjects rescreening after the original 28-day screening period has ended must repeat all screening procedures including being re-consented. However, a tuberculosis test that was negative at the original screening does not need to be repeated as long as the subject has not had exposure to active tuberculosis after the original screening tuberculosis test was completed.

9.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 2-1 and Table 2-3). On-study visits may be completed within a visit window of ± 1 day for phase 1b and ± 2 days for phase 2a from the scheduled dose date. The date of the first dose of investigational product is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Investigational product should be administered after all other study procedures have been completed, except at day 1 and week 12 in the phase 1b part of the study per the Schedule of Activities (Table 2-1).

9.1.3 Follow-up/Safety Follow-up/End of Study for Phase 1b

After the 12-week treatment period, subjects in the phase 1b part of the study will be followed for an additional 6 weeks up until week 18 for collection of additional safety, PK and PD data as described in the Schedule of Activities (Table 2-2). For subjects who complete the study at week 18, the visit includes all required safety follow-up data collection. All subjects who terminate the study early (ie, prior to completing the week 18 visit), will complete an Early Termination visit consisting of all assessments included in the week 12 day 85 pre-dose visit. In addition, a safety follow-up visit will occur 6 weeks (± 3 days) after the last dose of investigational product to collect all required safety data including adverse events, serious adverse events, disease related events, concomitant therapies, safety labs/assessments, anti-AMG 592 antibody, and urine pregnancy test.

[redacted]

9.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required timepoints.

9.2.1 General Assessments

9.2.1.1 Informed Consent

All subjects must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

9.2.1.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally demographic data will be used to study the impact on biomarkers variability and pharmacokinetics of the protocol-required therapies.

9.2.1.3 Medical History

The Investigator or designee will collect a relevant medical and surgical history that started within 5 years or as necessary for chronic or co-morbid conditions prior to enrollment through the start of the adverse event reporting period. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. In addition to the medical history above, RA history must date back to the original diagnosis. The current toxicity grade will be collected for each condition that has not resolved.

9.2.1.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

9.2.1.5 Physical Measurements

Weight in kilograms and height in centimeters should be measured without shoes.

9.2.1.6 Substance Use History

For the phase 1b part of the study, obtain a detailed history of prior and/or concurrent use of alcohol and of nicotine or tobacco containing products.

9.2.2 Efficacy Assessments

[redacted]

9.2.2.2 DAS28-CRP

The DAS28-CRP will be calculated in the phase 1b part of the study to determine subject eligibility during screening.

[redacted]

[redacted]

[redacted]

9.2.3 Safety Assessments

Planned timepoints for all safety assessments are listed in the Schedule of Activities.

9.2.3.1 Adverse Events

9.2.3.1.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

9.2.3.1.1.1 Disease-related Events

Disease-related events are defined in Appendix 4.

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur after the first dose of investigational product(s) through the safety follow-up are reported using the Event CRF.

Disease-related events assessed by the investigator to be more severe than expected and/or related to the investigational product(s)/study treatment/protocol-required therapies, and determined to be serious, must be reported on the Event CRF as serious adverse events.

Disease-related events pre-defined for this study include joint pain, joint stiffness, joint swelling, worsening of rheumatoid arthritis.

9.2.3.1.1.2 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) and is described in Appendix 4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product through the safety follow-up are reported using the Event CRF.

9.2.3.1.1.3 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the safety follow-up are reported using the Event CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

9.2.3.1.1.4 Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. Per local requirements in some countries, investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

The method of recording, evaluating, and assessing causality of adverse events, disease-related events, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 4.

9.2.3.1.1.5 Serious Adverse Events That Are Not to be Reported by the Sponsor to Regulatory Agencies in an Expedited Manner

Not applicable

9.2.3.1.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

9.2.3.1.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

If subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Aggregate analyses may also be unblinded by the Safety Assessment Team (SAT) as appropriate. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

9.2.3.1.5 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and, if indicated, female partners of male subjects will be collected after the start of study treatment and until 6 weeks after the last dose of investigational product.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Appendix 5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Appendix 5.

9.2.3.2 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

9.2.3.3 Electrocardiograms

Phase 1b

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. ECGs should be performed in a standardized method, in triplicate, and run consecutively (ie, < 30 seconds apart), prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

- ≥ 3 baseline ECGs collected ≥ 30 minutes apart, with each baseline ECG in triplicate run consecutively (ie, < 30 seconds apart [ie, total ≥ 9 ECGs])
- Triplicate ECGs at screening and timepoints after baseline per the Schedule of Activities

Baseline is defined as day -1.

The PI or designated site physician, will review all ECGs. ECGs will be transferred electronically to an ECG central reader for analysis per Amgen instructions. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen. Standard ECG machines should be used for all study-related ECG requirements. Amgen will provide standard ECG machines for use by the site.

[redacted]

9.2.4 Clinical Laboratory Assessments

All screening and on-study laboratory samples will be processed and sent to the central laboratory with the exception of erythrocyte sedimentation rate (ESR), urine pregnancy, PPD, and Quantiferon (may be done by central or local laboratory). The central laboratory will be responsible for all screening and on-study serum chemistry,

hematology, serum pregnancy, urinalysis, hepatitis C antibody, hepatitis B surface antigen and core antibody, high sensitivity CRP, and any other laboratory tests required. ESR, urine pregnancy and PPD testing, if applicable, will be performed locally with kits provided by the central laboratory (except PPD). The results of this testing will be maintained in the source documents at the site.

Subjects in the phase 1b part of the study will abstain from strenuous exercise for 72 hours before each blood collection for clinical laboratory tests.

Amgen or designee will be responsible for biomarker and pharmacogenetic assessments, and the central laboratory will ship the samples to Amgen or a specialty laboratory for assay (depending on the assessment). The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all samples. All blood samples will be obtained by venipuncture before investigational product administration. The date and time of sample collection will be recorded in the source documents at the site.

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities.

After baseline, CRP results as well as PK/PD parameters that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded. ESR will be performed locally. The results of the ESR performed after the subject has been randomized must be maintained in a blinded fashion so that it may not be viewed by other staff who perform any study assessments with the subjects.

9.2.4.1 Tuberculosis Testing

All subjects must receive either a PPD or Quantiferon test at screening per Section 6.2.

9.2.4.1.1 PPD

The PPD test must be read by a trained healthcare professional 48 to 72 hours after the test is placed. PPD reader must be identified on the delegation of authority for this responsibility.

9.2.4.1.2 Quantiferon

If a subject does not receive a PPD test, then a Quantiferon test must be performed per Section 6.2. Please refer to the central laboratory manual for instructions on sample collection, processing, and shipping of samples (if applicable).

9.2.4.1.3 Chest X-Ray

Subjects with a positive PPD test without a history of Bacillus Calmette-Guerin vaccination or subjects with a positive or indeterminate Quantiferon test will require a chest radiograph including posterior-anterior and lateral views. The radiograph report should be read by a radiologist or per local requirement and the report must be reviewed by the investigator before enrollment of the subject.

9.2.4.2 Human Immunodeficiency Virus, Hepatitis B Surface Antigen, and Hepatitis C Antibody

HIV testing at screening will be performed only in subjects in the phase 1b part of the study if HIV status is unknown. In both phase 1b and phase 2a, subjects will be assessed for HBsAg, and HepCAb titers at screening. The results of these tests must be negative and will be documented in the source document but will not be recorded on the eCRF.

9.2.4.3 Pregnancy Testing

A high sensitive (urine or serum) pregnancy test should be completed at screening and within 7 days of initiation of investigational product for females of childbearing potential.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Worksheet, see Figure 12-2). Refer to Appendix 5 for contraceptive requirements.

Additional pregnancy testing (urine) should be performed at monthly intervals during treatment with investigational product and 6 weeks (± 3 days) after the last dose of

investigational product. Positive urine pregnancy test should be confirmed with serum pregnancy test.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

9.2.4.4 Prespecified Biomarker Assessments

[redacted]

9.2.5 Pharmacokinetic Assessments

All subjects randomized to AMG 592 will have pharmacokinetic samples assessed.

Blood samples will be collected for measurement of serum concentrations of AMG 592 as specified in the Schedule of Activities (Table 2-1, Table 2-2 and Table 2-3). Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

[redacted]

[redacted]

9.2.7 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of inflammatory conditions and/or to identify subjects who may have positive or negative response to AMG 592. Additional samples are not collected for this part of the study. For subjects who consent to these analyses, DNA may be extracted.

The final disposition of samples will be described in Appendix 6.

9.2.8 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected according to the timepoints specified in the Schedule of Activities (Table 2-1, Table 2-2 and Table 2-3) for the measurement of anti-AMG 592 binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized. Additional blood samples may be obtained to rule out anti-AMG 592 antibodies during the study.

Subjects who test positive for anti-AMG 592 antibodies that cross-react with and neutralize native human IL-2 at the final scheduled study visit will be asked to return for additional follow-up testing. This testing is to occur approximately every 3 months starting from when the site has been notified of the positive result until: (1) IL-2 neutralizing antibodies are no longer detectable; or (2) the subject has been followed for a period of at least 1 year (± 4 weeks) post administration of AMG 592. All follow-up results, both positive and negative will be communicated to the sites. This notification is independent of and may be in advance of the time point when the entire study is planned to be unblinded. Refer to Section 7.3 for additional information regarding unblinding. More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing is not required where it is established that the subject did not receive AMG 592.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-AMG 592 antibody response

may also be asked to return for additional follow-up testing. Refer to the Schedule of Activities (Table 2-1 and Table 2-2), as applicable, for specific timepoints, and the laboratory manual for detailed collection and handling instructions.

9.2.9 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to AMG 592.

Blood samples are to be collected for biomarker development at the timepoints specified in the Schedule of Activities (Table 2-1, Table 2-2, and Table 2-3).

[redacted]

[redacted]

9.2.11 Other Assessments

Peripheral Blood Mononuclear Cell

Blood samples will be collected for subjects in the phase 1b part of the study at the timepoints indicated in the Schedule of Activities (Table 2-1, Table 2-2) for PBMC collection. Detailed instructions on sample collection, processing, and shipping will be provided in a separate manual.

10. Statistical Considerations

10.1 Sample Size Determination

10.1.1 Phase 1b

It is anticipated that approximately **48** subjects will be **randomized** in the phase 1b part of the study**,** with 8 subjects **randomized** to each **of cohorts 1 and 4 and approximately 16 subjects randomized to each of cohorts 2 and 3. The total sample size may be higher than 48 subjects if, following a DLRM recommendation, additional dosing cohorts are added and/or existing cohorts are expanded, or if subjects are replaced as per Section 5.2.1. Within each cohort subjects will be randomized to AMG 592 or placebo in a 3:1 ratio.**

The sample size of the phase 1b part of the study is based on practical considerations. **For cohorts 1 and 4, with** 6 subjects receiving AMG 592 **in each** cohort, there is an 82% chance of at least 1 subject **within a cohort** experiencing an adverse event, if the true event rate is 25%. The chance of at least 1 subject experiencing an adverse event **within a cohort** will be 74% if the event rate becomes 20%.

For cohorts 2 and 3, with 12 subjects receiving AMG 592 in each cohort, the chance of at least 1 subject experiencing an adverse event within a cohort increases to 97% and 93% for true event rates of 25% and 20%, respectively. In addition, with a total of 36 subjects planned to receive AMG 592 in **the** phase 1b **part of the study, the** chance of at least 1 subject experiencing an adverse event **across the cohorts increases to 30% and 84**% if the true event **rates are 1% and 5%, respectively.**

Additional subjects may be enrolled at a randomization ratio of 3:1 to AMG 592 or placebo to enable all screened eligible subjects to participate in the study, for addition and/or expansion of cohorts based on DLRM recommendations, or for replacement of subjects as per Section 5.2.1.

[redacted]

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

10.2.1.1 Phase 1b

10.2.1.1.1 Safety Analysis Set

The safety analysis set for phase 1b will consist of all subjects who received at least 1 dose of investigational product. The safety analysis set will be used for the phase 1b analyses unless otherwise specified. Subjects will be analyzed according to the actual treatment received.

10.2.1.1.2 Pharmacokinetic Concentration Analysis Set

The PK concentration analysis set for phase 1b will contain all subjects who have received AMG 592 and have at least one quantifiable PK sample collected.

10.2.1.1.3 Pharmacokinetic Parameter Analysis Set

The PK parameter analysis set for phase 1b will consist of all subjects who have received AMG 592 and for whom at least one PK parameter can be adequately estimated.

[redacted]

[redacted]

10.2.2 Covariates

10.2.2.1 Phase 1b

There are no pre-specified covariates.

[redacted]

10.2.3 Subgroups

10.2.3.1 Phase 1b

There are no pre-specified subgroup analyses.

[redacted]

10.2.4 Handling of Missing and Incomplete Data

10.2.4.1 Phase 1b

All endpoints in the phase 1b part of the study will be analyzed as-is and no imputation is planned.

[redacted]

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To

preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 5.3.1.

10.3.1 Planned Analyses

10.3.1.1 Interim Analysis and Early Stopping Guidelines

Phase 1b

There is no formal interim analysis for phase 1b.

[redacted]

10.3.1.2 Primary Analysis

10.3.1.2.1 Phase 1b

The primary analysis will be done after all subjects have had the opportunity to complete the study and performed the safety follow-up.

[redacted]

10.3.2 Methods of Analyses

10.3.2.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, PD, and biomarker data. Descriptive statistics on continuous measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Data will be presented and summarized by treatment and also by time as appropriate.

10.3.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Phase 1b The primary endpoint of phase 1b is not an efficacy endpoint. [redacted]
Secondary	
Exploratory	

10.3.2.3 Safety Analyses

10.3.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	Phase 1b: The primary endpoint for phase 1b is safety. Please refer to section 10.3.2.3.2 to 10.3.2.3.6 below for analyses of safety endpoints. [redacted]

10.3.2.3.2 Adverse Events and Disease-related Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other

protocol-required therapies, and significant treatment emergent adverse events will also be provided.

10.3.2.3.3 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics at selected timepoints by treatment group. Shifts in grades of safety laboratory values between the baseline and the worst on-study value will be tabulated.

10.3.2.3.4 Vital Signs

The analyses of vital signs will include summary statistics at selected timepoints. Shifts in vital sign values between the baseline and the worst on-study value will be tabulated.

10.3.2.3.5 Physical Measurements

The analyses of physical measurements will include summary statistics at selected timepoints by treatment group.

10.3.2.3.6 Electrocardiogram

Phase 1b

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters. Subjects' maximum change from baseline in QTcF, QTcB will be categorized and the number and percentage of subjects in each group will be summarized. Subjects' maximum post baseline values will also be categorized and the number and percentage of subjects in each group will be summarized. All on-study electrocardiogram (ECG) data will be listed.

10.3.2.3.7 Antibody Formation

The incidence and percentage of subjects who develop anti-AMG 592 or anti-IL-2 antibodies (binding and if positive, neutralizing) at any time will be tabulated by treatment group.

10.3.2.3.8 Exposure to Investigational Product

The number of days on investigational product, the total dose of investigational product will be summarized using descriptive statistics. Subject-level data may be provided instead of the summary if the subject incidence is low or single dose is given.

10.3.2.3.9 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term or category for each treatment group as coded by the World Health Organization Drug dictionary.

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12. Appendices

Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ACR	American College of Rheumatology
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
Anti-CCP	anti-cyclic citrullinated peptide
AUC_{tau}	area under the concentration-time curve
BLRM	Bayesian logistic regression model
[redacted]	
C_{max}	maximum observed concentration
CRF	case report form
CRP	C-reactive protein
CTCAE	common terminology criteria for adverse events
DAS28-CRP	disease activity score (28 joint) calculated using the C-reactive protein formula
DAS28-ESR	disease activity score (28 joint) calculated using the erythrocyte sedimentation rate formula
DILI	drug-induced liver injury
DLRM	dose level review meeting
DMARD	disease modifying anti-rheumatic drug
DNA	deoxyribonucleic acid
DRT	data review team
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
EDC	electronic data source
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
ESR	erythrocyte sedimentation rate
Exposure-Response Analysis	mechanism-based modeling & simulation and statistical analyses based on individual pharmacokinetic [PK] exposure (eg, population pharmacokinetic modeling) and response, which may include biomarkers, pharmacodynamic (PD) effects, efficacy and safety endpoints.
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End of Study for Individual Subject (EOS)	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early

Abbreviation or Term	Definition/Explanation
End of Study (end of trial)	defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, safety follow-up), as applicable
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
FIH	first in human
FSH	follicle stimulating hormone
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GVHD	graft versus host disease
HCP	health care provider
HepCAb	hepatitis c antibody
[redacted]	[redacted]
HIV	human immunodeficiency virus
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IL-2	interleukin 2
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IUD	intrauterine device
IRB	Institutional Review Board
Interactive Voice Response System (IVRS)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information
MAD	multiple ascending dose
MDRD	Modification of Diet in Renal Disease
NK cells	natural killer cells
NKT cells	natural killer T cells
NOAEL	no observed adverse effect level
NSAID	non-steroidal anti-inflammatory drug
PCR	polymerase chain reaction
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics
PK	pharmacokinetic
POS	probability of success
PPD	purified protein derivative
PR Interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG

Abbreviation or Term	Definition/Explanation
QRS interval	QRS interval is the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles
QT interval	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG.
QTc interval	QT interval corrected for heart rate using accepted methodology
[redacted]	
RA	rheumatoid arthritis
RF	rheumatoid factor
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
[redacted]	
SFU	Safety follow-up
SAT	safety assessment team
SC	subcutaneous
[redacted]	
SLE	systemic lupus erythematosus
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
TBL	total bilirubin
[redacted]	[redacted]
Teff	T effector cells
T_{max}	time of maximum observed concentration
TNF	tumor necrosis factor
Treg	T regulatory cells
ULN	upper limit of normal
[redacted]	[redacted]

Appendix 2. Clinical Laboratory Tests

The tests detailed in **Table 12-1** will be performed by the central laboratory and/or by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections **6.1** **to** **6.2** of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 12-1. Analyte Listing

Chemistry	Urinalysis	Hematology	Other Labs
Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or Urea Creatinine[b] Total bilirubin Direct bilirubin Alkaline phosphatase AST (SGOT) ALT (SGPT)	Specific gravity pH Blood Protein Glucose Ketones Urobilinogen Bilirubin Microscopic (reflex testing if abnormal)	Red blood cells White blood cells ANC Hemoglobin Hematocrit MCV MCH MCHC RDW Reticulocytes Platelets White blood cells differential • Total neutrophils or segmented neutrophils • Bands • Eosinophils • Basophils • Lymphocytes • Monocytes	Central Laboratory: Quantiferon[d] Hepatitis B surface Antigen Hepatitis B core antibody Hepatitis C virus antibody HIV FSH[c] Serum pregnancy[a] High sensitivity CRP Rheumatoid Factor Anti-CCP antibody [redacted] PBMC AMG 592 PK Anti-AMG 592 antibodies Biomarker development Optional pharmacogenetics sample **Urine drug/alcohol screen** Local Laboratory: Urine Pregnancy PPD ESR

Footnotes is defined on next page

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Hep = hepatitis; HIV = human immunodeficiency virus;; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell count; RDW = Red cell distribution width; PBMC = peripheral blood mononuclear cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT - serum glutamic-pyruvic transaminase; WBC = white blood cell count; Modification of Diet in Renal Disease = MDRD; PK = pharmacokinetics; PBMC = peripheral blood mononuclear cell; FSH = Follicle stimulating hormone; Anti-CCP = anti-cyclic citrullinated peptide antibody; CRP = C28-reactive protein; ESR = erythrocyte sedimentation rate; PPD = positive purified derivative
[a] Only at screening
[b] Glomerular filtration rate will be calculated by Modification of MDRD formula
[c] Can be done as a part of the clinical chemistry
[d] Quantiferon testing can be done locally or by the central laboratory

After baseline, CRP results as well as PK/PD parameters that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded. ESR will be performed locally. The results of the ESR performed after the subject has been randomized must be maintained in a blinded fashion so that it may not be viewed by other staff who perform any study assessments with the subjects.

Appendix 3. Study Governance Considerations

Dose Level Review Meetings and Data Review Team

Dose Level Review Meetings

The phase 1b part of the study will employ Dose Level Review Meetings (**DLRMs**). The DLRM team will be composed of the investigator(s), Amgen Medical Monitor, and Amgen Global Safety Officer or designee. Other optional Amgen representatives (eg, Amgen biostatistics representative, Clinical Trial Manager) may be included as appropriate. A quorum, defined as > 50% of the participating investigators who have enrolled at least 1 subject in the study or their qualified designee (ie, sub-investigator or research nurse or study coordinator possessing hard copy documentation [eg, email] of the investigator's vote regarding the dose level review), must be in attendance for the DLRM. The DLRM will be rescheduled if a quorum is not reached.

DLRM members will vote on dosing recommendations (followed by an Amgen decision). Voting members of the DLRM will include the Amgen Medical Monitor, the Amgen Global Safety Officer or designated Safety Scientist, and all participating investigators who have enrolled at least 1 subject in the study or their qualified medical doctor designee(s). The majority opinion of the investigators will count as 1 vote; the Medical Monitor will cast 1 vote and the Global Safety Officer will cast 1 vote. A unanimous positive vote indicating an acceptable safety profile for the investigational product is required to recommend dose level escalation to the next planned dose or to an intermediate dose. Only in the following limited circumstances, dose decisions can be made by the Amgen Medical Monitor and Amgen Global Safety Officer without convening a DLRM:

- The Amgen Medical Monitor and Amgen Global Safety Officer may decide to begin the next cohort using a de-escalated dose (de-escalated from the dose level of the most recent cohort), if this de-escalated dose had been previously evaluated during a DRLM.

All other recommendations regarding dose modification and/or cohort continuation/expansion will require a majority DLRM vote (ie, ≥ 2 of 3 votes).

All available study data including demographics, medical history, concomitant therapies, adverse events, electrocardiograms, vital signs, laboratory results, and emerging pharmacokinetic and pharmacodynamics data will be reviewed. Data to be reviewed may be unqueried. The DLRM vote and final dosing decision will be summarized in a DLRM memo which the study investigators will receive via email notification.

Data Review Team

A Data Review Team (DRT) will review unblinded safety data periodically in the phase 2a part of the study only. A DRT is a group, internal to Amgen but external to the relevant AMG 592 product team, that reviews accumulating data from the ongoing clinical trial to ensure no avoidable increased risk for harm to subjects. In order to maintain trial integrity, the unblinded data reviewed by the DRT will be restricted and not accessible by the AMG 592 product team. The DRT is composed of members that are external to the study team and include a clinician, a safety physician, and a biostatistician. Membership, procedures, and meeting timing will be described in detail in the study DRT charter.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen

- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations, ICH guidelines, the IRB/IEC, and all other applicable local regulations

Informed Consent Process

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects will then be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent [and the subject's agreement or refusal of his/her notification of the primary care physician] is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 8.

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject.

A subject who is rescreened is not required to sign another informed consent form if the rescreening occurs within 28 days from the previous informed consent form signature date.

The informed consent form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with [governmental regulations/ICH GCP Guidelines], it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the [IRB/IEC] direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:

Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in

ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above.

Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

All persons designated as authors must qualify for authorship, and all those who qualify are to be listed.

Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- A recognized expert in the therapeutic area
- An Investigator who provided significant contributions to either the design or interpretation of the study
- An Investigator contributing a high number of eligible subjects

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, [IRB/IEC] review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Quality, Compliance, and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Retention of study documents will be governed by the Clinical Trial Agreement.

Amgen (or designee) will perform Self-Evident Corrections (SEC) to obvious data errors in the clinical trial database. SECs will be documented in the CRF Standard Instructions and the CRF Specific Instructions, both of these will be available through the EDC system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date with different visit, [eg, week 4 and early termination]) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

CRFs must be completed in English. TRADENAMES® (if used) for concomitant therapies may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

Source Documents

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the Interactive Voice Response System (IVRS) system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen

- Investigational product-related correspondence including [Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable]

Retention of study documents will be governed by the Clinical Trial Agreement.

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Disease-related Event

Disease-related Event Definition

• Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. See Section 9.2.3.1.1.1 for the list of disease-related events.
• Disease-related events that would qualify as an adverse event or serious adverse event:
  o An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol-required therapies and disease worsening, this must be reported as an adverse event or serious adverse event.
• Disease-related events that do not qualify as adverse events or serious adverse events:
  o An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a disease-related event.

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Events Meeting the Adverse Event Definition
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
• **Results in death (fatal)**
• **Immediately life-threatening** The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
• **Requires in-patient hospitalization or prolongation of existing hospitalization** In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
• **Results in persistent or significant disability/incapacity** The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
• **Is a congenital anomaly/birth defect**
• **Other medically important serious event** Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events, Disease-related Events (if applicable), and Serious Adverse Events

Adverse Event, Disease-related Event (if applicable) and Serious Adverse Event Recording

• When an adverse event, disease-related event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
• The investigator will then record all relevant adverse event/disease-related event/serious adverse event information in the Event case report form (CRF).
  o Additionally, the investigator is required to report a fatal disease-related event on the Event CRF.
• The investigator must assign the following adverse event attributes:
  o Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  o Dates of onset and resolution (if resolved);
  o Severity (or toxicity defined below);
  o Assessment of relatedness to investigational product, other protocol-required therapies; and
  o Action taken.
• If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event CRF.
• It is not acceptable for the investigator to send photocopies of the subject's medical records to the sponsor in lieu of completion of the Event CRF page.

Adverse Event, Disease-related Event (if applicable) and Serious Adverse Event Recording
• If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity
The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on: The **Common Terminology Criteria for Adverse Events (CTCAE)**, version 4.0 which is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Assessment of Causality
• The investigator is obligated to assess the relationship between investigational product, protocol-required therapies, and/or study-mandated procedure and each occurrence of each adverse event/serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality. • There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data. • The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed Event CRF. • The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system via the Safety Report Form. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an electronic Serious Adverse Event (eSAE) Contingency Report Form (see Figure 12-1) within 24 hours of the investigator's knowledge of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data.   • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on a paper Serious Adverse Event Report Form (see Figure 12-1).

Adverse Device Effects: Recording, Evaluating and Reporting

- Any adverse event resulting from an adverse device effect that occur during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the Event CRF page.
- It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by Amgen at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident.

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Form

AMGEN Study # 20170149 AMG 592	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term:
and start date: Day ____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day Month Year

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	Serious, enter Serious Criteria code (see codes below)	Relationship: Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP?								Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
						<Device> No	<Device> Yes	<Device> No	<Device> Yes	<Device> No	<Device> Yes	<Device> No	<Device> Yes		
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device:		Prior to, or at time of Event: Date of Initial Dose Day Month Year	Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 592	☐blinded ☐open label							Lot # _____ ☐Unknown Serial # _____ ☐Unavailable / Unknown
<<IPDevice>>	☐blinded ☐open label							Lot # _____ ☐Unknown Serial # _____ ☐Unavailable / Unknown

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AMGEN Study # 20170149 AMG 592	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Test											
	Unit											

8. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20170149 AMG 592	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION *(Provide narrative details of events listed in section 3)* Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - _____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the Investigator for this study, or by a Qualified Medical Person authorized by the Investigator for this study.*	Title	Date

Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for females of childbearing potential are outlined in Section 6.2.

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and for 6 weeks (± 3 days) after the last dose of protocol-required therapies.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception and for an increased length of time. In addition, male subjects may also be required to use contraception. The investigator must discuss these contraceptive changes with the subject.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

  Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.

- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

Note: Failure rate of <1% per year when used consistently and correctly.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Unacceptable Methods of Birth Control for Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhoea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 6 weeks (± 3 days) after the last dose of investigational product.
- Information will be recorded on the Pregnancy Notification Worksheet (see Figure 12-2). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.)
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 6 weeks (±3 days) after the last dose of investigational product. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue investigational product (see Section 8.1 for details).

Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment]

- In the event a male subject fathers a child during treatment, and for an additional 6 weeks (± 3 days) after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Figure 12-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.)
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 6 weeks after the last dose of investigational product.
- Information will be recorded on the Lactation Notification Worksheet (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 227.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 6 weeks after discontinuing protocol-required therapies.

Figure 12-2. Pregnancy and Lactation Notification Worksheet

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20170149

Study Design: ■ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (____)_____ Fax (____)_____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject DOB: mm / dd / yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm /dd /yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm /dd /yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm / dd / yyyy_____ ☐ Unknown

Estimated date of delivery mm_____ / dd_____/ yyyy_____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm_____ / dd_____/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm / dd / yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: March 27, 2011 Page 1 of 1

Print Form

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20170149

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (_____)_____ Fax (_____)_____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Date of Birth: mm_____ / dd_____ / yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: 03 April 2012, version 2. Page 1 of 1

Appendix 6. Sample Storage and Destruction

Any blood samples collected according to the Schedule of Activities (Table 2-1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand inflammatory conditions, the dose response and/or prediction of response to AMG 592, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, [biomarker development,] or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining [sample types (eg, blood, tumor)] samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no

longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

See Appendix 3 for subject confidentiality.

Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed for possible DILI according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 12-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5x ULN (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then investigational product is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 12-2) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified in the above, require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Appendix 4

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 12-2 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- Complete blood count (CBC) with differential to assess for eosinophilia
- Serum total immunoglobulin IgG, anti-nuclear antibody, anti-smooth muscle antibody, and liver kidney microsomal antibody -1 to assess for autoimmune hepatitis

- Serum acetaminophen (paracetamol) levels
- A more detailed history of:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- Creatine phosphokinase (CPK), haptoglobin, lactate dehydrogenase (LDH), and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant therapies and laboratory results must be captured in the corresponding CRFs.

Amendment 3

Protocol Title: A Phase 1b/2a Study to Evaluate the Safety and Efficacy of AMG 592 in Subjects With Active Rheumatoid Arthritis With Inadequate Response to Standard of Care Therapy

Amgen Protocol Number AMG 592 20170149

Amendment Date: 06 June 2019

Rationale:

The rationale for this protocol amendment is:

1. To update the phase 1b sample size language throughout the protocol to allow flexibility for expansion and/or addition of cohorts per DLRM recommendation, for replacement of subjects who discontinue investigational drug product prior to completing week 4 of the study and to allow overenrollment of additional eligible screened subjects in each cohort.
2. To expand phase 1b dosing cohorts 2 and 3 by 8 subjects per cohort in order to gain additional pharmacokinetic, pharmacodynamic and safety data at these doses. Due to a large number of early drop outs the pharmacokinetic and pharmacodynamic data from these cohorts was insufficient to understand dose - response relationships.
3. To update the Risks section of the protocol to align with updates to the Investigator Brochure.
4. To update the dose for cohort 3 from [redacted] to reflect the DLRM recommendation that this dose be increased.
5. To reduce the thresholds for white blood cell count and absolute neutrophil count in the exclusion criteria because leukopenia is common in this patient population.

Description of Changes

Section: Global

Change: Version date updated throughout document from 26 July 2018 to **06 June 2019**.

Section: Global

Change: Editorial changes (including typographical, grammatical, and formatting) have been made throughout the document.

Section: Title Page

Replace: Name: [redacted] MD

With: Name: [redacted] **MD and** [redacted] **MD**

Section: Title Page

Replace: Email Address: [redacted]

With: Email Address: [redacted]

Section: Title Page

Add: Amendment 3 06 Jun 2019

Section: 1 Protocol Synopsis, Overall Design

Replace: The phase 1b will include 4 dosing-cohorts. Subjects within a dosing-cohort will be randomized in a 3:1 ratio to AMG 592 (n = 6) or placebo (n = 2) as follows: cohort 1 [redacted] cohort 2 [redacted] cohort 3 [redacted] and cohort 4 [redacted] in addition to standard of care therapy. Dosing cohorts will enroll sequentially with the exception of cohorts 2 and 3, which will enroll concurrently. A Dose Level Review Meeting (DLRM) will convene after the last subject in each cohort completes the week 4 visit. The exception is for cohorts 2 and 3 where the DLRM will convene after the last subject enrolled in both cohorts completes the week 4 visit.

With: The phase 1b will include 4 **planned** dosing-cohorts. Subjects within a dosing-cohort will be randomized in a 3:1 ratio to AMG 592 (n = 6) or placebo (n = 2) as follows: cohort 1 [redacted] cohort 2 [redacted] cohort 3 [redacted] and cohort 4 [redacted] in addition to standard of care therapy. **Approximately 8 additional subjects (6 AMG 592; 2 placebo) may be**

enrolled into each of cohorts 2 and 3. Dosing cohorts will enroll sequentially with the exception of cohorts 2 and 3, which will enroll concurrently. A Dose Level Review Meeting (DLRM) will convene after the last subject in each cohort completes the week 4 visit. The exception is for cohorts 2 and 3 where ~~the~~**an initial** DLRM will convene after the ~~last subject~~**first 16** enrolled **subjects (8** in ~~both cohorts completes~~**each cohort) complete** the week 4 visit **and a second DLRM will convene after the remaining 16 enrolled subjects (8 in each cohort) complete the week 4 visit**.

Section: 1 Protocol Synopsis, Overall Design

[redacted]

Section: 1 Protocol Synopsis, Number of Subjects

Replace: Approximately 32 subjects will be randomized in the phase 1b part of the study (24 to AMG 592 and 8 to placebo).

With: In the phase 1b part of the study**, sufficient subjects will be randomized to yield approximately 48 subjects** (~~24~~**approximately 36 randomized** to AMG 592 and ~~8~~**12 randomized** to placebo**; see Section 5.2.1**). **The total sample size may be higher than 48 subjects if, following a DLRM recommendation additional dosing cohorts are added and/or existing cohorts are expanded, or if subjects are replaced as per Section 5.2.1. Additional subjects may be enrolled in each cohort to enable all screened eligible subjects to participate in the study. Within each cohort subjects will be randomized to AMG 592 or placebo in a 3:1 ratio.**

Section: 1 Protocol Synopsis, Treatments

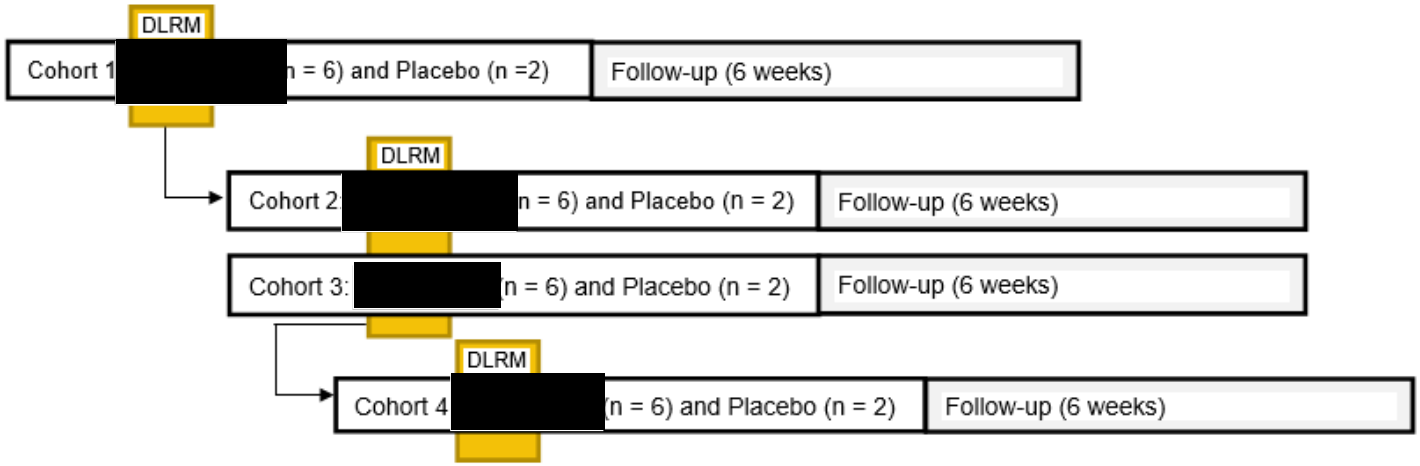
Replace: In the phase 1b part of the study, 4 dose cohorts are planned (cohort 1: [redacted] cohort 2: [redacted] cohort 3: [redacted] and cohort 4: [redacted]

With: In the phase 1b part of the study, 4 dose cohorts are planned (cohort 1: [redacted]; cohort 2: [redacted]; cohort 3: [redacted] and cohort 4: [redacted]

Section: 2.1 Study Schema

Replace:

Figure 2-1. Study Shema Phase 1b



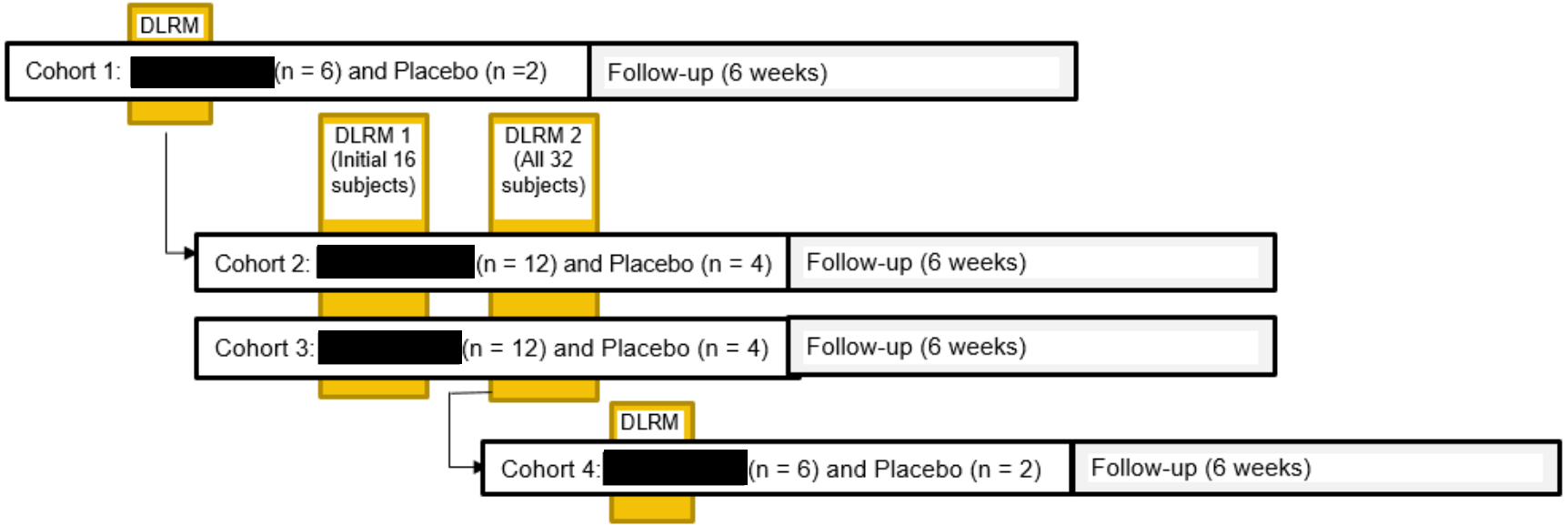
[redacted]

Doses and size of subsequent treatment cohorts may change as determined by safety, BLRM by logistic regression modeling, and pharmacokinetic/pharmacodynamic modeling:

- DLRM: 4 weeks after last subject in cohort enrolled except for cohorts 2 and 3 where the DLRM will convene after the last subject in each cohort has completed the week 4 visits.
- Treatment Period: 12 weeks
- Follow-up: 6 weeks after week 12 for collection of additional safety, pharmacokinetic, pharmacodynamics data. For subjects who complete the study at week 18, the visit includes all required safety follow-up collection. All subjects who terminate the study early (ie, prior to completing the week 18 visit) will complete an Early Termination visit consisting of all assessments included in the week 12, day 85 pre-dose visit. In addition, a safety follow-up visit will occur 6 weeks (± 3 days) after the last dose of investigational product to collect all required safety data including of adverse events, serious adverse events, disease related events, concomitant therapies, safety labs/assessments, anti-AMG 592 antibody, and urine pregnancy test.

With:

Figure 2-1. Study Shema Phase 1b



[redacted]

Doses and size of subsequent treatment cohorts may change as determined by safety, BLRM by logistic regression modeling, and pharmacokinetic/pharmacodynamic modeling:

- DLRM: 4 weeks after last subject in cohort enrolled except for cohorts 2 and 3 where an initial DLRM (DLRM 1) will convene after the first 16 enrolled subjects (8 in each cohort) completes the week 4 visit and a second DLRM (DLRM 2) will convene after the remaining 16 enrolled subjects (8 in each cohort) complete the week 4 visit.
- Treatment Period: 12 weeks
- Follow-up: 6 weeks after week 12 for collection of additional safety, pharmacokinetic, pharmacodynamics data. For subjects who complete the study at week 18, the visit includes all required safety follow-up collection. All subjects who terminate the study early (ie, prior to completing the week 18 visit) will complete an Early Termination visit consisting of all assessments included in the week 12, day 85 pre-dose visit. In addition, a safety follow-up visit will occur 6 weeks (± 3 days) after the last dose of investigational product to collect all required safety data including of adverse events, serious adverse events, disease related events, concomitant therapies, safety labs/assessments, anti-AMG 592 antibody, and urine pregnancy test.

[redacted]

Section: 3.2.5 Risk Assessment

Replace: Single doses of AMG 592 ranging from [redacted] have been administered to 8 cohorts of healthy subjects in a phase 1a FIH single ascending and multiple dose study of AMG 592 (Study 20140324). Treatment with AMG 592 resulted in a dose-dependent increase in Treg cells with minimal expansion of CD4+ and CD8+ [redacted] or NK cells. No deaths, serious adverse events, or concerning safety signals have been observed. The most common adverse events include mild (grade 1) painless erythema at or near the injection site, sometimes accompanied by pruritus, that is self-resolving. Please refer to the Investigator's Brochure for further details.

With: ~~Single doses of AMG 592 ranging from [redacted] have been administered to 8 cohorts of healthy subjects in a phase 1a FIH single ascending and multiple dose study of AMG 592 (Study 20140324). Treatment with AMG 592 resulted in a dose-dependent increase in Treg cells with minimal expansion of CD4+ and CD8+ [redacted] or NK cells. No deaths, serious adverse events, or concerning safety signals have been observed.~~ **As of 12 March 2019, approximately 100 subjects have received at least 1 dose of AMG 592. Repeated subcutaneous doses of up to [redacted] have been studied for up to 3 months in subjects with RA and systemic lupus erythematosus.** The most common adverse event~~s include~~ **experienced by subjects was** mild (grade 1) painless erythema at or near the injection site, sometimes accompanied by pruritus, that ~~i~~**was** self-resolving. ~~Please refer to~~**Two serious hypersensitivity reactions to AMG 592 have been reported. In addition, worsening arthritis deemed related to AMG 592 has been reported in the ongoing 20170149 study. The majority of these events were reported by a single site. No clinically significant therapeutic related abnormalities in electrocardiograms, hematological or biochemical laboratory investigations, or vital signs have been reported. More detailed information about the known and expected risks and reasonably expected adverse events of AMG 592 may be found in** the Investigator's Brochure.

Section: 5.1.1 Phase 1b Study Design

Replace: Dosing cohorts will enroll sequentially with the exception of cohorts 2 and 3, which will enroll concurrently and share a single dose level review meeting (DLRM).

After the last subject enrolled in each cohort completes the week 4 visit, a dose level review meeting (DLRM) will convene to determine the acceptability of dose escalation. The exception is for cohorts 2 and 3 where the DLRM will convene after the last subject enrolled in both cohorts completes the week 4 visit.

With: Dosing cohorts will enroll sequentially with the exception of cohorts 2 and 3, which will enroll concurrently and share ~~a single~~ dose level review ~~meeting~~ (~~DLRM~~**meetings (DLRMs**).

After the last subject enrolled in each cohort completes the week 4 visit, a ~~dose level review meeting (~~DLRM~~)~~ will convene to determine the acceptability of dose escalation. The exception is for cohorts 2 and 3 where ~~the~~**an initial** DLRM will convene after the ~~last subject~~**first 16** enrolled **subjects (8** in ~~both cohorts completes~~**each cohort) complete the week 4 visit and a second DLRM will convene after the remaining 16 enrolled subjects (8 in each cohort) complete** the week 4 visit.

Section: 5.1.1 Phase 1b Study Design

Replace: Additional dosing cohorts may be added or substituted based on emerging data.

With: Additional dosing cohorts may be added **and/**or ~~substituted~~**existing cohorts may be expanded** based on emerging data.

Section: 5.2 Number of Subjects

Replace: Approximately 32 subjects will be randomized in the phase 1b part of the study (24 to AMG 592 and 8 to placebo). [redacted]

With: ~~Approximately 32 subjects will be randomized in the phase 1b part of the study (24 to AMG 592 and 8 to placebo).~~**In the phase 1b part of the study, sufficient subjects will be randomized to yield approximately 48 evaluable subjects (approximately 36 randomized to AMG 592 and 12 randomized to placebo; see Section 5.2.1). The total sample size may be higher than 48 subjects if, following a DLRM recommendation, additional dosing cohorts are added and/or existing cohorts are expanded, or if subjects are replaced as per Section 5.2.1. Additional subjects may be enrolled in each cohort to enable all screened eligible subjects to participate in the study. Within each cohort subjects will be randomized to AMG 592 or placebo in a 3:1 ratio.**

Section: 5.2.1 Replacement of Subjects

Replace: In the phase 1b part of the study subjects who have been randomized but withdraw prior to administration of investigational product will be replaced.

With: In the phase 1b part of the study subjects who ~~have been~~**are** randomized but ~~withdraw prior to administration of~~**discontinue** investigational **medicinal** product ~~will~~**before completing the week 4 visit may** be replaced.

Section: 5.2.2 Number of Sites

Replace: Approximately 14 sites in North America and Europe will participate in the phase 1b part of the study [redacted]

With: Approximately ~~14~~**18** sites in North America and Europe will participate in the phase 1b part of the study [redacted]

[redacted]

Section: 6.2 Exclusion Criteria

Replace:

209 Positive drug or alcohol urine test at screening.

With:

209 **Phase 1b only:** Positive drug or alcohol urine test **for illicit drugs** at screening. **Prescription medications detected by the drug test are allowed if they are being taken under the direction of a physician.**

Section: 6.2 Exclusion Criteria

Replace:

225 Presence of laboratory abnormalities at screening including the following:

- Aspartate aminotransferase (AST) or alanine amino transferase (ALT) at screening > 1.5X upper limit of normal (ULN)
- Serum total bilirubin (TBL) ≥ 1.5 mg/dL (≥ 26 µmol/L)
- Hemoglobin ≤ 10.5 g/dL(≤ 105 g/L)
- Platelet count < 100,000/mm^3 (< 100 x 10^9/L)
- White blood cell count < 3,000 cells/mm^3 (< 3.0 x 10^9/L)
- Absolute neutrophil count (ANC) < 1,500/mm^3 (< 1.5 x 10^9/L)
- Calculated glomerular filtration rate of ≤ 50 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) formula

With:

225 Presence of laboratory abnormalities at screening including the following:

- Aspartate aminotransferase (AST) or alanine amino transferase (ALT) at screening > 1.5X upper limit of normal (ULN)
- Serum total bilirubin (TBL) ≥ 1.5 mg/dL (≥ 26 µmol/L)
- Hemoglobin ≤ 10.5 g/dL(≤ 105 g/L)
- Platelet count < 100,000/mm^3 (< 100 x 10^9/L)
- White blood cell count < ~~3,000~~**2,500** cells/mm^3 (< ~~3.0~~**2.5** x 10^9/L)
- Absolute neutrophil count (ANC) < 1,~~500~~**000**/mm^3 (< 1.~~5~~**0** x 10^9/L)
- Calculated glomerular filtration rate of ≤ 50 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) formula

Section: 7.1.1.1.1 Dosage Adminsitration and Schedule

Replace: In the phase 1b part of the study, AMG 592 or placebo will be administered by SC injection [redacted] starting on day 1. The following dose cohorts are planned in the phase 1b portion of the study:

[redacted]

With: In the phase 1b part of the study, AMG 592 or placebo will be administered by SC injection [redacted] starting on day 1. The following dose cohorts are planned in the phase 1b portion of the study:

[redacted]

Section: 7.4.2.1 Dose Level Review Meetings

Replace: After all evaluable subjects within a cohort have completed the week 4 visit, a DLRM will be held to review data and make dose escalation/de-escalation decisions (see Appendix 3).

With: After all evaluable subjects within a cohort have completed the week 4 visit, a DLRM will be held to review data and make dose escalation/de-escalation decisions (see Appendix 3). **The exception is for cohorts 2 and 3 where an initial DLRM will convene after the first 16 enrolled subjects (8 in each cohort) complete the week 4 visit and a second DLRM will convene after the remaining 16 enrolled subjects (8 in each cohort) complete the week 4 visit.**

Section: 7.4.2.2 Dose Cohort Stopping Rules

Replace:

Table 7-1. Dose Cohort Stopping Rules

Scenario	Action
Occurrence of a CTCAE version 4.0 Grade 3 adverse event deemed related to investigational product in 2 or more subjects within in a single dosing cohort	Stop dosing and convene DLRM (if event occurs outside the regularly scheduled DLRM) Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance Consider unblinding, as appropriate[a] Upon majority vote by the DLRM members, one of the following decisions may be made • stop enrollment of the cohort (if applicable) • enrollment of the cohort may resume as planned • the cohort may be expanded at the same dose • enrollment of the study may continue at a lower dose OR Upon unanimous vote by the DLRM members, 1 of the following decisions may be made: • escalation to an intermediate dose (a dose lower than the next planned dose) may take place • escalation to the next planned dose may occur
Any occurrence of a CTCAE version 4.0 ≥ Grade 4 adverse event	Stop dosing additional subjects in the cohort and convene DLRM (if the event occurs outside the regularly scheduled DLRM) Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance. Consider unblinding to determine relatedness to investigational product[a] If the adverse event is determined by majority vote of the DLRM members to be related to the investigational product and clinically or medically significant, no further doses should be administered at this dose and no dose escalation should proceed. Enrollment of the study may continue at a lower dose or a lower dose cohort may be added to the study. Otherwise, upon majority vote of the DLRM members, one of the following decisions may be made: • enrollment of the cohort may resume as planned • the cohort may be expanded at the same dose • enrollment of the study may continue at a lower dose or a lower dose cohort may be added to the study

With:

Table 7-1. Dose Cohort Stopping Rules

Scenario	Action
Occurrence of a CTCAE version 4.0**3** Grade 3 adverse event deemed related to investigational product in 2 or more subjects within in a single dosing cohort	Stop dosing and convene DLRM (if event occurs outside the regularly scheduled DLRM) Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance Consider unblinding, as appropriate[a] Upon majority vote by the DLRM members, one of the following ~~decisions~~**recommendations** may be made • stop enrollment of the cohort (if applicable) • enrollment of the cohort may resume as planned • the cohort may be expanded at the same dose • enrollment of the study may continue at a lower dose OR Upon unanimous vote by the DLRM members, 1 of the following ~~decisions~~**recommendations** may be made: • escalation to an intermediate dose (a dose lower than the next planned dose) may take place • escalation to the next planned dose may occur
Any occurrence of a CTCAE version 4.0**3** ≥ Grade 4 adverse event	Stop dosing additional subjects in the cohort and convene DLRM (if the event occurs outside the regularly scheduled DLRM) Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance. Consider unblinding to determine relatedness to investigational product[a] If the adverse event is determined by majority vote of the DLRM members to be related to the investigational product and clinically or medically significant, no further doses should be administered at this dose and no dose escalation should proceed. Enrollment of the study may continue at a lower dose or a lower dose cohort may be added to the study. Otherwise, upon majority vote of the DLRM members, one of the following ~~decisions~~**recommendations** may be made: • enrollment of the cohort may resume as planned • the cohort may be expanded at the same dose • enrollment of the study may continue at a lower dose or a lower dose cohort may be added to the study

Section: 10.1.1 Phase 1b

Replace: It is anticipated that approximately 32 subjects will be enrolled in the phase 1b part of the study with 8 subjects assigned to each cohort (3:1 ratio AMG 592 vs placebo).

The sample size of the phase 1b part of the study is based on practical considerations. With 6 subjects receiving AMG 592 per cohort, there is an 82% chance of at least 1 subject experiencing an adverse event, if the true event rate is 25%. The chance of at least 1 subject experiencing an adverse event will be 74% if the event rate becomes 20%. With a total of 24 subjects planned to receive AMG 592 in phase 1b, there is a 21% chance of at least 1 subject experiencing an adverse event with a true event rate of 1%. The chance of at least 1 subject experiencing an adverse event will be 71% if the true event rate becomes 5%.

With: It is anticipated that approximately ~~32~~**48** subjects will be ~~enrolled~~**randomized** in the phase 1b part of the study**,** with 8 subjects ~~assigned~~**randomized** to each **of cohorts 1 and 4 and approximately 16 subjects randomized to each of cohorts 2 and 3**~~(3:1 ratio AMG 592 vs placebo)~~**. The total sample size may be higher than 48 subjects if, following a DLRM recommendation, additional dosing cohorts are added and/or existing cohorts are expanded, or if subjects are replaced as per Section 5.2.1. Within each** cohort **subjects will be randomized to AMG 592 or placebo in a 3:1 ratio.**

The sample size of the phase 1b part of the study is based on practical considerations. ~~With~~ **For cohorts 1 and 4, with** 6 subjects receiving AMG 592 ~~per~~**in each** cohort, there is an 82% chance of at least 1 subject **within a cohort** experiencing an adverse event, if the true event rate is 25%. The chance of at least 1 subject experiencing an adverse event **within a cohort** will be 74% if the event rate becomes 20%. ~~With a total of 24 subjects~~

For cohorts 2 and 3, with 12 subjects receiving AMG 592 in each cohort, the chance of at least 1 subject experiencing an adverse event within a cohort increases to 97% and 93% for true event rates of 25% and 20%, respectively. In addition, with a total of 36 subjects planned to receive AMG 592 in **the** phase 1b~~, there is a 21% chance of at least 1 subject experiencing an adverse event with a true event rate of 1%. The~~ **part of the study, the** chance of at least 1 subject

experiencing an adverse event ~~will be 71~~**across the cohorts increases to 30% and 84**% if the true event ~~rate becomes 5%.~~**rates are 1% and 5%, respectively.**

Additional subjects may be enrolled at a randomization ratio of 3:1 to AMG 592 or placebo to enable all screened eligible subjects to participate in the study, for addition and/or expansion of cohorts based on DLRM recommendations, or for replacement of subjects as per Section 5.2.1.

Amendment 2

Protocol Title: A Phase 1b/2a Study to Evaluate the Safety and Efficacy of AMG 592 in Subjects With Active Rheumatoid Arthritis With Inadequate Response to Standard of Care Therapy

Amgen Protocol Number (AMG 592) 20170149

NCT Number: NCT03410056

EudraCT Number 2017-001944-36

Amendment Date: 26 July 2018

Rationale:

This protocol is being amended to change subject urine drug/alcohol testing, during screening, from the local laboratory to the central laboratory.

Amendment 1

Protocol Title: A Phase 1b/2a Study to Evaluate the Safety and Efficacy of AMG 592 in Subjects With Active Rheumatoid Arthritis With Inadequate Response to Standard of Care Therapy

Amgen Protocol Number (AMG 592) 20170149

Amendment Date: 23 May 2018

Rationale:

The purpose of this protocol amendment is to:

- Update language to clarify aspects of Early Termination and Safety Follow-up visits, as previously outlined in clarification memos for authorities.
- Change exclusion criterion 217 to allow up to 3 prior biologic or oral synthetic DMARD therapies; update wash out periods for these prior therapies.
- Clarify exclusion criterion 221, prohibition of as needed nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen and/or analgesics, applies to phase 2a only.
- Clarify exclusion criterion 223 and prohibited medications to allow Vitamin D and calcium to be taken.
- Replace sentinel dosing in Phase 1b with longer direct observation after the first dose and close telephone follow-up after the second dose of investigational product for *all* subjects.
- Incorporate a cohort stopping rule of ≥ 2 Grade 3 adverse events to replace the existing ≥ 3 Grade 3 adverse event cohort stopping rule.
- Clarify that Pharmacokinetic, pharmacodynamic, and antibody blood samples may not be drawn through a central or peripheral line.
- Include pharmacokinetic sampling at day 92, 99, and 113 to align with other studies in AMG 592 program.
- Include earlier clinical lab assessments prior to day 15 for additional safety review.
- Updated language within protocol to align with latest version of the DLRM SOP.