Title Page

Protocol Title:		A Phase 1b/2 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Efavaleukin Alfa in Adult Subjects With Steroid Refractory Chronic Graft Versus Host Disease
Short Protocol Title:		Safety and Efficacy of Efavaleukin Alfa in Subjects With Steroid Refractory Chronic Graft versus Host Disease
Protocol Number:		20160283
Investigational Product:		Efavaleukin Alfa
Trade Name:		Not applicable
Sponsor	**Name of Sponsor:**	Amgen Inc.
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EudraCT Number:		2017-000763-33
NCT Number:		NCT03422627
Protocol Date:		**Document Version** / **Date** Original / 13 April 2017 Amendment 1 / 22 August 2017 Amendment 2 / 04 December 2018 Amendment 3 / 26 August 2019 Amendment 4 / 08 December 2020 **Amendment 5** / **22 June 2021**
Version/Date:		**Data Element Standards Version** / **Date** 5.0 / 20 March 2015

Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled A Phase 1b/2 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Efavaleukin Alfa in Adult Subjects With Steroid Refractory Chronic Graft Versus Host Disease, dated **22 June 2021**, and agree to abide by all provisions set forth therein.

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

I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my subinvestigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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

_____

Signature

_____ _____

Name of Investigator Date (DD Month YYYY)

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[redacted]

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1. Protocol Synopsis

Protocol Title: A Phase 1b/2 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Efavaleukin Alfa in Adult Subjects With Steroid Refractory Chronic Graft Versus Host Disease

Short Protocol Title: Safety and Efficacy of Efavaleukin Alfa in Subjects With Steroid Refractory Chronic Graft versus Host Disease

Study Phase: 1b/2

Indication: Chronic graft versus host disease (cGVHD)

Rationale

This is an open-label, phase 1b/2 study to evaluate the safety and efficacy of efavaleukin alfa (AMG 592) in subjects with steroid refractory cGVHD. The phase 1b part of the study will evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of efavaleukin alfa and will define the maximum tolerated dose (MTD) and/or a biologically optimal dose. [redacted]

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
Phase 1b • To evaluate the safety and tolerability of multiple ascending doses of efavaleukin alfa in subjects with steroid refractory cGVHD in order to estimate the MTD [redacted]	**Phase 1b** • Incidence of dose limiting toxicities (DLTs) at first 4 weeks • Incidence of all treatment-related and treatment-emergent adverse events and serious adverse event
[redacted]	
Secondary	
[redacted]	

Objectives	Endpoints
Secondary (continued)	
[redacted]	

Hypotheses

Phase 1b

Efavaleukin alfa will be safe and well-tolerated in subjects with steroid refractory cGVHD.

[redacted]

Overall Design

This is an open-label, multi-center, phase 1b/2 study to evaluate the safety and efficacy of efavaleukin alfa in subjects with steroid refractory cGVHD. The study will be conducted in 2 portions as described below.

Phase 1b

The phase 1b part of this study will be conducted as a multiple ascending dose (MAD) study. Each dosing cohort will consist of between 3 and 6 DLT−evaluable subjects who will receive efavaleukin alfa SC either every week (QW) or every 2 weeks (Q2W) plus protocol permitted background therapy for 52 weeks. The DLT evaluation period is defined as 4 weeks after the first dose of study drug. At the discretion of the Sponsor, following discussion and agreement between the principal investigator and medical monitor, subjects responding to efavaleukin alfa (as assessed by the end of week 50), who wish to continue treatment, may continue to receive efavaleukin alfa treatment at their current dosing regimen for up to an additional 52 weeks. The remaining subjects will complete the week 52/EOT visit. All subjects who continue to receive efavaleukin alfa during the extended dosing period will be reevaluated at week 76 for their response to treatment. Following discussion and agreement between the principal investigator and medical monitor, the Sponsor may decide to allow these subjects to continue treatment through week 102 (Q2W dose) or week 103 (QW dose). Subjects participating in extended dosing **through week 104** will complete the week 104/**end of extended treatment (**EOET**)** visit (see Table 2-3). **At the discretion of the Sponsor, following discussion and agreement between the principal investigator and medical monitor, subjects responding to efavaleukin alfa (as assessed by the end of week 104), who wish to continue treatment beyond week 104, may continue to receive efavaleukin alfa treatment at their current dosing regimen for up to an additional 156 weeks. Only subjects who are deemed eligible to continue extended dosing beyond week 102 or week 103 will complete dosing at week 104. The remaining subjects will complete the week 104/EOET visit. All subjects who continue to receive efavaleukin alfa during the extended dosing period will be reevaluated every 6 months for their response to treatment. Following discussion and agreement between the principal investigator and medical monitor, the Sponsor may decide to allow these subjects to continue treatment through week 258 (Q2W dose) or week 259 (QW dose). Subjects participating in extended dosing through week 258 or 259 will complete the week 260/EOET visit (see Table 2-6).** All subjects will complete the 6-week safety follow-up after the last dose of efavaleukin alfa.

Five dose levels are planned: [redacted] µg Q2W (cohort 1a), [redacted] µg QW (cohort 2a), [redacted] µg Q2W (cohort 3), [redacted] µg QW (cohort 4), and [redacted] µg Q2W (cohort 5). Dose levels 1a ([redacted] µg Q2W) and 2a ([redacted] µg QW) will be enrolled concurrently. Three subjects each will be assigned to cohorts 1a ([redacted] µg Q2W) and 2a ([redacted] µg QW) alternately (total of

6 subjects). After the last subject completes the DLT evaluation period, a dose level review meeting (DLRM) will occur and if deemed necessary, 3 additional subjects each will be assigned to cohorts 1a and 2a alternately (total of 6 subjects) to gain additional information. After the last subject completes the DLT evaluation period, a DLRM will occur and if dose escalation is deemed appropriate, subjects will be enrolled in cohorts 3 ([redacted] µg Q2W), 4 ([redacted] µg QW), and 5 ([redacted] µg Q2W) as follows: first, 3 subjects will be enrolled in cohort 3. An internal safety review will be conducted by the Amgen Medical Monitor and Global Safety Officer after the first 3 subjects complete the DLT evaluation period. If concerning safety issues are identified, a DLRM will occur to assess if it is safe to proceed with additional enrollment in cohort 3 and concurrent enrollment in cohort 4. If no concerning safety issues are identified in these first 3 subjects, enrollment of the remaining 3 subjects in cohort 3 will proceed without a DLRM. Concurrently, enrollment of 6 subjects in cohort 4 will begin with alternate assignment of subjects between cohorts 3 and 4 until enrollment of cohort 3 has completed. Enrollment of 6 subjects in cohort 5 will begin after the DLRM for cohort 4 is complete. DLRMs for cohorts 3, 4, and 5 will occur after the last subject in that cohort completes the DLT evaluation period.

All planned dose levels for a given cohort may be adjusted at any time based on emerging data. Additional dosing cohorts may be added, removed, or substituted at any time based on emerging data and the results of continuous modelling.

After there is at least 1 DLT observed at any dose level, a Bayesian logistic regression model (BLRM) (Bailey et al, 2009; Neuenschwander et al, 2008) will be used to inform dose escalation and the results of this analysis will be provided to the DLRM.
Three toxicity probability intervals (TPI) of DLT will be defined: target TPI (20% to 30%), excessive TPI (30% to 60%), and unacceptable TPI (60% to 100%). Adverse events meeting DLT criteria after week 4 and PD information may also be included in the model, as available. The model will recommend an MTD as the dose with the highest probability in the target TPI, but with less than 25% probability in excessive TPI and unacceptable TPI. Lower dose levels, intermediate dose levels, or alternative dosing schedules may be considered based on all available information as long as they do not exceed the estimated MTD per the model. In addition, Amgen may add subjects to dose levels below the MTD in order to better characterize PK and PD. After DLT is observed, the BLRM model will be run after each dosing cohort and may be run at any time to continuously update the MTD information. For technical details of BLRM, please refer to the statistical analysis plan (SAP).

During or after completion of the dose escalation part of the study, Amgen may enroll approximately 10 subjects in an optional dose expansion cohort in order to gain additional safety and efficacy information prior to the selection of an [redacted].
Determination of the dose for the dose expansion cohort will be based on review of all available information, including but not limited to BLRM model, other safety data, PK/PD, and efficacy. This dose cannot exceed the model predicted MTD. A dose that has not been previously explored may also be considered. The BLRM model may be run anytime during the dose expansion cohort, and Amgen may change the expansion cohort dose level or add additional subjects for dose expansion based on emerging information.

After all subjects in the phase 1b part of the study have had the opportunity to undergo assessment for the week 16 visit Amgen will review all the available information, including but not limited to the BLRM model, other safety data, PK/PD, and efficacy, to select the [redacted].

All phase 1b subjects will continue efavaleukin alfa treatment at their current dose until the [redacted] is established. Subjects still receiving or planned to receive efavaleukin alfa treatment at the time that the [redacted] is established may change their efavaleukin alfa dose to the [redacted] dose at the discretion of the Sponsor, following discussion and agreement between the principal investigator and medical monitor, and **may** continue study treatment **through** the week **260**/EOET visit **if they remain eligible for extended dosing** (see **Table 2-6**).

[redacted]

Number of Subjects

Approximately 40 subjects will be enrolled in phase 1b of the study, with about 30 subjects in the dose escalation cohorts and approximately 10 subjects in the optional dose expansion cohort. The total sample size may be higher than 40 subjects if, following a DLRM recommendation or Amgen decision to evaluate additional doses, dosing cohorts are added and/or existing cohorts are expanded; or subjects are replaced as per Section 5.2.1. Additional subjects may be enrolled in each cohort to enable all screened eligible subjects to participate in the study.

[redacted]

Summary of Subject Eligibility Criteria

The study will enroll subjects who are recipients of an allogeneic hematopoietic stem cell transplant (HSCT), have been diagnosed with moderate to severe steroid-refractory cGVHD per the 2014 cGVHD NIH Consensus Criteria, have received no more than 3 previous treatments for cGVHD (excluding topical agents), have a Karnofsky performance status score ≥ 50%, have adequate renal, cardiac and bone marrow function, have adequate hepatic and pulmonary function (unless related to cGVHD), and an estimated life expectancy of greater than 3 months. Subjects who are receiving systemic corticosteroids at baseline must be on a stable corticosteroid dose from 2 weeks prior to the first dose of efavaleukin alfa and must have an ongoing systemic prednisone requirement ≤ 1 mg/kg/day (or equivalent). Subjects who are receiving non-corticosteroid immunosuppressants at baseline must be on a stable dose from 2 weeks prior to the first dose of efavaleukin alfa. Subjects will be excluded from the study if they have active morphologic relapse/progression of hematologic malignancy post transplantation, received a donor lymphocyte infusion T-cell depleting, B-cell depleting or IL-2 signaling targeted medication within 12 weeks prior to starting efavaleukin alfa, received T regulatory cell expanding therapies, ibrutinib, imatinib, bortezomib, entospletinib, ruxolitinib or other JAK inhibitor, or an investigational drug or

device within 4 weeks prior to starting efavaleukin alfa, or have a known history of active tuberculosis.

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

Treatments

Subjects will receive a SC dose of efavaleukin alfa QW or Q2W starting on day 1 until week 50 (Q2W dose) or 51 (QW dose). Subjects in phase 1b may continue to receive efavaleukin alfa at their current dosing regimen (QW or Q2W) for up to an additional **208** weeks (through week **258** or week **259**, respectively) at the discretion of the Sponsor, following discussion and agreement between the principal investigator and medical monitor.

Efavaleukin alfa will be provided in glass vials.

Efavaleukin alfa will be stored between 2°C and 8°C. All doses will be fixed, and the qualified site personnel will prepare the appropriate dose for each subject.

Procedures

Written informed consent must be obtained from all subjects before any study-specific screening procedures are performed. Among the procedures performed, blood samples will be collected from subjects for serum chemistry, hematology, PK samples, [redacted], lymphocyte subsets, biomarker development, optional pharmacogenetic sample, and PBMC.

All subjects in the study will have their disease response assessed using the NIH cGVHD Response assessment (NIH Form A). [redacted]

Safety assessments including adverse events, serious adverse events, and disease-related events assessments will be performed throughout the duration of the study.

For a full list of study procedures, including the timing of each procedure, please refer to Section 9.2 and the Schedule of Activities in Table 2-1, Table 2-2, Table 2-3, Table 2-4, Table 2-5, **Table 2-6**, **Table 2-7**, and **Table 2-8**.

Statistical Considerations

The baseline demographics, disease characteristics, and the exposure to efavaleukin alfa by dose level will be summarized using descriptive statistics. Summary descriptive statistics by dose level group will be provided. For categorical endpoints, the descriptive statistics will contain the frequency and percentage. For continuous endpoints, the descriptive statistics will include the number of observations, mean, standard deviation, median, minimum, and maximum.

Statistical testing will be performed with statistical significance level of 0.025 for 1-sided tests, and with 0.05 statistical significance level for 2-sided tests, unless specified otherwise. No multiplicity adjustment will be provided, unless specified otherwise.

Primary Efficacy Endpoint

[redacted]

[redacted]

Secondary Endpoints

[redacted]

Safety Endpoints:

The Medical Dictionary for Regulatory Activities (MedDRA version 20.0 or later) will be used to code all adverse events to a system organ class and a preferred term. Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, and adverse events leading to withdrawal from investigational product or other protocol-required therapies will also be provided. In addition, summary statistics and shifts in grades of selected safety laboratory values and summary statistics for vital signs will be provided.

The incidence and percentage of subjects who develop [redacted] at any time will be tabulated by dose level. The incidence and percentage of subjects who develop [redacted] will also be tabulated.

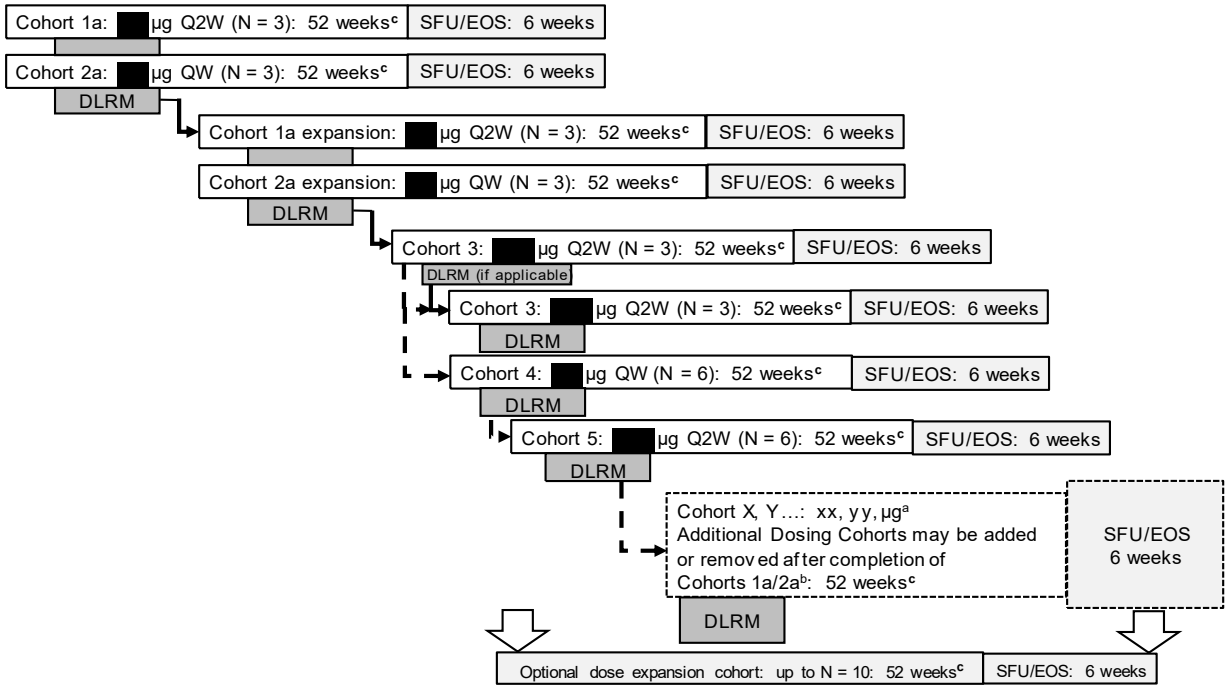
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor Name: Amgen Inc.

2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Study Schema Phase 1b



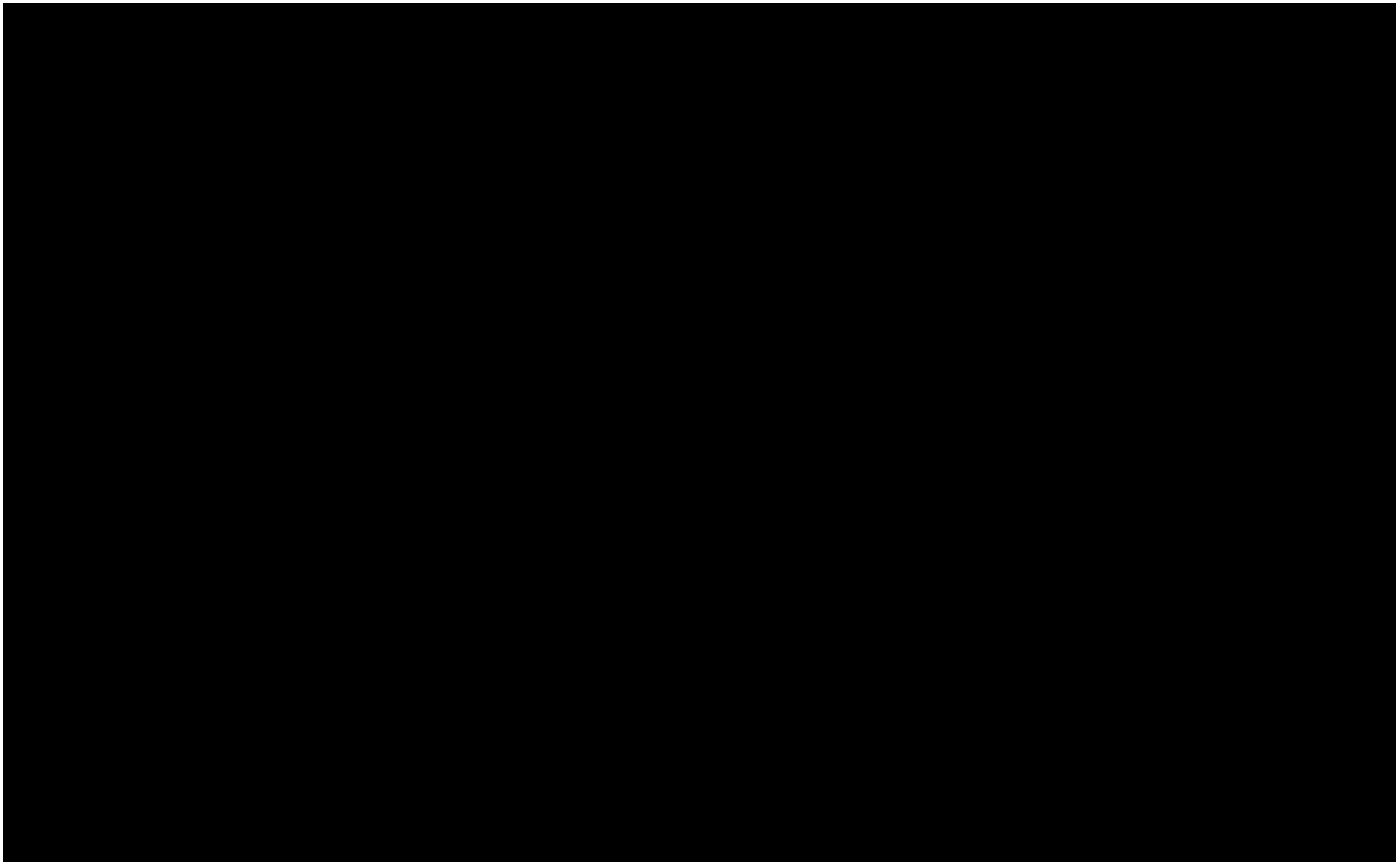
DLRM = dose level review meeting; **EOET = end of extended treatment;** EOS = end of study; PD = pharmacodynamics; PK = pharmacokinetics; SFU = safety follow-up; TPI = toxicity probability interval; Q2W = every 2 weeks; QW = every week;

[a] Doses for subsequent cohorts will be determined by results of Bayesian TPI and PK/PD modeling of previous cohorts.

[b] A DLRM is required for escalation to higher doses but not for allocation of additional subjects to doses equivalent to or lower than previously given that have been deemed tolerable.

[c] At the discretion of the Sponsor, following discussion and agreement between the principal investigator and medical monitor, subjects responding to efavaleukin alfa (as assessed by the end of week 50), who wish to continue treatment, will complete week 52 assessments and may continue to receive efavaleukin alfa treatment at their current dosing regimen for up to an additional 52 weeks. The remaining subjects will complete the week 52/EOT visit. All subjects who continue to receive efavaleukin alfa during the extended dosing period will be reevaluated at week 76 for their response to treatment. Following discussion and agreement between the principal investigator and medical monitor, the Sponsor may decide to allow these subjects to continue treatment through week 102 (Q2W dose) or week 103 (QW dose). Subjects participating in extended dosing **through week 104** will complete the week 104/EOET visit (see Table 2-3). **At the discretion of the Sponsor, following discussion and agreement between the principal investigator and medical monitor, subjects responding to efavaleukin alfa (as assessed by the end of week 104), who wish to continue treatment beyond week 104, may continue to receive efavaleukin alfa treatment at their current dosing regimen for up to an additional 156 weeks. Only subjects who are deemed eligible to continue extended dosing beyond week 102 or week 103 will complete dosing at week 104. The remaining subjects will complete the week 104/EOET visit. All subjects who continue to receive efavaleukin alfa during the extended dosing period will be reevaluated every 6 months for their response to treatment. Following discussion and agreement between the principal investigator and medical monitor, the Sponsor may decide to allow these subjects to continue treatment through week 258 (Q2W dose) or week 259 (QW dose). Subjects participating in extended dosing through week 258 or 259 will complete the week 260/EOET visit (see Table 2-6).** All subjects will complete the 6-week safety follow-up after the last dose of efavaleukin alfa.

Note: All subjects will continue treatment with efavaleukin alfa at their current dose until the [redacted] Subjects who discontinue treatment early (prior to week 50 [Q2W dosing] or week 51 [QW dosing]) for any reason will complete an end of treatment visit. Subjects in the extended dosing period who discontinue treatment prior to week **258** (Q2W dosing) or week **259** (QW dosing) for any reason will complete an EOET visit **within a window of ± 7 days of the next regularly scheduled visit after the last dose of efavaleukin alfa, consisting of all assessments included in the week 260 visit**. All subjects will complete a safety follow-up visit 6 weeks (± 3 days) after the last dose of efavaleukin alfa.



2.2 Schedule of Activities

Table 2-1. Phase 1b Schedule of Activities – Screening Through Week 5

	Screening	Baseline	Treatment Period[a] Visits for Weekly and Biweekly dosing																										
Study Week																2	3	4									5	PD Visit	SFU/EOS[b]
Study Day	-28	-1	1								2	3	4	8	11	15	22	29					30	31	32	36	Anytime	
Hours post dose			Pre-dose	0	0.25	0.5	1	2	6	12	24	48	72					Pre-dose	0	6	12	24	48	72			
GENERAL AND SAFETY ASSESSMENTS																													
Informed Consent	X																												
Demographics	X																												
Medical History	X																												
GVHD/Transplant History	X																												
Physical Examination	X																									X			
Vital Signs	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X								X	X		
Height	X																												
Weight	X	X																X											
ECG[c]	X	X																									X	X	
Chest X-ray[d]	X																												
[redacted]																													
Prior/Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Corticosteroid use[e]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease-Related Events				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
cGVHD DISEASE ASSESSMENTS																													
NIH cGVHD Response Assessment (NIH Form A)[f]		X																									X		
GVHD Staging[q]	X																												
Pulmonary Function Test[g]		X[h]																									X		

Footnotes defined on last page of table

Table 2-1. Phase 1b Schedule of Activities – Screening Through Week 5

	Screening	Baseline	Treatment Period[a] Visits for Weekly and Biweekly dosing																										
Study Week																2	3	4									5	PD Visit	SFU/EOS[b]
Study Day	-28	-1	1								2	3	4	8	11	15	22	29				30	31	32	36	Anytime	
Hours post dose			Pre-dose	0	0.25	0.5	1	2	6	12	24	48	72					Pre-dose	0	6	12	24	48	72			
CLINICAL OUTCOME ASSESSMENTS																													
[redacted]																													
LABORATORY ASSESSMENTS																													
Clinical Chemistry and Hematology	X	X									X			X		X	X	X							X	X	X
Urinalysis	X																												
Pregnancy Test[j]	X	X																X										X
Coagulation (PT, INR, and aPTT)	X																												
FSH Test (postmenopausal only)[k]	X																												
HIV, Hepatitis B & C	X																												
Drug and Alcohol Screen	X																												
Tuberculosis Testing[l]	X																												
Lymphocyte Subsets[m]			X								X		X	X	X	X	X	X				X		X	X			
Biomarker Development Sample[m]			X								**X**		**X**	X		X	X	X										
Pharmacogenetic sample[m,n]			X																										
PBMC[m]			X											X				X										
PHARMACOKINETIC AND ANTIBODY ASSESSMENTS																													
[redacted]																													

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Footnotes defined on last page of table

Table 2-1. Phase 1b Schedule of Activities – Screening Through Week 5

	Screening	Baseline	Treatment Period[a] Visits for Weekly and Biweekly dosing																										
Study Week																	2	3	4									5	PD Visit	SFU/EOS[b]
Study Day	-28	-1	1								2	3	4	8	11	15	22	29						30	31	32	36	Anytime	
Hours post dose			Pre-dose	0	0.25	0.5	1	2	6	12	24	48	72					Pre-dose	0	6	12	24	48	72				
DOSING[p]																													
Weekly Efavaleukin Alfa Administration				X										X		X	X		X								X		
Biweekly Efavaleukin Alfa Administration				X												X			X										

aPTT = activated partial thromboplastin time; cGVHD = chronic graft versus host disease; CRF = case report form; ECG = electrocardiogram; EOS = end of study for individual subject; EOT = end of treatment; FSH = follicle stimulating hormone; GVHD = graft versus host disease; HIV = human immunodeficiency virus; INR = international normalized ratio; IP = investigational product; NIH = National Institutes of Health; PBMC = peripheral blood mononuclear cell; PD = progressive disease; PFT = pulmonary function test; PK = pharmacokinetics; PPD = positive purified derivative; PT = prothrombin time; [redacted] SFU = safety follow-up

[a] Subjects who withdraw early from treatment will complete the EOT visit and Safety follow-up visit **within a window of ± 7 days of the next regularly scheduled visit after the last dose of efavaleukin alfa, consisting of all assessments included in the week 52 visit**.

[b] Safety follow-up visit will be done 6 weeks (± 3 days) after the last dose of efavaleukin alfa. Women of childbearing potential will be required to complete a pregnancy test at this visit.

[c] A single ECG will be collected prior to blood draws or other invasive procedures. See Section 9.2.3.3.

[d] Only for subjects with a positive tuberculosis test (ie, positive PPD, indeterminate Quantiferon, or T-SPOT test).

[e] Record steroid use and/or changes to dose on concomitant medication CRF page.

[f] A 2 or 6 minute walk test is optional for the NIH Form A assessment.

[g] PFTs (spirometry) will be used in the NIH Form A assessment unless the subject is unable to comply. PFTs must be obtained at the Baseline visit unless they were performed at the Screening visit. Thereafter PFTs are strongly preferred at all visits which include the NIH Form A assessment and must be performed for all subjects who have an abnormal PFT at Baseline, who have known pulmonary GVHD or who have new pulmonary symptoms. If PFTs cannot be performed as part of the NIH Form A assessment, the lung symptom score should be substituted.

[h] PFTs performed at the Screening visit or between the Screening and Baseline visits may be substituted for the Baseline PFT. However, if historical PFTs are used at Screening then PFTs must be performed at the Baseline visit. Historical PFTs must have been performed within 2 years of the Screening visit.

[redacted]

[j] For women of childbearing potential, serum pregnancy test is required at screening. All other pregnancy tests are urine.

[k] Can be done as a part of the clinical chemistry

[l] Either a PPD, Quantiferon, or T-SPOT test will be done during screening.

[m] Blood samples must be collected prior to administration of investigational product, where appropriate. Acceptable windows for the timing of blood sample collection are as follows: within 12 hours prior to dose administration for samples collected on days when the investigational product is administered and within ± 12 hours of scheduled timepoint for samples collected on days when the investigational product is not administered.

[n] In subjects who consent to the optional pharmacogenetics testing.

[redacted]

Table 2-2. Phase 1b Schedule of Activities – Week 6 Through Week 52

TREATMENT PERIOD[a]																																										
	Visits for weekly dosing	Visits for weekly and biweekly dosing																																							PD Visit	SFU/ EOS[b]
Study Week	**19,21,23,25, 27,29,31,33, 35,37,39,41, 43,45,47,49,51**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52/ EOT[c]**	**Any-time**	
Study Day	**134,148,162, 176,190,204, 218,232,246, 260,274,288, 302,316,330, 344,358**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**120**	**127**	**141**	**155**	**169**	**183**	**197**	**211**	**225**	**239**	**253**	**267**	**281**	**295**	**309**	**323**	**337**	**351**	**365**		
GENERAL ASSESSMENTS																																										
Physical Examination																																X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight				X								X					X						X								X										
ECG[d]				X								X					X						X								X	X	X								
[redacted]																																										
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Corticosteroid use[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Disease-Related Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Footnotes defined on last page of table

Table 2-2. Phase 1b Schedule of Activities – Week 6 Through Week 52

TREATMENT PERIOD[a]																																								
	Visits for weekly dosing	Visits for weekly and biweekly dosing																																			PD Visit	SFU/ EOS[b]
Study Week	**19,21,23,25, 27,29,31,33, 35,37,39,41, 43,45,47,49,51**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52/ EOT[c]**	**Any-time**	
Study Day	**134,148,162, 176,190,204, 218,232,246, 260,274,288, 302,316,330, 344,358**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**120**	**127**	**141**	**155**	**169**	**183**	**197**	**211**	**225**	**239**	**253**	**267**	**281**	**295**	**309**	**323**	**337**	**351**	**365**		
cGVHD DISEASE ASSESSMENTS																																								
NIH cGVHD Response Assessment (NIH Form A)[f]				X								X[g,n]					X						X								X	X	
Pulmonary Function Test[h]				X								X					X						X								X	X	
CLINICAL OUTCOME ASSESSMENTS																																								
[redacted]																																								
LABORATORY ASSESSMENTS																																								
Clinical Chemistry and Hematology		X	X	X				X				X			X		X		X		X		X		X		X		X		X	X	X	
Pregnancy Test[j]				X				X				X			X		X		X		X		X		X		X		X		X			X	
PHARMACOKINETIC AND ANTIBODY ASSESSMENTS																																								
[redacted]																																								

Footnotes defined on last page of table

Table 2-2. Phase 1b Schedule of Activities – Week 6 Through Week 52

TREATMENT PERIOD[a]																																									
	Visits for weekly dosing	Visits for weekly and biweekly dosing																																						PD Visit	SFU/ EOS[b]
Study Week	**19,21,23,25, 27,29,31,33, 35,37,39,41, 43,45,47,49,51**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52/ EOT[c]**	**Any-time**	
Study Day	**134,148,162, 176,190,204, 218,232,246, 260,274,288, 302,316,330, 344,358**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**120**	**127**	**141**	**155**	**169**	**183**	**197**	**211**	**225**	**239**	**253**	**267**	**281**	**295**	**309**	**323**	**337**	**351**	**365**		
OTHER																																								
Lymphocyte Subsets[l]		X	X	X	X	X	X	X		X		X	X		X		X		X		X		X		X		X		X		X									
Biomarker Development Sample[l]		X		X		X		X				X			X		X		X		X		X		X		X		X		X									
PBMC[l]												X																													
DOSING[m]																																								
Weekly Efavaleukin Alfa Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[n]									
Biweekly Efavaleukin Alfa Administration[g]		X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[n]									

CRF = case report form; cGVHD = chronic graft versus host disease; ECG = electrocardiogram; EOS = end of study for individual subject; EOT = end of therapy; GVHD = graft versus host disease; NIH = National Institutes of Health; PBMC = peripheral blood mononuclear cell; PD = progressive disease; PFT = pulmonary function test; PK = pharmacokinetics; Q2W = every 2 weeks; [redacted] SFU = safety follow-up

[a] Subjects who withdraw early from treatment will complete the EOT visit and Safety follow-up visit **within a window of ± 7 days of the next regularly scheduled visit after the last dose of efavaleukin alfa, consisting of all assessments included in the week 52 visit**.

[b] Safety follow-up visit will be done 6 weeks (± 3 days) after the last dose of efavaleukin alfa. Women of childbearing potential will be required to complete a pregnancy test at this visit.

[c] At the discretion of the Sponsor, following discussion and agreement between the principal investigator and medical monitor, subjects responding to efavaleukin alfa (as assessed by the end of week 50), who wish to continue treatment, will complete week 52 assessments and may continue to receive efavaleukin alfa treatment at their current dosing regimen for up to an additional 52 weeks (see Table 2-3). The remaining subjects will complete the week 52/EOT visit and 6-weeks of safety follow-up after the last dose of efavaleukin alfa.

[d] A single ECG will be collected prior to blood draws or other invasive procedures. See Section 9.2.3.3.

[e] Record steroid use and/or changes to dose on concomitant medication CRF page.

[f] A 2 or 6 minute walk test is optional for the NIH Form A assessment.

[g] For subjects on biweekly dosing arm, beginning at week 18, subjects come in for biweekly visits.

[h] PFTs (spirometry) will be used in the NIH Form A assessment unless the subject is unable to comply. PFTs must be obtained at the Baseline visit unless they were performed at the Screening visit. Thereafter PFTs are strongly preferred at all visits which include the NIH Form A assessment and must be performed for all subjects who have an abnormal PFT at Baseline, who have known pulmonary GVHD or who have new pulmonary symptoms. If PFTs cannot be performed as part of the NIH Form A assessment, the lung symptom score should be substituted.

[redacted]

For women of childbearing potential, on study pregnancy tests are urine

[redacted]

Doses of investigational product must be given within ± 1 day of the scheduled time point. Subjects will remain at the site for at least 1 hour following the first and second dose of efavaleukin alfa and for 30 minutes following all remaining doses. Once [redacted] has been selected, investigational product will be administered within ± 2 days.

[n] Subjects continuing to receive treatment during the extended dosing period will receive efavaleukin alfa treatment at the week 52 visit per their current dosing regimen.

Table 2-3. Phase 1b Schedule of Activities – Extended Dosing Period Subjects Only (Week 53 Through Week 104)

Treatment Period[a]																														
	Visits for weekly dosing	Visits for weekly and biweekly dosing																											PD Visit	SFU/ EOS[b]
Study Week	**53,55,57,59,61, 63,65,67,69,71, 73,75,77,79,81, 83,85,87,89,91, 93,95,97,99,101, 103**	**54**	**56**	**58**	**60**	**62**	**64**	**66**	**68**	**70**	**72**	**74**	**76[c]**	**78**	**80**	**82**	**84**	**86**	**88**	**90**	**92**	**94**	**96**	**98**	**100**	**102**	**104/ EOET[d]**	**Any-time**	
Study Day	**372,386,400,414, 428,442,456,470, 484,498,512,526, 540,554,568,582, 596,610,624,638, 652,666,680,694, 708,722**	**379**	**393**	**407**	**421**	**435**	**449**	**463**	**477**	**491**	**505**	**519**	**533**	**547**	**561**	**575**	**589**	**603**	**617**	**631**	**645**	**659**	**673**	**687**	**701**	**715**	**729**		
GENERAL ASSESSMENTS																														
Physical Examination																												X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight													X														X		
ECG[e]													X														X	X	X
[redacted]																														
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Corticosteroid use[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease-Related Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NIH cGVHD Response Assessment (NIH Form A)[g]													X														X	X	
Pulmonary Function Test[h]													X														X	X	

Footnotes defined on last page

Table 2-3. Phase 1b Schedule of Activities – Extended Dosing Period Subjects Only (Week 53 Through Week 104)

	Treatment Period[a]																														
	Visits for weekly dosing	Visits for weekly and biweekly dosing																												PD Visit	SFU/ EOS[b]
Study Week	53,55,57,59,61, 63,65,67,69,71, 73,75,77,79,81, 83,85,87,89,91, 93,95,97,99,101, 103	54	56	58	60	62	64	66	68	70	72	74	76[c]	78	80	82	84	86	88	90	92	94	96	98	100	102	104/ EOET[d]	Any-time	
Study Day	372,386,400,414, 428,442,456,470, 484,498,512,526, 540,554,568,582, 596,610,624,638, 652,666,680,694, 708,722	379	393	407	421	435	449	463	477	491	505	519	533	547	561	575	589	603	617	631	645	659	673	687	701	715	729		
CLINICAL OUTCOME ASSESSMENTS																													
[redacted]																													
LABORATORY ASSESSMENTS																													
Clinical Chemistry and Hematology			X		X		X		X		X		X		X		X		X		X		X		X		X	X	X
Pregnancy Test[j]			X		X		X		X		X		X		X		X		X		X		X		X		X	X	X
PHARMACOKINETIC AND ANTIBODY ASSESSMENTS																													
[redacted]																													
OTHER																													
Lymphocyte Subsets[l]					X				X				X				X				X						X		
Biomarker Development Sample[l]					X				X				X				X				X						X		
DOSE																													
Weekly Efavaleukin Alfa Administration[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[n]		
Biweekly Efavaleukin Alfa Administration[m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[n]		

CRF = case report form; cGVHD = chronic graft versus host disease; ECG = electrocardiogram; EOS = end of study for individual subject; EOET = end of extended treatment; GVHD = graft versus host disease; NIH = National Institutes of Health; PD = progressive disease; PFT = pulmonary function test; PK = pharmacokinetics; Q2W = twice weekly; QW = every week; [redacted]; SFU = safety follow-up

[a] **Subjects who withdraw early from treatment will complete the EOET visit and Safety follow-up visit within a window of ± 7 days of the next regularly scheduled visit after the last dose of efavaleukin alfa, consisting of all assessments included in the week 104 visit.**

[b] Safety follow-up visit will be done 6 weeks (± 3 days) after the last dose of efavaleukin alfa. Women of childbearing potential will be required to complete a pregnancy test at this visit.

[c] Re-assessment of subject's response to efavaleukin alfa treatment will be conducted at week 76 and a decision may be made by the Sponsor, following discussion and agreement between the principal investigator and medical monitor, to allow subjects who wish to, to continue treatment through week 102 (Q2W dose) or week 103 (QW dose).

[d] Subjects in the extended dosing period who discontinue treatment prior to week **258** (Q2W dosing) or week **259** (QW dosing) for any reason will complete an EOET visit and 6-weeks of safety follow-up after the last dose of efavaleukin alfa.

[e] A single ECG will be collected prior to blood draws or other invasive procedures. See Section 9.2.3.3.

[f] Record steroid use and/or changes to dose on concomitant medication CRF page.

[g] A 2 or 6 minute walk test is optional for the NIH Form A assessment.

[h] PFTs (spirometry) will be used in the NIH Form A assessment unless the subject is unable to comply. PFTs must be obtained at the Baseline visit unless they were performed at the Screening visit. Thereafter PFTs are strongly preferred at all visits which include the NIH Form A assessment and must be performed for all subjects who have an abnormal PFT at Baseline, who have known pulmonary GVHD or who have new pulmonary symptoms. If PFTs cannot be performed as part of the NIH Form A assessment, the lung symptom score should be substituted.

[redacted]

[redacted]

Doses of investigational product must be given within ± 1 day of the scheduled time point. Subjects will remain at the site for at least 30 minutes following doses of investigational product. Once [redacted] has been selected, investigational product will be administered within ± 2 days.

[n] **At the discretion of the Sponsor, following discussion and agreement between the principal investigator and medical monitor, subjects responding to efavaleukin alfa (as assessed by the end of week 104), who wish to continue treatment beyond week 104, may continue to receive efavaleukin alfa treatment at their current dosing regimen for up to an additional 156 weeks. Only subjects who are deemed eligible to continue extended dosing beyond week 102 or week 103 will complete dosing at week 104. The remaining subjects will complete the week 104/EOET visit.**

Table 2-4. Phase 1b Schedule of Activities – Extended Dosing Period Subjects Only (Week 105 Through Week 158)

TREATMENT PERIOD[a]																															
	Visits for weekly dosing	Visits for weekly and biweekly dosing																												PD Visit	SFU/ EOS[b]
Study Week	105,107,109,111, 113,115,117,119, 121,123,125,127, 129,131,133,135, 137, 139, 141, 143, 145,147,149,151, 153,155,157	106	108	110	112	114	116	118	120	122	124	126	128	130[c]	132	134	136	138	140	142	144	146	148	150	152	154	156	158	Any-time	
GENERAL ASSESSMENTS																															
Physical Examination																													X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Weight														X													X			
ECG[d]														X													X			
[redacted]																															
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Corticosteroid use[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NIH cGVHD Response Assessment (NIH Form A)[f]														X													X			
Pulmonary Function Test[g]														X													X			
CLINICAL OUTCOME ASSESSMENTS																															
[redacted]																															
LABORATORY ASSESSMENTS																															
Clinical Chemistry and Hematology							X							X						X							X		X	X
Pregnancy Test[i]							X							X						X							X		X	X

Footnotes are defined on the last page of the table.

Table 2-4. Phase 1b Schedule of Activities – Extended Dosing Period Subjects Only (Week 105 Through Week 158)

TREATMENT PERIOD[a]																																
	Visits for weekly dosing	Visits for weekly and biweekly dosing																													PD Visit	SFU/ EOS[b]
Study Week	105,107,109,111, 113,115,117,119, 121,123,125,127, 129,131,133,135, 137, 139, 141, 143, 145,147,149,151, 153,155,157	106	108	110	112	114	116	118	120	122	124	126	128	130[c]	132	134	136	138	140	142	144	146	148	150	152	154	156	158	Any-time	
PHARMACOKINETIC AND ANTIBODY ASSESSMENTS																																
[redacted]																																
OTHER																																
Lymphocyte Subsets[k]														X													X				
Biomarker Development Sample[k]							X							X						X							X				
DOSE																																
Weekly Efavaleukin Alfa Administration[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Biweekly Efavaleukin Alfa Administration[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

CRF = case report form; cGVHD = chronic graft versus host disease; ECG = electrocardiogram; EOS = end of study for individual subject; EOET = end of extended treatment; GVHD = graft versus host disease; NIH = National Institutes of Health; PD = progressive disease; PFT = pulmonary function test; PK = pharmacokinetics; Q2W = every 2 weeks; QW = every week; [redacted]; [redacted]
SFU = safety follow-up
Subjects in the extended dosing period who discontinue treatment prior to week 258 (Q2W dosing) or week 259 (QW dosing) for any reason will complete an EOET visit and 6-weeks of safety follow-up after the last dose of efavaleukin alfa. See Table 2-6.

[a] Subjects who withdraw early from treatment will complete the EOET visit and Safety follow-up visit within a window of ± 7 days of the next regularly scheduled visit after the last dose of efavaleukin alfa, consisting of all assessments included in the week 260 visit.

[b] Safety follow-up visit will be done 6 weeks (± 3 days) after the last dose of efavaleukin alfa. Women of childbearing potential will be required to complete a pregnancy test at this visit.

[c] Re-assessment of subject's response to efavaleukin alfa treatment will be conducted every 6 months and a decision may be made by the Sponsor, following discussion and agreement between the principal investigator and medical monitor, to allow subjects who wish to, to continue treatment through week 258 (Q2W dose) or week 259 (QW dose).

[d] A single ECG will be collected prior to blood draws or other invasive procedures. See Section 9.2.3.3.

[e] **Record steroid use and/or changes to dose on concomitant medication CRF page.**
[f] **A 2 or 6 minute walk test is optional for the NIH Form A assessment.**
[g] **PFTs (spirometry) will be used in the NIH Form A assessment unless the subject is unable to comply. PFTs must be obtained at the Baseline visit unless they were performed at the Screening visit. Thereafter PFTs are strongly preferred at all visits which include the NIH Form A assessment and must be performed for all subjects who have an abnormal PFT at Baseline, who have known pulmonary GVHD or who have new pulmonary symptoms. If PFTs cannot be performed as part of the NIH Form A assessment, the lung symptom score should be substituted.**

[redacted]

For women of childbearing potential, on study pregnancy tests are urine.

[redacted]

[l] **Doses of investigational product in phase 1b must be given within ± 3 days from the scheduled visit for subjects in Q2W dosing and ± 2 days from the scheduled visit for QW dosing. Subjects will remain at the site for at least 30 minutes following doses of investigational product. Once** [redacted] **has been selected, investigational product will be administered within ± 2 days.**

Table 2-5. Phase 1b Schedule of Activities – Extended Dosing Period Subjects Only (Week 159 Through Week 222)

TREATMENT PERIOD[a]																																
	Visits for weekly dosing	Visits for weekly and biweekly dosing																													PD Visit	SFU/ EOS[b]
Study Week	159,161,163,165, 167,169,171,173, 175,177,179,181, 183,185,187,189, 191,193,195,197, 197,199,201,203, 205,207,209,221	160	162	164	166	168	170	172	174	176	178	180	182[c]	184	186	188	190	192	194	196	198	200	202	204	206	208[c]	210	222	Any-time	
GENERAL ASSESSMENTS																																
Physical Examination																													X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight													X													X				
ECG[d]													X													X			X	X
[redacted]																																
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Corticosteroid use[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NIH cGVHD Response Assessment (NIH Form A)[f]													X													X			X		
Pulmonary Function Test[g]													X													X			X		
CLINICAL OUTCOME ASSESSMENTS																																
[redacted]																																
LABORATORY ASSESSMENTS																																
Clinical Chemistry and Hematology						X							X						X							X			X	X	
Pregnancy Test[i]						X							X						X							X			X	X	

Footnotes are defined on the last page of the table.

Table 2-5. Phase 1b Schedule of Activities – Extended Dosing Period Subjects Only (Week 159 Through Week 222)

TREATMENT PERIOD[a]																																
	Visits for weekly dosing	Visits for weekly and biweekly dosing																													PD Visit	SFU/ EOS[a]
Study Week	159,161,163,165, 167,169,171,173, 175,177,179,181, 183,185,187,189, 191,193,195,197, 197,199,201,203, 205,207,209,221	160	162	164	166	168	170	172	174	176	178	180	182	184	186	188	190	192	194	196	198	200	202	204	206	208	210	222	Any-time	
PHARMACOKINETIC AND ANTIBODY ASSESSMENTS																																
[redacted]																																
OTHER																																
Lymphocyte Subsets[k]													X													X					
Biomarker Development Sample[k]						X							X						X							X					
DOSE																																
Weekly Efavaleukin Alfa Administration[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Biweekly Efavaleukin Alfa Administration[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				

CRF = case report form; cGVHD = chronic graft versus host disease; ECG = electrocardiogram; EOS = end of study for individual subject; EOET = end of extended treatment; GVHD = graft versus host disease; NIH = National Institutes of Health; PD = progressive disease; PFT = pulmonary function test; PK = pharmacokinetics; Q2W = every 2 weeks; QW = every week; [redacted]
SFU = safety follow-up
Subjects in the extended dosing period who discontinue treatment prior to week 258 (Q2W dosing) or week 259 (QW dosing) for any reason will complete an EOET and 6-weeks of safety follow-up after the last dose of efavaleukin alfa. See Table 2-6.

[a] Subjects who withdraw early from treatment will complete the EOET visit and Safety follow-up visit. within a window of ± 7 days of the next regularly scheduled visit after the last dose of efavaleukin alfa, consisting of all assessments included in the week 260 visit

[b] Safety follow-up visit will be done 6 weeks (± 3 days) after the last dose of efavaleukin alfa. Women of childbearing potential will be required to complete a pregnancy test at this visit.

[c] Re-assessment of subject's response to efavaleukin alfa treatment will be conducted every 6 months and a decision may be made by the Sponsor, following discussion and agreement between the principal investigator and medical monitor, to allow subjects who wish to, to continue treatment through week 258 (Q2W dose) or week 259 (QW dose).

[d] A single ECG will be collected prior to blood draws or other invasive procedures. See Section 9.2.3.3.

[e] **Record steroid use and/or changes to dose on concomitant medication CRF page.**
[f] **A 2 or 6 minute walk test is optional for the NIH Form A assessment.**
[g] **PFTs (spirometry) will be used in the NIH Form A assessment unless the subject is unable to comply. PFTs must be obtained at the Baseline visit unless they were performed at the Screening visit. Thereafter PFTs are strongly preferred at all visits which include the NIH Form A assessment and must be performed for all subjects who have an abnormal PFT at Baseline, who have known pulmonary GVHD or who have new pulmonary symptoms. If PFTs**

[redacted]

For women of childbearing potential, on study pregnancy tests are urine.

[redacted]

e

scheduled visit for QW dosing. Subjects will remain at the site for at least 30 minutes following doses of investigational product. Once [redacted] **has been selected, investigational product will be administered within ± 2 days.**

Table 2-6. Phase 1b Schedule of Activities – Extended Dosing Period Subjects Only (Week 223 Through Week 260)

TREATMENT PERIOD[a]																					
	Visits for weekly dosing	Visits for weekly and biweekly dosing																		PD Visit	SFU/ EOS[b]
Study Week	223,225,227,229, 231,233,235,237, 239,241,243,245, 247,249,251,253, 257,259	224	226	228	230	232	234[c]	236	240	242	244	246	248	250	252	254	256	258	260/ EOET[d]	Any-time	
GENERAL ASSESSMENTS																					
Physical Examination																					
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight							X												X	X	
ECG[e]							X												X	X	X
[redacted]																					
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Corticosteroid use[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease-Related Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NIH cGVHD Response Assessment (NIH Form A)[g]							X												X	X	
Pulmonary Function Test[h]							X												X	X	
CLINICAL OUTCOME ASSESSMENTS																					
[redacted]																					
LABORATORY ASSESSMENTS																					
Clinical Chemistry and Hematology							X						X						X		X
Pregnancy Test[j]							X						X						X		X

Footnotes are defined on the last page of the table.

Table 2-6. Phase 1b Schedule of Activities – Extended Dosing Period Subjects Only (Week 223 Through Week 260)

TREATMENT PERIOD[a]																					
	Visits for weekly dosing	Visits for weekly and biweekly dosing																		PD Visit	SFU/ EOS[a]
Study Week	223,225,227,229, 231,233,235,237, 239,241,243,245, 247,249,251,253, 257,259	224	226	228	230	232	234	236	240	242	244	246	248	250	252	254	256	258	260/ EOET	Any-time	
PHARMACOKINETIC AND ANTIBODY ASSESSMENTS																					
[redacted]																					
OTHER																					
Lymphocyte Subsets[l]							X												X	X	
Biomarker Development Sample[l]							X						X						X		
DOSE																					
Weekly Efavaleukin Alfa Administration[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Biweekly Efavaleukin Alfa Administration[m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

CRF = case report form; cGVHD = chronic graft versus host disease; ECG = electrocardiogram; EOS = end of study for individual subject; EOET = end of extended treatment; GVHD = graft versus host disease; NIH = National Institutes of Health; PD = progressive disease; PFT = pulmonary function test; PK = pharmacokinetics; Q2W = every 2 weeks; QW = every week; [redacted]; SFU = safety follow-up

[a] Subjects who withdraw early from treatment will complete the EOET visit and Safety follow-up visit within a window of ± 7 days of the next regularly scheduled visit after the last dose of efavaleukin alfa, consisting of all assessments included in the week 260 visit.

[b] Safety follow-up visit will be done 6 weeks (± 3 days) after the last dose of efavaleukin alfa. Women of childbearing potential will be required to complete a pregnancy test at this visit.

[c] Re-assessment of subject's response to efavaleukin alfa treatment will be conducted every 6 months and a decision may be made by the Sponsor, following discussion and agreement between the principal investigator and medical monitor, to allow subjects who wish to, to continue treatment through week 258 (Q2W dose) or week 259 (QW dose).

[d] Subjects in the extended dosing period who discontinue treatment prior to week 258 (Q2W dosing) or week 259 (QW dosing) for any reason will complete an EOET visit and 6-weeks of safety follow-up after the last dose of efavaleukin alfa.

[e] A single ECG will be collected prior to blood draws or other invasive procedures. See Section 9.2.3.3.

[f] Record steroid use and/or changes to dose on concomitant medication CRF page.

[g] A 2 or 6 minute walk test is optional for the NIH Form A assessment.

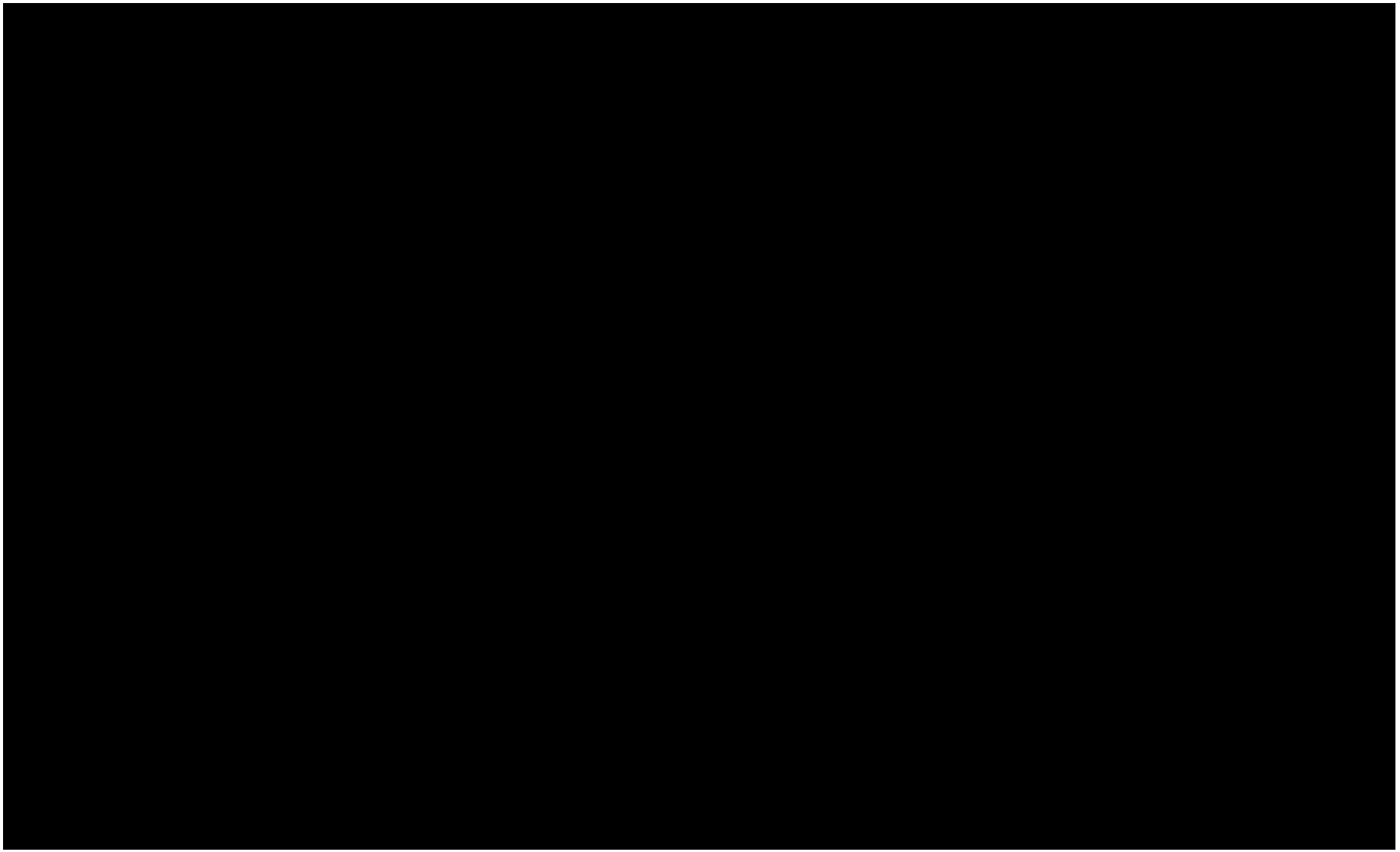
[h] **PFTs (spirometry) will be used in the NIH Form A assessment unless the subject is unable to comply. PFTs must be obtained at the Baseline visit unless they were performed at the Screening visit. Thereafter PFTs are strongly preferred at all visits which include the NIH Form A assessment and must be performed for all subjects who have an abnormal PFT at Baseline, who have known pulmonary GVHD or who have new pulmonary symptoms. If PFTs cannot be performed as part of the NIH Form A assessment, the lung symptom score should be substituted.**

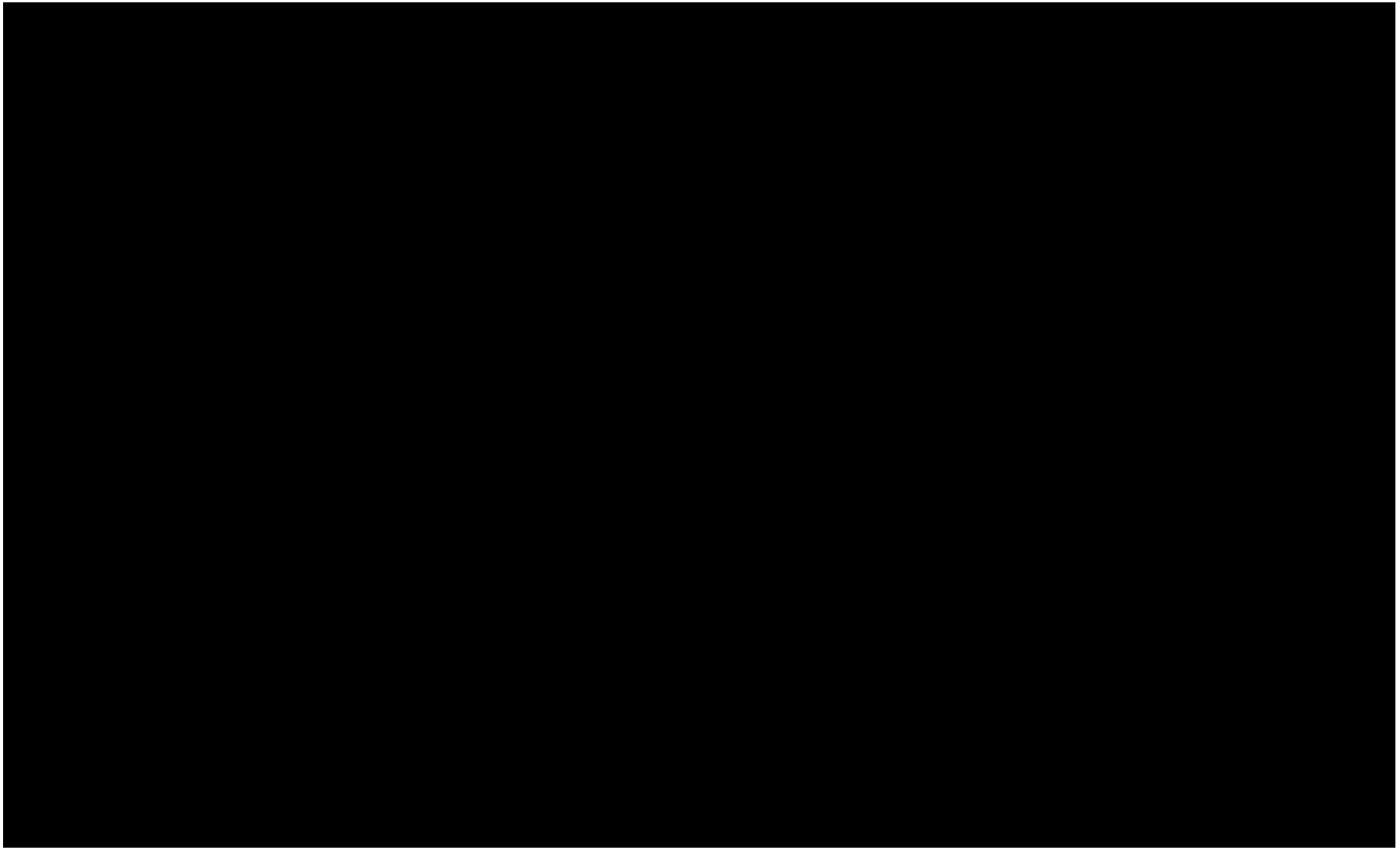
[redacted]

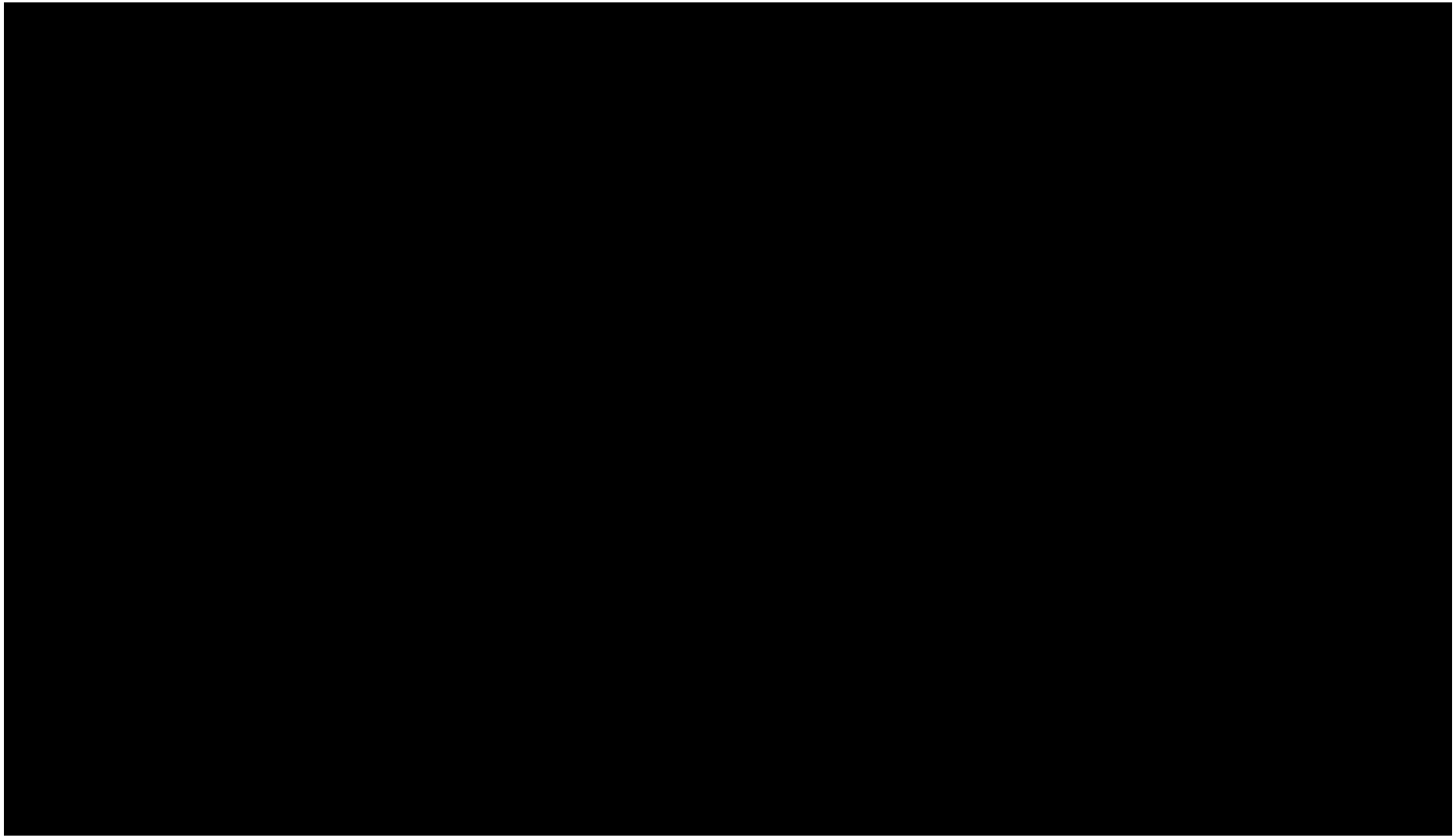
[j] **For women of childbearing potential, on study pregnancy tests are urine.**

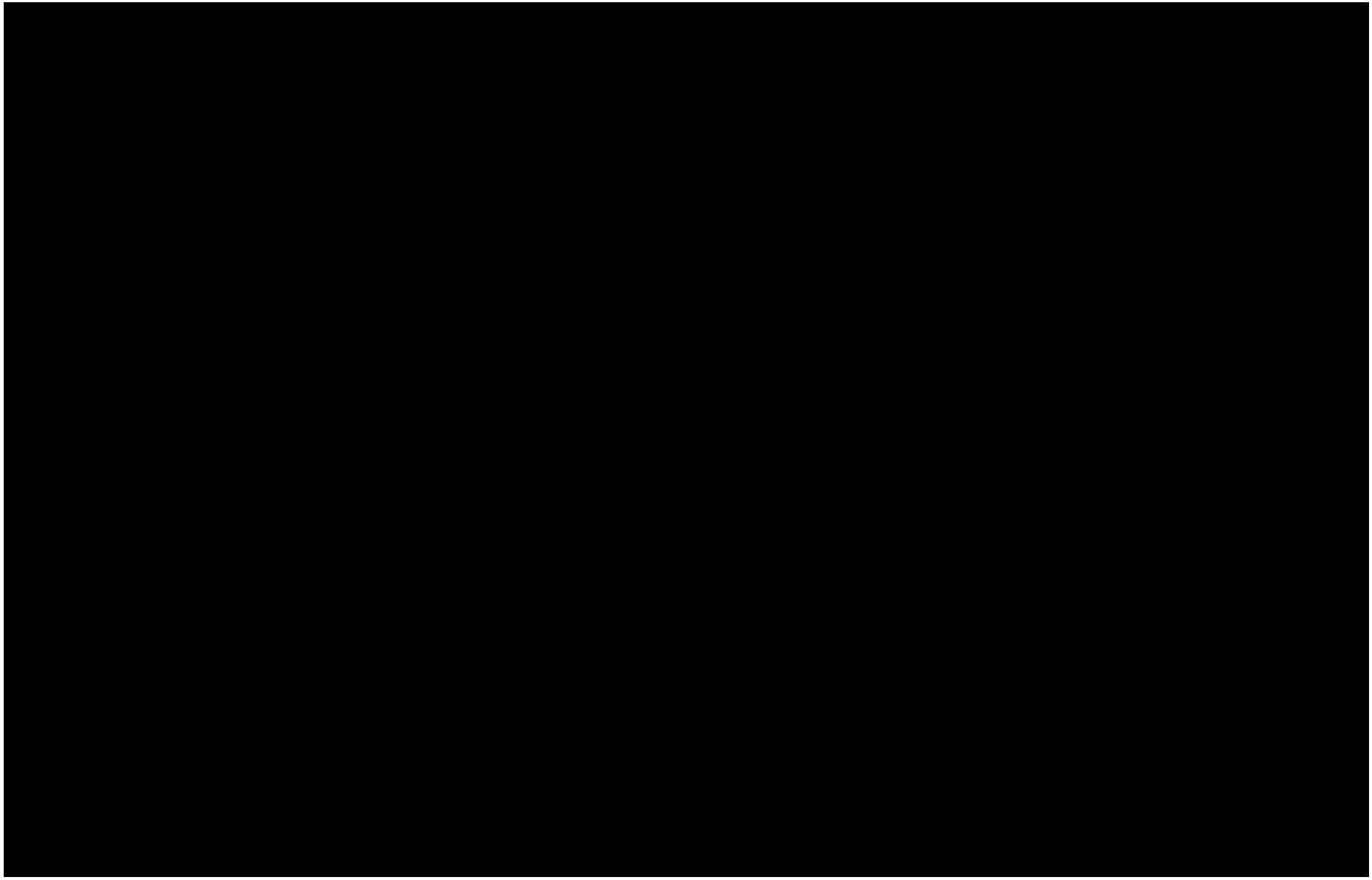
[redacted]

[m] **Doses of investigational product in phase 1b must be given within ± 3 days from the scheduled visit for subjects in Q2W dosing and ± 2 days from the scheduled visit for QW dosing. Subjects will remain at the site for at least 30 minutes following doses of investigational product. Once [redacted] has been selected, investigational product will be administered within ± 2 days.**









3. Introduction

3.1 Study Rationale

This open-label, multicenter, phase 1b/2 study is planned to evaluate the safety and efficacy of efavaleukin alfa (AMG 592) in subjects with steroid refractory chronic graft versus host disease (cGVHD). The phase 1b part of the study will evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of efavaleukin alfa and will define the maximum tolerated dose (MTD) and/or a biologically optimal dose. [redacted]

3.2 Background

3.2.1 Disease

Chronic graft-versus-host disease (cGVHD) is a systemic inflammatory disorder that is associated with considerable morbidity and mortality and develops in more than half of long term survivors after hematopoietic stem-cell transplantation (HSCT) (Kahl, 2007). It is the most common long-term complication of allogeneic HSCT and the leading cause of [redacted] The median time to onset is 4 to 6 months after HSCT but 5% to 10% of cases are diagnosed at greater than 1 year after HSCT (Lee and Flowers, 2008). Per 21 CFR 312.300, cGVHD meets the definition of a serious condition as it is a condition associated with morbidity that has a substantial impact on day to day function. Improved treatment for cGVHD is a major unmet need.

First line therapy for moderate to severe cGVHD consists of systemic glucocorticoid therapy or calcineurin inhibitors. Treatment with systemic glucocorticoids has limited efficacy, with half of patients requiring second-line therapy, and is associated with substantial long-term toxicity.

Second-line therapy for those who fail systemic glucocorticoids is not well established. Estimated response rates to experimental therapy are confounded by the lack of controlled trials and the non-standardized use of outcome measures. [redacted]. However, few multi-center controlled trials have replicated these high response rates. For instance, a recent multi-center randomized controlled phase 2 cross-over trial comparing imatinib versus rituximab for cutaneous sclerosis associated

with cGVHD reported a significant clinical response in 26% of patients in the imatinib arm versus 27% of subjects in the rituximab arm. Furthermore, only 17% of imatinib-treated subjects and 14% of rituximab-treated subjects achieved 'treatment success', defined as a significant clinical response without cross-over, relapse, or death (Arai et al, 2016).

With regard to the expected response rate with current standard of care (SOC), few studies include an SOC arm for comparison. The largest relevant study (n = 151 evaluable patients), a double-blind, randomized controlled trial comparing mycophenolate mofetil (MMF) plus SOC versus SOC alone, demonstrated that only 18% in the SOC arm versus 23% in the MMF plus SOC met the primary endpoint of complete withdrawal of systemic immunosuppressant therapy after 2 years (p = NS) (Martin, 2009). A study of Extra Corporeal Photophoresis (ECP) versus SOC reported a blinded evaluation of the Total Skin Score of 8.5% in the SOC arm versus 14.5% in the ECP arm (Flowers, 2008).

There is currently 1 approved, commercially available drug in the US and Canada for the treatment of patients with steroid-refractory cGVHD. Ibrutinib, an inhibitor of Bruton's tyrosine kinase (BTK), was approved in 2017 for the treatment of adults with cGVHD after failure of 1 or more lines of systemic therapy. [redacted]

The pathogenesis of cGVHD is complex and incompletely understood. It is characterized by aberrant negative selection of autoreactive T cells due to thymic dysfunction, autoantibody production, and fibrotic injury (Cutler et al, 2017; MacDonald et al, 2017; Soci and Ritz, 2014; Blazar et al, 2012).

Regulatory T cells (Treg) are a subset of cluster of differentiation (CD)4 T cells that suppress inflammation and whose numbers and function are maintained by interleukin-2 (IL-2). A loss in the homeostatic balance between Treg and other lymphocytes is considered a causative factor in many inflammatory conditions, including cGVHD. Low dose IL-2 and recombinant IL-2 (Proleukin® [aldesleukin]) have been studied in active cGVHD subjects (Koreth et al, 2016; Koreth et al, 2011). Disease improvement has generally been associated with sustained Treg expansion *in vivo* without increases in rates of infection or cancer relapse. However, the narrow window between adequate Treg enrichment and side effects (nausea, fever, fatigue) due to stimulation of T effector

cells (Teff) and natural killer (NK) cells may limit achievement of optimal Treg expansion (Koreth et al, 2011). Notably, a dose of 3 x 10^6 IU/m^2 induced persistent National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03) grade 1 constitutional symptoms (fever, malaise, and arthralgia), necessitating a 50% dose reduction, and indicating a narrow therapeutic window between adequate Treg enrichment and stimulation of effector cells (Koreth et al, 2011).

3.2.2 Amgen Investigational Product Background: Efavaleukin Alfa

Efavaleukin alfa is an Fc IL-2 mutein fusion protein designed to increase Treg selectivity, which has been developed to expand Tregs in subjects with inflammatory diseases (refer to the Investigator's Brochure). Interleukin-2 is a key growth factor for Tregs and is essential for Treg development, homeostasis and function. At low dose IL-2 binds preferentially to the α subunit (CD25) of the high-affinity IL-2 receptor which is expressed constitutively by Tregs and is absent on naive Tcells and unactivated T memory cells. This results in selective activation of Tregs. However, at higher doses IL-2 also activates other immune cells such as CD4+ and CD8+ T effector cells, NK cells and natural killer T cells (NKT) via the dimeric low affinity IL-2 receptor. Compared with aldesleukin, efavaleukin alfa exhibits greatly improved selectivity for Tregs over Teff and NK cells both in vitro and in vivo, potentially resulting in an improved therapeutic margin. In addition, the Fc domain of efavaleukin alfa provides a prolonged half-life compared with aldesleukin, thus reducing dosing frequency to maintain Treg enrichment. Treatment in subjects with steroid-refractory cGVHD with efavaleukin alfa is anticipated to provide greater sustained Treg expansion and an improved safety profile, leading to greater efficacy and tolerability.

A detailed description of the chemistry, pharmacology, efficacy, and safety of efavaleukin alfa is provided in the Investigator's Brochure.

3.2.2.1 Toxicology

In the 1- and 3-month repeat-dose toxicology studies in the cynomolgus monkey (dose levels up to 300 and 100 µg/kg, respectively, weekly subcutaneous [SC] injection), the no observed adverse effect level (NOAEL) dose was 30 µg/kg based on the observation of increased heart rate with attenuated diurnal rhythm at 100 µg/kg or greater. In addition, reversible decreases in red blood cell (RBC) mass, platelet and neutrophil counts were observed at 300 µg/kg in the 1-month study. In the rat single-dose safety pharmacology study evaluating respiratory function (dose levels: 100, 500, and 2000 µg/kg, single SC injection), audible respiration, decreased tidal volume and

increased respiration rate were observed at 2000 µg/kg. The heart rate, hematologic and respiratory changes were reversible, and are considered clinically monitorable.

3.2.2.2 Human Exposure

The observed efavaleukin alfa human exposures from cohorts 1 through 8 (to µg) of the single ascending dose (SAD) first in human (FIH) study in healthy subjects and all available PK data from 3 phase 1b studies: 20170103 (up to µg every 2 weeks [Q2W] in subjects with systemic lupus erythematosus [SLE]); 20170149 (up to µg Q2W in subject with rheumatoid arthritis [RA]); and this study, 20160283 (up to µg Q2W) were used to predict efavaleukin alfa exposures in humans following and µg doses given every week (QW) and and µg doses given Q2W. Accumulation of efavaleukin alfa is not expected, therefore at steady state, exposures (area under the concentration-time curve [AUC] and maximum observed concentration [C_{max}]) are predicted to be within the range of attained after a single dose (Table 3-1). Safety margins (Table 3-1) based on the efavaleukin alfa AUC and C_{max} observed at the NOAEL of 30 µg/kg from the 3-month repeat-dose GLP toxicology study in cynomolgus monkey are predicted to be 9.1-fold and 1.3-fold at the administration of µg Q2W, the dose expected to result in the highest exposures and support administration of this dose.

Table 3-1. Predicted Efavaleukin Alfa Steady State Exposures After 16 Weekly Subcutaneous Administrations of Efavaleukin Alfa in cGVHD Subjects for the Proposed Doses and Margins Relative to the 3-month GLP Repeat-dose Cynomolgus Monkey Exposure at the NOAEL of 30 µg/kg (Study 20160283)

	Median (IQR)		Exposure Margin[b]	
Clinical Dose (µg)	AUC_{tau}[a] (hr•ng/mL)	C_{max}[a] (ng/mL)	AUC	C_{max}
[redacted] (Q2W)	549 (373-801)	18.9 (15.0-23.1)	35	4.7
[redacted] (QW)	274 (195-395)	10.3 (8.1-12.6)	35	8.5
[redacted] (Q2W)	1028 (719-1488)	35.4 (28.3-43.4)	18	2.5
[redacted] (QW)	553 (399-778)	20.3 (16.5-25.0)	17	4.3
[redacted] (Q2W)	2070 (1401-2938)	70.3 (55.6-86.7)	9.1	1.3

AUC = area under the concentration-time curve; AUC_{tau} = area under the concentration-time curve over a dosing interval; C_{max} = maximum observed concentration; GLP = good laboratory practice; IQR = interquartile range; NOAEL = no observed adverse effect level; QW = every week; Q2W = every 2 weeks

[a] Exposure after the first and last doses are predicted to be similar, steady state C_{max} and AUC_{tau} (AUC for the last dosing interval) are used for margin calculation.

[b] Toxicokinetic results (Study 118065) in monkey last week of dosing at 30 µg/kg once weekly, mean $AUC_{7,wk13}$ (area under the concentration-time profile from day 1 to day 7 of week 13) = 9490 hr•ng/mL, last dose mean $C_{max,wk13}$ = 88 ng/mL from 4 of 8 animals that sustained efavaleukin alfa exposure throughout the 3-month administration period: Exposure margin for AUC for Q2W dosing was based on 9490 hr•ng/mL x 2.

3.2.2.3 Clinical Experience

As of 22 September 2020, approximately 136 subjects have received single or multiple doses of efavaleukin alfa, including healthy subjects in a phase 1a FIH study (20140324), Japanese healthy subjects in a phase 1a study (20180132), subjects with RA in a phase 1b study (20170149), and subjects in 2 ongoing clinical studies in subjects with SLE (20170103; phase 1b), and steroid-refractory cGHVD (20160283; phase 1b/2). Detailed information about clinical experience with efavaleukin alfa may be found in the Investigator's Brochure.

3.2.3 Risk Assessment

The most common adverse events experienced by subjects included mild (grade 1) painless erythema at or near the injection site, sometimes accompanied by pruritus, that was self-resolving. As of 22 September 2020, 2 serious hypersensitivity reactions to efavaleukin alfa have been reported. The 2 events (grade 2 and 3, respectively)

occurred within the first 24 hours after initial dose and resolved without sequalae with symptomatic treatment (ie, systemic corticosteroids). More detailed information about the safety risks of efavaleukin alfa may be found in the Investigator's Brochure.

3.2.4 Experience With Other Similar Biological Agents

Low dose recombinant IL-2 has been administered SC to healthy subjects as well as to small numbers of patients in clinical trials in multiple indications including cGVHD, Type 1 Diabetes, SLE, alopecia areata and HCV vasculitis (He et al, 2016; Koreth et al, 2016; Hartemann et al, 2013; Castela et al, 2014; Ito et al, 2014; Koreth et al, 2011; Sadoun et al, 2011). Dosing regimens have ranged between 0.33 million IU and 3 million IU/m^2 daily with varying treatment intervals. The overall safety profile of low dose IL-2 has been acceptable. The most common reported adverse events across trials include flu-like constitutional symptoms (malaise, fatigue, arthralgia, and myalgia), typically grade 1 to 3, which resolved upon dose reduction or cessation of treatment. Grade 1 to 3 injection site reactions were also commonly reported. Five grade 3 or higher infections were reported in 63 cGVHD patients (Koreth et al, 2016; Koreth et al, 2011) and one grade 2 dental abscess was reported in 10 patients with HCV vasculitis treated with low dose recombinant IL-2 (Sadoun et al, 2011). Increased rates of infection have not been reported. Treatment with low dose IL-2 administered SC has not been associated with capillary leak syndrome, cytokine release syndrome, pulmonary edema, cardiac toxicities or other severe IL-2 related toxicities. In summary, efavaleukin alfa is expected to be well-tolerated compared to aldesleukin due to its wider therapeutic window and the safety profile observed to date in healthy subjects who have received a single dose of efavaleukin alfa. However, subjects will be monitored closely throughout the study.

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
Phase 1b • To evaluate the safety and tolerability of multiple ascending doses of efavaleukin alfa in subjects with steroid refractory cGVHD in order to estimate the MTD and establish the [redacted]	**Phase 1b** • Incidence of dose limiting toxicities (DLTs) at first 4 weeks • Incidence of all treatment-related and treatment-emergent adverse events and serious adverse event
[redacted]	
Secondary	
[redacted]	

Objectives	Endpoints
[redacted]	

Exploratory
[redacted]

4.2 Hypotheses

Phase 1b

Efavaleukin alfa will be safe and well-tolerated in subjects with steroid refractory cGVHD.

[redacted]

5. Study Design

5.1 Overall Design

This is an open-label, multi-center phase 1b/2 study to evaluate the safety and efficacy of efavaleukin alfa in subjects with steroid refractory cGVHD. The study will be conducted in 2 phases:

5.1.1 Phase 1b

The phase 1b part of this study will be conducted as a multiple ascending dose (MAD) study. Each dosing cohort will consist of between 3 and 6 DLT-evaluable subjects who will receive efavaleukin alfa SC either QW or Q2W plus protocol permitted background therapy for 52 weeks. The DLT evaluation period is 4 weeks after the first dose of study drug. At the discretion of the Sponsor, following discussion and agreement between the principal investigator and medical monitor, subjects responding to efavaleukin alfa (as assessed by the end of week 50), who wish to continue treatment, may continue to receive efavaleukin alfa treatment at their current dosing regimen for up to an additional 52 weeks. The remaining subjects will complete the week 52/EOT visit. All subjects who continue to receive efavaleukin alfa during the extended dosing period will be reevaluated at week 76 for their response to treatment. Following discussion and agreement between the principal investigator and medical monitor, the Sponsor may decide to allow these subjects to continue treatment through week 102 (Q2W dose) or week 103 (QW dose). Subjects participating in extended dosing **through week 104** will complete the week 104/**end of extended treatment (**EOET**)** visit (see Table 2-3). **At the discretion of the Sponsor, following discussion and agreement between the principal investigator and medical monitor, subjects responding to efavaleukin alfa (as assessed by the end of week 104), who wish to continue treatment beyond week 104, may continue to receive efavaleukin alfa treatment at their current dosing regimen for up to an additional 156 weeks. Only subjects who are deemed eligible to continue extending dosing beyond week 102 or week 103 will complete**

dosing at week 104. The remaining subjects will complete the week 104/EOET visit. All subjects who continue to receive efavaleukin alfa during the extended dosing period will be reevaluated every 6 months for their response to treatment. Following discussion and agreement between the principal investigator and medical monitor, the Sponsor may decide to allow these subjects to continue treatment through week 258 (Q2W dose) or week 259 (QW dose). Subjects participating in extended dosing through week 258 or 259 will complete the week 260/EOET visit (see Table 2-6). All subjects will complete the 6-week safety follow-up after the last dose of efavaleukin alfa.

Five dose levels are planned: [redacted] µg Q2W (cohort 1a), [redacted] µg QW (cohort 2a), [redacted] µg Q2W (cohort 3), [redacted] µg QW (cohort 4), and [redacted] µg Q2W (cohort 5). Dose levels 1a ([redacted] µg Q2W) and 2a ([redacted] µg QW) will be enrolled concurrently. Three subjects each will be assigned to cohorts 1a ([redacted] µg Q2W) and 2a ([redacted] µg QW) alternately (total of 6 subjects). After the last subject completes the DLT evaluation period, a dose level review meeting (DLRM) will occur and if deemed necessary, 3 additional subjects each will be assigned to cohorts 1a and 2a alternately (total of 6 subjects) to gain additional information. After the last subject completes the DLT evaluation period, a DLRM will occur and if dose escalation is deemed appropriate, subjects will be enrolled in cohorts 3 ([redacted] µg Q2W) ,4 ([redacted] µg QW), and 5 ([redacted] µg Q2W) as follows: first, 3 subjects will be enrolled in cohort 3. An internal safety review will be conducted by the Amgen Medical Monitor and Global Safety Officer after the first 3 subjects complete the DLT evaluation period. If concerning safety issues are identified, a DLRM will occur to assess if it is safe to proceed with additional enrollment in cohort 3 and concurrent enrollment in cohort 4. If no concerning safety issues are identified in these first 3 subjects, enrollment of the remaining 3 subjects in cohort 3 will proceed without a DLRM. Concurrently, enrollment of 6 subjects in cohort 4 will begin with alternate assignment of subjects between cohorts 3 and 4 until enrollment of cohort 3 has completed. Enrollment of 6 subjects in cohort 5 will begin after the DLRM for cohort 4 is complete. DLRMs for cohorts 3, 4 and 5 will occur after the last subject in that cohort completes the DLT evaluation period.

All planned dose levels for a given cohort may be adjusted at any time based on emerging data. Additional dosing cohorts may be added, removed, or substituted at any time based on emerging data and the results of continuous modelling.

After there is at least 1 DLT observed at any dose level, a Bayesian logistic regression model (BLRM) (Bailey et al, 2009; Neuenschwander et al, 2008) will be used to inform dose escalation and the results of this analysis will be provided to the DLRM.
Three toxicity probability intervals (TPI) of DLT will be defined: target TPI (20% to 30%), excessive TPI (30% to 60%), and unacceptable TPI (60% to 100%). Adverse events meeting DLT criteria after week 4 and PD information may also be included in the model, as available. The model will recommend an MTD as the dose with highest probability in the target TPI, but with less than 25% probability in excessive TPI and unacceptable TPI. Lower dose levels, intermediate dose levels or alternative dosing schedules may be considered based on all available information as long as they do not exceed the estimated MTD per the model. In addition, Amgen may add subjects to dose levels below the MTD in order to better characterize PK and PD. After DLT is observed, the BLRM model will be run after each dosing cohort and may be run at any time to continuously update the MTD information. For technical details of BLRM, please refer to Statistical Analysis Plan (SAP).

During or after completion of the dose escalation part of the study, Amgen may enroll approximately 10 additional subjects in an optional dose expansion cohort in order to gain additional safety and efficacy information prior to the selection of an [redacted] dose. Determination of the dose for the dose expansion cohort will be based on review of all available information, including but not limited to BLRM model, other safety data, PK/PD, and efficacy. This dose cannot exceed the model predicted MTD. A dose that has not been previously explored may also be considered. The BLRM model may be run anytime during the dose expansion cohort, and Amgen may change the expansion cohort dose level or add additional subjects for dose expansion based on emerging information.

After all subjects in the phase 1b part of the study have had the opportunity to undergo assessment for the week 16 visit Amgen will review all the available information, including but not limited to the BLRM model, other safety data, PK/PD, and efficacy, to select the [redacted]

All phase 1b subjects will continue efavaleukin alfa therapy at their current dose until the [redacted] is established. Subjects still receiving or planned to receive efavaleukin alfa treatment at the time that [redacted] is determined may change their efavaleukin alfa dose to the [redacted] dose at the discretion of the Sponsor, following discussion and agreement between the principal investigator and medical monitor, and **may** continue study

treatment **through** the week **260**/EOET visit **if they remain eligible for extended dosing** (see **Table 2-6**).

[redacted]

5.2 Number of Subjects

Approximately 40 subjects will be enrolled in phase 1b of the study, with about 30 subjects in the dose escalation cohorts and approximately 10 subjects in the optional dose expansion cohort. The total sample size may be higher than 40 subjects if, following a DLRM recommendation or Amgen decision to evaluate additional doses, dosing cohorts are added and/or existing cohorts are expanded; or if subjects are replaced as per Section 5.2.1. Additional subjects may be enrolled in each cohort to enable all screened eligible subjects to participate in the study.

[redacted]

Subjects in this clinical investigation shall be referred to as “subjects.”

5.2.1 Replacement of Subjects

Subjects enrolled in the phase 1b portion of the study may be replaced if they receive fewer than 4 doses of efavaleukin alfa prior to discontinuing study participation.

Subjects enrolled in the [redacted]

5.2.2 Number of Sites

Approximately 14 sites in North America, Europe, and Asia will participate in the phase 1b portion of the study and [redacted] Sites that do not enroll subjects within approximately 3 months of site initiation may be closed.

5.3 End of Study

5.3.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the [redacted]

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

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

5.3.2 Study Duration for Subjects

The study will consist of up to a 28-day screening period, a 52 week treatment period (up to **260** weeks for subjects in phase 1b who enter the extended dosing period), and a 6 week safety follow-up period. The maximum duration of trial participation for an individual subject is approximately 14 months (up to **62** months for subjects in phase 1b who enter the extended dosing period) from screening through safety follow-up.

5.4 Justification for Investigational Product Dose

Based on data from Study 20160283 as of 27 October 2020, efavaleukin alfa has demonstrated acceptable safety and tolerability in patients with cGVHD at doses up to [redacted] µg Q2W administered for up to 54 weeks. Efavaleukin alfa has also demonstrated pharmacodynamic selectivity with greater fold increase in the mean blood Treg counts compared to mean CD4 Tcon counts across all the doses and dosing frequencies tested although high inter-subject variability in response was observed. The increases in CD4+ Tcon were minimal and demonstrated both inter-subject and inter-visit variability. The observed safety profile and pharmacodynamics of efavaleukin alfa in cGVHD patients support further dose escalation to investigate whether higher Treg expansion can be achieved with continued maintenance of selectivity.

The additional efavaleukin alfa dose of [redacted] µg Q2W was selected based on about 2-fold higher predicted drug exposures than the [redacted] µg Q2W dose with about 9-fold and 1.3-fold exposure margins of AUC and C_{max} relative to the NOAEL dose in the 3-month toxicology study. The observed exposures of efavaleukin alfa in cGVHD patients are approximately dose proportional. The proposed dose of [redacted] µg Q2W was selected to minimize overlap in exposures compared to the observed exposures at the [redacted] µg Q2W dose (Table 3-1). The cohort 5 dose of [redacted] µg Q2W is predicted to have good separation in exposure based on the estimated interquartile ranges (IQRs) of AUC and C_{max} at the [redacted] µg Q2W dose.

Population PK/PD modeling was performed to predict efavaleukin alfa Treg expansion in humans following [redacted] and [redacted] µg doses given QW and [redacted] and [redacted] µg doses given Q2W. Exposure response relationships were modelled using observed efavaleukin alfa human exposures and pharmacodynamic outputs from cohorts 1 through 8 ([redacted] to [redacted] µg) of the SAD, FIH study in healthy subjects and all available PK/PD data from 3 phase 1b studies: 20170103 (up to [redacted] µg Q2W in subjects with SLE); 20170149 (up to [redacted] µg Q2W in subject with RA); and this study, 20160283 (up to [redacted] µg Q2W). For each dosing frequency (QW or Q2W), predicted [redacted] consistent with observed data. The [redacted] µg Q2W dose is predicted to produce a roughly 30% increase in the [redacted] compared to the [redacted] µg Q2W dose.

[redacted]

[redacted]

6. Study Population

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

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

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

6.1 Inclusion Criteria

For both phase 1b and [redacted] subjects are eligible to be included in the study only if all of the following criteria apply:

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

102 Subject is an adult ≥ 18 years old at the time of signing the informed consent.

103 Subject is a recipient of an allogeneic HSCT.

104 Subject has moderate to severe steroid-refractory cGVHD as defined by all of the following criteria:

- Diagnosed with cGVHD per the 2014 cGVHD NIH Consensus Criteria (Jagasia, 2015; Appendix 8).
- Steroid refractory cGVHD, defined as having persistent signs and symptoms of cGVHD despite ≥ 4 weeks of prednisone (or equivalent) dosed at ≥ 0.25 mg/kg/day (or ≥ 0.5 mg/kg every other day).
- Moderate to severe cGVHD (in accordance with 2014 cGVHD NIH Consensus Criteria [Jagasia, 2015; Appendix 9]) at screening with involvement of at least 1 of the following organs at the screening and baseline visits: skin, mouth, eyes, gastrointestinal (GI) tract, liver, lungs, and joint and fascia.

105 Subject has received no more than 3 previous treatments for cGVHD, excluding topical agents.

- Treatment with corticosteroids is considered a treatment for cGVHD and should be included in determining the number of previous treatments.
- Lines of therapy consisting of concurrent medications or interventions (eg, tacrolimus and corticosteroids; ECP and corticosteroids) count as 2 separate treatments.
- If cGVHD has worsened during a taper of immunosuppressive agents, restoring the agents to therapeutic level is permitted and does not count as an additional treatment.

106 Subject may be receiving corticosteroid therapy provided that the dose is ≤ 1 mg/kg/day of systemic prednisone or equivalent and has been stable for at least 2 weeks prior to first dose of efavaleukin alfa.

107 Subject may be receiving other non-corticosteroid immunosuppressive therapies provided that the immunosuppressant dose is stable for at least 2 weeks prior to first dose of efavaleukin alfa. Adjustments to dose of calcineurin inhibitor or sirolimus are allowed only to maintain drug levels within therapeutic range.

108 Subject has a Karnofsky performance status score ≥ 50%.

109 Subject has an estimated life expectancy of > 3 months.

110 Subject must have adequate hepatic function, defined below, unless the treating physician documents the abnormal LFTs as consistent with hepatic cGVHD:

- total bilirubin < 2.0 mg/dL (34.2 µmol/L) [elevated values due to Gilbert's Syndrome or of non-hepatic origin are excluded].
- aspartate transaminase [AST; SGOT]/Alanine transaminase [ALT; SGPT] ≤ 2x upper limit of normal (ULN).
- If LFT abnormalities are deemed consistent with hepatic cGVHD by the investigator, a liver biopsy will not be mandated.

111 Subject must have adequate pulmonary function defined as: forced expiratory volume in 1 second (FEV1) ≥ 50% or hemoglobin-adjusted diffusion capacity for

carbon monoxide (D_{LCO} Hb) ≥ 40% of predicted, unless pulmonary dysfunction is deemed to be due to cGVHD.

112 Subject must have adequate renal function defined as: a calculated glomerular filtration rate of > 50 mL/min/1.73 m^2 using the MDRD formula.

113 Subject must have adequate cardiac function defined as: no history within 6 months prior to screening of myocardial infarction, unstable angina, New York Heart Associate Class III or IV heart failure, or stroke. No findings on the screening electrocardiogram (ECG) that in the opinion of the investigator requires further cardiovascular evaluation, including severe uncontrolled ventricular arrhythmias, electrocardiographic evidence of acute ischemia or active conduction system abnormalities.

114 Subject must have adequate bone marrow function indicated by ANC > 1.00 x 10^9/L and platelets > 50 x 10^9/L without growth factors or transfusions within the 4 weeks prior to starting efavaleukin alfa.

6.2 Exclusion Criteria

Subjects in both phase 1b and 2 are excluded from the study if any of the following criteria apply.

201 Subject is concurrently receiving treatment with calcineurin-inhibitor plus sirolimus (either agent alone is acceptable).

202 Subject has received ibrutinib, imatinib, bortezomib, entospletinib, ruxolitinib or other JAK inhibitor, or treatment with any investigational drug or device within 4 weeks prior to starting efavaleukin alfa.

203 Subject has received treatment with T-cell depleting, B-cell depleting or IL-2 signaling targeted medication (eg, ATG, alemtuzumab, basiliximab, denileukin diftitox, IL-2, rituximab) within 12 weeks prior to starting efavaleukin alfa.

204 Subject has received treatment with T regulatory cell expanding therapies (ie, PUVA, UVB, adoptively transferred T regulatory cells) within 4 weeks prior to starting efavaleukin alfa.

205 Subject has received a donor lymphocyte infusion within 12 weeks prior to starting dose of efavaleukin alfa.

206 Subject with active morphologic relapse/progression of hematologic malignancy post transplantation. Persistent CLL early after transplantation that subsequently entered remission will not be excluded.

207 Subject has a history of malignancy, other than the indication for hematopoietic cell transplantation, with the following exceptions:

- adequately treated nonmelanoma skin cancers without current evidence of disease
- adequately treated cervical carcinoma in situ without current evidence of disease
- adequately treated breast ductal cancer in situ without current evidence of disease

- any malignancy treated with curative intent and with no evidence of active disease present for more than 5 years prior to screening and felt to be at low risk for recurrence by the treating physician

208 Subject has a history of thrombotic microangiopathy, hemolytic-uremic syndrome or thrombotic thrombocytopenic purpura.

209 Subject has an active infection requiring treatment with intravenous antibiotics or has been hospitalized for treatment of an active infection in the 4 weeks prior to starting dose of efavaleukin alfa.

210 Subject has known history of active tuberculosis.

211 Positive test for tuberculosis during screening defined as either:

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

212 Subject is positive for hepatitis B surface antigen, hepatitis B core antibody (confirmed by hepatitis B deoxyribonucleic acid [DNA] polymerase chain reaction [PCR] test) or detectable hepatitis C virus ribonucleic acid (RNA) by PCR (screening is generally done by hepatitis C antibody [HepCAb], followed by hepatitis C virus RNA by PCR if HepCAb is positive). Subjects with a history of hepatitis B vaccination without history of hepatitis B are allowed.

213 Subject has positive test results for Human Immunodeficiency Virus (HIV) or known to be HIV-positive.

214 Phase 1b subject has a drug or alcohol urine test positive for illicit drugs at the screening visit. Medications detected by the drug test are allowed if they are being taken under the direction of a physician or if permitted for recreational purposes as per country regulations.

215 Phase 1b subject cannot be a current smoker, nor have used any nicotine or tobacco containing products within the last 6 months prior to screening. These types of products include but are not limited to: snuff, chewing tobacco, cigars, cigarettes, pipes, or nicotine patches.

216 Phase 1b subject is unable to avoid alcohol during the 4-week DLT evaluation period or tobacco consumption for the duration of the study.

217 Subject has known sensitivity to efavaleukin alfa or its excipients to be administered during dosing.

218 Subject likely to be unable to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments [COAs]) to the best of the subject and investigator's knowledge.

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

220 Females who are pregnant or breastfeeding, or planning to become pregnant or breastfeed during treatment and for an additional 6 weeks after the last dose of efavaleukin alfa.

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

222 Females of childbearing potential who are unwilling to use 1 highly effective method of contraception during treatment and for an additional 6 weeks after receiving the last dose of efavaleukin alfa. Refer to Appendix 5 for additional contraception information.

223 Subject has previously entered this study.

6.3 Lifestyle Restrictions

6.3.1 Alcohol and Tobacco (Phase 1b)

Phase 1b subjects will be required to avoid alcohol consumption during the 4-week DLT evaluation period. After the 4-week DLT evaluation period, alcohol consumption is strongly discouraged and is prohibited in those subjects with hepatic GVHD, underlying hepatic abnormalities, or elevated liver function tests at the baseline visit.

Phase 1b subjects must not use any nicotine or tobacco containing products within 6 months prior to screening and throughout the study. These types of products include but are not limited to: snuff, chewing tobacco, cigars, cigarettes, pipes, or nicotine patches.

6.4 Subject Enrollment

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

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

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria and has been enrolled via the Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS). The investigator is to document this decision and date, in the subject's medical record and it will be transferred from the IVRS/IWRS to the subject's enrollment case report form (CRF).

Subjects will be screened to determine eligibility 28 days prior to baseline visit (see Table 2-1 and Table 2-7).

Each subject who enters into the screening period for the study receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned using the IVRS/IWRS. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

6.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected in the source documents that includes demography, screen failure details, eligibility criteria, and any serious adverse events.

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

7. Treatments

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

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

Efavaleukin alfa will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. It is a liquid formulation presented in glass vials. An Investigational Product Instruction Manual (IPIM), containing detailed information regarding the storage, formulation, preparation, and administration of investigational product will be provided separately.

7.1 Treatment Procedures

7.1.1 Investigational Products

Table 7-1. Study Treatments

Study Treatment Name	Amgen Investigational Product: Efavaleukin Alfa
Dosage Formulation	Efavaleukin alfa is a liquid formulation presented in glass vials
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	Phase 1b Cohort 1: [redacted] µg biweekly Cohort 2 [redacted] µg weekly Cohort 3: [redacted] µg biweekly Cohort 4 [redacted] µg weekly Cohort 5: [redacted] µg biweekly [redacted]
Route of Administration	Subcutaneous injection
Accountability	The amount of investigational product used in preparation, total volume of preparation, quantity administered, start date, start time, frequency, and lot number of efavaleukin alfa are to be recorded on each subject's CRF.
Dosing Instructions	A qualified staff member at the site will administer all SC injections in the abdomen, upper arm or thigh. A physician must be available at the time of administration of efavaleukin alfa Phase 1b: Subjects will receive weekly or biweekly SC doses of efavaleukin alfa at the site administered by study personnel for the duration of the study. Subjects will remain at the site for at least 1 hour following the first and second dose of efavaleukin alfa and for 30 minutes following all remaining doses. [redacted]

7.1.2 Non-investigational Products

Non-investigational products will not be used in this study.

7.1.3 Medical Devices

No investigational medical devices will be used in this study

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

Non-investigational medical devices (eg, syringes, sterile needles, and vials required for investigational product dilution) will be provided by Amgen. These items will be listed specifically in the IPIM.

7.1.4 Other Protocol-required Therapies

There are no other protocol-required therapies.

7.1.5 Other Treatment Procedures

There are no other treatment procedures in this study.

7.1.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, **combination product,** or device after it is released for distribution to market or clinic by either **(1)** Amgen or **(2)** distributors or partners for whom Amgen manufactures the material. **This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.**

This includes any drug(s), device(s) or combination product(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product. For this study, Amgen will collect product complaints for efavaleukin alfa.

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

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

Subjects may not initiate treatment with donor lymphocyte infusions, ECP, recombinant IL-2 (eg, aldesleukin, ILTOO), with T-cell depleting (eg, ATG, alemtuzumab), IL-2 signaling targeted medication (eg, basiliximab, daclizumab, denileukin dififtitox) or Treg

cell expanding therapies (ie, recombinant IL-2, adoptively transferred Treg cells) during study participation.

7.2 Method of Treatment Assignment

This study includes a single arm, open-label, multiple ascending dose stage followed by [redacted]. Subjects will be assigned to the dose levels in the order described in Section 5.1.1. In the phase 1b stage of the study, enrollment of alternating concurrent dosing cohorts will be facilitated by IVRS. [redacted]. The treatment assignment date is to be documented in the subject's medical record and on the enrollment case report form (CRF).

7.3 Blinding

This is an open-label study; blinding procedures are not applicable.

7.4 Dose Modification

7.4.1 Phase 1b Dose-cohort Study Escalation/De-escalation

7.4.1.1 Dose Level Review Meetings

After all DLT-evaluable subjects within a cohort have completed the 4-week DLT evaluation period, a DLRM will be held to review data, monitor safety, and make dose change decisions. See Appendix 3 for more details on the DLRM.

7.4.1.2 Definition of Dose Limiting Toxicities for Phase 1b

The DLT evaluation period for each subject is 4 weeks from the first dose of efavaleukin alfa. To be evaluable for a DLT subjects must have received at least 2 doses of efavaleukin alfa or have experienced a DLT within the DLT evaluation period. All subjects who experience a DLT will discontinue study therapy and complete safety follow-up. Dose limiting toxicity events will be used to guide dose escalation decisions and to determine the MTD as described in Section 5.1.1.

The following DLT criteria apply only to the phase 1b part of the study:

- Non-hematological toxicity ≥ grade 4 related to efavaleukin alfa. Non-hematological laboratory abnormalities without clinical significance will not be considered DLTs (based upon the investigator's discretion in conjunction with Amgen).
- Hematological toxicity ≥ grade 4 related to efavaleukin alfa defined as decreases in peripheral counts (ANC or platelets) persisting longer than 72 hours, as measured by 2 separate results, that are not related to malignant disease relapse, infection, or other etiologies.
- Constitutional events (ie, fever, fatigue) ≥ grade 3 that are classified as serious adverse events by the investigator and related to efavaleukin alfa.

- Infection: Infection is considered an expected complication of cGVHD and its treatment. cGVHD itself increases the risk of infection, including life-threatening infection. Therefore only grade 4 or 5 infections considered by the investigator to be related to efavaleukin alfa will be reviewed by the DLRM to determine whether the infection is considered a DLT.

Subjects who develop an uncontrolled grade 4 life-threatening infection (eg, sepsis, ARDS), as assessed by the investigator, will discontinue efavaleukin alfa and remain in the study for safety follow-up (see Section 9.1.5).

After completing the 4-week DLT evaluation period, phase 1b subjects will be evaluated by standard safety reporting.

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

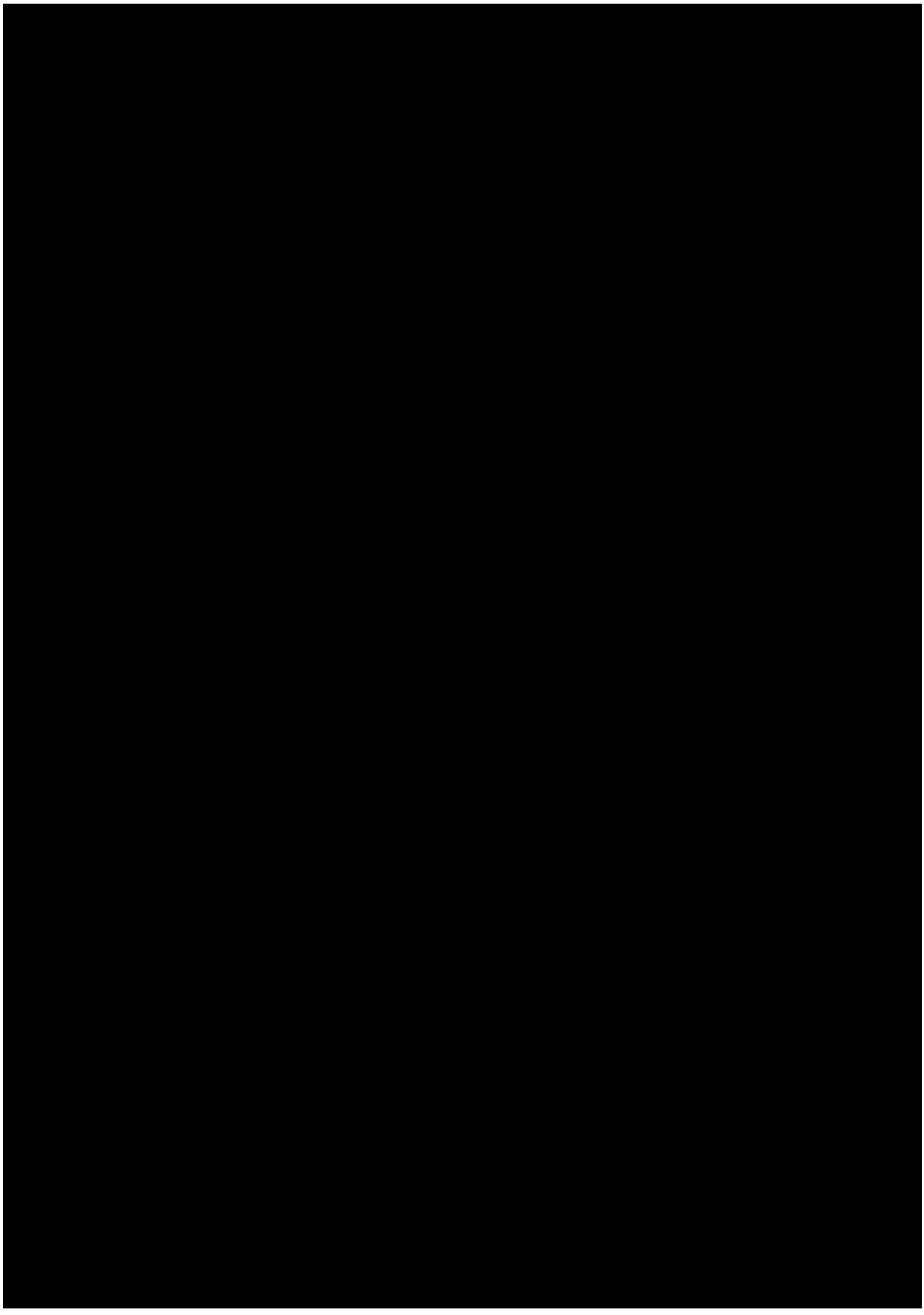
7.4.2.1 Amgen Investigational Product: Efavaleukin Alfa

The reason for dose change of efavaleukin alfa is to be recorded on each subject's CRF.

7.4.2.1.1 Phase 1b

Dose adjustment of efavaleukin alfa for individual subjects is not allowed until the [redacted] is determined. The Medical Monitor should be informed of withholding of efavaleukin alfa for acute clinical events such as acute infection or major surgery. Once the [redacted] dose is determined, all phase 1b subjects may continue study therapy at the [redacted] dose and frequency (at the discretion of the Sponsor, following discussion and agreement between the principal investigator and medical monitor) and will be subject to the dose adjustment guidelines in Section 7.4.2.1.2. A subject experiencing worsening of cGVHD that requires the addition of new immunosuppressive medication(s) at any time during the study or initiation of an increase in systemic corticosteroid dose above baseline after week 4 of the study (at the discretion of the treating investigator) will be deemed a treatment failure. These subjects will discontinue treatment and will have a safety follow-up visit (see Section 9.1.5).

[redacted]



[redacted]

7.4.3 Hepatotoxicity Stopping and Rechallenge Rules

Elevated hepatic laboratory values may be observed in subjects with cGVHD who have hepatic involvement. In the phase 1b part of the study, the Medical Monitor should be consulted regarding management of subjects whose abnormal hepatic laboratory values are, in the opinion of the Investigator, attributable to underlying cGVHD. Subjects in the

[redacted]

7.5 Preparation/Handling/Storage/Accountability

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

7.6 Treatment Compliance

Subjects will receive the SC doses of **efavaleukin alfa** at the research facility administered by qualified study personnel for the duration of the study.

7.7 Treatment of Overdose

The effects of overdose of this product are not known.

7.8 Prior and Concomitant Treatment

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

All other therapies including steroids, other immunosuppressive medications, prophylactic therapies for infections, and other medications considered supportive care for GVHD will not be provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining these therapies.

7.8.1 Prior Treatment

Prior therapies that were being taken from 12 weeks prior to enrollment through the first dose of investigational product should be collected. Collect complete prior therapy history for GVHD. For prior therapies, collect therapy name, indication, dose, unit, frequency, route, start date and if applicable, stop date.

7.8.2 Concomitant Treatment

Concomitant therapies are to be collected from first dose of investigational product through safety follow-up in the source documents and the eCRF.

For all therapies, collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

7.8.2.1 Corticosteroids

7.8.2.2 Other Immunosuppressive Medications

Subjects will continue other systemic immunosuppressive background therapies (eg, tacrolimus, sirolimus, MMF, ECP) concomitantly with efavaleukin alfa. Addition or substitution of systemic immunosuppressive therapies beyond dose adjustments to maintain therapeutic levels will be considered a treatment failure. Dose reductions in background therapy are not allowed in the first 8 weeks of the study but may be reduced thereafter in responders at the discretion of the investigator. Disease flares during immunosuppressant taper will not be counted as GVHD progression or treatment failure if the subject can be managed by return to the baseline immunosuppressant dose. Topical immunosuppressant (ie, mouthwash, eye drops, genitourinary ointments) are allowed at the discretion of the investigator.

7.8.2.3 Prophylaxis for Infection

Prophylaxis for infection, including routine viral bacterial and fungal prophylaxis (ie, Bactrim, acyclovir, azole fungals), will be managed according to institutional guidelines. Antimicrobial treatment including antivirals, antibiotics and antifungals will be left to the discretion of the investigator.

7.8.2.4 Other Allowed Therapies

Supportive medications in accordance with standard practice (such as emesis, diarrhea, red blood cell [RBC] or neutrophil growth factors) are permitted per investigator discretion. Other allowed therapies include medications considered supportive care or prophylactic therapy for cGVHD including but not limited to ursodeoxycholic acid, INH, azithromycin, and montelukast.

8. Discontinuation Criteria

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

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

8.1 Discontinuation of Study Treatment

Subjects can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 2-1, Table 2-2, Table 2-3, Table 2-4, Table 2-5, **Table 2-6**, **Table 2-7**, and **Table 2-8**) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and disease-related events, as applicable and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

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

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

- Decision by Sponsor
- Lost to follow-up
- Death
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Adverse event
- Subject request
- cGVHD progression
- Requirement for alternative therapy
- Protocol-specified reasons as described in Section 7.4.1.2 and Section 7.4.2.1.2
- Pregnancy

8.2 Discontinuation From the Study

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

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

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

Not applicable.

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

8.3 Lost to Follow-up

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

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

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

- For subjects who are lost to follow-up, the investigator can search publicly available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

9. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 2-1, Table 2-2, Table 2-3, Table 2-4, Table 2-5, **Table 2-6**, **Table 2-7**, and **Table 2-8**).

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

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

9.1 General Study Periods

9.1.1 Screening, Enrollment and/or Randomization

The general study assessments and procedures will apply to subjects in both the phase 1b and [redacted] portions of the study.

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

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

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening 2 times in consultation with Amgen medical monitor.

Rescreen subjects must first be registered as screen failures in IVRS/IWRS and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 28-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 28 days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated.

9.1.2 Treatment Period

Visits will occur per the Schedule of Activities (see Table 2-1, Table 2-2, Table 2-3, Table 2-4, Table 2-5, **Table 2-6**, **Table 2-7**, and **Table 2-8**). In the phase 1b part of the study, visits may be completed within a visit window of ± 1 day through the week 4 visit. After the week 4 visit, the visit window may increase to ± 3 days from the scheduled visit date for those phase 1b subjects on Q2W dosing and ± 2 days from the scheduled dose date for those subjects on QW dosing. [redacted]

[redacted]

9.1.3 Progressive Disease Visit

A progressive disease visit should be performed any time during the study, if the investigator suspects progressive disease and the subject is experiencing worsening of cGVHD that requires the addition of new immunosuppressive medication(s) or initiation of an increase in systemic corticosteroid dose above baseline after week 4 of the study. Efavaleukin alfa should be discontinued, followed by an end of treatment visit (see Section 9.1.4) and a safety follow-up visit (see Section 9.1.5).

9.1.4 End of Treatment

Subjects discontinuing treatment prior to week 52 for any reason (see Section 8.1) will be asked to complete an End of Treatment visit within a window of ± 7 days of the next regularly scheduled visit after the last dose of efavaleukin alfa, consisting of all assessments included in the week 52 visit according to the Schedule of Activities (see Table 2-2). If the End of Treatment visit for a subject occurs < 7 days after a progressive

disease visit, then the procedures completed at the End of Treatment visit should only be those NOT performed at the progressive disease visit.

For phase 1b subjects participating in the extended dosing period, subjects discontinuing treatment prior to week **102 or week 103 will be asked to complete the EOET visit within a window of + 7 days of the next regularly scheduled visit after the last dose of efavaleukin alfa, consisting of all assessments included in week 104 visit according to the Schedule of Activities (see Table 2-3). Subjects continuing treatment after week 104 but discontinuing treatment before week 258** (Q2W dosing) or week **259** (QW dosing) will be asked to complete an EOET visit within a window of ± 7 days of the next regularly scheduled visit after the last dose of efavaleukin alfa, consisting of all assessments included in the week **260** visit according to the Schedule of Activities (see **Table 2-6**). If the EOET visit for a subject occurs < 7 days after a progressive disease visit, then the procedures completed at the EOET visit should only be those NOT performed at the progressive disease visit.

9.1.5 Safety Follow-up/End of Study

Upon completion of the treatment period or permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately 6 weeks (± 3 days) after the last dose of efavaleukin alfa as described in the Schedule of Activities (see Table 2-1, Table 2-2, Table 2-3, Table 2-4, Table 2-5, **Table 2-6**, **Table 2-7**, and **Table 2-8**). Women of childbearing potential will be required to complete a pregnancy test at this visit.

9.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points. These assessments apply to subjects in both phase 1b and [redacted] unless otherwise indicated.

9.2.1 General Assessments

9.2.1.1 Informed Consent

All subjects must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed for both the phase 1b and [redacted] portions of the study.

9.2.1.2 Demographics

Demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

Additionally, demographic data will be used to study the impact of biomarker variability and PK of efavaleukin alfa.

9.2.1.3 Medical History

The Investigator or designee will collect complete medical and surgical history within 5 years prior to enrollment. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. In addition to the medical history above, cGVHD history must date back to the original diagnosis. The current severity will be collected for each condition that has not resolved.

9.2.1.4 GVHD Staging Evaluation

The clinician will complete the GVHD Staging Evaluation form at screening to document that study subjects meet the criteria for moderate-to-severe cGVHD per the 2014 cGVHD NIH Consensus Criteria. [redacted] is not required for the Staging Evaluation. Please see Appendix 9 for algorithm for calculation of cGVHD severity.

9.2.1.5 Physical Examination

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

9.2.1.6 Physical Measurements

Height measurement in centimeters without shoes and weight measurement in kilograms and without shoes will be performed at the time points specified in the Schedule of Activities.

9.2.1.7 Substance Abuse History

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

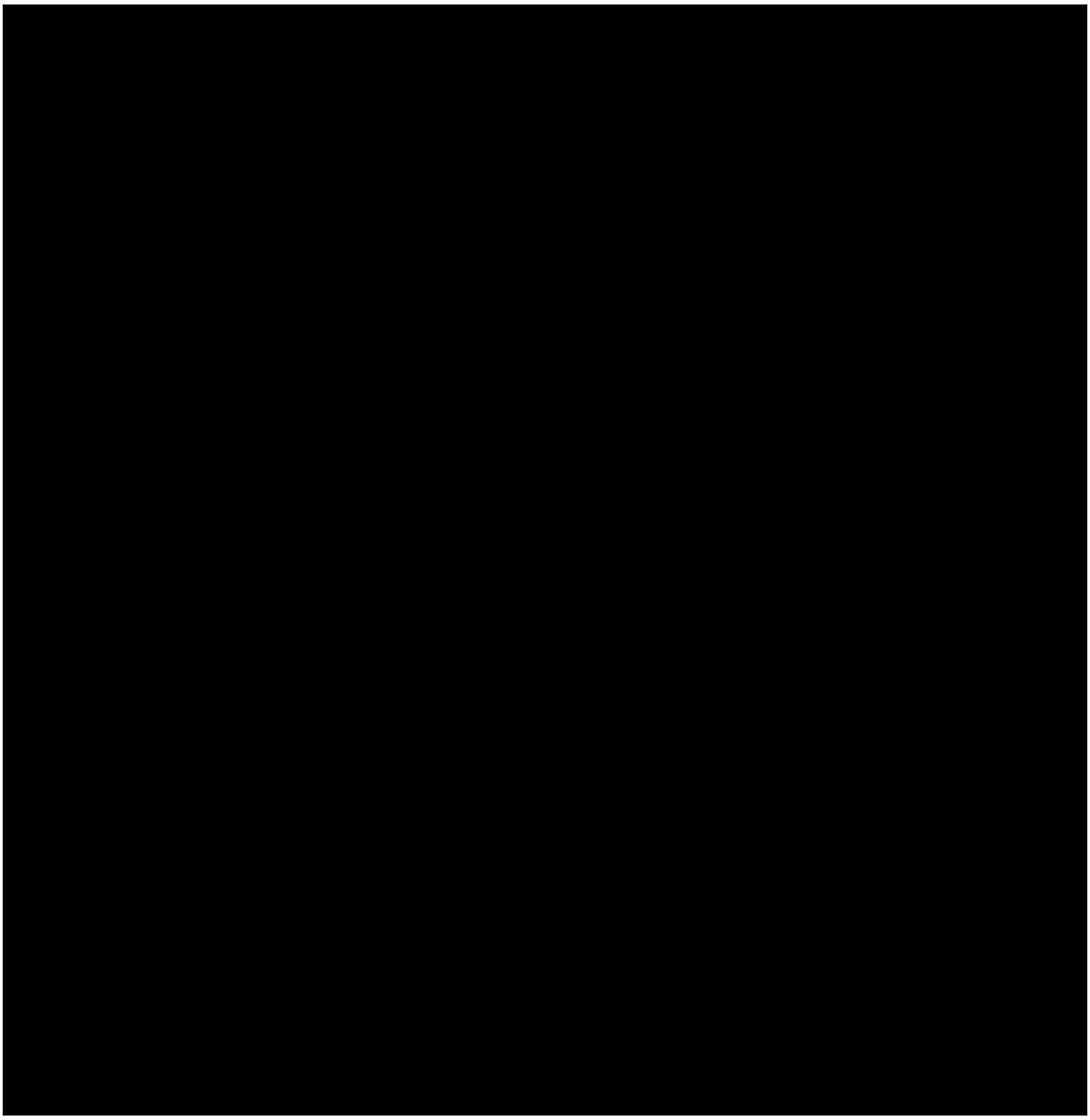
[redacted]

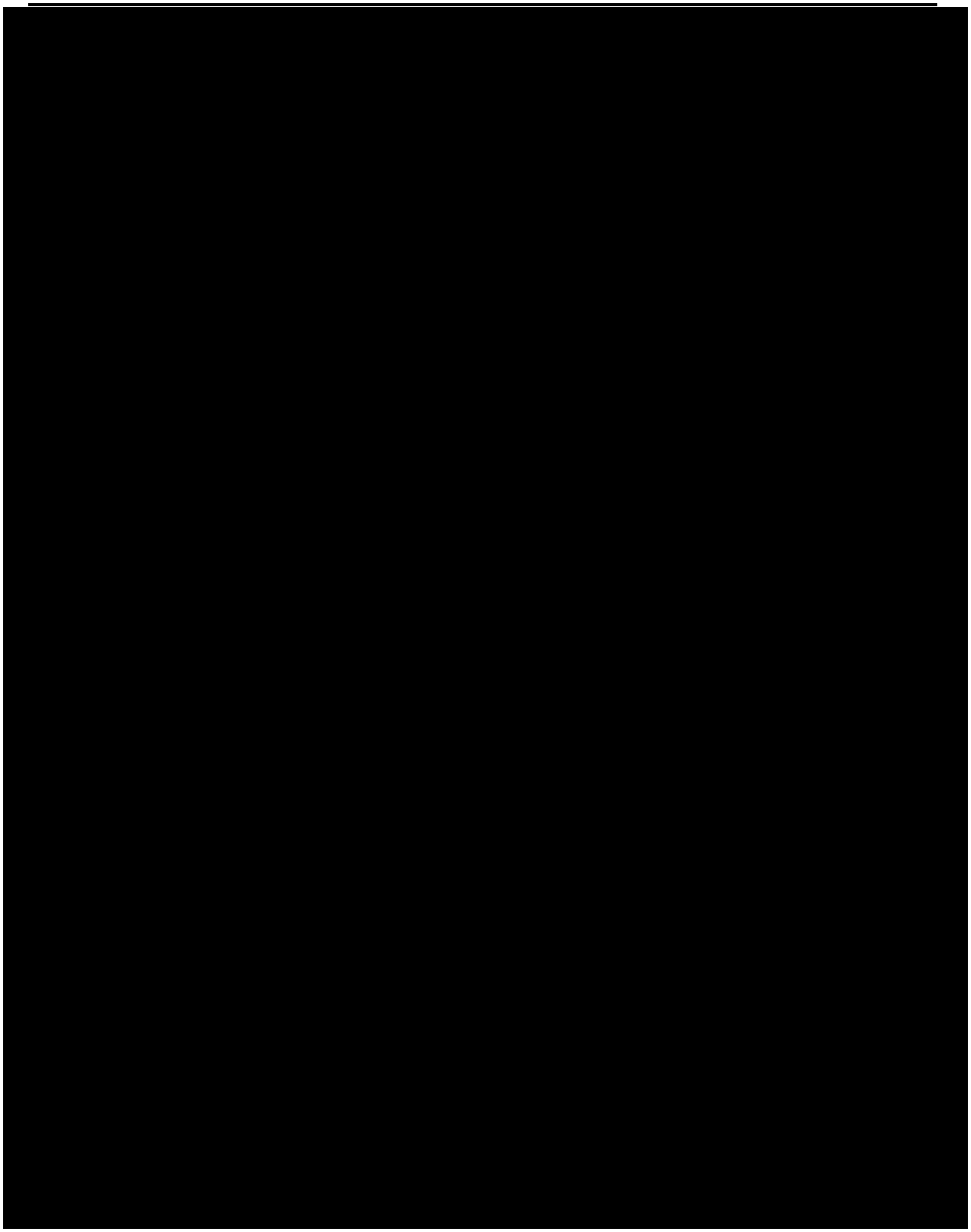
9.2.2 Efficacy Assessments

9.2.2.1 Response Assessment: NIH cGVHD Response Assessment (NIH Form A)

All subjects in the study will have their clinical response assessed using the NIH cGVHD Response assessment (NIH Form A) per the 2014 cGVHD NIH Consensus Criteria

(2014 Response Criteria Working Group; Measurement of Therapeutic Response, ASBMT Web site) in accordance with the Schedule of Activities (see Table 2-1, Table 2-2, Table 2-3, Table 2-4, Table 2-5, **Table 2-6**, **Table 2-7**, and **Table 2-8**). Subjects will undergo repeat detailed assessment of ocular, oral, cutaneous, musculoskeletal, gastrointestinal, hepatic, and pulmonary systems per the [redacted]. Both standard and [redacted] response assessments will be captured on the NIH cGVHD Response Assessment (NIH Form A).





9.2.3 Safety Assessments

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

9.2.3.1 Adverse Events and Serious Adverse Events

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

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

9.2.3.1.1.1 Disease-related Events

Disease-related events are defined in Appendix 4.

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

All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated serious disease-related event data to the sponsor within 24 hours of it being available.

Disease-related events assessed by the investigator to be more severe than expected and/or related to the investigational product(s)/study treatment/protocol-required therapies, and determined to be serious, must be reported on the Event CRF as serious adverse events and recorded and reported per Section 9.2.3.1.1.3 and Appendix 4.

Disease-related events pre-defined for this study are listed in Appendix 11.

9.2.3.1.1.2 Adverse Events

The adverse event grading scale to be used for this study will be the CTCAE version 4.03 and is described in Appendix 4.

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

9.2.3.1.1.3 Serious Adverse Events

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

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

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

9.2.3.1.1.4 Serious Adverse Events After the Protocol-required Reporting Period

If the investigator becomes aware of serious adverse events after the protocol-required reporting period **(as defined in Section 9.2.3.1.1.3) is complete**, these serious adverse events **will** be reported to Amgen **(regardless of causality)**. **The investigator will** report serious adverse events to Amgen within 24 hours following the investigator's **awareness** of the event.

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

If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

9.2.3.1.2 Method of Detecting Adverse Events and Serious Adverse Events

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

9.2.3.1.3 Follow-up of Adverse Events and Serious Adverse Events

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

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records.

Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

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

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

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

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

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

9.2.3.1.5 Pregnancy and Lactation

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

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

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

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

9.2.3.2 Vital Signs

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

9.2.3.3 Electrocardiograms (ECGs)

Single ECGs will be collected at screening and at time points per the Schedule of Activities (see Table 2-1, Table 2-2, Table 2-3, Table 2-4, Table 2-5, **Table 2-6**, **Table 2-7**, and **Table 2-8**).

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

The investigator 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. In certain circumstances Amgen may be able to provide a standard ECG machine if a site is unable to provide one.

9.2.4 Clinical Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (see Table 2-1, Table 2-2, Table 2-3, Table 2-4, Table 2-5, **Table 2-6**, **Table 2-7**, and **Table 2-8**) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. The investigator must determine whether an abnormal value in an individual study subject represents a

clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

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

9.2.4.1 Human Immunodeficiency Virus (HIV) Status

Human immunodeficiency virus antibody titers will be assessed as specified in the Schedule of Activities. The result must be negative and will be documented in the source document but will not be recorded on the eCRF.

9.2.4.2 Hepatitis B and C Status

The following should be followed for the determination of hepatitis B and C status:

- if hepatitis B and/or hepatitis C status is known to be positive by serology no additional laboratory testing procedures are required
- if hepatitis B and/or hepatitis C status is not known to be positive by serology, the following laboratory testing is required:

Hepatitis B surface antigen

- if results are hepatitis B surface antigen positive, no additional testing is necessary

Hepatitis B Core Antibody

- if results are hepatitis B core antibody positive but negative for hepatitis B surface antigen, additional testing is necessary for hepatitis B virus DNA by polymerase chain reaction

Hepatitis C virus antibody

- if results are hepatitis C virus antibody positive, no additional testing is necessary.

9.2.4.3 Tuberculosis Testing

All subjects must receive either a PPD**,** Quantiferon, or T-SPOT test at screening.

9.2.4.3.1 Purified Protein Derivate (PPD)

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

responsibility. PPD test kits will not be provided by the sponsor and must be procured locally.

9.2.4.3.2 Quantiferon or T-SPOT Testing

If a subject does not receive a PPD test they must have Quantiferon or T-SPOT testing per Section 6.2. If testing is performed by central laboratory then refer to the central laboratory manual for instructions on sample collection, processing, and shipping of samples.

9.2.4.3.3 Chest Radiograph

Subjects with a positive PPD test without a history of Bacillus Calmette-Guerin vaccination or subjects with a positive or indeterminate Quantiferon or T-SPOT test will require a chest radiograph including posterior-anterior and lateral views performed within 3 months before the first dose of investigational product. The radiograph report should be read by a radiologist or per local requirement and the report must be reviewed by the investigator before enrollment of the subject.

9.2.4.4 Pregnancy Testing

A high sensitive (serum) pregnancy test should be completed at screening for females of childbearing potential.

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

For women of childbearing potential, additional urine pregnancy testing should be performed at monthly intervals during treatment with efavaleukin alfa and 6 weeks (± 3 days) after the last dose of protocol-required therapies. On visits where required, urine pregnancy tests must be given prior to dosing with investigational product. If a urine pregnancy test is positive, investigational product must be withheld; if pregnancy is confirmed, then investigational product must be discontinued.

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

9.2.4.5 Prespecified Biomarker Assessments

No prespecified biomarkers will be collected.

9.2.5 Pharmacokinetic Assessments

[redacted]

[redacted]

9.2.6 Pharmacodynamic Assessments

Lymphocyte Subsets: Blood samples will be collected for all subjects at the time points indicated in the Schedule of Activities. These samples will be used to evaluate Treg, Tcon, and NK cells. Sampling time points for lymphocyte subsets may be modified based on emerging data.

9.2.7 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of cGVHD and/or to identify subjects who may have positive or negative response to investigational product or protocol-required therapies. No additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted.

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

9.2.8 Antibody Testing Procedures

[redacted]

9.2.9 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to investigational product(s) (eg, Amgen or non-Amgen investigational product or protocol-required therapies.

Blood samples are to be collected for biomarker development at the time points specified in the Schedule of Activities (see Table 2-1, Table 2-2, Table 2-3, Table 2-4, Table 2-5, **Table 2-6**, **Table 2-7**, and **Table 2-8**).

9.2.10 Clinical Outcome Assessments

[redacted]

9.2.11 Other Assessments

9.2.11.1 Peripheral Blood Mononuclear Cell

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

9.2.11.2 Hospitalizations

If a subject is hospitalized anytime during the [redacted]

[redacted]

10. Statistical Considerations

10.1 Sample Size Determination

10.1.1 Phase 1b

Approximately 40 subjects are planned to be enrolled in the phase 1b portion of the study. Approximately 30 subjects will be enrolled in dose escalation cohorts and approximately 10 subjects may be enrolled in optional dose expansion cohort. The total sample size may be higher than 40 subjects if, following a DLRM recommendation, additional dosing cohorts are added and/or existing cohorts are expanded; or if subjects are replaced as per Section 5.2.1. With 40 subjects receiving efavaleukin alfa, there is an 87% chance of detecting an adverse event with a true incidence rate of 5%. Without optional dose expansion cohort (ie, with 30 subjects), the chance of detecting an adverse event with a true incidence rate of 5% reduces to 79%.

[redacted]

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

Phase 1b

- Safety Analysis Set: The safety analysis set is defined as all subjects who have received at least 1 dose of efavaleukin alfa in phase 1b portion of the study. All phase 1b analyses will be conducted on the safety analysis set unless noted otherwise.
- DLT Analysis Set: The analysis of DLT will be restricted to DLT analysis set which consists of DLT-evaluable subjects in the phase 1b portion of the study. The DLT evaluation period for each subject is 4 weeks from the first dose of efavaleukin alfa. To be evaluable for a DLT subjects must have received at least 2 doses of efavaleukin alfa or have experienced a DLT within the DLT evaluation period.

[redacted]

10.2.2 Covariates

No covariates will be used for this study.

10.2.3 Subgroups

Subgroup analyses may be conducted for primary endpoint and selected secondary efficacy endpoints in [redacted] Subgroups may include but are not limited to age, region, cancer type, time from transplant, time from cGVHD diagnosis, cGVHD severity, radiation received (yes/no), and conditioning regimen (myeloablative versus non-myeloablative) as well as [redacted] at baseline and at 1 week.

10.2.4 Handling of Missing and Incomplete Data

Please refer to Section 10.4.2.2 for discussion of missing data imputation.

10.3 Adaptive Design

The adaptive design elements implemented for this study are:

- Bayesian logistic regression model to assist dose escalation in phase 1b

[redacted]

10.4 Statistical Analyses

The SAP will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 5.3.1.

10.4.1 Planned Analyses

10.4.1.1 Interim Analysis and Early Stopping Guidelines

Phase 1b

The interim analysis of the phase 1b part of the study will be performed after the last subject in the phase 1b part completes 16 weeks or early terminates. The objective of this analysis is to review all the available safety, tolerability, and efficacy data and [redacted]. No formal hypothesis testing is planned in this analysis.

[redacted]

10.4.1.3 Final Analysis

A final analysis will be performed after the end of the study, ie, after the last subject in the study completes the study (including the treatment period and the safety follow-up period), or early terminates. All analyses described in Section 10.4.2 based on final study data will be performed at this time.

10.4.2 Methods of Analyses

10.4.2.1 General Considerations

The baseline demographics, disease characteristics, and the exposure to efavaleukin alfa by dose level will be summarized using descriptive statistics. Summary descriptive statistics by dose level will be provided. For categorical endpoints, the descriptive statistics will contain the frequency and percentage. For continuous endpoints, the descriptive statistics will include the number of observations, mean, standard deviation, median, minimum, and maximum.

Statistical testing will be performed with statistical significance level of 0.025 for 1-sided tests, and with 0.05 statistical significance level for 2-sided tests, unless specified otherwise. No multiplicity adjustment will be provided, unless specified otherwise.

10.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	[redacted]
Secondary	

Endpoint	Statistical Analysis Methods
Secondary (continued)	[redacted]
Exploratory	Will be described in the SAP finalized before database lock

10.4.2.3 Safety Analyses

10.4.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	**Phase 1b** The Medical Dictionary for Regulatory Activities (MedDRA version 20.0 or later) will be used to code all adverse events to a system organ class and a preferred term. Data will be summarized as described in the sections below.

10.4.2.3.2 Adverse Events and Disease-related Events

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

10.4.2.3.3 Laboratory Test Results

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

10.4.2.3.4 Vital Signs

The analyses of vital signs will include summary statistics at selected time points, post-baseline maximum/minimum and change from baseline to post-baseline maximum/minimum by dose level.

10.4.2.3.5 Physical Measurements

The analyses of physical measurements will include summary statistics at selected time points and by dose level (phase 1 only).

10.4.2.3.6 Electrocardiogram

The ECG measurements will be performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

10.4.2.3.7 Antibody Formation

[redacted]

10.4.2.3.8 Exposure to Investigational Product

The number of days on investigational product and the total dose of investigational product **by** each dose level will be summarized using descriptive statistics.

10.4.2.3.9 Exposure to Concomitant Medication

Number and proportion of subjects receiving **medications**/therapies of interest will be summarized by preferred term or category as coded by the World Health Organization Drug (WHODRUG) dictionary.

10.4.2.4 Other Analyses

10.4.2.4.1 Pharmacokinetic Analysis

Summary of [redacted] will be provided.

10.4.2.4.2 Pharmacodynamic Analysis

[redacted] at selected time points will be summarized by dose level.

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12. Appendices

Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ADL	activities of daily living
AIHA	autoimmune hemolytic anemia
ALP	alkaline phosphatase
ALT	alanine transaminase
ANA	anti-nuclear antibody
ANC	absolute neutrophil count
ARDS	acute respiratory distress syndrome
AST	aspartate transaminase
ATG	antithymocyte globulin
AUC	area under the concentration-time curve
AUC_{last}	AUC from time 0 to the time of the last quantifiable sample
AUC_{tau}	area under the concentration-time curve over a dosing interval
BIL	bilirubin
BLRM	Bayesian logistic regression model
BOOP	bronchiolitis obliterans organizing pneumonia
BOS	bronchiolitis obliterans syndrome
BSA	body surface area
BTK	Bruton's tyrosine kinase
CBC	complete blood count
CD	cluster of differentiation
CFR	Code of Federal Regulations
cGVHD	chronic graft versus host disease
CIOMS	Council for International Organizations of Medical Sciences
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed concentration
CNS	central nervous system
COA	clinical outcome assessments
CPK	creatine phosphokinase
CVVH	continuous veno-venous hemofiltration
[redacted]	[redacted]
CRF	case report form
CTCAE	common terminology criteria for adverse events
DILI	drug-induced liver injury
D_{LCO} Hb	hemoglobin-adjusted diffusion capacity for carbon monoxide

Abbreviation or Term	Definition/Explanation
DLT	dose limiting toxicity
DLRM	dose level review meeting
DLRT	Dose Level Review Team
DRE	disease related event
ECG	electrocardiogram
ECP	Extra Corporeal Photophoresis
eCRF	electronic case report form
eSAE	electronic Serious Adverse Event
EDC	electronic data capture
End of Study (primary completion)	The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the [redacted] part primary endpoint(s), [redacted]) for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.
End of Study (end of trial)	The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, safety follow-up), as applicable.
EOET	end of extended treatment
EOS	End of Study, defined as the last day that protocol-specified procedures are conducted for an individual subject.
EU	European Union
Fc	fragment, crystallizable
FVC	forced vital capacity
FEV1	forced expiratory volume in 1 second
[redacted]	[redacted]
FIH	first in human
Foxp3	forkhead box P3
FSH	follicle stimulating hormone
GCP	good clinical practice
GI	gastrointestinal
GLP	good laboratory practice
GU	genitourinary
GVHD	graft versus host disease
HCV	Hepatitis C virus
HepCAb	hepatitis C virus ribonucleic acid
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation or Term	Definition/Explanation
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
HSCT	hematopoietic stem cell transplant
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IL-2	interleukin 2
INH	isoniazid
INR	international normalized ratio
Interactive Voice Response System (IVRS)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information
Interactive Web Response System (IWRS)	web based technology that is linked to a central computer in real time as an interface to collect and process information
IP	investigational product
IPIM	Investigational Product Instruction Manual
IQR	interquartile range
IRB	Institutional Review Boards
ITP	idiopathic thrombocytopenic purpura
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LKM1	liver kidney microsomal antibody -1
LOCF	last observation carried forward
LTFU	long term follow-up
MDRD	modification of diet in renal disease
MedDRA	medical dictionary for regulatory activities
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
MMF	mycophenolate mofetil
NASH	nonalcoholic steatohepatitis
NCI	National Cancer Institute
NK cells	natural killer cells
NKT cells	natural killer T cells

Abbreviation or Term	Definition/Explanation
NIH	National Institutes of Health
NOAEL	no observed adverse effect level
NRI	nonresponder imputation
[redacted]	[redacted]
NS	not significant
[redacted]	[redacted]
[redacted]	[redacted]
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamics or progressive disease
PFT	pulmonary function test
PI	principal investigator
PK	pharmacokinetic
PPD	positive purified derivative
POR	proof of receipts
[redacted]	[redacted]
PUVA	psoralen and ultraviolet A
RA	rheumatoid arthritis
RBC	red blood cell
[redacted]	[redacted]
RNA	ribonucleic acid
[redacted]	[redacted]
ROM	range of motion
SAD	single ascending dose
SAP	statistical analysis plan
SC	subcutaneous
[redacted]	[redacted]
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SLE	systemic lupus erythematosus
S/N	signal to noise
SOC	standard of care

Abbreviation or Term	Definition/Explanation
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
SUSAR	suspected unexpected serious adverse reactions
TB	tuberculosis
TBL	total bilirubin
Tcon	conventional T cells
T_{max}	time of maximum observed concentration
TMA	thrombotic microangiopathy
TPI	toxicity probability interval
Teff	T effector cells
Treg	regulatory T cells
QW	every week
Q2W	every 2 weeks
ULN	upper limit of normal
UVB	ultraviolet B

Appendix 2. Clinical Laboratory Tests

All laboratory samples will be processed and sent to the central laboratory with the exception of:

- urine pregnancy
- Quantiferon, which may be done by central or local laboratory
- T-SPOT, which may be done by local laboratory with kits provided by the sites
- PPD – done locally with kits provided by sites per Section 9.2.4.3.1
- Hepatotoxicity monitoring as per Appendix 7

The central laboratory will be responsible for all screening and on-study serum chemistry, hematology, serum pregnancy, hepatitis C antibody, hepatitis B surface antigen and core antibody, and any other laboratory tests required. The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all samples. All blood samples will be obtained by venipuncture before investigational product administration. The date and time of sample collection will be recorded in the source documents at the site.

Specific analytes for serum chemistry, hematology, urinalysis, and other testing to be conducted on blood and urine samples are listed in Table 12-1. **Additional analyte test results may be reported by the local or central laboratory, in accordance with standard laboratory procedures (eg, components of a hematology panel).**

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

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

Table 12-1. Analyte Listing

Central Laboratory				
Chemistry[a]	**Hematology[a]**	**Coagulation[b]**	**Urinalysis[b]**	**Other**
Albumin	Hematocrit	PT	Bilirubin	FSH[d]
ALP	Hemoglobin	aPTT	Blood	Serum pregnancy[b]
ALT	MCH	INR	Glucose	Quantiferon[e]
AST	Platelet count		Ketones	HIV Status
Calcium	MCHC		pH	Hepatitis B surface Antigen
Corrected calcium	MCV		Protein	Hepatitis B core antibody
Bicarbonate	RDW		Specific gravity	Hepatitis C virus antibody
Direct bilirubin	Reticulocytes		Urobilinogen	[redacted]
Total bilirubin	Red blood cells		Microscopic exam (performed at the discretion of the Investigator):	Biomarker development sample
Blood urea nitrogen	White blood cells Differential		• Bacteria	Lymphocyte subsets
Chloride	• Total neutrophils or segmented neutrophils and band cells		• Casts	PBMC
Complete lipid profile[b]	• Eosinophils		• Crystals	Optional pharmacogenetics sample
Creatinine[c]	• Lymphocytes		• Epithelial cells	Urine drug/alcohol
Creatine kinase	• Basophils		• Red blood cells	**Local Laboratory**
GGT	• Monocytes		• White blood cells	Urine pregnancy
Glucose				PPD
Magnesium				T-SPOT
Phosphorus				
Potassium				
Total protein				
Sodium				
Coagulation				

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MDRD = Modification of Diet in Renal Disease; PK = pharmacokinetics; PBMC = peripheral blood mononuclear cell; RDW = red cell distribution width.
[a] The screening chemistry and hematology to be collected after an 8 hour overnight fast.
[b] Only at screening
[c] Glomerular filtration rate will be calculated by MDRD formula
[d] Can be done as a part of the clinical chemistry
[e] Quantiferon testing can be done locally or by the central laboratory

Appendix 3. Study Governance Considerations

Dose Level Review Meetings

After all dose limiting toxicity (DLT)-evaluable subjects within a cohort have completed the 4-week DLT evaluation period, a dose level review meeting (DLRM) will be conducted to review and interpret safety data for the purposes of making recommendations about dose-level changes and evaluating safety signals. In addition, ad hoc DLRMs may be convened by the Medical Monitor at any time for review of emerging safety events.

The required Dose Level Review Team (DLRT) members are the Medical Monitor, Global Safety Officer (GSO), and Site Investigators. Optional non-voting Amgen representatives may also attend as needed at the discretion of the Medical Monitor, including but not limited to representatives from Study management, Biostatistics, Clinical Pharmacology, and Clinical Biomarkers.

For a DLRM to occur, the Medical Monitor must be in attendance and cannot be represented by a voting designee or delegate. Voting designees can be identified as appropriate by the GSO or Site Investigator(s). In addition, a quorum of Site Investigators must attend. A quorum is defined as greater than 50% of the participating investigators or their qualified designee. The DLRM will be rescheduled if these requirements are not met. A Site Investigator may identify a delegate (eg, Sub-investigator) who is listed in the Delegation of Authority. If a delegate attends in place of a Site Investigator, the Site Investigator must provide written agreement with the delegate's vote.

The DLRT members will be responsible for dosing recommendations, which may include escalation to the next planned dose, adding additional cohorts, escalation to an intermediate dose (a dose lower than the next planned dose), de-escalation to a lower dose; continuation, delay, or termination of dosing; or removal, repetition or expansion of a cohort.

All available study data including demographics, investigational product administration, medical history, concomitant medications, adverse events, electrocardiograms (ECGs), vital signs, and laboratory results. All available safety data, including data collected after the DLT evaluation period will be included. Data to be reviewed may be unqueried.

DLRM voting will occur as follows. There will be a total of 3 votes: 1 for the Medical Monitor, 1 for the GSO or delegate, and 1 for all of the Site Investigators or delegates

combined. Regardless of how many Site Investigators there are, all of the Site Investigators combined will have a total of one vote decided by a majority of the investigators (defined as greater than or equal to 50%).

DLRT recommendations to escalate to the next planned cohort, or to an intermediate cohort, must be by unanimous vote. If the DLRT is not able to reach a unanimous recommendation on whether to escalate to the next planned cohort or to an intermediate cohort, then this should be reflected in the DLRM Memo. Other recommendations, such as expanding a cohort or lowering a dose can be made by a majority vote.

The dosing change recommendations will be documented in the DLRM Memo. After receiving the DLRT recommendation, Amgen will render a final decision and will issue a written notification of the dose change decision to study investigators. Amgen retains final decision-making authority on all dose escalation/changes.

Dose Level Determination

The Medical Monitor will determine if a DLRM is necessary based on the cohort status and all available safety data. Recommendations to escalate to a higher dose cohort will only occur when the previous dose regimen(s) has (have) been found to be reasonably tolerated based on available study data through the last subject in a dosing cohort's 4-week DLT evaluation period and upon unanimous agreement of the 3 DLRM votes. Dosing recommendations will be made on a treatment cohort basis (not on an individual basis).

Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Informed Consent Process

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

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

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

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

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

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

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

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

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

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for

exploratory research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

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

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

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

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

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

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

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

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does

not guarantee authorship. The criteria described below are to be met for every publication.

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

Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

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

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

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

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

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

Investigator Signatory Obligations

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

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

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

Data Quality Assurance

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

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

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

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

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

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

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

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Quality, Compliance, and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage

areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

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

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

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

Source Documents

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

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

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

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

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

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including [Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable

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

Study and Site Closure

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

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

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

Compensation

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

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

Definition of Disease-related Event

Disease-related Event Definition

• Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. See Appendix 11 for a list of disease-related events. All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours.
• Disease-related events that would qualify as an adverse event or serious adverse event:
  ○ An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol-required therapies and disease worsening, this must be reported as an adverse event or serious adverse event.
• Disease-related events that do not qualify as adverse events or serious adverse events:
  ○ An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a disease-related event.

Definition of Adverse Event

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

Events Meeting the Adverse Event Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition

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

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
• **Results in death (fatal)**
• **Immediately life-threatening** The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
• **Requires in-patient hospitalization or prolongation of existing hospitalization** In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
• **Results in persistent or significant disability/incapacity** The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
• **Is a congenital anomaly/birth defect**
• **Other medically important serious event** Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

Adverse Event, Disease-related Event (if applicable) and Serious Adverse Event Recording
• When an adverse event, disease-related event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
• The investigator will then record all relevant adverse event/disease-related event/serious adverse event information in the Event case report form (CRF).

- Additionally, the investigator is required to report a fatal disease-related event on the Event CRF.

- The investigator must assign the following adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Did the event start prior to first dose of investigational product;
  - Assessment of seriousness;
  - Severity (or toxicity defined below);
  - Assessment of relatedness to efavaleukin alfa;
  - Action taken; and
  - Outcome of 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.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to the sponsor in lieu of completion of the Event CRF page.
- If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:

The Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 which is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Assessment of Causality

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

Follow-up of Adverse Event and Serious Adverse Event

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

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool

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

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

AMGEN
Study # 20160283
AMG 592

Electronic Serious Adverse Event Contingency Report Form

For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day_____ Month____ Year_____

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

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

		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 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
IP/Amgen Device:								
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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AMGEN
Study # 20160283
AMG 592

Electronic Serious Adverse Event Contingency Report Form

For Restricted Use

Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year)	Test / Unit											
	Test											
	Unit											

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

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AMGEN Study # 20160283 AMG 592	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

Signature of Investigator or Designee -	Title	Date
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.		

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

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

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and after the last dose of protocol-required therapies.

Definition of Females of Childbearing Potential

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

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

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

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

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

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

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

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

Unacceptable Methods of Birth Control for Female Subjects

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

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

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

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

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

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 6 weeks.
- Information will be recorded on the Lactation Notification Worksheet (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 220.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 6 weeks after discontinuing protocol-required therapies.

Figure 12-2. Pregnancy and Lactation Notification Worksheet

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20160283

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm___ / dd___ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm___/dd___/yyyy____

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

If yes, provide product (or study drug) stop date: mm___/dd___/yyyy____

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

5. Pregnancy Information

Pregnant female's LMP mm___ / dd___ / yyyy____ ☐ Unknown

Estimated date of delivery mm___ / dd___ / yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm___ / dd___ / yyyy____

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

If yes, provide date of delivery: mm___ / dd___ / yyyy____

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

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

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

AMGEN® Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: 20160283

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

2. Contact Information

Investigator Name _____ **Site #** _____
Phone (____)_____ **Fax** (____)_____ **Email** _____
Institution _____
Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm____ / dd____/ yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No
If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____
Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No
If No, provide stop date: mm_____/dd_____/yyyy_____
Infant date of birth: mm_____/dd_____/yyyy_____
Infant gender: ☐ Female ☐ Male
Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

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

Form Completed by:
Print Name: _____ **Title:** _____
Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

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Appendix 6. Sample Storage and Destruction

Any blood sample collected according to the Schedule of Activities (see Table 2-1, Table 2-2, Table 2-3, Table 2-4, Table 2-5, **Table 2-6**, **Table 2-7**, and **Table 2-8**) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

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

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

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

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as

appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Appendix 3 for subject confidentiality.

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

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

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

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

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

- GVHD
- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, and parvovirus)
- Protozoal infections (eg, toxoplasmosis, schistosomiasis)
- 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 (NASH)
- Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

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

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

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

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

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

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

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

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

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

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

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

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

Additional Clinical Assessments and Observation

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

Additional laboratory assessments for hepatotoxicity monitoring will be performed locally.

Assessments that are to be performed during this period include:

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

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

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

- Complete blood count (CBC) with differential to assess for eosinophilia
- Serum total immunoglobulin IgG, anti-nuclear antibody (ANA), anti smooth muscle antibody, and liver kidney microsomal antibody -1 (LKM1) to assess for autoimmune hepatitis

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

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

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

Appendix 8. NIH Defined Diagnostic or Distinctive Features of Chronic GVHD

Organ or site	Diagnostic (sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive[a] (Seen in Chronic GVHD, but insufficient Alone to Establish a Diagnosis of Chronic GVHD)	Other Features or Unclassified Entities[b]	Common[c] (Seen with Both Acute and Chronic GVHD)
Skin	Poikiloderma Lichen planus-like features Sclerotic features Morphea-like features Lichen sclerosus-like features	Depigmentation Papulosquamous lesions	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails	-	Dystrophy Longitudinal ridging, splitting, or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric; affects most nails)[b]	-	-
Scalp and body hair	-	New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Loss of body hair Scaling	Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes) Premature gray hair	-
Mouth	Lichen-type features	Xerostomia Mucocele Mucosal atrophy Ulcers Pseudomembranes	-	Gingivitis Mucositis Erythema Pain

Organ or site	Diagnostic (sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive[a] (Seen in Chronic GVHD, but insufficient Alone to Establish a Diagnosis of Chronic GVHD)	Other Features or Unclassified Entities[b]	Common[c] (Seen with Both Acute and Chronic GVHD)
Eyes	-	New onset dry, gritty, or painful eyes Cicatricial conjunctivitis Keratoconjunctivitis sicca Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	-
Genitalia	Lichen planus-like features Lichen sclerosus-like features Females Vaginal scarring or clitoral/labial agglutination Males Phimosis or urethral/meatus scarring or stenosis	Erosions Fissures Ulcers	-	-
GI Tract	Esophageal web Strictures or stenosis in the upper to mid third of the esophagus	-	Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive (infants and children)
Liver	-	-	-	Total bilirubin, alkaline phosphatase > 2 x ULN ALT or AST > 2 x ULN

Organ or site	Diagnostic (sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive[a] (Seen in Chronic GVHD, but insufficient Alone to Establish a Diagnosis of Chronic GVHD)	Other Features or Unclassified Entities[b]	Common[c] (Seen with Both Acute and Chronic GVHD)
Lung	Bronchiolitis obliterans diagnosed with lung biopsy Bronchiolans obliterans syndrome (BOS)[d]	Air trapping and bronchiectasis on chest CT	Cryptogenic organizing pneumonia (COP)[e] Restrictive lung disease[e]	
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to sclerosis	Myositis or polymyositis[f]	Edema Muscle cramps Arthralgia or arthritis	-
Hematopoietic and immune	-	-	Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hyper-gammaglobulinemia Autoantibodies (AIHA and ITP) Raynaud's phenomenon	-
Other	-	-	Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	-

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[a] In all cases, infection, drug effect, malignancy, or other causes must be excluded.
[b] Can be acknowledged as part of the chronic GVHD manifestations if diagnosis is confirmed.
[c] Common refers to shared features by both acute and chronic GVHD.
[d] BOS can be diagnostic for lung chronic GVHD only, if distinctive sign or symptom present in another organ.
[e] Pulmonary entities under investigation or unclassified.
[f] Diagnosis of chronic GVHD requires biopsy.
Source: Jagasia et al, 2015

Appendix 9. NIH Global Severity of cGVHD

Mild chronic GVHD	1 or 2 organs involved with no more than score 1 AND Lung Score 0
Moderate chronic GVHD	3 or more organs involved with no more than score 1 OR At least 1 organ (not lung) with a score of 2 OR Lung score 1
Severe chronic GVHD	At least 1 organ with a score of 3 OR Lung score of 2 or 3

Key Points:

In skin: higher of the 2 scores to be used for calculating global severity.

In lung: FEV1 is used instead of clinical score for calculating global severity

If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.

If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Source: Jagasia et al, 2015

Appendix 11. Disease Related Events Table

Below is a list of common Disease-Related Events. This list is not meant to be comprehensive. All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours.

Organ System	Disease Related Event
Skin	Scleroderma (superficial or fasciitis), lichen planus, vitiligo, scarring alopecia, hyperkeratosis pilaris, contractures from skin immobility, nail bed dysplasia
Mucous membranes	Lichen planus, non-infectious ulcers, corneal erosions/non-infectious conjunctivitis, xerostomia, keroconjunctivitis sicca
GI tract	Esophageal strictures, steatorrhea, anorexia, malabsorption, weight loss, abdominal pain
Liver	None
GU tract	Vaginal stricture, lichen planus
Musculoskeletal /Serosa	Non-septic arthritis, myositis, myasthenia, polyserositis, contractures from joint immobilization
Hematologic	None
Lung	Bronchiolitis obliterans

Amendment 5

Protocol Title: A Phase 1b/2 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Efavaleukin Alfa in Adult Subjects With Steroid Refractory Chronic Graft Versus Host Disease

Amgen Protocol Number efavaleukin alfa 20160283

Amendment Date: 22 June 2021

Rationale:

The rationale for this protocol amendment is:

- To update the phase 1b part of the study to allow for continued access to efavaleukin alfa for up to an additional 156 weeks following week 102 (Q2W dose) or week 103 (QW dose) at the discretion of the Sponsor, following discussion and agreement between the principal investigator and medical monitor, for subjects who are responding to efavaleukin alfa (as assessed by week 104) and who wish to continue on treatment.
- Administrative and editorial updates.

Amendment 4

Protocol Title: A Phase 1b/2 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Efavaleukin Alfa in Adult Subjects With Steroid Refractory Chronic Graft versus Host Disease

Amgen Protocol Number efavaleukin alfa 20160283

Amendment Date: 08 December 2020

Summary of Changes:

- Add cohort 5 ([redacted] µg every 2 weeks) for the purpose of exploring the safety, pharmacokinetics (PK), pharmacodynamics (PD) of higher efavaleukin alfa (AMG 592) doses in patients with steroid refractory chronic graft versus host disease. The highest doses tested to date, [redacted] µg every 2 weeks and [redacted] µg every week, were determined at a dose level review meeting to have acceptable safety in this patient population. The following changes were made:
  - Include description of cohort 5 and enrollment to cohort 5 to study design
  - Remove statement that efavaleukin alfa dose level not to exceed [redacted] µg weekly since this statement is no longer applicable
  - Update study schema phase 1b to include cohort 5
  - Increase the sample size from up to 34 subjects to approximately 40 subjects sample size to reflect the addition of cohort 5
  - Update human exposure and justification for investigational product dose sections (Section 3.2.2.2 and Section 5.4) to support the cohort 5 dose
- Change name of investigational product from AMG 592 to efavaleukin alfa
- Edit a secondary [redacted]
- Consolidate risk assessment section and note that serious hypersensitivity reactions to efavaleukin alfa have been reported
- Remove timing window for National Institutes of Health (NIH) Form A for week 16 footnote since no longer applicable (Table 2-2)
- Add footnote to clarify that the 2 or 6 minute walk test is optional for the NIH Form A assessment to [redacted] schedule of activities
- Update timing windows for immunogenicity and biomarker blood sample collection
- Update visit window for treatment period

- Remove the following assessments from the schedule of activities:

[redacted]

- Update and consolidate clinical experience information
- Updates to maintain consistency regarding criteria for the progressive disease visit
- Add permission for recreational drug use as per country regulations to exclusion criterion 214
- Clarify that the medical monitor is to be informed when efavaleukin alfa is withheld for acute clinical events
- Minor corrections to statistical considerations section to provide additional clarity including:
  - Clarify that improvement of 20% is equivalent to absolute improvement of 20% in the sample size section
  - Include the test used in EAST 6.4 for sample size calculation

[redacted]

  - Establish analyses to be performed as part of the final analysis

[redacted]

  - Move [redacted] from secondary efficacy endpoints to a new section (other analyses)
  - Add summary of subject incidence of events of interest to analyses of adverse events and disease-related events
  - Add post-baseline maximum/minimum and change from baseline to post-baseline maximum/minimum and remove tabulation of shifts in selected vital sign values between baseline and the worst on-study value to analyses of vital signs.
  - Add summary of signal to noise (S/N) ratio for subjects who develop [redacted] to analyses of antibody formation
  - Remove summary of proportion of subjects receiving each dose level (phase 1b only) from the analyses of exposure to investigation product. Remove plan to provide subject-level data instead of the summary if the subject incidence is low or single dose is given to analyses of exposure to investigation product
  - Clarify that concomitant medication will include medications and therapies
  - Editorial updates
- Provide more details for serious adverse event reporting via the electronic data collection tool
- Clarify that the disease-related events table presented in Appendix 11 is not inclusive
- Administrative and editorial updates

Amendment 3

Protocol Title: A Phase 1b/2 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 592 in Adult Subjects With Steroid Refractory Chronic Graft Versus Host Disease

Amgen Protocol Number: AMG 592 20160283

Amendment Date: 26 August 2019

Rationale:

The rationale for this protocol amendment is:

- To update the phase 1b part of the study to allow for continued access to AMG 592 for up to an additional 52 weeks following week 50 (Q2W dose) or week 51 (QW dose) at the discretion of the Sponsor, following discussion and agreement between the principal investigator and medical monitor, for subjects who are responding to AMG 592 (as assessed by week 50) and who wish to continue on treatment.
- To clarify that phase 1b subjects still receiving or planned to receive AMG 592 treatment at the time that the [redacted] is established may change their AMG 592 dose to the [redacted] dose at the discretion of the Sponsor, following discussion and agreement between the principal investigator and medical monitor, and may continue study treatment until completion of the week104/EOT visit.
- To correct inconsistencies in the Schedules of Assessments for the phase 1b part of the study with regard to corticosteroid use, adverse events, serious adverse events, and disease-related events.
- To clarify requirements for recording and reporting disease-related events.

Amendment 2

Protocol Title: A Phase 1b/2 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 592 in Adult Subjects With Steroid Refractory Chronic Graft versus Host Disease

Amgen Protocol Number (AMG 592) 20160283

EudraCT Number: 2017-000763-33

NCT Number: NCT03422627

Amendment Date: 04 December 2018

Rationale:

The main purpose of this protocol amendment is to update the Phase 1b study design in order to provide more robust data. In addition this amendment includes edits that clarify eligibility criteria and study conduct rules, remove restrictions that decrease subject retention, and align the protocol with current Amgen guidelines. The following changes were made:

Changes to Study Design:

- Increased Phase 1b cohort size of future dosing cohorts from n = 3 to up to n = 6 in order to provide more robust PK/PD and safety data for each dose level
- Clarified that dosing cohorts may be added or removed at any time after completion of the first cohorts
- Removed optional cohorts 1b/2b as these do not need to be depicted as optional cohorts may be added at any time in the study as needed
- Added 1a/2a dose expansion cohorts to align with DLRM decision
- Made final dose expansion cohort of n = 10 subjects optional
- Revised study schema to align with Study Design language

Clarification of Entry Criteria and Study Conduct Rules:

- Clarified that for inclusion criterion 105, lines of therapy consisting of concurrent medications or interventions count as 2 separate treatments
- Clarified that inclusion criteria 106 and 107 do not require subjects to be taking corticosteroids or other immunosuppressants at study entry, but do require those subjects who are taking these medications at study entry to be on stable doses

- Clarified that the intent of the urine toxicology screen is to exclude illicit drugs; prescription medications taken under the direction of a physician are not exclusionary
- Clarified that PFTs are strongly preferred as part of the NIH Form A efficacy assessment and are required at the Baseline or Screening visit and in all subsequent NIH Form A assessments for those subjects with abnormal PFTs at baseline, known pulmonary GVHD or new respiratory symptoms.
- Clarified that the 2 (or 6) minute walk test is not required for the NIH Form A assessment
- [redacted] Individual subject dose reduction is not permitted in the Phase 1b part of the study.
- Clarified rules for use of systemic corticosteroids for GVHD flares occurring in the first 4 weeks of study participation
- Specified that Phase 1b subjects who discontinue study participation before receiving fewer than 4 doses (instead of 2) of AMG 592 will be replaced to ensure adequate PK and PD information
- Added T-SPOT to the list of acceptable assays for TB testing to reflect standard of care. Added criteria for inclusion for subjects with an indeterminate Quantiferon or T-SPOT test, given the high prevalence of anergy in this immunosuppressed population

[redacted]

<u>Changes to Improve Subject Retention:</u>

- Revised entry criterion 104, definition of moderate to severe steroid refractory cGVHD:
  - Remove requirement for diagnosis within the past 2 years
  - Remove requirement to be steroid refractory within the past 12 months
- Modified alcohol restrictions after the 4-week DLT evaluation period in eligible subjects
- Increased visit window duration after the week 16 visit
- [redacted] as part of the Staging and NIH Form A evaluations.

<u>Changes to Align with Current Amgen Guidelines:</u>

- Revised Appendix 3 DLRM and Section 5.1.1 Phase 1b study design to align with new Early Development Review Committee Guidelines

Other Miscellaneous Changes:

- [redacted]
- [redacted]
- Changed subject urine drug/alcohol testing, during screening, from the local laboratory to the central laboratory for operational ease
- Changed to 1-sided test with a significance level of 0.025, which was a request from the IRB of the lead PI site

Amendment 1

Protocol Title: A Phase 1b/2 Open-label Study Evaluating the Safety, Tolerability, pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 592 in Adult Subjects with Steroid Refractory Chronic Graft versus Host Disease

Amgen Protocol Number AMG 592 20160283

Amendment Date: 22 August 2017

Rationale:

The changes to this protocol include the following:

- Administrative, typographical, abbreviation clarifications and formatting changes were made throughout the protocol. The template was updated to match the new Amgen template Version 15.2; 14 April 2017.
- Key Sponsor Contact and supporting information was updated to [redacted], MD.
- The primary objective for the phase 1b portion of the study was updated to clarify the intent to use the phase 1 data to determine the maximum tolerated dose and support the determination of the [redacted]
- Due to nonclinical safety findings the maximum dose to be administered in the study has been changed to [redacted] µg administered every other week (Q2W). Information associated with the steady state exposures and corresponding safety exposure margins have been updated to include the [redacted] µg Q2W dose. The [redacted] µg Q2W dose is predicted to achieve similar Treg expansion as seen in chronic GVHD (cGVHD) subjects treated with low-dose IL-2 at 12 weeks while still maintaining adequate safety margins relative to the no adverse effect level in the 3-month toxicology study in cynomolgus monkeys.
- To accommodate the change in formulation, the information regarding product packaging has been updated to indicate that AMG 592 is a liquid formulation that will be provide in glass vials. In addition to the abdomen, administration of AMG 592 was updated to include the upper arm and thigh as sites for the SC injection. In addition, observation following study drug administration was updated to indicate that the subject will remain for at least 1 hour following the first and second dose of AMG 592 followed by 30 minutes for all remaining doses.

[redacted]

- A GVHD Staging procedure was added to the screening visit in the Schedule of Activities to clarify the procedures required for determining potential subject eligibility to participate in the study. The inclusion criteria were updated to clarify that based on this assessment, subjects had moderate to severe cGVHD present at both the screening along with the diagnostic history. The continued presence of symptoms at the baseline visit were also included.
- Information was added to clarify those procedures which are specific for phase 1b or [redacted] Including the reduction in the duration of time where immunosuppressive background therapy dose reductions are not permitted from 16 weeks to 8 weeks.

[redacted]

- Clarifying language was added regarding the eligibility and continued participation of subjects with elevations in liver function tests and abnormalities in pulmonary function associated with cGVHD. In addition, the assessment of drug induced liver injury (DILI) was clarified to indicate that DILI would be assessed by the PI to determine if the abnormality was related to cGVHD or should be evaluated as a potential DILI event. The evaluation of DILI was also clarified to indicate that associated testing may be performed by the local laboratory.
- Removed eligibility exception for elevated total bilirubin for subjects with Gilbert's Syndrome.
- Pharmacokinetics will be determined using serum samples rather than plasma samples.
- Subgroup analyses were updated to include prior radiation status and conditioning regimen (myeloablative versus non-myeloablative).
- The NIH defined diagnostic or distinctive features of cGVHD and the NIH Global Severity were updated to match the 2014 criteria.
- For consistency throughout the protocol, the current Common Terminology Criteria for Adverse Events (CTCAE) grades are presented without associated laboratory values.
- Updates for the timing of assessments in both phase 1b and [redacted] were included to ensure the alignment of the collection of appropriate efficacy and safety data.
- The Safety Follow-Up Visit was updated to require in-clinic assessment of the subjects rather than a phone call assessment. Urine pregnancy testing was also added for women of childbearing potential to confirm pregnancy status up to 6 weeks posttreatment.