**Title: A Randomized, Double Blind Placebo Controlled, First in Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending Subcutaneous Doses of AMG 570 in Healthy Subjects**

Amgen Protocol Number (AMG 570) 20140322

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## Confidentiality Notice



NCT Number: NCT02618967
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**Investigator's Agreement**

I have read the attached protocol entitled "A Randomized, Double Blind Placebo Controlled, First in Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending Subcutaneous Doses of AMG 570 in Healthy Subjects", dated 24 January 2018 and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) 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)

## Protocol Synopsis

**Title:** A Randomized, Double Blind Placebo Controlled, First in Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending Subcutaneous Doses of AMG 570 in Healthy Subjects

**Study Phase:** 1

**Indication:** Systemic Lupus Erythematosus

**Primary Objective:** To assess the safety and tolerability of single subcutaneous (SC) doses of AMG 570 in healthy subjects.

**Secondary Objective(s):**

- To characterize the PK of single subcutaneous (SC) doses of AMG 570 in healthy subjects.
- To evaluate the PD effects (B7RP-1 occupancy and inhibition of B cell survival) of single subcutaneous (SC) doses of AMG 570 in healthy subjects.
- To evaluate the immunogenicity of AMG 570.

**Exploratory Objective(s):**

- To evaluate the relationship between PK, B7RP-1 occupancy, [redacted] and changes in percentage and absolute counts of naïve and memory B cells following single subcutaneous (SC) doses of AMG 570 in healthy subjects.
- To evaluate the PD effect of single subcutaneous (SC) doses of AMG 570 in healthy subjects on serum IgG and IgM.

**Hypotheses:** A single SC dose administration of AMG 570 will achieve an acceptable safety and tolerability profile in healthy subjects within the proposed dose ranges (SC: 7 to 700 mg AMG 570).

**Primary Endpoint:** Subject incidences of treatment-emergent adverse events, including clinically significant changes in physical examinations, vital signs, laboratory safety tests, and electrocardiograms (ECGs).

**Secondary Endpoint(s):**

- AMG 570 PK parameters (eg, maximum observed concentration [$C_{max}$], time at $C_{max}$ [$t_{max,}$], and area under the concentration-time curve [AUC]).
- Anti-AMG 570 binding antibodies.
- Peripheral blood B7RP-1 receptor occupancy.
- Peripheral blood changes in percentage and absolute counts of naïve and memory $CD19^+$ B cells (naïve = $IgD^+CD27^-$, memory = $IgD^-CD27^+$).

**Exploratory Endpoint(s):** Exploratory biomarkers may include but are not limited to the following:

- [redacted].
- Serum IgG and IgM.

**Study Design:** This is a randomized, placebo-controlled, double-blind, single ascending dose (SAD) study in healthy subjects. The study consists of 7 SC cohorts. Subjects will be randomized in a 3:1 ratio to receive AMG 570 or placebo accordingly.

**Dose Levels**

| Cohort # | Planned Dose (mg) | Route | N (active:placebo) |
|---|---|---|---|
| 1 | 7 | SC | 8 (6:2) |
| 2 | 21 | SC | 8 (6:2) |
| 3 | 70 | SC | 8 (6:2) |
| 4 | 140 | SC | 8 (6:2) |
| 5 | 210 | SC | 8 (6:2) |
| 6 | 420 | SC | 8 (6:2) |
| 7 | 700 | SC | 8 (6:2) |

The actual dose to be administered may be adjusted based on safety, tolerability, and preliminary PK and PD data of previous dose levels. Dose adjustments may involve either an increase or a decrease in the planned dose, but will not exceed pharmacokinetic criteria defined in the rationale for dose selection Section 2.4.5.

**Sample Size:** Approximately 56 healthy subjects will be enrolled into 7 cohorts (6 active: 2 placebo in each cohort).

**Summary of Subject Eligibility Criteria:** Subjects in this study will be males and females between ages of 18 and 65 years, and the females must be of non-reproductive potential. Subjects should have a body mass index of ≥ 18.0 and ≤ 30.0 kg/m$^2$. For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2.

**Investigational Product**

**Amgen Investigational Product Dosage and Administration:**

This first in human study will utilize sentinel dosing for the first two subjects of each cohort. The sentinel pair (the first 2 subjects in each cohort) will be dosed with one subject receiving a single dose of AMG 570 and the other receiving placebo. The remaining subjects of each cohort may be dosed 24 hours after the sentinel pair.

For subcutaneous dosing in Cohorts 1 & 2, diluent will be used. For subcutaneous dosing in Cohorts 3 to 5, doses will be administered in a 1.0 mL per injection format (up to 3 x 1 mL injections depending on treatment arm). For subcutaneous dosing in Cohort 6, doses will be administered in a 1.5 mL per injection format (4 x 1.5 mL injections). For subcutaneous dosing in Cohort 7, doses will be administered in a 2 mL per injection format (5 x 2.0 mL injections).

**Dosage and IP Administration**

| Product Name | AMG 570 | Placebo | Diluent |
|---|---|---|---|
| Formulation Description | 10 mM acetate, 9.0% (w/v) sucrose, 0.01% (w/v) polysorbate 80 | 10 mM acetate, 9.0% (w/v) sucrose, 0.004% (w/v) polysorbate 20 | 10 mM acetate, 9.0% (w/v) sucrose, 0.004% (w/v) polysorbate 20 |
| Dosage Form | Solution | Solution | Solution |
| Unit dose Strength | 70 mg/ml | NA | NA |

**Procedures:** After signing the informed consent, subjects will be screened to determine eligibility. The screening period is 42 days. Prior to enrollment, baseline assessments will be performed. Subjects who meet the inclusion and exclusion criteria after completion of all screening and baseline procedures will be enrolled in the study.

Subjects will be confined to the research facility from day -1 to day 3, where critical clinical safety and study evaluations will be performed including physical examination, vital signs, clinical laboratory tests, ECGs, PK, and biomarker sample collections.

On study day 1, subjects will complete pre-dose assessments and receive a single SC dose of AMG 570 or placebo. Subjects may check out of the research facility on Day 3 after all assessments have been completed. If needed to facilitate study evaluation at specified time points subjects may also stay at the research facility up to Day 11. After discharge from the research facility, subjects must return to the research facility on an outpatient basis at specified time points for collection of blood samples for PK and PD measurements and completion of safety assessments (including blood samples for antibody analysis). All adverse events, including serious adverse events, and use of concomitant medication will be collected for the duration of the study.

Subjects' participation in the study will conclude with the completion of the end of study procedures. However, if an end of study test result demonstrates a significant clinical or laboratory abnormality, the subject will be followed until resolution of the abnormality or until it is considered clinically stable by the Principal Investigator. If a subject's $CD3^{-}CD19^{+}$ B cell counts are < 107 cells/µL (the lower limit of normal for healthy volunteers), the subject will return for further testing of B cell counts every 3 months until the subject has B cell counts ≥ 107 cells/µL. Such follow-up visit(s) for B cell counts will continue every 3 months, up to 12 months after the end of study.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 8).

**Statistical Considerations:** Descriptive statistics will be provided for selected demographics, safety, immunogenicity, PK, PD, and biomarker end points. 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 may also be presented by time as appropriate.

The number and percent of subjects reporting any adverse events will be tabulated by system organ class and preferred term and may be further classified by severity and relationship to treatment. Subject incidence of clinically significant changes in vital signs, physical examinations, clinical laboratory safety tests, ECGs, and the development of AMG 570 binding antibodies will be noted. For a full description of statistical analysis methods, please refer to Section 10.



**Sponsor:**

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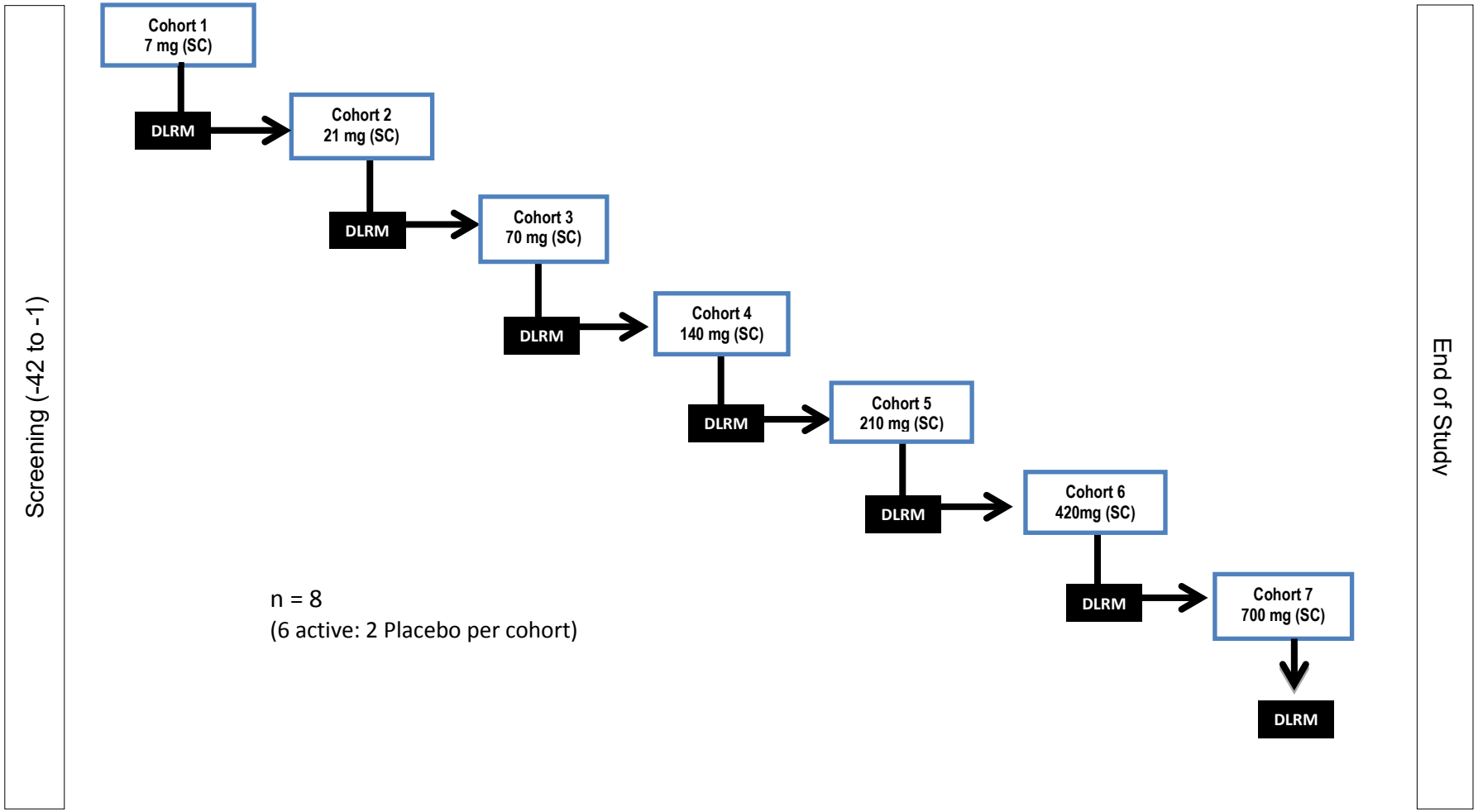
## Study Design and Treatment Schema



## Study Glossary

| Abbreviation or Term | Definition/Explanation |
|---|---|
| ADA | Anti-drug antibodies |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| BAFF | B cell activating factor |
| B7RP-1 | B7-related protein-1 (also known as ICOSL) |
| BMI | body mass index |
| CI | confidence interval |
| $C_{max}$ | maximum observed concentration |
| CRF | case report form |
| DLRM | dose level review meeting |
| DLT | dose limiting toxicity |
| DCs | dendritic cells |
| DILI | drug-induced liver injury |
| ECG | Electrocardiogram |
| eCRF | electronic case report form |
| EOS | end of study |
| EMEA | European Medicines Agency |
| end of study for individual subject | defined as the last date that protocol-specified procedures are conducted for an individual subject |
| end of treatment | defined as the date of final assessment for the protocol specified treatment phase of the study 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 purposes of final collection of data for the primary endpoint(s). |
| end of trial | defined as the date when the last subject is assessed or receives an intervention for evaluation in the study; if the study includes multiple parts (eg, safety follow-up), the end of study would include these additional parts |
| FIH | First in Human |
| FSH | Follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GSO | Global Safety Officer |
| HBcAb | hepatitis B core antibody |
| HepBsAg | hepatitis B surface antigen |

| Abbreviation or Term | Definition/Explanation |
|---|---|
| HepCAb | hepatitis C antibody |
| HIV | human immunodeficiency virus |
| Ig | Immunoglobulin |
| $IC_{50}$ | inhibitory concentration at 50% |
| $IC_{90}$ | inhibitory concentration at 90% |
| $IC_{99}$ | inhibitory concentration at 99% |
| ICF | informed consent form |
| ICOS | inducible co-stimulator |
| ICOSL | inducible co-stimulator ligand |
| ICH | International Conference On Harmonisation |
| IV | intravenous |
| IP | Investigational Product |
| IPIM | Investigational Product Instruction Manual |
| IPRO | Immunophenotyping and Receptor Occupancy |
| IRB | Institutional Review Board |
| LLN | lower limit of normal |
| LLOQ | lower limit of quantification |
| MABEL | Minimum Anticipated Biological Effect Level |
| MRSD | maximum recommended starting dose |
| NOAEL | no observed adverse effect level |
| PD | pharmacodynamic |
| PK | pharmacokinetic |
| PR | the interval measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by electrocardiogram |
| QRS | the interval between the Q wave and the S wave in the heart's electrical cycle as measured by electrocardiogram; represents the time it takes for depolarization of the ventricles |
| QT | 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 electrocardiogram |
| QTc | QT interval corrected for heart rate using accepted methodology |
| RO | receptor occupancy |
| RNA | ribonucleic acid |
| SRBC | sheep red blood cells |
| SC | Subcutaneous |
| SLE | Systemic Lupus Erythematosus |

| Abbreviation or Term | Definition/Explanation |
|---|---|
| study day 1 | defined as the first day that protocol specified investigational product is administered to the subject |
| Th1 | T helper type 1 |
| Th2 | T helper type 2 |
| $t_{max}$ | time to maximum concentration |
| ULN | upper limit of normal |

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# 1. OBJECTIVES

## 1.1 Primary

To assess the safety and tolerability of single subcutaneous (SC) doses of AMG 570 in healthy subjects.

## 1.2 Secondary

- To characterize the PK profile of single subcutaneous (SC) doses of AMG 570 in healthy subjects.
- To evaluate the PD effects (B7RP-1 occupancy and inhibition of B cell survival) of single subcutaneous (SC) doses of AMG 570 in healthy subjects.
- To evaluate the immunogenicity of AMG 570.

## 1.3 Exploratory

- To evaluate the relationship between PK, B7RP-1 occupancy, [redacted] and changes in percentage and absolute counts of naïve and memory B cells following single subcutaneous (SC) doses of AMG 570 in healthy subjects.
- To evaluate the PD effect of single subcutaneous (SC) doses of AMG 570 in healthy subjects on serum IgG and IgM.

# 2. BACKGROUND AND RATIONALE

## 2.1 Disease

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease of unknown cause with diverse clinical manifestations that disproportionately affects minorities (in particular, blacks and Hispanics) and women of childbearing potential (Tsokos, 2011; Rahman and Isenberg, 2008; Kotzin, 1996). The prevalence of SLE in the United States varies widely in different studies but is generally thought to be underestimated due to the difficulty in diagnosis of the disease and obtaining reliable data to estimate the true numbers of subjects with this disease. The prevalence of SLE in the population varies from 20 to 150 cases per 100,000 (Pons-Estel, 2010; Helmick, 2008; Lawrence, 2008; Chakravarty, 2007). There are significant racial differences in prevalence rates with 164 (white) to 406 (African American) per 100,000 (Chakravarty, 2007). In the US, one-third of patients diagnosed with lupus have moderate to severe SLE.

SLE is a heterogeneous disease that is characterized by periods of remission and flares that range from mild to severe. It is associated with highly variable inter-individual symptoms and can be fatal. SLE can affect the skin (rash), musculoskeletal system (arthritis, bone tissue death), nervous system (seizures, psychosis), lungs (pleuritis, pneumonitis), and the blood (venous or arterial clots, anemia). In addition, approximately 65% of patients will develop lupus nephritis, which is an inflammatory

condition of the kidney that can range from mild focal to severe diffuse proliferative glomerulonephritis (Adams et al, 2006). Lupus nephritis can also lead to kidney failure and is a serious complication of SLE.

The treatment options and duration of SLE are highly individualized and depend on symptoms, organ involvement, and disease severity. Antimalarial and nonsteroidal anti-inflammatory drugs (NSAIDs) are useful in the treatment of mild symptoms such as arthralgia and cutaneous manifestations. Oral corticosteroids and cytotoxic agents are used in more severe disease. Other medications (cyclophosphamide, immunosuppressive agents, and tacrolimus) may be used depending on the severity and organ systems involved. Belimumab (anti-BAFF) is a newer agent that is approved for patients with mild to moderate disease currently taking standard therapy.

Although the clinical heterogeneity of SLE presents diagnostic challenges, antibodies to nuclear components represent a common manifestation of the disease. The presence of class-switched immunoglobulin G (IgG) autoantibodies implicate immune dysregulation as a driving force for disease pathogenesis, with T cells appearing to play a role in the development of autoantibody production by B cells. T cells are believed to be drivers of many different autoimmune diseases including SLE and rheumatoid arthritis (RA) due to their central role in the control of immune system function. Simultaneous blockade of the B7-related protein-1 (B7RP-1)/ inducible co-stimulator (ICOS) pathway and B cell-activating factor (BAFF) with AMG 570 is hypothesized to result in blockade of T-cell activation, B-cell maturation, and antibody production.



## 2.2 Amgen Investigational Product Background

### 2.2.1 Pharmacology

AMG 570 is a bispecific molecule inhibiting both BAFF and B7RP-1. AMG 570 contains two tandem copies of BAFF-binding peptides identical to the BAFF binding peptides of blisibimod (also known as AMG 623) fused to the C-terminus of AMG 557, a fully human IgG2 against B7RP-1 currently in clinical development for SLE. In terms of anti-BAFF effect, AMG 570 has similar binding affinity and cellular potency to blisibimod. AMG 570 has 29 pM $K_D$ BAFF binding affinity and 0.86 nM $IC_{50}$ in a BAFF cellular assay. Blisibimod was reported to have an $IC_{50}$ of 0.2 nM. For anti-B7RP-1 effect, AMG 570 has similar binding affinity and inhibitory activity to AMG 557. AMG 570 has 28 pM $K_D$ B7RP-1 binding affinity and 1.36 nM $IC_{50}$ in a B7RP-1 cellular assay. AMG 557 has 17 pM $K_D$ B7RP-1 binding affinity and AMG 557 parental antibody 16H has 1.35 nM $IC_{50}$ in a B7RP-1 cellular assay. AMG 570 binds and inhibits cynomolgus monkey

BAFF and B7RP-1, but not rodent B7RP-1. A mouse surrogate BAFF/B7RP-1 bispecific molecule showed dual-target inhibition in vivo and was more efficacious than the single B7RP-1 or BAFF inhibitors in the mouse NZB/NZW lupus model. We hypothesize that targeting both BAFF and B7RP-1 by AMG 570 will achieve a large effect size in the treatment of SLE.

### 2.2.2 Pharmacokinetics

The pharmacokinetics (PK) of AMG 570 after a single IV or SC administration was characterized in male cynomolgus monkeys.

PK profiles of AMG 570 and AMG 557 were similar in cynomolgus monkeys (Table 1).

**Table 1. Comparison of AMG 570 and AMG 557 Mean ± SD Pharmacokinetic Parameters in Cynomolgus Monkey**

| | 10 mg/kg SC | | | 10 mg/kg IV | | |
|---|---|---|---|---|---|---|
| **Molecule** | **$C_{max}$ (µg/mL)** | **AUC (µg•day/ mL)** | **CL or CL/F (mL/day/kg)** | **$C_0$ (µg/mL)** | **AUC (µg•day/ mL)** | **CL or CL/F (mL/day/ kg)** |
| AMG 570 | 90.0 ± 8.54 | 693 ± 102 | 13.9 ± 2.63 | 323 ± 30.6 | 1140 ± 219 | 9.03 ± 1.80 |
| AMG 557 | 112 ± 9.50 | 991.6 ± 144 | 10.3 ± 1.5 | 264 ± 23.3 | 1087.5 [a] | 9.31[a] |

[a] n=2
$C_0$ = extrapolated initial concentration after IV administration; $C_{max}$ = Maximum observed drug concentration during a dosing interval; AUC= area under the concentration-time curve from zero to end of dosing interval; CL = clearance after IV administration; CL/F = apparent drug clearance after SC administration; F = Bioavailability of drug

[redacted]

Serum AMG 557 exposures in the FIH study ($C_{max}$ and AUC) increased more than dose proportionally at lower doses after either single or multiple SC doses. However, an approximately dose-proportional increase in exposure was observed at higher doses (≥ 140 mg for SAD; ≥ 70 mg for MAD). Maximum concentration of AMG 557 was reached in 3-7 days ($t_{max}$) after SC administration. Bioavailability after SC dosing was estimated to be ~57%.

### 2.2.3 Toxicology

[redacted]



## 2.3 Risk Assessment

This is the first single dose study proposed in human subjects with AMG 570.

The assessment of potential side effects of AMG 570 is based on the pre-clinical studies conducted to date (Section 2.2.3) and by observations of safety and tolerability of AMG 557 and blisibimod clinical studies. Summaries of findings from the pre-clinical studies with AMG 570 can be found in the AMG 570 Investigator's Brochure (IB).

The proposed risk assessment and management plan for the study has been developed in accordance with the requirements of regulatory guidelines and strategies to identify and mitigate risks for FIH clinical trials with investigational medicinal products.
Please refer to the AMG 570 IB, Section 7 for a description of these potential side effects.



## 2.4 Rationale

The interaction of ICOS on T cells with its sole ligand, B7RP-1 on antigen presenting cells, including B cells, plays a role in T cell effector functions including cytokine production, T cell differentiation, T cell-dependent help for B cell differentiation and immunoglobulin (Ig) isotype switching (Moore et al, 2011; Paulos et al, 2010; Dong and Nurieva, 2003; McAdam et al, 2001; Coyle et al, 2000). ICOS is elevated on T cells in patients with SLE, RA and Sjögren's syndrome (Ma et al, 2012; Simpson et al, 2010;

Hu et al, 2009; Hutloff et al, 2004). B7RP-1 is expressed on B cells, dendritic cells (DCs), monocytes and macrophages, and to a lesser degree on T cells and non-lymphoid cells like endothelial cells, where it is up-regulated by inflammatory stimuli (Kroczek et al, 2004; Groom et al, 2002; Khayyamian et al, 2002; Yoshinaga et al, 1999).

BAFF is mainly expressed by monocytes, neutrophils and DCs (Chu et al, 2007; Rickert et al, 2011). BAFF supports naïve and transitional B cell survival through binding to the BAFF receptor expressed on B cells (Mackay and Browing, 2002). Increased levels of BAFF have been observed in patients with SLE, RA, and Sjögren's syndrome (Mariette et al, 2003; Groom et al, 2002; Cheema et al, 2001, Zhang et al, 2001). Elevated levels of BAFF may cause excessive survival signals to autoreactive B cells, possibly as they pass through critical tolerance checkpoints while maturing in the spleen and lymphoid tissues. Indeed, increased dependence on BAFF for autoantigen binding B cells was demonstrated in a monoclonal Ig-transgenic model (Lesley et al, 2004). At target-saturating doses, belimumab has modest efficacy, validating the BAFF pathway yet also demonstrating a strong need for therapies with better efficacy.

The combination of a T cell modulator, AMG 557 (Amgen's anti-B7RP-1 mAb), and BAFF binding peptides as in the B7RP-1-BAFF bispecific, AMG 570, has the potential for better efficacy than belimumab.

Dual BAFF and B7RP-1 inhibition is likely to be well-tolerated. Separate inhibition of BAFF or B7RP-1 has moderate impact on the immune system. BAFF inhibitors (belimumab and blisibimod) are well-tolerated in the clinic. AMG 557 is in early clinical development and has an acceptable safety profile to date.

For proof-of-concept, a mouse surrogate bispecific molecule was generated by fusion of two tandem copies of BAFF-binding peptides from AMG 523 to the C-terminus of anti-mouse B7RP-1 blocking antibody 1B7 (described by Hu et al, 2009). AMG 523 has structure similar to blisibimod with two additional amino acids (Leu, Pro) at the N-terminus. AMG 523 has binding specificity, affinity and cellular potency similar to blisibimod. The surrogate bispecific inhibits mouse BAFF induced B cell proliferation with potency similar to the BAFF peptibody AMG 523. The surrogate also inhibited mouse B7RP-1-Fc binding to ICOS on mouse T cells with potency similar to anti-mouse B7RP-1 antibody 1B7. The surrogate bispecific PK property was evaluated in mouse. Male CD-1 mice were given single dose intravenous (IV) administration via lateral tail vein of surrogate bispecific (5mg/kg), anti-B7RP-1 mAb 1B7 (4.68mg/kg), or anti-BAFF

peptibody AMG 523 (1.88mg/kg). Doses of the bispecific and single parental inhibitors were adjusted based on MW to be molar equivalents. The surrogate bispecific has PK properties similar to 1B7 in mouse with no detectable clipping of the BAFF-binding peptides.

To investigate the dual PD effects of the surrogate bispecific, we evaluated the surrogate bispecific effect on B cells, memory T cells and antibody responses in the sheep red blood cell (SRBC) challenge model. BALB/c mice (n=5) were immunized with sheep red blood cell (SRBC) on day 0 and boosted on day 28. Mice were treated with mIgG1 isotype control (5mpk), anti-mouse B7RP-1 antibody 1B7 (5mpk), anti-BAFF peptibody AMG 523 (5mpk), combination of 1B7 (5mpk) and AMG 523 (5mpk), or surrogate bispecific (1, 5 or 10 mpk) twice per week for 5 weeks starting on day 0. Spleen cells were collected on day 35 for FACS analysis and B cell numbers were measured as a PD marker to monitor BAFF inhibition. AMG 523 treatment led to more than 50% reduction of splenic B cells, whereas no significant B cell reduction was observed with anti-B7RP-1 mAb 1B7 treatment or isotype control. To monitor the B7RP-1 inhibitory PD effect, memory T cells (CD4+CD44hiCD62Lo) in spleen were measured by FACS analysis. Splenic memory T cells were significantly reduced in the 1B7 treated group, but not in the AMG 523 treatment or isotype treatment groups. Unlike single agent treatment, surrogate bispecific treatment resulted in reduction of both B cells and memory T cells, suggesting dual BAFF and B7RP-1 inhibition. The dual PD effect of the surrogate bispecific was comparable to the combination of anti-BAFF and anti-B7RP-1 treatment group. In addition, and importantly for a bispecific approach, the effective doses for B cell vs. memory T cell reduction were in a similar range.

The surrogate bispecific was compared with single agent treatment in the NZB/NZW lupus model, a mouse model of spontaneous disease, in both prophylactic and therapeutic mode. Surrogate bispecific treatment resulted in B cell reduction similar to that observed with combination or AMG 523 treatment and B7RP-1 occupancy similar to combination or 1B7 treatment groups. Altogether, prophylactic treatment with surrogate bispecific was comparable to combination therapy and more efficacious than single agents in the NZB/NZW lupus model.

The surrogate bispecific was also compared with single agents in NZB/NZW mice with delayed initiation of treatment starting at 7.5 months of age when mice had developed anti-dsDNA IgG. Similarly, surrogate bispecific treatment had a modest yet significant effect in improving survival, with p=0.0029 compared with isotype control (Kaplan Meier

Plot). Combination treatment also had modest yet significant effect in improving survival, with p=0.0239 vs isotype control. No significant difference between other groups was observed.

### 2.4.1 AMG 570, AMG 557 and Blisibimod Molecular Structure Information

The bispecific AMG 570 antibody has a peptide-linker-peptide-linker construct fused to the C-terminus of each heavy chain of AMG 557. AMG 557 is a human IgG2. Blisibimod has a peptide-linker-peptide-linker construct fused to the N-terminus of each chain of a human Fc. The peptides in AMG 570 are BAFF-binding peptides identical to those in blisibimod. Molecular weights of AMG 570, AMG 557 and blisibimod are approximately 161, 148, and 64 kDa, respectively.

### 2.4.2 AMG 557 Clinical Background

Single dose administration of AMG 557 to subjects with mild, stable SLE with subcutaneous (SC) doses of 1.8, 6, 18, 60, 140, and IV dosing of 210 mg and 18 mg demonstrated an acceptable safety profile with no observed neutralizing antibodies (study 20060132). AMG 557 demonstrated nonlinear pharmacokinetic properties, as expected for a therapeutic targeting a cell surface receptor. The degree of target occupancy was dose/concentration-related, reversible, and achieving maximal levels in the 140 mg SC group. Consistent pharmacodynamic effects on immunophenotype or KLH responses were not observed following single doses of AMG 557.

The estimated mean AMG 557 target occupancy $IC_{50}$ was 0.0888 µg/mL (0.60 nM), $IC_{90}$ of 0.8 µg/mL (5.4 nM), and $IC_{99}$ of 8.8 µg/mL (59.5 nM).

### 2.4.3 Blisibimod Clinical Background

Subjects with mild to moderate SLE were treated with blisibimod single SC doses of 0.1, 0.3, 1.0, or 3.0 mg/kg or IV doses of 1.0, 3.0, or 6.0 mg/kg in a first-in-human study (study 20040147) and multiple dose 0.3, 1.0, 3.0 (SC) or 6.0 (IV) mg/kg in phase1b (study 20040250). Blisibimod treatment led to a significant decrease in naïve B cells ($IgD^+CD27^-$) and an increase in class-switched memory B cells ($IgD^-CD27^+$) (Stohl et al, 2015). This significant reduction in naïve B-cells was observed when blisibimod concentration was 3 µg/mL (47 nM) or higher. No consistent effects on T cells, NK cells, plasmablasts, or plasma cells were evident. The Phase 2 study of blisibimod in subjects with moderate-to-severe SLE (Furie, 2014) demonstrated significantly higher SLE Responder Index (SRI-5) responses in subjects randomized to the highest dose of blisibimod 200 mg once-weekly (QW at Week 20 (p=0.02)).

### 2.4.4 AMG 570 Clinical Background

AMG 570 is currently being evaluated in this ongoing FIH study in healthy subjects. As of 1 January 2018, 48 subjects have received a single SC dose of AMG 570 or placebo at the following doses: 7, 21, 70, 140, 210, or 420 mg. All dose levels have demonstrated acceptable safety and tolerability with no severe, life-threatening, or fatal events reported. A multiple ascending dose study in patients with rheumatoid arthritis (study 20150196) has also been initiated with 9 subjects receiving 6 doses of AMG 570 at 70 mg SC q 2 weeks. Subjects at this dose level have demonstrated acceptable safety and tolerability with no severe, life-threatening, or fatal events reported. Preliminary safety, pharmacokinetics, and pharmacodynamics results from the cohorts receiving 7-140 mg of study 20140322, are described in Sections 6.1 and 6.2. of the Investigator's Brochure.

### 2.4.5 Rationale for Dose Selection

The proposed doses for AMG 570 first-in-human (FIH) clinical study were selected based on predicted human exposures utilizing clinical PK and pharmacodynamics (PD) human data from AMG 557,as well as PK, pharmacology, and toxicology data from AMG 570, and data from blisibimod clinical studies.

The exposure margins were computed from serum AMG 570 exposures at the NOAEL of 200 mg/kg in cynomolgus monkeys determined in a 3 month Good Laboratory Practice (GLP) toxicology study, and from the projected human PK exposures for the proposed doses. AMG 570 and AMG 557 PK in cynomologus monkeys were comparable based on PK studies for AMG 570 and AMG 557, as shown in Table 1. The projected AMG 570 human PK simulations were initially conducted using mean PK/PD parameters derived from modeling AMG 557 phase-1 data in SLE patients. The PK predictions have since been updated based on emerging data from this study (Table 2).

Given the safety and tolerability of AMG 557 and blisibimod, the established PK/PD relationships, and the NOAEL of 200 mg/kg, the first dose level of this study will be 7 mg SC, derived from the US FDA guidance on the maximum recommended starting dose (MRSD)(CDER, 2005). This dose is expected to demonstrate intermediate B7RP-1 occupancy in peripheral blood based on simulated relationship between predicted AMG 570 exposure and effective concentration but no reduction in naïve B cells or any other biologic effect based on predicted AMG 570 serum level and blisibimod PD data. Subsequent dose levels are 21, 70, 140, 210, 420, and 700 mg SC. Planned clinical dose levels are also supported by adequate margin based on NOAEL

from the 3-month AMG 570 GLP toxicology study in the cynomolgus monkey (Table 2). Observed and/or predicted exposure margins are shown in Table 2 below.

**Table 2. Observed or Predicted AMG 570 Pharmacokinetic Parameters and Exposure Margins**

Using the US FDA MRSD guidance for starting doses in healthy volunteers, a safety factor of 10, and a NOAEL of 200 mg/kg (2400 mg/m$^2$), the human equivalent dose would be 4500 mg (2400 mg/m$^2$ = 65 mg/kg for a 70 kg individual) and MRSD of AMG 570 would be 450 mg or 65-times the proposed starting dose of 7 mg. [redacted] (Table 2).

As outlined in Section 6.1 of the Investigator's Brochure, preliminary assessment of data from this study indicates dose-related and reversible receptor occupancy of B7RP-1 (now referred to as ICOSL in the Investigator's Brochure). Preliminary assessment on total circulating B cells indicates a significant reduction in B cell relative to baseline at day 57 in cohorts 2 (21 mg) and 3 (70 mg) compared to the accumulated placebo. Preliminary assessment of IgM and IgG levels indicate that relative to baseline, AMG 570 has demonstrated no dose-related changes compared to the accumulated placebo group.

Based on the 3-month GLP toxicology study in cynomolgus monkeys and interim pharmacokinetics data from this ongoing FIH study, it is anticipated that a 700 mg SC dose of AMG 570 in humans would not exceed the exposure associated with the AMG 570 NOAEL in cynomolgus monkeys. At this highest planned SC dose, the exposure margins are 44- and 10-fold below the $C_{max}$ and AUC at the NOAEL in monkeys. Based on interim pharmacokinetics and pharmacodynamics data from this ongoing study, it is also anticipated that a 700 mg SC dose of AMG 570 is expected to result in 90% or more B7RP-1 RO at day 8 and B cell depletion of up to 40% compared to baseline by day 57. Significant changes to circulating IgG and IgM levels are not anticipated based on interim data.

In summary, the dose range of 7 mg to 700 mg SC is projected to result in human exposures less than the exposures tested in the cynomolgus monkey 3-month GLP toxicology study. This dose range is expected to be well tolerated and to result in pharmacological activity useful for dose selection in subsequent clinical trials.



### 2.4.6 Rationale for Key Aspects of Study Design

Healthy volunteers are to be enrolled in this single ascending dose (SAD) study. The understanding of both targets of AMG 570, B7RP-1 and BAFF, and previous experience with AMG 557 and blisibimod with their acceptable safety and tolerability profiles justifies testing in healthy volunteers. Further, a single dose of AMG 570 is not expected to provide great benefit in subjects with autoimmune disease.

The single ascending dose design requires thorough evaluation of the safety profile for dose escalation. Subjects will be carefully monitored for adverse events and safety laboratory results, including peripheral blood B cell numbers and serum IgG. Testing in this population will provide initial information on the PK of AMG 570, which is expected to be similar to AMG 557.

Biomarkers include B7RP-1 target occupancy on peripheral blood B cells and [redacted]. The percentage and absolute counts of total lymphocytes, monocytes, granulocytes and lymphocyte populations including CD3+ T cells, CD16/56+ NK cells and naïve and memory $CD19^+$ B cells (naïve = $IgD^+CD27^-$; memory = $IgD^-CD27^+$) will be determined. The levels of serum IgG and IgM immunoglobulins and [redacted] will also be measured.

### 2.5 Clinical Hypotheses

A single SC dose administration of AMG 570 will achieve acceptable safety and tolerability profiles in healthy subjects within the proposed dose ranges (7 to 700 mg SC AMG 570).

## 3. EXPERIMENTAL PLAN

### 3.1 Study Design

This is a randomized, placebo-controlled, double-blind, SAD study in healthy subjects. The study consists of 7 SC cohorts. Subjects will be randomized in a 3:1 ratio to receive AMG 570 or placebo according to Table 3. The overall study design is described by a study schema at the end of the protocol synopsis section. The study endpoints are defined in Section 10.1.1.

### 3.2 Number of Sites

Three sites in the US will be utilized in this study. Additional sites may be added at the discretion of the medical monitor.

### 3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”. Approximately 56 healthy subjects will be enrolled into 7 cohorts (6 active: 2 placebo in each cohort). See Section 10.2 for the sample size rationale.

### 3.4 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study prior to receiving AMG 570 will be replaced at the discretion of the Amgen Medical Monitor and Principal Investigator by notifying the unblinded study pharmacist or designee. The new subject will receive the identical treatment as the replaced subject, but will be assigned a replacement number associated with this new record. The unblinded study pharmacist or designee will retain the randomization list.

### 3.5 Estimated Study Duration

#### 3.5.1 Study Duration for Subjects

The planned length of participation in the study will be approximately 5 months (13 visits) which includes up to 6 weeks for screening, 1 day for drug dosing, 15 weeks for evaluation of drug distribution, followed by end of study (EOS) visit.

Subject's participation in the study will conclude at the completion of the end of study procedures. Once complete, this will conclude the subject's participation in the study. However, if an end of study test result demonstrates a significant clinical or laboratory abnormality, the subject will be followed until resolution of the abnormality or until it is considered clinically stable by the Principal Investigator. If a subject's $CD3^{-}CD19^{+}$ B cell counts are < 107 cells/µL (the lower limit of normal for healthy volunteers (Becton, Dickinson , 2015)), the subject will return for further testing of B cell counts every 3 months until the subject has B cell counts ≥ 107 cells/µL. Follow-up visits for B cell counts will continue every 3 months, for up to 12 months after the end of study.

Subject participation may be adjusted based on treatment-emergent data. All adjustments or modifications to the schedule outline above will be agreed upon by the Investigator in consultation with the Sponsor. The Institutional Review Board (IRB) will be informed via written correspondence.

#### 3.5.2 End of Study

Primary Completion: the time when the last subject has completed the EOS visit as outlined in the Schedule of Assessments (Table 8).

End of Trial: the time when the last subject has completed either the EOS visit or the last safety follow-up visit. See Section 3.5.1 for details.

As noted previously, the EOS for each cohort may be prolonged pending treatment- emergent data.

## 4. SUBJECT ELIGIBILITY

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).

### 4.1 Inclusion Criteria

A subject that has provided written informed consent may be eligible for inclusion in this study only if the following criteria are met:

101 Male and female subjects ≥ 18 to ≤ 65 years of age, at the time of signing the informed consent

102 Healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, neurological examination, laboratory tests and cardiac assessment

103 Body weight ≥ 50 kg and a body mass index (BMI) within the range of 18-30 kg/$m^2$ (inclusive)

104 Normal or clinically acceptable ECG (12-lead reporting ventricular rate and PR, QRS, QT, QTc) at screening and prior to dosing (QTc < 450 msec based on 3 measures taken approximately 60 seconds apart ) as deemed acceptable by the site investigator

105 Female subjects must be of documented non-reproductive potential (ie, postmenopausal [see definition below]; OR history of hysterectomy; OR history of bilateral salpingectomy; OR history of bilateral oophorectomy)

- Female subjects will be considered postmenopausal if no vaginal bleeding or spotting for at least 12 months and:
- If less than 55 years of age, follicle stimulating hormone (FSH) and estradiol must be within the laboratory's reference range for postmenopausal females. (FSH >40MIU/ml and estradiol < 40pg/ml (<147 pmol/L))
- If 55 to 59 years of age and there is uncertainty regarding menopausal status, FSH must be within the laboratory's reference range for postmenopausal females
- If 60 years of age or older, evaluation of FSH is not needed to confirm postmenopausal status

106 Male subjects must agree to practice a highly effective method of birth control for the duration of the study and continuing for 20 weeks after the last dose of study drug. Highly effective methods of birth control include sexual abstinence, vasectomy, a partner who is of non-childbearing potential (surgically sterile or postmenopausal), or a condom with spermicide (men) in combination with the following methods used by the female partner: hormonal birth control or intrauterine device or use of a barrier method.

107 Male subjects must agree to not donate sperm for the duration of the study and continuing for 20 weeks after the last dose of study drug

108 Subjects must be current for all vaccinations recommended by the CDC within a year of and at least 30 days prior to enrollment. Seasonal influenza vaccine need only be administered during influenza season (October through May).

109 Capable of giving signed informed consent which includes compliance with the requirement and restriction listed in the consent form and in the protocol

### 4.2 Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

201 Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)

202 History of active infections (viral, bacterial, or fungal) within 21 days of receiving the study medication.

203 History or diagnosis of obstructive sleep apnea

204 History of significant respiratory disorder

205 History or current evidence of febrile seizures, epilepsy, convulsions or significant head injury

206 Positive serology for HIV antibodies, Hepatitis B surface Antigen (HepBsAg), Hepatitis B core antibody(HBcAb) or Hepatitis C Antibodies (HepCAb) (confirmed by Polymerase Chain Reaction (PCR) or RIBA) at screening

207 Where participation in the study would result in donation of blood or blood products in excess of 500mL within a 56-day period

208 History of regular alcohol consumption exceeding 7 units weekly for female subjects and 14 units weekly for male subjects within 6 months of screening. This is equivalent to a half-pint (240 mL) of beer, 1 glass (125 mL) of wine, or a (25 mL) measure of spirits daily for women and one pint (480 mL) of beer, 2 glasses (250 mL) of wine, or 2 measures (50 mL) of spirits daily for men.

209 History of tobacco or nicotine-containing product use within 6 months of screening.

210 The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigation product (whichever is longer)

211 History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that in the opinion of the investigator or medical monitor (if appropriate), contraindicates their participation

212 Subject received a vaccine (either live attenuated or non-live) within 30 days of randomization or plan to receive live attenuated vaccine within 30 days and 5 half-lives of the last dose of study medication

213 Exposure to more than four new chemical entities within 12 months prior to the first dosing day

214 Evidence of renal disease, defined as:

Calculated glomerular filtration rate < 80 mL/min using the Cockcroft-Gault equation:

$$\frac{[(140-\text{age}) \times \text{Body Weight (kg)}]^*}{72 \times \text{serum creatinine (mg/dL)}}$$

*(For female subjects multiply by 0.85)

215 Evidence of liver disease (eg, serum ALT or AST > 2x upper limit of normal)

216 Total WBC < 4 x $10^9$/L or Platelet count < 140 x $10^9$/L

217 Circulating IgG or IgM levels < LLN at screening

218 $CD3^-CD19^+$ B cell counts < 107 cells/µL at screening

219 Underlying condition that predisposes the subject to infections (eg, uncontrolled diabetes - HbA1c ≥ 7%, history of splenectomy)

220 Known sensitivity to mammalian derived products

221 Positive serum βhCG at screening or positive serum βhCG or urine hCG prior to dosing

## 5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board (IRB) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (Section 11.2). All subjects must personally sign and date the ICF 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 the enrollment decision and date, in the subject's medical record and in/on the enrollment eCRF.

Each subject who enters into the screening period for the study, which is the first time that a subject undergoes detailed assessments to determine their potential for eligibility into the study, receives a unique subject identification number before any study procedures are performed. The subject identification number will be assigned manually. 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. A screen failed subject may be rescreened up to two times at the discretion of the PI with the agreement of the Amgen Medical Monitor.

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. The identification number will be 11 digits: the first 3 are the protocol identifier (322), the next 5 digits represent the site number which consists of the 2-digit country code (66) and 3-digit study-specific site number (001), and the last 3 digits are assigned in sequential order as subjects are screened (eg, 001, 002, 003, etc.). Thus, the first subject screened at site 66002 would be 32266002001, and the second subject

would be 32266002002, and so forth. This number will not be the same as the randomization number assigned for the study.

### 5.1 Randomization/Treatment Assignment

Randomization to AMG 570 or placebo will be based on a randomization schedule prepared by Amgen before the start of the study and retained by the unblinded study pharmacist or designee. On Day 1, once eligibility for study participation has been confirmed (based on data collected during screening visits and on Day -1), eligible subjects will be randomized to receive either AMG 570 or placebo. The randomization date is to be documented in the subject's medical record and on the enrollment eCRF.

Unique randomization numbers will be assigned in sequential order according to when each subject met the eligibility criteria. At no time will the same randomization number be assigned to more than one subject.

In the event a subject is randomized, but withdraws before receiving study medication, or during the study for reasons other than adverse events (Section 9.1), a replacement subject may be enrolled at the discretion of the Amgen Medical Monitor and Principal Investigator. The unblinded study pharmacist or designee will be notified. The new subject will receive the identical treatment as the replaced subject but will be assigned a replacement number per the randomization list.

### 5.2 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study or may potentially impact the safety of subjects currently enrolled or subjects in subsequent cohorts. Unblinding at the study site for any other reason will be considered a protocol deviation. The investigator is strongly encouraged to contact the Amgen Clinical Study Manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event.

Treatment assignments will be unblinded after the initial database lock at the end of the trial. After initial database lock and receipt of written authorization from Amgen to unblind, the unblinded pharmacist will release the specified unblinded pharmacy records to site staff designated to enter the subject treatment into each subject's Investigational Product Administration Electronic Case Report Form (eCRF).

# 6. TREATMENT PROCEDURES

## 6.1 Classification of Product(s)

The Amgen Investigational Product and/or placebo used in this study include: AMG 570 and placebo. The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of AMG 570 and placebo.

## 6.2 Investigational Product

All investigational products will be administered at the research facility by a qualified staff member. A physician must be present at the time of investigational product administration.

### 6.2.1 Amgen Investigational Product AMG 570

AMG 570 will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. AMG 570, which is a clear colorless sterile solution, will be packaged in open label 5mL glass vials containing 70 mg/ml of AMG 570 formulated with 10mM acetate, 9.0%(w/v) sucrose, 0.01%(w/v) polysorbate 80 at pH 5.2. Placebo will be presented in identical containers and stored/packaged the same as AMG 570, but will not contain AMG 570 protein. Diluent for lower doses will also be supplied as a clear colorless sterile solution in 10mL glass vials. All AMG 570, placebo and diluent supplies will be shipped to the study site and should be stored at 2°C to 8°C with limited exposure to light.

For more information regarding investigational product handling and preparation please see the study specific IPIM which is provided as a separate document.

#### 6.2.1.1 Dosage, Administration, and Schedule

All study drug will be administered (Table 3) at the research facility by a qualified staff member. A physician must be available during each administration of investigational product. The date, time, lot number and volume of investigational product administered will be recorded on the individual subject's electronic case report form (eCRF). Subject will be randomized only once to one of 7 Cohorts starting with Cohort 1 and continuing in a sequential manner to Cohort 7. Within each cohort, subjects will be randomized to receive a single SC of AMG 570 or placebo in a ratio of 3:1. Once a dose is selected for a cohort, no dose adjustments will be made for an individual subject within the cohort. Each subject will only receive one dose of the investigation product.

A sentinel dosing strategy will be used. The first 2 subjects in each cohort will be randomized such that 1 subject receives AMG 570 and 1 subject receives placebo. This sentinel pair will be dosed first and will be observed for at least 24 hours before study drug is administered to the remainder of the cohort. An informal safety review will be held after the sentinel subjects of each cohort are dosed and prior to dosing the subsequent 6 subjects. The decision to continue with the cohort as planned will be based on available data for vital signs and adverse events occurring in the prior 24 hours, and will be reviewed by the PI, medical monitor, and GSO or designee.

**Table 3. Dose Levels**

| Cohort # | Planned Dose (mg) | Route | N(active:placebo) |
|---|---|---|---|
| 1 | 7 | SC | 8 (6:2) |
| 2 | 21 | SC | 8 (6:2) |
| 3 | 70 | SC | 8 (6:2) |
| 4 | 140 | SC | 8 (6:2) |
| 5 | 210 | SC | 8 (6:2) |
| 6 | 420 | SC | 8 (6:2) |
| 7 | 700 | SC | 8 (6:2) |

#### 6.2.1.2 Dose Level Review Meeting (DLRM) Membership

The DLRM members will be composed of the investigator(s), Amgen Medical Monitor, Amgen Global Safety Officer (GSO) or designee, Early Development Leader or designee, Clinical Study Manager or designee, and Biostatistics representative or designee. Additional members may be added as needed (eg, PK Scientist). The DLRM voting members will include the investigator(s), Amgen Medical Monitor and Amgen GSO or designee.

#### 6.2.1.3 Dose-Cohort Study Escalation and Stopping Rules

**Dose-Cohort Study Escalation**

The decision to dose escalate will be based on the review of safety data during the dose level review meeting. Within each cohort, the safety data will be assessed after all 8 subjects have been enrolled and at least 6 subjects have completed the day 57 visit. Emerging PK and PD data will be reviewed in a blinded fashion at the DLRM as these data become available. Peripheral blood B cell number and serum IgG levels through day 57 post-dose for individual cohorts will be incorporated into each DLRM assessment.

The DLRM voting members will be responsible for dosing decisions, which may include:

1) escalation to the next planned dose
2) escalation to an intermediate dose (a dose lower than the next planned dose)
3) de-escalation to a lower dose
4) continuation, delay, or termination of dosing
5) repetition or expansion of a cohort.

Dose adjustments (if any) will be made on a treatment cohort basis and not on an individual basis, and will be agreed upon by Amgen after reviewing emerging safety, PK, and/or PD data.

**Dose Stopping and Review**

Further dosing of AMG 570 will be either stopped or modified to a lower dose if suspected adverse drug reactions and/or changes in safety data (including but not limited to vital signs, ECGs, clinical laboratory results, or laboratory parameters reflecting humoral immune status) are observed and these changes pose a health risk. A DLRM is held when a dose limiting toxicity (DLT) has occurred. A DLT is defined as any treatment-related fatal, life threatening or disabling serious adverse event (SAE). In addition, any adverse event or change in vital signs, clinical laboratory test value, or ECG which is considered drug related, and poses a significant health risk, as determined by the Investigators and Sponsor, would also constitute a DLT and form the basis for stopping dose escalation in the study. If a decision is made not to proceed following dosing of sentinel subjects, a Dose Level Review Meeting (DLRM) will be held. In addition, dosing will be stopped or modified if any of the scenarios shown in Table 4 are met.

**Dose Cohort Stopping Rules**

This section addresses how subject safety will be monitored through adherence to rules for stopping dosing within a dose cohort (which precludes any further dose escalation). Table 4 describes the dose stopping rules to be used for stopping dosing within a cohort.

**Table 4. Dose Cohort Stopping Rules**

| Scenario | Action |
|---|---|
| Any occurrence of a CTCAE **Grade 2** adverse event of the same system class (eg, hepatobiliary, cardiovascular) observed in 2 or more subjects in the same cohort | Stop dosing additional subjects in the cohort and convene DLRM.<br>Review AE and all relevant safety data for evidence of relationship to treatment and clinical significance. Consider unblinding to determine relatedness to investigational product.*<br>Upon unanimous decision of the review team, one of the following decisions may be made:<br>• Enrollment of the cohort may resume,<br>• The cohort may be expanded at the same dose,<br>• A lower dose cohort may be added to the study,<br>• Escalation to the next planned dose may occur,<br>• Escalation to an intermediate dose (a dose lower than the next planned dose) may take place. |
| Any occurrence of a CTCAE **Grade 3 or greater** adverse event in a dose cohort | Stop dosing additional subjects in the cohort and convene DLRM.<br>Review AE and all relevant safety data for evidence of relationship to treatment and clinical significance. Consider unblinding to determine relatedness to investigational product.*<br>If Grade 3 adverse event is determined to be related to study drug, and clinically significant by the DLRM, no further dose escalation to proceed.<br>Otherwise, upon unanimous decision of the review team, one of the following decisions may be made:<br>• Enrollment of the cohort may resume,<br>• The cohort may be expanded at the same dose,<br>• 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 subjects in subsequent cohorts

### Vital Signs Stopping Rules

If 2 subjects within the same cohort develop persistent out of range vital sign assessments (3 repeated measurements) as specified in Table 5 below in the first 3 days following dose administration, additional subjects within the cohort (if applicable) will not be dosed and a DLRM will be convened.

**Table 5. Dose Stopping Values for Vital Signs**

| Vital Sign Assessments |
|---|
| Temperature > 38.5° C<br>Heart rate < 42 or > 120 bpm<br>Blood Pressure (supine, sustained):<br>• Systolic < 80 or > 160 mm Hg;<br>• Diastolic > 105 mm Hg |

### ECG Stopping Rules

Should a subject in a dose cohort present with an ECG result (in triplicate readings) greater than the values provided in Table 6 below after dosing, the ECG will be repeated in triplicate and the etiology of the ECG abnormality will be evaluated. If the increased interval is thought to be drug-related, the patient should be monitored closely until the abnormality resolves. If 2 subjects within the same cohort develop treatment-related ECG abnormalities as specified in Table 6 below, additional subjects within the cohort (if applicable) will not be dosed and a DLRM will be convened.

**Table 6. Dose Stopping Values for ECG**

| ECG assessments |
|---|
| PR interval > 220 msec<br>QRS interval > 125 msec<br>QTc > 500 msec |

### Clinical Laboratory Value Stopping Rules

Should a subject in a dose cohort have a laboratory value or assessment that meets the criteria in Table 7 below, the laboratory assessment(s) will be repeated within 5 days. If the out-of-range laboratory assessment result persists after the repeated assessment(s) in 2 or more subjects, additional subjects within the cohort (if applicable) will not be dosed and a DLRM will be convened.

**Table 7. Dose Stopping Values for Clinical Laboratory Results**

| Chemistry Laboratory Findings | |
|---|---|
| Sodium | < 130 or > 150 mmol/L |
| Potassium | < 3.1 or > 5.4 mmol/L |
| Glucose | < 50 or fasting > 125 mg/dL |
| Creatinine | > 50% increase above subject's baseline |
| Calcium | < 8.0 or >12 mg/dL |
| CPK | > 5 x ULN without known alternative etiology |
| Magnesium | < 1.0 mg/dL |
| AST | > 2.5 x ULN |
| ALT | > 2.5 x ULN |
| Bilirubin | > 2 x ULN |
| **Hematology Laboratory Findings** | |
| Hemoglobin | < 10 gm/dL |
| WBC | < 2000 or >15,000/$mm^3$ |
| Platelets | < 100,000/$mm^3$ |
| Neutrophils | < 1,000/$mm^3$ |
| Lymphocytes | < 500/$mm^3$ |

**Humoral Immune Status Stopping Rules**

Humoral immune status will be monitored by peripheral blood B cell counts and total serum IgG. Values of these parameters will affect dosing of AMG 570 by the following two conditions:

1) If any subject exhibits a peripheral blood B cell count < 107 cells/μl accompanied by a serum IgG level < 639 mg/dl (Agarwal, 2007) at any time during the study, further dose escalation will be postponed until B cell counts and IgG levels recover without development of infectious complications in these subjects.
2) If any subject in a dose cohort has a peripheral blood B cell count < 107 cells/μl and a serum IgG level < 639 mg/dl at day 57 post-dose (Agarwal, 2007), patients rather than healthy subjects will be enrolled in subsequent cohorts.

Infections will be monitored and classified per CTCAE guidelines with stopping rules delineated in Table 4.

#### 6.2.1.4 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

This protocol allows for some alterations from the currently outlined dosing schedule, but the maximum dose will not exceed 700 mg.

The actual dose to be administered may be adjusted by the DLRM voting members based on safety, tolerability, and preliminary PK data of previous dose levels. Dose adjustments may involve either an increase or a decrease in the planned dose, but will

not exceed pharmacokinetic criteria defined in the Rationale for Dose Selection (Section 2.4.5).

If consistent adverse events of moderate or severe intensity occur in the group, or if unacceptable pharmacological effects, reasonably attributable in the opinion of the investigator to dosing with AMG 570, are observed in more than 2 subjects in a group, the dose escalation will be temporarily halted and no additional subjects will be dosed until a full safety review by DLRM of the study has taken place. Relevant data will be reviewed and discussed with the investigator, appropriate Amgen personnel, and IRB prior to resumption of dosing.

Clinically or medically significant suspected adverse drug reactions, and serious adverse events considered to be related to study procedures will be followed until resolved or considered stable. The study may be terminated at any point in time at the discretion of the sponsor.

## 6.3 Hepatotoxicity Stopping and Rechallenge Rules

### 6.3.1 Criteria for Permanent Withholding of AMG 570 due to Potential Hepatotoxicity

Following the single-dose administration of study drug, subjects should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- TBL > 2x upper limit of normal (ULN) or INR > 1.5

**AND**

- increased AST or ALT from the relevant baseline value as specified below:

| Baseline AST or ALT Value | AST or ALT Elevation |
|---|---|
| < ULN | ≥ 3x ULN |

**AND**

- no other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or elevated 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, rhabdomyolysis, hemolysis)

### 6.4 Concomitant Therapy

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care.

Concomitant therapies are to be collected from informed consent through the EOS. Acetaminophen (up to 2 g per day) for analgesia will be allowed. Other concomitant medication may be allowed on a case by case basis by the investigator in consultation with the Amgen Medical Monitor if required. Details (name, indication, dose, frequency, and dates) of all concomitant medications will be recorded in the subject's source documents and on the eCRF.

Concomitant medications will not be collected after the EOS visit for subjects returning for additional IPRO monitoring.

### 6.5 Alcohol, Tobacco Restrictions and Exercise Restriction

- Prior to admission to the clinic of each clinic visit, subject will abstain from alcohol consumption for 24 hours.
- Use of tobacco, nicotine or nicotine-containing product is not allowed from 6-months prior to screening until after the final follow-up visit.
- Subjects are required to refrain from strenuous exercise 48 hours prior to each blood collection for clinical laboratory testing. Subjects may participate in light recreational activities during the study.

## 7. STUDY PROCEDURES

### 7.1 Schedule of Assessments

## Table 8. AMG 570 Schedule of Assessments

| Activity | Screen | Treatment and Evaluation (each dosing session) | | | | | | | | | | | | | | | | | | EOS[1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Month | | | | | | | | | | | | | | | | ~1m | | | ~2m | 3.5m |
| Study Day | Screening[8] | Day -1 | Day 1 | | | | | Day 2 | Day 3 | Day 4 | Day 6[2] | Day 8 | Day 11[2] | Day 15 | Day 22[2] | Day 29 | Day 43 | Day 57 | Day 71 | Day 105 |
| Window | -42 to -1 | | | | 10m (+/-) | 15m (+/-) | 30m (+/-) | 30m (+/-) | 60m (+/-) | 6h (+/-) | 1d (+/-) | 1d (+/-) | 1d (+/-) | 1d (+/-) | 2d (+/-) | 2d (+/-) | 4d (+/-) | 4d (+/-) | 4d (+/-) | 4d (+/-) |
| Relative to Dosing(h) | | | Pre | 0 | 0.5 | 6 | 12 | 24 | 48 | 72 | 120 | 168 | 240 | 336 | 504 | 672 | 1008 | 1344 | 1680 | 2496 |
| **General Assessment** | | | | | | | | | | | | | | | | | | | | |
| ICF | X | | | | | | | | | | | | | | | | | | | |
| Eligibility | X | | | | | | | | | | | | | | | | | | | |
| Medical/Med/Drug/Alcohol History | X | | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | | |
| BMI (Ht & Wt) | X | | | | | | | | | | | | | | | | | | | |
| **General Safety Assessments** | | | | | | | | | | | | | | | | | | | | |
| Physical Exam [2] | X | X | | | | | | | X | | | | | | | X | | X | | X |
| Vitals | X | X | X | X | X | X | X | X | X | | | X | | X | | X | | X | | X |
| ECG[3] | X | X | | | | X | X | | X | | | X | | | | X | | X | | X |
| AEs & Con. Meds | | | ← | | | | | | | | | | | | | | | | | |
| SAE | ← | | | | | | | | | | | | | | | | | | | |
| Lab Assessments | | | | | | | | | | | | | | | | | | | | |
| Drug/ Alcohol/Cotinine screen | X | **X** | | | | | | | | | | | | | | | | | | |
| HIV, HepC, HepB | X | | | | | | | | | | | | | | | | | | | |
| Hem/Chem/Urinalysis[4] | X | **X** | | | | | | | X | | | | | | | X | | X | | X |
| Pregnancy Test | X | **X** | | | | | | | | | | | | | | | | | | X |
| FSH/Estradiol | X | | | | | | | | | | | | | | | | | | | |
| **Dosing** | | | | | | | | | | | | | | | | | | | | |
| Treatment Assignment | | X | | | | | | | | | | | | | | | | | | |
| AMG 570 or Placebo | | | | X | | | | | | | | | | | | | | | | |

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Footnotes defined on the last page of this table.

## Table 8. AMG 570 Schedule of Assessments

| Activity | Screen | Treatment and Evaluation (each dosing session) | | | | | | | | | | | | | | | | | | EOS[1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Month | | | | | | | | | | | | | | | | ~1m | | | ~2m | 3.5m |
| Study Day | Screening | Day -1 | Day 1 | | | | | Day 2 | Day 3 | Day 4 | Day 6 | Day 8 | Day 11 | Day 15 | Day 22 | Day 29 | Day 43 | Day 57 | Day 71 | Day 105 |
| Window | -42 to -1 | | | | 10m (+/-) | 15m (+/-) | 30m (+/-) | 30m (+/-) | 60m (+/-) | 6h (+/-) | 1d (+/-) | 1d (+/-) | 1d (+/-) | 1d (+/-) | 2d (+/-) | 2d (+/-) | 4d (+/-) | 4d (+/-) | 4d (+/-) | 4d (+/-) |
| Relative to Dosing(h) | | | Pre | 0 | 0.5 | 6 | 12 | 24 | 48 | 72 | 120 | 168 | 240 | 336 | 504 | 672 | 1008 | 1344 | 1680 | 2496 |
| PK Assessments of AMG 570 | | | | | | | | | | | | | | | | | | | | |
| Cohort 1 to 6 | | | X | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Biomarker & Immunological Assessments | | | | | | | | | | | | | | | | | | | | |
| Immunophenotyping and Receptor Occupancy (IP & RO) assays[5] | X | | X | | | | | | | | | X | | | | X | | X | | X |
| ADA | | | X | | | | | | | | | | | | | X | | X | | X |
| IgG and IgM serum | X | | X | | | | | | | | | X | | | | X | | X | | X |
| [redacted] | | | | | | | | | | | | | | | | | | | | |
| Exploratory Biomarkers[6] | | | X | | | | | | | | | X | | | | X | | X | | X |
| Pharmacogenetic | | | | | | | | | | | | | | | | | | | | |
| Blood for cell pellets[7] | | | X | | | | | | | | | | | | | | | | | |



[1] If a subject's $CD3^-CD19^+$ B cell counts are < 107 cells/uL (the lower limit of normal for healthy volunteers, the subject will return for further testing of B cell counts every 3 months until the subject has B cell counts ≥ 107 cells/uL. Follow-up visits for B cell counts will continue every 3 months, for up to 12 months after the end of study.
[2] A complete physical will be performed at screening and EOS. A brief physical will be performed at all other timepoints unless required for evaluation of AEs.
[3] On day -1 baseline, three sets of triplicate baseline ECGs will be collected ≥ 30 minutes apart and at other time-points single triplicate ECGs will be collected, (ie, <30 seconds between subsequent ECGs)
[4] All Subjects must fast from all food and drink (except water) for at least 8 hours prior to any clinical lab evaluation.
[5] The AMG 570 IPRO assay will measure absolute counts for CD3+ T cells, CD16/56+ NK cells, CD19+ B cells as well as: 1) naïve B cell % of B cells and counts; 2) memory B cell % of B cells and counts; 3) free B7RP-1 MFI (or MESF) on memory B cells and: 4) total B7RP-1 MFI (or MESF) on memory B cells. Receptor occupancy will be calculated from the measurements of free and total B7RP-1.
[6] Exploratory biomarkers will include collection of serum, plasma and PAX gene RNA for future use.
[7] Blood for cell pellet sample will be obtained from the exploratory biomarker sample
[8] Subjects who require vaccination must receive vaccination(s) at least 30 days prior to receiving IP (tetanus booster and flu vaccinations may be administered by the investigator site during the screening window). Seasonal influenze vaccine need only be administered during influenza season (October through May).

## 7.2 General Study Procedures

Adherence to the study design requirements, including those specified in the Schedule of Assessments (Table 8) are essential and required for study conduct.

This section lists the procedure and parameters of each planned study assessment. The exact timing of each assessment is listed in the Schedule of Assessments (Section 7).

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the assessment should occur in the following order: ECGs, vital signs, blood draws. The timing of the assessment should allow the blood draw to occur at the exact nominal time.

The timing and number of planned study assessments, including: Safety, PK, PD and Immunogenicity assessment may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentration) to ensure appropriate monitoring.

The IRB will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

No more than 500 mL of blood, including from any extra assessments that may be required, will be collected over the duration of the study.

Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the Investigator's discretion.



### 7.2.1 Informed Consent

Before any study-related screening or baseline procedure can be completed, a subject must sign and date the IRB approved ICF.

### 7.2.2 Screening

After informed consent, all screening procedures will be performed between Day -42 and Day -1. Study eligibility must be met per inclusion/exclusion criteria prior to enrollment. The following procedures will be completed during the screening period at time points designated in the Schedule of Assessments (Table 8).

- Informed Consent (confirmation that the ICF has been signed)
- Medical, Medication, Drug and Alcohol History
- Demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety
- BMI calculated using height and weight

- Compete Physical Examination
- Electrocardiogram (triplicate)
- Vital Signs
- Drug, Alcohol, and Cotinine Screen
- HIV (human immunodeficiency virus), HBcAb (hepatitis B core antibody), HepBsAg (hepatitis B surface antigen),HepCAb (Hepatitis C antibody)
- Laboratory Assessments (including creatinine clearance, chemistry, hematology, and urinalysis)
- Follicle-Stimulating Hormone and estradiol (postmenopausal females only) and Pregnancy Test (females only)
- IPRO assay, IgG and IgM
- subjects may be rescreened only with permission of the Amgen medical monitor (Section 5)

Given the potential of AMG 570 to modulate IgG levels and possible safety risks to healthy subjects with low IgG levels, all subjects with a screening IgG level of below 800 mg/dl (8 g/L) will be discussed with the Amgen Medical Monitor prior to enrollment in the study. Such subjects will have the entirety of their screening immune status parameters reviewed prior to approval of suitability for the study.

### 7.2.3 Day -1, Day 1 and Day 2 and Other Treatment

Subjects will be admitted to the clinical unit on Day -1 at which time the following assessments will be obtained:

- Brief Physical Examination
- ECG (triplicate sets)
- Vital Signs
- Drug, Alcohol, and Cotinine Screen
- Laboratory Assessments (chemistry, hematology, and urinalysis)
- Pregnancy Testing (females only)
- Treatment Assignment (can occur any time prior to dosing)

Subject will stay overnight and then undergo Day 1 assessments as follows:

- ECG (triplicate)
- Vitals
- IPRO, ADA, IgG, IgM, [redacted] Exploratory Biomarkers, blood for cell pellets
- PK
- Dosing

Prior to the subject being discharged, the following assessments will be completed or samples obtained:

- Brief Physical Examination
- ECG (triplicate)
- Vitals
- Laboratory Assessments (chemistry, hematology, and urinalysis)
- PK

If subject stays in house up to Day 11, then subject does not have to be discharged from research facility on Day 3. After discharge, subject will return to clinical unit on an outpatient basis for scheduled study procedures including blood draws for PK assessment, safety, immunogenicity, and other assessment as per Schedule of Assessments (Table 8).

### 7.2.4 End of Study Visit/ Early Termination

The following procedures will be completed at the EOS visits as per Schedule of Assessments (Table 8):

- Complete Physical Examination
- ECG (triplicate)
- Vitals
- Laboratory Assessments (chemistry, hematology, and urinalysis)
- Pregnancy Testing (females only)
- PK
- IPRO, ADA, IgG, IgM, [redacted] Exploratory Biomarkers

As noted previously, the EOS for each cohort may be prolonged pending treatment emergent data.

### 7.2.5 Medical History

The Investigator or designee will collect a complete medical history. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history eCRF.

### 7.2.6 Adverse Event

Adverse event and serious adverse event assessments will be made throughout the study and will be evaluated and recorded in the source documents and on the eCRF for the duration of the study. Determination of the severity of all adverse events will be consistent with CTCAE Version 4.0 unless specified otherwise.

### 7.2.7 Concomitant Medications

Concomitant medication(s) will be recorded throughout the study in the source documents and eCRF. Sites will collect therapy name, indication, dose, unit, frequency, route, and start and stop dates for all concomitant medications.

### 7.2.8 Physical Examination

A physical examination will be performed by the investigator or designated physician or nurse practitioner at time points specified in the Schedule of Assessments (Table 8).

Pre-Dose abnormal findings will be reported on the medical history eCRF. Abnormal findings found after the subject has received study medication will be reported on the Event eCRF. A complete physical examination will include, at a minimum, assessment of cardiovascular, respiratory, gastrointestinal and neurological systems. A brief physical examination will include assessment of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

### 7.2.9 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Record all measurements on the vital signs eCRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs eCRF. Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be recorded by the principal investigator or designee at time points specified in the Schedule of Assessments (Table 8).

Blood pressure will be measured in the following manner:

- Subjects should be lying in a semi-supine or supine position quietly and comfortably for at least 5 minutes. The upper arm should be bare without constrictive clothing and supported at heart level.
- Exercise should be avoided for at least 30 minutes prior to measurement.
- An appropriately sized cuff (cuff bladder encircling at least 80 percent of the arm) should be used to ensure accuracy. At least 2 measurements should be made and the average recorded.
- Neither the subject nor the observer (measurer) should talk during measurement.

Subjects should be lying in a semi-supine or supine position quietly and comfortably for at least 5 minutes for respiratory and heart rate assessments. Abnormal measurements may be repeated upon investigator discretion. Record all measurements on the vital signs eCRF.

### 7.2.10 Height, Weight, and Body Mass Index

Height in centimeters will be measured without shoes at screening.

Weight in kilograms will be measured without shoes at time point specified in the Schedule of Assessments (Table 8).

Subject BMI will be calculated using height and weight measurements taken at screening according to the following formula:

$$BMI\ (kg/m^2) = weight\ (kg) / (height\ [cm]/100)^2$$

### 7.2.11 Electrocardiograms

During the study, 12-lead electrocardiograms (ECG) will be performed at the time points indicated in the Schedule of Assessments (Table 8).

The subject must be in supine position in a rested and calm state for at least 5 minutes before the ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position 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 sets of triplicate baseline ECGs collected ≥ 30 minutes apart between each set and within each baseline set ECG in triplicate will be run consecutively (ie, <30 seconds between subsequent ECGs) [ie, total ≥ 9 ECGs]
- 1 set of triplicate ECGs at all other time points, single triplicate ECGs run consecutively (ie, <30 seconds between subsequent ECGs)

The Principal Investigator or designated site physician or nurse practitioner will review all ECGs. 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.

### 7.2.12 Estimated Glomerular Filtration Rate (eGFR)

For determining eligibility, estimated glomerular filtration rate (eGFR) will be calculated using the Cockcroft-Gault formula based on serum creatinine, age, sex and weight at time point indicated in the Schedule of Assessments (Table 8).

### 7.2.13 Clinical Chemistry

All laboratory tests must be reviewed and signed by the principal investigator or qualified designee. Additional safety laboratory assessments may be performed for subject

safety. Blood samples for clinical chemistry will be collected at time points specified in the Schedule of Assessments (Table 8).

The tests listed below will be conducted and analyzed by standard laboratory procedures:

**Table 9. Clinical Chemistry**

| | |
|---|---|
| Albumin | Blood urea nitrogen or Urea |
| Calcium | Chloride |
| Glucose | Phosphorus |
| Potassium | Creatinine |
| Magnesium | Sodium |
| Carbon Dioxide or Bicarbonate | Uric acid |
| Aspartate aminotransferase (AST) | Alanine aminotransferase (ALT) |
| Cholesterol | Total bilirubin (TBIL) |
| Alkaline phosphatase (ALP) | Direct bilirubin |
| Total protein | Triglycerides |
| High-density lipoprotein | Creatine Phosphokinase (CPK) |
| | Hemoglobin A1C** |

* All Subjects must fast from all food and drink (except water) for at least 8 hours prior to any clinical lab evaluation.
**Hemoglobin A1C will be collected only at screening.

### 7.2.14 Hematology

All laboratory tests must be reviewed and signed by the principal investigator or qualified designee. Additional safety laboratory assessments may be performed for subject safety. Blood samples for hematology tests will be collected at time points specified in the Schedule of Assessments (Table 8).

The tests listed below will be conducted and analyzed by standard laboratory procedures:

**Table 10. Hematology**

| | |
|---|---|
| Red blood cells<br>Hemoglobin<br>Hematocrit<br>Mean corpuscular volume<br>Mean corpuscular hemoglobin<br>Platelet count<br>Mean corpuscular hemoglobin concentration | White blood cells with differential count:<br>• Total neutrophils (OR segmented neutrophils and band cells)<br>• Eosinophils<br>• Lymphocytes<br>• Basophils<br>• Monocytes |

* All Subjects must fast from all food and drink (except water) for at least 8 hours prior to any clinical lab evaluation.

### 7.2.15 Urinalysis

All laboratory tests must be reviewed and signed by the principal investigator or qualified designee. Additional safety laboratory assessments may be performed for subject safety. Urine samples will be collected at time points specified in the Schedule of Assessments (Table 8).

The tests listed below will be conducted and analyzed by standard laboratory procedures:

**Table 11. Urinalysis**

| | |
|---|---|
| Specific gravity | pH |
| Blood | Protein |
| Glucose | Ketones |
| Bilirubin | Urobilinogen |
| Microscopic exam (performed at the discretion of the principal investigator or qualified designee): | |
| White blood cells | Red blood cells |
| Epithelial Cells | Bacteria |
| Casts | Crystals |

* All Subjects must fast from all food and drink (except water) for at least 8 hours prior to any clinical lab evaluation.

### 7.2.16 Drug, Alcohol, and Cotinine Screen

The drug and alcohol tests will include at minimum testing for drugs with a high potential for abuse, including amphetamines, barbiturates, benzodiazepines, cocaine, ethanol, opiates, and cannabinoids.

Subjects who test positive for drug, alcohol, and cotinine will not qualify for investigational product administration. The intention is to detect drugs of abuse and not

those prescribed therapeutically. Subjects with a positive drug test may be retested once at the discretion of the investigator. Drug, alcohol, and cotinine assessments are to be completed at time points indicated in the Schedule of Assessments (Table 8).

### 7.2.17 Hepatitis B, Hepatitis C and HIV Status

Hepatitis B surface antigen (HepBsAg), hepatitis B core antibody (HBcAb), hepatitis C antibody (HepCAb), and HIV status will be assessed. If the results show a negative HepBsAg and positive for HBcAb: a hepatitis B virus DNA by polymerase chain reaction (PCR) is necessary. If the results show a positive HepCAb: hepatitis C virus ribonucleic acid (RNA) by PCR is necessary. The test must be confirmed negative at screening for the subject to be eligible for this study.

### 7.2.18 Serum Follicle-stimulating Hormone and Estradiol

Additional serum will be collected for an FSH and estradiol for females who are at least 1 year postmenopausal at screening unless 60 years or older. Results must be consistent with postmenopausal status per local laboratory ranges to be eligible for this study. Postmenopausal status will be recorded on the medical history eCRF.

### 7.2.19 Pregnancy Test

A serum pregnancy test must be completed for all females at screening. A serum or highly sensitive urine pregnancy test will be collected at Day -1 and EOS as specified in the Schedule of Assessments (Table 8). The screening (serum) and Day -1 (serum or urine) pregnancy test must be confirmed negative for the subject to be eligible for this study.

### 7.2.20 Pharmacokinetic Blood Sample Collection for AMG 570 Serum Concentrations

Blood samples will be collected for determination of AMG 570 serum concentrations at time points indicated in the Schedule of Assessments (Table 8). Instructions for collecting, processing, and shipping samples are provided in a separate document from Amgen.

### 7.2.21 Immunophenotyping and Receptor Occupancy (IPRO) Assay Blood Collections

Whole blood samples for Immunophenotyping and Receptor Occupancy (IPRO) will be collected at timepoints indicated in the Schedule of Assessments (Table 8). The Immunophenotyping assay will measure B cells and B cell subsets. The Receptor Occupancy assay will measure B7RP-1 receptor occupancy. Instructions for collecting, processing, and shipping the IPRO samples will be provided in a separate document

from Amgen. Immunophenotyping blood collection instructions for collecting, processing, and shipping samples are provided in a separate document from Amgen.

[redacted]

### 7.2.23 IgG and IgM Blood Collection

Blood samples will be collected for determination of serum Immunoglobulin IgG and IgM levels at time points indicated in the Schedule of Assessments (Table 8). Instructions for collecting, processing, and shipping samples will be provided in a separate document from Amgen.

### 7.2.24 Anti-Drug Antibody Testing (ADA)

Blood samples for antibody testing are to be collected at day 1, 29, 57, and the EOS time point (Schedule of Assessments, Table 8) for the measurement of anti-AMG 570 binding antibodies. Samples testing positive for binding antibodies may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. Additional blood samples may be obtained to rule out anti AMG 570 antibodies during the study. In the event of safety-related concerns, more frequent testing (eg, every month) or testing for a longer period of time may be requested. Follow-up testing is not required where it is established that the subject did not receive AMG 570.

Subjects who test positive for binding antibodies, and have clinical sequelae that are considered potentially related to an anti-AMG 570 antibody response may also be asked to return for additional follow-up testing. Refer to the Schedule of Assessments (Table 8), as applicable, for specific time points and the laboratory manual for detailed collection and handling instructions.

## 7.3 Exploratory Biomarker Samples for Future Use

Exploratory biomarker blood samples will be collected for serum, plasma and Paxgene RNA at the time points indicated in the Schedule of Assessments (Table 8). Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarker development samples 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 570.

### 7.4 Pharmacogenetic Sample of Blood for Cell Pellets

A blood sample will be analyzed for pharmacogenetic analyses at the time point indicated in the Schedule of Assessments (Table 8). Pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease activity and/or responsiveness to AMG 570. The goals include the use of genetic markers to help in the investigation to identify subjects who may have positive or negative response to AMG 570. No additional samples will be collected for this part of the study; however for those subjects who consent to these studies, DNA will be extracted from samples already collected from the exploratory biomarker sample.

### 7.5 Sample Storage and Destruction

Any blood sample collected according to the Schedule of Assessment (Table 8) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects.

This analysis includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. The analysis 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 the dose response and/or prediction of response to AMG 570, characterize antibody response, 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 nor 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, nor 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 blood 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 Section 11.3 for subject confidentiality.



## 8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

### 8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

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, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

#### 8.1.1 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product and/or other protocol required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

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 Section 12.1.

### 8.1.2 Reasons for Removal From Treatment

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

- subject request
- safety concern (eg, due to an adverse event, protocol deviation, non-compliance, pregnancy)
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)

### 8.1.3 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

## 9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

### 9.1 Definition of Safety Events

### 9.1.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, and gout) has increased in severity, frequency, and/or duration more than expected by the investigator's assessment. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study, or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

#### 9.1.2 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria.

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug induced liver injury (DILI) (see Appendix A for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

### 9.2 Safety Event Reporting Procedures

#### 9.2.1 Adverse Events

##### 9.2.1.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment through the end of study are reported using the Event CRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity

- Assessment of relatedness to investigational product
- Action taken.

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE). The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to the investigational product. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product.

The investigator is responsible for reviewing laboratory test results and determining 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.

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. The investigator is expected to follow reported adverse events until stabilization or reversibility.



#### 9.2.1.2 Reporting Procedures for 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 EOS are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via fax.

See Appendix B for a sample of the Serious Adverse Event Worksheet.

The investigator must assess whether the serious adverse event is possibly related to any study mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure"?

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

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

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. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.



#### 9.2.1.3 Reporting 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. In some countries (eg, European Union [EU] member states), 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 for the purposes of expedited reporting.

### 9.3 Pregnancy Reporting

If a pregnancy occurs in a female partner of a male subject, while the subject is taking protocol-required therapies, report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies through 20 weeks for the female partner of a male subject.

The pregnancy should be reported to Amgen's Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C).

## 10. STATISTICAL CONSIDERATIONS

### 10.1 Study Endpoints, Analysis Sets, and Covariates

### 10.1.1 Study Endpoints

#### 10.1.1.1 Primary Endpoints

Subject incidences of treatment-emergent adverse events, including clinically significant changes in physical examinations, vital signs, laboratory safety tests, and electrocardiograms (ECGs).

#### 10.1.1.2 Secondary Endpoints

- To characterize the PK profile of single subcutaneous (SC) doses of AMG 570 in healthy subjects
- To determine the PD effects (B7RP-1 occupancy and inhibition of B cell survival) of single subcutaneous (SC) doses of AMG 570 in healthy subjects
- To determine the immunogenicity of AMG 570

#### 10.1.1.3 Exploratory Endpoints

Exploratory biomarkers may include but are not limited to the following:

- [redacted].
- Serum IgG and IgM.

### 10.1.2 Analysis Sets

For safety, pharmacokinetic concentration, pharmacokinetic parameter and pharmacodynamic analyses, subjects will be analyzed according to the treatment they received, not the treatment to which they are randomized.

#### 10.1.2.1 Safety Analysis Set

The safety set will consist of all subjects who have received AMG 570/placebo.

#### 10.1.2.2 Pharmacokinetic (PK) Concentration Analysis Set

The PK concentration analysis set will contain all subjects who have received AMG 570 and have at least one quantifiable PK sample collected.

#### 10.1.2.3 Pharmacokinetic (PK) Parameter Analysis Set

The PK parameter analysis set will consist of all subjects who have received AMG 570 and for whom at least one PK parameter can be adequately estimated.

#### 10.1.2.4 Pharmacodynamic (PD) Analysis Set

The PD analysis set will consist of all subjects who have received AMG 570/placebo and for whom at least one PD parameters have quantifiable baseline sample (not needed for B7RP-1 occupancy) and at least one quantifiable post-baseline PD sample collected.

### 10.1.3 Covariates and Subgroups

No subgroup analysis is planned.

## 10.2 Sample Size Considerations

Approximately 56 healthy subjects will be enrolled into 7 cohorts (6 active: 2 placebo in each cohort). This sample size is based on practical considerations and is typical for this type of study. For safety considerations, for a cohort, with 6 subjects receiving AMG 570, there is an 82% chance of at least one subject experiencing an adverse event with a true incidence rate of 25% and a 74% chance of at least one subject experiencing an adverse event with 20% true incidence rate. With a total of 42 subjects expected to receive AMG 570 across all 7 cohorts, there is a 34% chance of at least 1 subject experiencing an adverse event with a true incidence rate of 1% and the chance of at least 1 subject experiencing an adverse event increases to 88% and 99% with a true incidence rate of 5% and 10%, respectively.

## 10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Amgen staff and their designees involved in the study will not be blinded, but will only be given treatment assignments when there is a need to use the information for analysis, discussion and internal decision making.

Access to treatment assignments and other restricted data will be managed as described in the Managing Access to Restricted Study Data Document. Unblinded individuals are to ensure unblinding and potentially unblinding information not be distributed to the investigators or subjects prior to the study being formally unblinded at the end of the trial.

## 10.4 Planned Analyses

### 10.4.1 Data Monitoring Committee (DMC), Data Review Team (DRT) or Dose Level Review Team (DLRT)

A Dose Level Review Team (DLRT) will be used to oversee progress of the study and make recommendations relating to early closure/extension or alteration of the study based on ongoing monitoring of the study data. The DLRT members will consist of the principal investigator or designee, Amgen Medical Monitor, Amgen Global Safety Officer or designee, Amgen Clinical Research Study Manager or designee, and biostatistics representative or designee. Additional members may be added as needed (eg, PK scientist). The key objectives of the DLRT are to review data, monitor safety, and make dose change decisions.

### 10.4.2 Primary Analysis

The primary analysis will occur after all subjects have completed the study.

## 10.5 Planned Methods of Analysis

### 10.5.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, immunogenicity, 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 by time as appropriate.

The number and percent of subjects reporting any adverse events and each adverse event will be tabulated by system organ class and preferred term and may be further classified by severity and relationship to treatment. Subject incidence of clinically significant changes in vital signs, physical examinations, clinical laboratory safety tests, ECGs, and the development of AMG 570 binding antibodies will be noted.

### 10.5.2 Primary Endpoint

#### 10.5.2.1 Adverse Event

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The number and percentage of subjects reporting adverse events will be evaluated for each treatment group and will be tabulated by relationship to the study drug. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies will also be provided.

#### 10.5.2.2 Clinical Laboratory Tests

Clinical chemistry, hematology, and urinalysis data will be reviewed for each subject.

Values outside the normal laboratory reference ranges will be flagged as high or low. The analyses of safety laboratory endpoints may include summary statistics over time and/or changes from baseline by treatment. Shifts in grades of safety laboratory values between the baseline and the worst on-study value may be tabulated by treatment group. Clinically significant changes in clinical laboratory test values will be noted.

#### 10.5.2.3 Vital Signs

Vital signs data will be reviewed for each subject. Depending on the size and scope of the changes, the analyses of vital signs may include summary statistics over time and/or changes from baseline over time by treatment. Clinically significant changes in vital signs will be noted.

#### 10.5.2.4 Electrocardiograms

Descriptive summary statistics of ECG values over time and/or changes from baseline to post-baseline maximum and post-baseline minimum may be provided for each ECG parameters.

Subjects' maximum change from baseline in QTcF 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.

#### 10.5.2.5 Study Disposition and Demographic Data

The number of subjects who are randomized, have received investigational product and have completed the study will be tabulated. Demographic characteristics will be summarized using descriptive statistics.

### 10.5.3 Secondary Endpoint(s)

#### 10.5.3.1 PK Analysis

Serum AMG 570 concentrations will be determined using a validated assay. Individual serum concentration-time plots for AMG 570 will be presented for each subject as well as mean concentration-time plots for each treatment.

The following pharmacokinetic parameters will be calculated but not limited to maximum observed concentration [$C_{max}$], time at $C_{max}$ [$t_{max}$], and area under the concentration-time curve [AUC] using non-compartmental methods. Actual dosing and sampling times will

be used for calculation of individual PK parameters. Summary statistics will be generated for each PK parameter for each treatment.

Additional analyses using compartmental methods or population PK analysis may be performed.

#### 10.5.3.2 Antibody Analysis

Anti-AMG 570 binding antibody will be assessed using a validated assay. The number and percentage of subjects who have developed anti- AMG 570 antibodies at any time, at baseline and during post-baseline visits will be summarized by treatment group.

#### 10.5.3.3 PD Analysis

PD end points (including but not limited to peripheral blood B7RP-1 receptor occupancy, peripheral blood changes in percentage and absolute counts of naive and memory $CD19^{+}$B cells) will be summarized by treatment using descriptive statistics at each visit and may be listed by subject if deemed necessary.

### 10.5.4 Exploratory Endpoints

Biomarker end points (including but not limited to [redacted] and serum IgG and IgM immunoglobulins levels) will be summarized by treatment using descriptive statistics at each visit and may be listed by subject if deemed necessary.

## 11. REGULATORY OBLIGATIONS

### 11.1 Informed Consent

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 template are to be communicated formally in writing from the Amgen Clinical Study Manager to the investigator. The written informed consent document is to be prepared in the language(s) of the potential subject population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific screening procedures or any investigational product(s) is/ are administered.

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. 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 The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject. Refer to ICH GCP guideline, Section 4.8.9.

### 11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB for written approval. 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.

The investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be sent to Amgen.

### 11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained:

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the demographics page, in addition to the unique subject identification number, include the age at the 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 date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in strict confidence by the investigator, except as described below.

In compliance with Federal 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 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 named such individuals to have access to his/her study related records, including personal information.

### 11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center 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

## 12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

### 12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the Investigator must be obtained. The IRB/ must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IRB to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the Investigator's participation in the study according to the study contract. The investigator is to notify the IRB 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 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 it is available commercially.

### 12.2 Study Documentation and Archive

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 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.

Elements to include:

- Subject files containing completed CRF, 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 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) documentation, as applicable.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

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

### 12.3 Study Monitoring and Data Collection

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.

The Clinical Monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study related records needed to verify the entries on the CRFs.

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.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing 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.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the electronic CRFs must be maintained and readily available.
- Updates to electronic CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that the investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.

Additional information on the current guidelines for publications can be found at the following location: http://www.icmje.org/.

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).

### 12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 8), the investigator can search publically 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.

### 12.5 Language

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

### 12.6 Publication Policy

To coordinate dissemination of data from this study, the investigator will solicit input and assistance from Amgen staff as appropriate.

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), which states:

- Authorship credit should 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. Authors should meet conditions 1, 2, and 3.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should 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 should qualify for authorship, and all those who qualify should be listed.
- Each author should 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 corporate review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

### 12.7 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.

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# 14. APPENDICES

## Appendix A. Additional Safety Assessment Information

### Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used and is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronicapplications/ctc.htm.]

### Drug-induced Liver Injury Reporting & 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 Section 6.3 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 the 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 Section 9.1.2.

### 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 Section 6.3.1 or who experience AST or ALT elevations > 3 x ULN 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:
  - Obtain complete blood count (CBC) with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis

  - Obtain serum acetaminophen (paracetamol) levels
  - Obtain 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
  - Obtain viral serologies
  - Obtain CPK, haptoglobin, LDH, and peripheral blood smear
  - Perform appropriate liver imaging if clinically indicated
- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. 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 medications and laboratory results must be captured in corresponding CRFs.

# Appendix B. Sample Serious Adverse Event Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for Studies using Electronic Data Capture (EDC))

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions:
The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Definitions:

- Adverse Event - Any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment.
- Serious Adverse Event – An adverse event that meets serious criteria
- Suspected Adverse Reaction (SAR) – An adverse event that is suspected to be related to an Amgen product in an observational study.
- Serious Suspected Adverse Reaction – An SAR that meets serious criteria

What types of events to report on this form:

| Type of Event | Clinical Trials |
|---|---|
| Adverse Event that is *not serious* | No |
| Serious Adverse Event (regardless of relationship) | Yes |

| Type of Event | Observational Studies |
|---|---|
| Suspected Adverse Reaction (SAR) | Yes |
| Serious Suspected Adverse Reaction | Yes |
| Serious Adverse Events that are not suspected to be related | ONLY if instructed by protocol or by local Amgen office or CRA |

1. Site Information

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. Subject Information

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

*If you are submitting follow-up information to a previous report, provide the adverse event form for the previous report as well as the start date for the initial event.*

3. Adverse Event

   Provide the date the Investigator became aware of this information

   Adverse Event Diagnosis or Syndrome* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started rather than the date of diagnosis or hospitalization. For serious events, the start date is the date the event started, not the date on which the event met serious criteria. This is a mandatory field.

   Date Ended – Enter date the adverse event ended. For serious events, this is not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the Investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to IP/drug under study* – The Investigator must determine and enter the relationship of the event to the IP/drug under study at the time the event is initially reported. *For observational studies, remember that SARs are, by definition, related to the drug under study.* This is a mandatory field.

Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for Studies using Electronic Data Capture (EDC))

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

**Relationship to Amgen device*** – The investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

**Outcome of Event*** – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field for serious events.**

- Resolved – End date is known
- Not resolved / Unknown – End date is unknown
- Fatal – Event led to death

**If event is related to a study procedure**, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP/drug under study or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**
If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

*At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.*

5. **IP/Drug Under Study Administration Including Lot # and Serial # when known / available.**
**Blinded or open-label** – If applicable, indicate whether the investigational product is blinded or open-label
**Initial Start Date** – Enter date the product was first administered, regardless of dose.
**Date of Dose Prior to or at the time of the Event** – Enter date the product was last administered prior to, or at the time of, the onset of the event.
**Dose, Route, and Frequency at or prior to the event** – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
**Action Taken with Product** – Enter the status of the product administration.

6. **Concomitant Medications**
**Indicate if there are any medications.**
**Medication Name, Start Date, Stop Date, Dose, Route, and Frequency** – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
**Co-suspect** – Indicate if the medication is co-suspect in the event
**Continuing** – Indicate if the subject is still taking the medication
**Event Treatment** – Indicate if the medication was used to treat the event

7. **Relevant Medical History**
Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.

8. **Relevant Laboratory Tests**
**Indicate if there are any relevant laboratory values.**
**For each test type**, enter the test name, units, date the test was run and the results.

9. **Other Relevant Tests**
**Indicate if there are any tests, including any diagnostics or procedures.**
**For each test type**, enter the date, name, results and units (if applicable).

*At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.*

10. **Case Description**
**Describe Event** – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the Investigator, designee must be identified on the Delegation of Authority form.*

| AMGEN Study 20140207 AMG 334 | Electronic 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

**[If the protocol provides instructions to submit certain types of events ONLY to Amgen Safety and not to the Clinical Trial Database, state that reason below and remove these instructions. If no protocol-specific reasons, remove these instructions and the following bullet.]**

Protocol specific reason(s):

☐ *<<Note protocol instruction/reason here and change text from italics to standard.>>*

*<<For completion by Amgen 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: ☐F ☐M | Race | If applicable, provide End of Study date |
|---|---|---|---|---|
| | | | | |

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. ADVERSE EVENT**

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

| Adverse Event diagnosis or syndrome<br>If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report.<br>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<br>Day Month Year | Date Ended<br>Day Month Year | Check only if event occurred before first dose of IP/drug under study | Is event serious? | Reason serious (see Serious Criteria codes (see codes below)) | Relationship<br>Is there a reasonable possibility that the Client may have been caused by IP/drug under study or an Amgen device used to administer the IP/drug under study? | | | | | | | | Outcome of Client<br>Resolved / Not resolved / Fatal / Unknown | Check only if event is related to study procedure<br>eg, biopsy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Relate<br>Yes | Relate<br>No | Relate<br>Yes | Relate<br>No | Relate<br>Yes | Relate<br>No | Relate<br>Yes | Relate<br>No | | |
| | | | | ☐ 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<br>Day Month Year | Date Discharged<br>Day Month Year |
|---|---|
| | |

AMGEN
Study 20140207
AMG 334

## Electronic Adverse Event Contingency Report Form
For Restricted Use

| Site Number | Subject ID Number |
|---|---|
| | |

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

| IP/Drug/Amgen Device | | Date of Initial Dose (Day Month Year) | Prior to or at time of Event: Date of Dose (Day Month Year) | Dose | Route | Frequency | Action Taken with Product (1 Still being Administered; 2 Permanently discontinued; 3 Withheld) | Lot # and Serial # |
|---|---|---|---|---|---|---|---|---|
| **IPDrug Device** | Delivered Dose Intact | | | | | | | Lot # ____ ☐ Unknown Serial # ____ ☐ Unavailable / Unknown |
| **IPDrug Device** | Delivered Dose Intact | | | | | | | Lot # ____ ☐ Unknown Serial # ____ ☐ Unavailable / Unknown |

**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 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | |
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| | | | | | | | | | | | |

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

| Date (Day Month Year) | Additional Tests | Results | Units |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

FORM-056005 Version 5.0 Effective Date: 07 JUL 2014

Page 2 of 3

| AMGEN Study 20140207 AMG 334 | Electronic Adverse Event Contingency Report Form<br>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.

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| Signature of Investigator or Designee -<br>*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 C. Pregnancy Notification Worksheet (Pregnancy in Partner of a Male Subject)

**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: _____

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: _____

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011 Page 1 of 1

**Amendment 4**

**Protocol Title: A Randomized, Double Blind Placebo Controlled, First in Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending Subcutaneous Doses of AMG 570 in Healthy Subjects**

Amgen Protocol Number AMG 570 20140322

Amendment Date: 24 January 2018

**Rationale:**

The protocol has been amended to include an additional cohort – Cohort 7. Enrollees in cohort 7 will receive a single subcutaneous (SC) dose of 700 mg AMG 570 or placebo (6 active and 2 placebo). The addition of this cohort will increase enrollment to a total of approximately 56 subjects and will provide high dose safety, pharmacokinetic, and pharmacodynamic data that will inform multiple dose paradigms in future studies. Available data for Cohorts 1-6 have been used to support updates to dose selection, study design, safety and biostatistical information throughout the protocol. Where available, observed data have replaced predicted values for increased accuracy.

Administrative, typographical and formatting changes have been made throughout the protocol where applicable.

**Description of Changes:**

Section: Global

**Change:** Minor corrections have been made throughout the protocol (eg, administrative updates, typographical and formatting errors).

Section: Global

**Change:** Addition of Cohort 7 with planned dose 700 mg SC,
N (active:placebo) = 8(6:2)

Section: Protocol Synopsis, Sample Size (global change)

**Replace:**

Approximately 48 healthy subjects will be enrolled into 6 cohorts (6 active: 2 placebo in each cohort).

**With:**

Approximately **56 healthy subjects** will be enrolled into **7 cohorts** (6 active: 2 placebo in each cohort).

Section: Protocol Synopsis, Study Design, Dose Levels (global change)

**Replace:**

The study consists of 6 SC cohorts.

**With:**

The study consists of **7** SC cohorts.

Section: Synopsis, Investigational Product Dosage and Administration

**Add:**

**For subcutaneous dosing in Cohort 7, doses will be administered in a 2 mL per injection format (5 x 2.0 mL injections).**

Section: Section 2.3 Risk Assessment

**Add:**

[redacted]

Section: 2.4.4 AMG 570 Clinical Background

**Replace:**

As of 15 January 2017, 32 subjects have received a single SC dose of AMG 570 or placebo at the following doses: 7, 21, 70, or 140 mg. Preliminary safety, pharmacokinetics, and pharmacodynamics results from study, are described in Sections 6.1 and 6.2. of the Investigator's Brochure.

**With:**

As of **1 January 2018**, **48** subjects have received a single SC dose of AMG 570 or placebo at the following doses: 7, 21, 70, 140 mg, **210 mg, or 420 mg**. Preliminary safety, pharmacokinetic, and pharmacodynamic results from the cohorts receiving 7-140 mg of AMG 570 are described in Sections 6.1 and 6.2 of the Investigator's Brochure. **All dose levels have demonstrated acceptable safety and tolerability with no severe, life-threatening, or fatal events reported. A multiple ascending dose study in patients with rheumatoid arthritis (study 20150196) has also been initiated with 9 subjects receiving 6 doses of 70 mg AMG 570 or placebo SC q 2 weeks. Subjects at this dose level have demonstrated acceptable safety and tolerability with no severe, life-threatening, or fatal events reported.**

Section: 2.4.5 Rationale for Dose Selection (Table 2)

**Add:**

- Observed AMG 570 Pharmacokinetic Parameters and Exposure Margins for 210 mg and 420 mg doses
- Predicted AMG 570 Pharmacokinetic Parameters and Exposure Margins for 700 mg dose

Section: 2.4.5 Rationale for Dose Selection

**Replace:**

Based on the 3-month GLP toxicology study in cynomolgus monkeys and interim pharmacokinetics data from this ongoing FIH study, it is anticipated that a 420 mg SC dose of AMG 570 in humans would not exceed the exposure associated with the AMG 570 NOAEL in cynomolgus monkeys. At this highest planned SC dose, the exposure margins are 160- and 48-fold below the Cmax and AUC at the NOAEL in monkeys. Based on interim pharmacokinetics and pharmacodynamics data from this ongoing study, it is also anticipated that a 420 mg SC dose of AMG 570 is expected to

result in 90% or more B7RP-1 RO at day 8 and B cell depletion of at least 40% compared to baseline. Significant changes to circulating IgG and IgM levels are not anticipated based on interim data.

**With:**

Based on the 3-month GLP toxicology study in cynomolgus monkeys and interim pharmacokinetics data from this ongoing FIH study, it is anticipated that a **700** mg SC dose of AMG 570 in humans would not exceed the exposure associated with the AMG 570 NOAEL in cynomolgus monkeys. At this highest planned SC dose, the exposure margins are **44-** and **10-**fold below the $C_{max}$ and AUC at the NOAEL in monkeys. Based on interim pharmacokinetics and pharmacodynamics data from this ongoing study, it is also anticipated that a **700** mg SC dose of AMG 570 is expected to result in 90% or more B7RP-1 RO at day 8 and B cell depletion of **up to** 40% compared to baseline **by day 57**. Significant changes to circulating IgG and IgM levels are not anticipated based on interim data.

Section: Section 3.3, Number of Subjects

**Replace:**

Approximately 48 healthy subjects will be enrolled into 6 cohorts.

**With:**

Approximately **56** healthy subjects will be enrolled in **7** cohorts.

Section: 10.2 Sample Size Considerations

**Replace:**

With a total of 36 subjects expected to receive AMG 570 across all 6 cohorts, there is a 30% chance of at least 1 subject experiencing an adverse event with a true incidence rate of 1% and the chance of at least 1 subject experiencing an adverse event increases to 84% and 98% with a true incidence rate of 5% and 10%, respectively.

**With:**

With a total of **42** subjects expected to receive AMG 570 across all **7** cohorts, there is a **34%** chance of at least 1 subject experiencing an adverse event with a true incidence rate of 1% and the chance of at least 1 subject experiencing an adverse event increases to **88%** and **99%** with a true incidence rate of 5% and 10%, respectively.

Section: 10.5.2.1 Adverse Event

**Delete:**

~~or from study, and significant treatment-emergent adverse events~~

Section 10.5.2.4 Electrocardiograms

**Replace:**

Descriptive summary statistics of ECG values over time and/or changes from baseline over time may be provided for each ECG parameters.

**With:**

Descriptive summary statistics of ECG values over time and/or changes from baseline **to post-baseline maximum and post-baseline minimum** may be provided for each ECG parameters.

Section: 10.5.3.2 Antibody Analysis

**Delete:**

~~The incidence of anti-AMG 570 antibodies will be listed for each subject~~

**Amendment 3**

**Protocol Title: A Randomized, Double Blind Placebo Controlled, First in Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending Subcutaneous Doses of AMG 570 in Healthy Subjects**

Amgen Protocol Number AMG 570 20140322

Amendment Date: 04 May 2017

**Rationale:**

The protocol has been amended to include an additional cohort – Cohort 6. Enrollees in cohort 6 will receive a single subcutaneous (SC) dose of 420 mg AMG 570. The addition of this cohort will extend enrollment to an additional 8 subjects for a total of 48 subjects. The addition of this cohort will provide additional safety, pharmacokinetics, and pharmacodynamics data that will facilitate the understanding of the exposure-response relationship to inform future studies with AMG 570. Available data for Cohorts 1-4 have been used to support updates to dose selection, study design, safety and biostatistical information throughout the protocol. Where available, observed data have replaced predicted values for increased accuracy.

Additional updates have been made to incorporate clarification and guidance previously released to sites regarding the following:

- Length of in-house stay – up to 11 days allowed for in-house residence
- CDC vaccine recommendation – flu season (October-May)
- Renal disease exclusion criteria – removal of additional criteria does not pose safety risk, does not interfere with ability to assess safety of subject, and does not affect scientific integrity of study.
- Screening IgG below 800 mg/dl – review with Amgen Medical Monitor prior to enrollment
- Delegation of responsibilities to designated physician or nurse practitioner
- Timing of consecutively run ECGs – ECGs should be run in as short a time as possible
- Self-evident corrections – updated template language has been incorporated into protocol

Administrative, typographical and formatting changes have been made throughout the protocol where applicable.

**Amendment 2**

**Protocol Title: A Randomized, Double Blind Placebo Controlled, First in Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending Subcutaneous Doses of AMG 570 in Healthy Subjects**

Amgen Protocol Number AMG 570 20140322

Change Summary Date: 08 January 2016

**Rationale:**

The AMG 570 20140322 protocol is being amended to allow for longer screening period so subjects are up to date on their vaccinations prior to screening for the study

Specifically, the following major changes are being made:

- Increase of screening window from 28 days to 42 days to allow required vaccination
- Increase timing for taking triplicate ECG from 30 sec to 60 sec
- Clarification of contraception language

Minor typographical errors were corrected and clarifications were made.

**Amendment 1**

**Protocol Title: A Randomized, Double Blind Placebo Controlled, First in Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending Subcutaneous Doses of AMG 570 in Healthy Subjects**

Amgen Protocol Number AMG 570 20140322

Change Summary Date: 27 October 2015

**Rationale:**

The AMG 570 20140322 protocol is being amended in response to FDA concerns for the potential of prolonged immune suppression in healthy subjects based on decreases in B cells and serum IgG levels observed in the 3-month repeat dose toxicology study in cynomolgus monkeys and inadequate nonclinical toxicology studies to support the IV route of administration.

Specifically, the following major changes are being made:

- Removal of all language pertaining to 210 mg and 420 mg intravenous (IV) administration
- Update to the Serum AMG 570 concentration-time profile
- Changes to Section 6.2.1.3 to include increasing length of DLRM interval from 28 to 57 days and addition of Humoral Immune Status Stopping Rules
- Update to Schedule of Assessments (SOA) pertaining to language about IV dosing
- Alignment of Endpoints listed in Section 10.1.1 with other sections of the protocol

Minor typographical errors were corrected and clarifications were made.