Ponesimod / ACT-128800

Chronic Graft versus Host Disease

Protocol AC-058C202

A Phase 2, open-label, single-arm, intra-subject dose-escalation study to investigate the biological activity, safety, tolerability, and pharmacokinetics of ponesimod in subjects with symptomatic moderate or severe chronic GVHD inadequately responding to first or second line therapy

Study Phase:	2
NCT Number:	**NCT02461134**
Date:	5 July 2016
Version and History:	Final Version 4
	Amendment 2, Final Version 3, 21 May 2015
	Amendment 1, Final Version 2, 28 January 2015
	Final Version 1, 16 December 2014

SPONSOR CONTACT DETAILS

SPONSOR	ACTELION Pharmaceuticals Ltd Gewerbestrasse 16 CH-4123 Allschwil Switzerland
Clinical Trial Physician	Daniele D'Ambrosio, MD, PhD ☎ [redacted] Fax e-mail [redacted]
MEDICAL HOTLINE Toll phone number:	☎ 1 (800) 540-5687 (USA) ☎ + 41 61 227 05 63 (Switzerland)

Site-specific toll telephone numbers and toll-free numbers for the Medical Hotline can be found in the Investigator Site File.

ACTELION CONTRIBUTORS TO THE PROTOCOL

Clinical Trial Scientist	[redacted]
Clinical Science Program Head	Daniele D'Ambrosio, MD, PhD
Clinical Trial Statistician	[redacted]
Clinical Project Statistician	[redacted]
Drug Safety Physician	[redacted]

NATIONAL PRIMARY INVESTIGATORS

[redacted]	[redacted]
[redacted]	National Institutes of Health

CONTRACT RESEARCH ORGANIZATIONS INFORMATION

CENTRAL LABORATORY	[redacted]
CENTRAL ENROLLMENT	[redacted]

A list of site-specific contact details for CROs can be found in the Investigator Site File.

SIGNATURE PAGE FOR ACTELION PHARMACEUTICALS LTD

Hereinafter called Actelion

Treatment name / number

Ponesimod / ACT-128800

Indication

Chronic graft versus host disease

Protocol number, study title

AC-058C202, A Phase 2, open-label, single-arm, intra-subject dose-escalation study to investigate the biological activity, safety, tolerability, and pharmacokinetics of ponesimod in subjects with symptomatic moderate or severe chronic GVHD inadequately responding to first or second line therapy

I approve the design of this study.

	NAME (TITLE)	DATE	SIGNATURE
Clinical Trial Physician	Daniele D'Ambrosio, MD, PhD	06 JUL 2016	[redacted]
Trial Statistician	[redacted]	6-Jul-2016	[redacted]

INVESTIGATOR SIGNATURE PAGE

Treatment name / number

Ponesimod / ACT-128800

Indication

Chronic graft versus host disease

Protocol number, study title

AC-058C202, A Phase 2, open-label, single-arm, intra-subject dose-escalation study to investigate the biological activity, safety, tolerability, and pharmacokinetics of ponesimod in subjects with symptomatic moderate or severe chronic GVHD inadequately responding to first or second line therapy

I agree to the terms and conditions relating to this study as defined in this protocol, the electronic Case Report Form (CRF), and any other protocol-related documents. I fully understand that any changes instituted by the investigator(s) without previous agreement with the sponsor would constitute a protocol deviation, including any ancillary studies or procedures performed on study subjects (other than those procedures necessary for the wellbeing of the subjects).

I agree to conduct this study in accordance with the Declaration of Helsinki principles, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws. I will obtain approval by an Institutional Review Board or Independent Ethics Committee (IRB/IEC) prior to study start and signed informed consent from all subjects included in this study. If an amendment to the protocol is necessary, I will obtain approval by an IRB/IEC and ensure approval by regulatory authorities (if applicable) have been obtained before the implementation of changes described in the amendment. I will allow direct access to source documents and study facilities to sponsor representative(s), particularly monitor(s) and auditor(s), and agree to inspection by regulatory authorities or IRB/IEC representative. I will ensure that the study treatment(s) supplied by the sponsor are being used only as described in this protocol. I confirm herewith that the sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to Health Authorities worldwide.

	Country	Site number	Town	Date	Signature
Site Principal Investigator					

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND ACRONYMS

ADL	Activities of daily living
AE	Adverse event
ALC	Absolute lymphocyte count
ALG	Anti-lymphocyte globulin
ALT	Alanine aminotransferase
ARR	Annualized relapse rate
AST	Aspartate aminotransferase
ATG	Anti-thymocyte globulin
ATS	American Thoracic Society
AV	Atrioventricular
BOS	Bronchiolitis obliterans syndrome
BP	Blood pressure
bpm	Beats per minute
BSA	Body surface area
CDC	The Centers for Disease Control and Prevention
CI	Confidence interval
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
COPD	Chronic obstructive pulmonary disease
CRO	Contract research organization
CsA	Cyclosporine
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
C_{trough}	Trough concentrations
CXR	Chest X-ray
DBO	Diastolic blood pressure
DDI	Drug-drug interaction
DL_{CO}	Diffusing capacity of lung for carbon monoxide
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EOS	End-of-Study
EOT	End-of-Treatment
ERS	European Respiratory Society
ES	Extension set
EVL	Everolimus
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEF	Forced expiratory flow
FEV_1	Forced expiratory volume in 1 second
FFS	Failure-free survival
FU	Follow-up
FVC	Forced vital capacity
GCP	Good Clinical Practice
GI	Gastrointestinal
GVHD	Graft versus host disease
Hb	Hemoglobin
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HR	Heart rate
HSCT	Hematopoietic stem cell transplantation
i.v.	Intravenous(ly)
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive response technology
IS	Immunosuppressant

ISF	Investigator site file
KCS	Keratoconjunctivitis sicca
kg	Kilogram
KPS	Karnofsky Performance Score
LOCF	Last observation carried forward
LSS	Lee Symptom Scale
MCP-Mod	Multiple Comparison Procedure – Modeling
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MMF	Mycophenolate mofetil
MMP-1	Matrix metalloproteinase-1
MOC	Methods of contraception
MPS	Mycophenolate sodium
mRNA	Messenger RNA
MS	Multiple sclerosis
MTX	Methotrexate
NIH	National Institutes of Health
NK	Natural killer
NRM	Non-relapse mortality
NYHA	New York Heart Association
o.d.	Once daily
OCT	Optical coherence tomography
OSB	Ophthalmology Safety Board
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamic
PDS	Pharmacodynamic analysis set
PFT	Pulmonary function test
PK	Pharmacokinetic
PKS	Pharmacokinetic analysis set
PML	Progressive multifocal leukoencephalopathy
PPS	Per-protocol Set

P-ROM	Photographic range of motion scale
PTEN	Phosphatase and tensin homolog
QTcB	QT corrected for heart rate on the basis of Bazett's formula
QTcF	QT corrected for heart rate on the basis of Fridericia's formula
ROM	Range of motion
RRMS	Relapsing remitting multiple sclerosis
S1P	Sphingosine 1-phosphate
$S1P_1$	Sphingosine 1-phosphate receptor 1
SAE	Serious adverse event
SAF	Safety Set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SIV	Site initiation visit
SMC	Study Monitoring Committee
SOC	System organ class
SOP	Standard operating procedure
SRL	Sirolimus
STD	Standard deviation
TAC	Tacrolimus
TB	Tuberculosis
TBL	Total bilirubin
ULN	Upper limit of the normal range
WBC	White blood cell
WOCBP	Women of child-bearing potential

SUBSTANTIAL GLOBAL AMENDMENT 3

Amendment rationale

This amendment rationale applies to global protocol AC-058C202 Version 3 dated 21 May 2015. The resulting amended global protocol is Version 4 dated 5 July 2016.

The main reason for this amendment is to improve the AC-058C202 study eligibility criteria to recruit subjects who are more representative of the chronic graft versus host disease (GVHD) population in the real world. To accomplish this, while still ensuring safety of subjects included in the study, the eligibility criteria based on pulmonary function test results (i.e., spirometry and diffusing capacity of lung for carbon monoxide [DL_{CO}]) have been changed, and the peripheral blood absolute lymphocyte count (ALC) eligibility threshold has been lowered. The exclusion criterion based on 1-s forced expiratory volume (FEV_1) has been modified to exclude subjects with predicted normal value < 60% rather than < 75%, and exclusion criteria based on forced vital capacity (FVC) and DL_{CO} results have been removed. The exclusion criterion based on ALC has been modified to exclude subjects with $< 0.5 \times 10^9$ cells/L rather than $< 0.8 \times 10^9$ cells/L. In line with these changes in eligibility criteria, adjustments were made to the guidance and criteria for interruption of study treatment in case of decreases in FEV_1, FVC, or ALC occurring during treatment.

The following rationale is provided to support these changes.

Rationale for lowering ALC exclusion threshold to $< 0.5 \times 10^9$ cells/L and ALC threshold for treatment interruption to $< 0.1 \times 10^9$ cells/L

Immune reconstitution is essential for the success of an allogeneic hematopoietic stem cell transplantation (HSCT), and a surrogate marker for immune reconstitution is ALC recovery. However, the rate of ALC recovery varies in allogeneic HSCT recipients and many patients will have low ALC several months after HSCT. Patients with chronic GVHD can be as early as 3–4 months after HSCT and they may receive multiple immunosuppressive treatments which may further decrease ALC. Although the presence of very low levels of ALC post-HSCT is associated with poor long-term outcomes [Kim 2015], subjects with ALC $> 0.5 \times 10^9$ cells/L do not show a significant increase in non-relapse mortality (NRM) [Yamamoto 2014].

Ponesimod is a selective and reversible sphingosine 1-phosphate receptor 1 ($S1P_1$) modulator which causes a marked and sustained blood lymphocyte count reduction. This is a well described pharmacological effect of $S1P_1$ modulators due to reversible inhibition of T and B lymphocyte egress from lymphoid organs [Brinkmann 2010]. In healthy subjects and patients with psoriasis or multiple sclerosis (MS), ponesimod has shown a clear dose dependent decrease of lymphocyte count with a mean decrease of approximately 30%, 50%, 65% from baseline with 5, 10, or 20 mg, respectively [Ponesimod IB]. Based

on these data, treatment of chronic GVHD patients with pre-existing low ALC (e.g., < 0.8 ≥ 0.5×10^9 cells/L) with 20 mg ponesimod may result in decreased ALC < 0.2×10^9 cells/L. However, such decrease will be the result of a targeted and reversible sequestration of discrete subsets of T and B cells in lymphoid organs.

In Phase 2 studies in MS and psoriasis patients, the overall rate of infections did not increase with ponesimod as compared to placebo, despite lymphocyte counts decreased < 0.5×10^9 cells/L in many subjects receiving placebo. Several studies with the non-selective S1P receptor modulator fingolimod as well as ponesimod have shown a predominant effect on naïve T cells and central memory CD4+ T cells with sparing of effector T cells [Mehling 2011, D'Ambrosio 2015]. Effector T cells, particularly CD8+, are thought to play a pivotal role in controlling viral infections. Preservation of effector T cell function may help to maintain control of viral replication and prevent the outbreak of infection.

Despite sequestration of T and B lymphocytes, available data in MS patients treated with the non-selective S1P receptor modulator fingolimod indicate no association between lymphocyte count reduction and the risk of infections as well as preserved antibody response to non-live vaccines [Francis 2014, Kappos 2015]. In the initial clinical studies with fingolimod, treatment was to be interrupted when lymphocyte counts were < 0.1×10^9 cells/L but later this threshold was increased to < 0.2×10^9 cells/L. As a consequence, lymphocyte counts < 0.2×10^9 cells/L have been observed in a substantial number of MS patients treated with fingolimod and in these patients the rate of infections did not appear higher than in patients treated with placebo [Francis 2014].

Importantly, and differently from fingolimod, lymphocyte count reduction by ponesimod is rapidly established, stable on treatment, and rapidly reversible after treatment discontinuation (within 1 week). Thus, in case of a clinically significant lymphopenia (e.g., ALC < 0.1×10^9 cells/L) or infection, ponesimod treatment may be interrupted and lymphocyte counts can be expected to return to the pre-treatment range within a few days, thus rapidly restoring the immune system function.

It is also relevant to emphasize that in this open label study ALC values will always be visible to the investigator, together with absolute and differential white cell counts, and the protocol allows treatment interruption at any time if this is considered in the best interest of the patient at the discretion of the investigator.

Taken together, these data justify lowering the ALC threshold for inclusion of subjects to < 0.5×10^9 cells/L from < 0.8×10^9 cells/L and also lowering the ALC threshold for interruption of ponesimod treatment to < 0.1×10^9 cells/L from < 0.2×10^9 cells/L, as these changes are expected to improve the external validity of the study without significantly increasing the risk for patients.

Rationale for changes to pulmonary function test exclusion criteria and for changes to the criteria for treatment interruption following bronchodilator challenge.

A number of pulmonary complications can occur after an allogeneic HSCT, including infection, neoplasia, pulmonary edema, peri-engraftment respiratory distress syndrome, idiopathic pneumonia and diffuse alveolar hemorrhage. Additionally, recipients of allogeneic HSCT patients who develop chronic GVHD may develop the bronchiolitis obliterans syndrome (BOS), sclerosis of the chest wall, myositis, and muscle weakness. As a result of these complications pulmonary function test (PFT) abnormalities with obstruction, restriction, or diffusion impairment are common in patients with chronic GVHD.

BOS is a serious irreversible obstruction, that does not respond to bronchodilators and is diagnosed by a decline in FEV_1 and FEV_1/FVC ratio < 0.7, and is associated with poor prognosis of chronic GVHD [Jagasia 2015]. Long-term observational data from 6-month survivors of allogeneic HSCT showed that obstruction, but not restriction or diffusion impairment, is associated with a significant increased mortality [Marras 2004].

Although a patient may experience a diffusion impairment (measured by a decline in DL_{CO}) after HSCT, BOS does not directly affect DL_{CO} values and restrictive changes are not characteristics of this manifestation. In 2015, the National Institutes of Health (NIH) Chronic GVHD Consensus Response Criteria Working Group removed DL_{CO} as an organ response measure for lung chronic GVHD. The working group recommends measuring changes in FEV_1 and pulmonary symptoms only as response measures for clinical trials in chronic GVHD [Lee 2015].

Bronchial obstruction has been observed with the non-selective S1P receptor modulator fingolimod, which has been approved for the treatment of MS since 2010 [Francis 2010]. There are no contraindications to the use of fingolimod in patients with lung disease or pulmonary function abnormalities. After treatment of several thousand patients for several years, no specific safety signals have been detected with fingolimod and the clinical relevance of pulmonary function changes remains unclear.

Similarly to fingolimod, ponesimod increases expiratory airflow resistance in a dose-dependent and reversible fashion. In MS patients, treatment with ponesimod 20 mg once daily (o.d.) induced a mean decrease of FEV_1 of approximately 6% while the mean decrease of FVC was less than 3%. These changes in pulmonary function were rapidly established, stable on treatment, and rapidly reversible (within 1 week) following treatment discontinuation and could also be reversed by administration of a short-acting β2 agonist. In animal studies with ponesimod, there were no indications of irreversible structural or smooth muscle pulmonary changes. Furthermore, data from an ongoing, long-term extension of the Phase 2 study in MS patients suggests that the decrease in FEV_1 is

largely stable and remains reversible after several years of treatment with ponesimod [Actelion data on file].

Chronic GVHD patients with BOS are excluded from this study as the potential effect of ponesimod on this GVHD manifestation is unknown and both the disease and the drug may have an additive effect on the obstructive deficit.

However, based on the above considerations, exclusion of subjects based on pre-existing low values of DL_{CO} or FVC is not justified as this leads to the exclusion of a substantial number of patients with a restriction deficit or diffusion impairment who may actually benefit from ponesimod treatment with no increased risk. Similarly, decreasing the FEV_1 exclusion threshold from 75% to 60% of the normal predicted value while maintaining the exclusion for subjects with FEV_1/FVC ratio < 0.7 will allow enrollment of subjects with restriction deficit but will exclude those with obstruction who may be more at risk.

As for the change made to the exclusion threshold based on ALC, the changes made to the pulmonary function exclusion criteria will improve external validity of this trial.

It is important to emphasize that spirometry and DL_{CO} are assessed frequently during the study with a significant effort to increase accuracy of the measurements. Spirometry test results are used to guide subject's management. Bronchodilator challenge and interruption of ponesimod treatment will continue to be performed whenever a relevant % decrease in normal predicted FEV_1 and FEV_1/FVC ratio are observed. However, the protocol-defined criteria that mandate bronchodilator challenge and ponesimod treatment interruption will be modified to reflect the change made in the inclusion criterion for FEV_1 (60% of the normal predictive FEV_1 value rather than 75%) and to still ensure that reversible obstructive changes, which may occur with ponesimod, are distinguished from the irreversible obstructive changes of BOS. These modifications to the protocol will continue to ensure early diagnosis of BOS and decreased risk of potential toxicity with ponesimod.

Rationale for additional changes to the protocol

Additional changes have been made to make the protocol less burdensome for subjects and investigators. These include allowing a serum pregnancy test prior to enrollment to confirm the first negative serum pregnancy test, reducing the washout duration for extracorporeal photopheresis (ECP), removing restrictions on topical immunosuppressant therapies, and removing the use of a central spirometry vendor.

A second serum pregnancy test may be performed at least 7 days after the Visit 1 test to confirm the negative pregnancy test result. The 3 week period required between the Visit 1 (screening) serum pregnancy test and the Visit 2 (Day 1) urine pregnancy test may be considered too long for women of child-bearing potential requiring a change in chronic

GVHD therapy. The subject may be enrolled as soon as the second serum pregnancy test negative results are available.

The washout duration following ECP has been reduced from 30 days to 15 days. For chronic GVHD patients ECP is typically performed every two weeks until a partial response is achieved and then the treatment schedule may become less frequent [Dignan 2014]. Eligible subjects for this study are likely to be on a two week treatment schedule. Additionally, the active agent in ECP, 8-MOP, has a half-life less than 4 hours following cross-linking. Consequently, the washout period of 15 days is sufficient for ECP and is a convenient duration for eligible subjects to switch from ECP to a new therapy.

The main objective of this study is to evaluate the safety, tolerability, and pharmacodynamic effect of ponesimod in patients with chronic GVHD. For the allowed concomitant topical calcineurin inhibitors (CNIs) and glucocorticoids, starting or increasing the dose will no longer be prohibited, but the protocol will recommend against changes in dose. Topical treatments have generally limited systemic immunosuppressive effects and it is often difficult to control the dose and application area of a topical treatment on a day-to-day basis. Therefore, it is reasonable to recommend no change rather than prohibit any change to concomitant topical CNIs/glucocorticoids in an effort to limit the confounding effects of these treatments.

The central spirometry vendor will no longer be required for this protocol. Spirometry and DL_{CO} testing can be performed using the equipment at the site's pulmonary function facility. Typically, both spirometry and DL_{CO} can be accomplished with a single PFT maneuver. Therefore, removing the central spirometry vendor reduces the burden of assessments for the subject by combining the spirometry and DL_{CO} assessments where appropriate equipment is available.

Other changes to the protocol include minor edits, corrections of typos, and clarifications including the responder definition in Section 6.3.3.

Changes to the protocol

Two versions of the amended protocol will be prepared: 1) a clean version and 2) a Word comparison document, showing deletions and insertions in comparison to the previous protocol version.

Amended protocol sections

The main sections of the protocol affected by this amendment are listed below. Where applicable, the same changes have also been made to the corresponding sections of the protocol synopsis:

4.4 Exclusion Criteria

5.1.10 Specific dose-reduction, interruption, or premature discontinuation criteria

5.2.2 Modifications to IS treatments

7.3.3 Spirometry

7.3.4 DL_{CO}

Summary of previous amendments

Amendment	Date	Main reason(s)
1	28 January 2015	The main reason for this amendment was to update the protocol according to feedback from the FDA.
2	21 May 2015	The main reason for this amendment was to add to the protocol: a longer safety follow-up period; an extension treatment period; and a second safety follow-up period. Subjects completing 24 weeks of ponesimod treatment will have the option to be treated with ponesimod for an additional 96 weeks, should they meet additional eligibility criteria. The protocol has been updated to refer to the initial 24 weeks of treatment as the "Core Treatment Period" with the addition of the "Extension Treatment Period."

PROTOCOL SYNOPSIS AC-058C202

TITLE	A Phase 2, open-label, single-arm, intra-subject dose-escalation study to investigate the biological activity, safety, tolerability, and pharmacokinetics of ponesimod in subjects with symptomatic moderate or severe chronic GVHD inadequately responding to first or second line therapy
OBJECTIVES	**Main objectives** • To investigate the dose response in peripheral absolute lymphocyte count reduction with ponesimod in subjects with chronic graft versus host disease (GVHD) • To investigate the safety and tolerability of ponesimod in subjects with chronic GVHD **Exploratory objectives** • To investigate the efficacy of ponesimod in subjects with chronic GVHD
DESIGN	Prospective, multi-center, open label, single-arm, intra-subject, dose-escalation Phase 2 study.
PERIODS	**Screening period** • This period lasts up to 30 days prior to the day final eligibility is established and includes the screening visit and all baseline assessments. **Core Treatment Period** • The Core Treatment Period starts at the time of first intake of study drug, and continues until the end of treatment at Week 24. • Visits during the Core Treatment Period consists of an enrollment visit (Day 1) and visits at Weeks 4, 8, 12, 16, 20, and 24. • The End-of-Treatment 1 (EOT1) visit takes place at Week 24, or earlier in case of premature discontinuation of study drug. In all cases, the EOT1 visit should take place not later than 7 days after the last dose of study drug. • All subjects will be treated according to local standard of care at investigator's discretion after EOT1. **Core Safety Follow-up Period 1**

	• All subjects will enter the core safety follow-up period after EOT1. • The follow-up period for subjects who were prematurely discontinued lasts for 30 days after the last dose of study drug and ends with the 30-day follow-up 1 (FU1) visit, which is also the End-of-Study (EOS) visit. • The follow-up period for subjects who were not prematurely discontinued lasts for 90 days after the last dose of study drug, and consists of the 30-day FU1 site visit and the 90-day follow-up 2 (FU2) visit, which is also the EOS visit. FU1 and FU2 are cancelled if the subject enrolls in Extension Treatment and visit EX-1 (Extension visit 1) occurs the day of or prior to the scheduled FU1 visit. FU2 is cancelled if the subject enrolls in Extension Treatment and visit EX-1 occurs the day of or prior to the scheduled FU2 visit. **Extension Treatment Period** • Subjects who were not prematurely discontinued from the Core Treatment Period, and whose chronic GVHD was assessed by National Institutes of Health (NIH) response criteria to have progressed versus EOT1 disease activity, may be restarted on study drug and enter the Extension Treatment Period. The assessment of progression and the re-initiation of ponesimod must both occur at least 7 days after EOT1 and no later than 90 days after EOT1. (Note: subjects must not have been started on immunosuppressant (IS) therapy other than agents used during the Core Treatment Period). • The Extension Treatment Period starts the day ponesimod is restarted, on visit EX-1, and continues for 96 weeks. Visits during the Extension Treatment Period will consist of visit EX-1 and visits at EX-Weeks 4, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, and 96. • The End-of-Treatment 2 (EOT2) visit will take place at EX-Week 96 or earlier in case of premature discontinuation of study drug. In all cases, the EOT2 visit should take place not later than 7 days after the last dose of study drug.

<table>
<tr><td></td><td>

- Subjects completing the EOT2 will be subsequently treated according to local standard of care at the investigator's discretion.

Extension Safety Follow-up Period 2

- All subjects will enter the safety follow-up period after EOT2 (Follow-up Period 2), which will last for 30 days after the last dose of study drug and end with the 30-day follow-up 3 (FU3) visit. This is also the EOS visit for these subjects.
</td></tr>
<tr><td>STUDY DISCONTINUATION CRITERIA</td><td>At any time during the treatment period, subjects meeting the study-specific criteria for premature discontinuation of study drug (described in Section 5.1.10) are to be prematurely discontinued from study drug and will perform EOT (1 or 2) and EOS visits.</td></tr>
<tr><td>PLANNED DURATION</td><td>Approximately 168 weeks
<table>
<tr><td>First subject First visit</td><td>Q2 2015</td><td>Last subject First visit</td><td>Q2 2016</td><td>Last subject Last visit</td><td>Q4 2018</td></tr>
</table></td></tr>
<tr><td>SITE(S) / COUNTRY(IES)</td><td>Approximately 10 sites in the USA (planned).</td></tr>
<tr><td>SUBJECTS / GROUPS</td><td>30 subjects in 1 group</td></tr>
<tr><td>INCLUSION CRITERIA FOR THE CORE TREATMENT PERIOD</td><td>

1. Signed informed consent prior to initiation of any study-mandated procedure.
2. Males and females aged 18 to 70 years.
3. Recipients of allogeneic hematopoietic stem cell transplant (HSCT) diagnosed with chronic GVHD.
4. Currently receiving systemic IS therapy at enrollment, with no dose changes in the 14 days prior to enrollment, consisting of systemic glucocorticoids AND/OR one of the following systemic agents: cyclosporine (CsA), tacrolimus (TAC), mycophenolate mofetil (MMF), mycophenolate sodium (MPS), everolimus (EVL), sirolimus (SRL), or methotrexate (MTX).
5. Subject needs a change of current systemic IS therapy, in the opinion of the investigator, based on all of the following conditions:
</td></tr>
</table>

	a) Symptomatic moderate or severe chronic GVHD per NIH global severity scoring assessed at screening. b) Glucocorticoid refractory, dependent, or intolerant status at screening [see Appendix 1 for guidance]. c) Evidence of GVHD progression at enrollment despite ≥ 4 weeks current systemic IS therapy, OR without evidence of GVHD improvement at enrollment despite ≥ 8 weeks current systemic IS therapy. Current systemic IS therapy must be the same as in inclusion criterion 4 [see Appendix 1 for guidance]. 6. Chronic GVHD manifestations involve at least one of the following organs: skin, mouth, eyes, joints and fascia, esophagus, upper or lower gastrointestinal (GI) tract. The qualifying manifestation should have an NIH chronic GVHD activity assessment score of at least 1 at enrollment [see Form A, Appendix 7]. 7. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test at screening and a negative urine or serum pregnancy test prior to enrollment, and must agree to undertake urine pregnancy tests every 4 weeks during the study and up to the protocol defined EOS. 8. WOCBP must agree to use acceptable methods of contraception during the study and up to the protocol defined EOS.
EXCLUSION CRITERIA FOR THE CORE TREATMENT PERIOD	**Cardiovascular** 1. Resting heart rate (HR) < 50 bpm measured by 12-lead electrocardiogram (ECG) at enrollment (prior to study drug administration). 2. Myocardial infarction within 24 weeks prior to screening or ongoing unstable ischemic heart disease. 3. Cardiac failure (NYHA class III or IV) or any severe cardiac disease at time of screening. 4. History or presence of valvular heart disease associated with symptoms or hemodynamic change.

	5. History or presence of cardiac rhythm disorders (e.g., sino-atrial heart block, symptomatic bradycardia, atrial flutter or atrial fibrillation, ventricular arrhythmias, cardiac arrest). 6. Presence of an increased QT corrected for HR on the basis of Fridericia's formula (QTcF) interval > 470 ms (females), > 450 ms (males) measured by 12-lead ECG at screening or pre-dose on Day 1. 7. History of syncope associated with cardiac disorders. 8. Systemic arterial hypertension not controlled by medication as judged by the investigator. **Hematologic** 9. Hemoglobin < 8.0 g/dL or need for red blood cell transfusion at screening. 10. Absolute neutrophil count < 1.5×10^9/L (< 1500 cells/mm^3) at screening. 11. Absolute lymphocyte count < 0.5×10^9/L (< 500 cells/mm^3) at screening. 12. Platelet count < 50×10^9/L (< 50,000 cells/mm^3) or need for platelet transfusion at screening. **Hepatic** 13. ALT and/or aspartate aminotransferase (AST) ≥ 3.0-fold the upper limit of normal (ULN) at screening. 14. Total bilirubin (TBL) > 1.5-fold ULN (unless in the context of known Gilbert's Syndrome) at screening. 15. Known chronic liver or biliary disease that is not due to chronic GVHD. **Infection and infection risk** 16. Active or uncontrolled bacterial, viral, or fungal infection (except onychomycosis and dermatomycosis); positive hepatitis B surface antigen or hepatitis C antibody tests at screening. 17. Cytomegalovirus (CMV) disease, including CMV pneumonia, CMV retinitis, and CMV gastroenteritis and/or subjects meeting institutional criteria for systemic therapy for CMV reactivation. (Subjects with positive CMV serology and/or CMV reactivation are not excluded

	if they do not have CMV disease and do not require systemic therapy). 18. Active or latent tuberculosis (TB), as assessed by chest X-ray performed at screening or within 90 days prior to screening, and interferon gamma release assay (QuantiFERON-TB-Gold®) at screening, except if there is documentation that the subject has received adequate treatment for TB previously. 19. Congenital or acquired severe immunodeficiency or known human immunodeficiency virus (HIV) or positive HIV testing at screening. **Malignancy** 20. New or recurrent malignancy or minimal residual disease. **Metabolic** 21. Type 1 or 2 diabetes that is poorly controlled according to investigator judgment, or diabetes complicated with organ involvement such as nephropathy or retinopathy. **Ophthalmologic** 22. Presence of macular edema. **Pregnancy and breastfeeding** 23. Breastfeeding, pregnant women or women planning to become pregnant during the study. **Pulmonary** 24. Subjects with a clinically significant pulmonary condition including asthma and chronic obstructive pulmonary disease (COPD) that is insufficiently controlled according to investigator judgment. 25. Subjects with diagnosed bronchiolitis obliterans syndrome. 26. Subjects with any hospitalization due to a clinically significant pulmonary condition including asthma or COPD exacerbation within 24 weeks prior to screening (with the exception of a fully resolved pulmonary infection).

	27. Subjects with abnormal pulmonary function tests: forced expiratory volume in 1 second (FEV_1) < 60% of predicted normal value or FEV_1/forced vital capacity (FVC) ratio < 0.7 at screening. **Renal** 28. Severe renal insufficiency defined as a calculated creatinine clearance < 30 mL/min/1.73 m^2 (Cockroft-Gault) at screening. **Treatments** 29. Systemic glucocorticoids at prednisone-equivalent dose > 1.0 mg/kg/day at screening. 30. Treatment within 15 days prior to enrollment with: • Azathioprine • β-blockers, diltiazem, verapamil, digoxin, digitoxin or any anti-arrhythmic or HR-lowering systemic therapy (a non-exhaustive list of drugs provided in Appendix 4) • CsA, TAC, MMF, MPS, EVL, SRL (with the exception of any therapy serving as a mandatory concomitant therapy, as per inclusion criterion 4 and Section 5.2). • Extracorporeal photopheresis • Isotretinoin • Thalidomide 31. Treatment within 30 days prior to enrollment with: • Acitretin • Cyclophosphamide • Etanercept • Imatinib • Vaccination with live vaccines 32. Treatment within 45 days prior to enrollment with: • Pulse methylprednisolone • MTX (with the exception if MTX serves as a mandatory concomitant therapy, as per inclusion criterion 4 and Section 5.2).

	33. Treatment within 60 days prior to enrollment with: • Basiliximab 34. Treatment within 24 weeks prior to enrollment with: • Anti-lymphocyte globulin • Anti-thymocyte globulin • Belimumab • Mesenchymal stem cell therapy • Ofatumumab • Pentostatin • Rituximab 35. Treatment within 36 weeks prior to enrollment with: • Hydroxychloroquine 36. Treatment within 48 weeks prior to enrollment with: • Alemtuzumab • Clofazamine 37. Treatment with any IS or immunomodulatory drug or technology not identified in items 30 to 37, unless discussed with the Sponsor to determine appropriate washout. Chemotherapy and radiation for conditioning treatment leading up to the stem cell transplant and growth factors are exempt and do not have to be discussed with the sponsor. **Other Categories** 38. Karnofsky Performance Score < 60%. 39. Known history of clinically significant drug or alcohol abuse. 40. Known allergy to any of the ponesimod formulation excipients. 41. Any other clinically relevant medical or surgical condition, which, in the opinion of the investigator, would put the subject at risk by participating in the study. 42. Subjects unlikely to comply with protocol, e.g., uncooperative attitude, inability to return for follow-up visits, or known likelihood of not completing the study including mental condition rendering the

	subject unable to understand the nature, scope, and possible consequences of the study.
INCLUSION CRITERIA FOR THE EXTENSION TREATMENT PERIOD	1. Signed informed consent prior to initiation of any study-mandated procedure. 2. Subject has completed the 24 weeks of treatment of the Core Treatment Period and the EOT1 visit. 3. Subject has experienced disease progression 7 to 90 days after EOT1 visit, versus EOT1 chronic GVHD activity assessment, for at least one previously involved organ. Progression is per NIH Consensus Development Project response criteria and is defined in Section 6.3.2. 4. WOCBP, as defined in Section 4.3.1, must have a negative urine pregnancy test at enrollment visit EX-1, and at all prior visits, and must agree to undertake monthly scheduled urine pregnancy tests during the study and up to the protocol defined EOS. 5. WOCBP must agree to use acceptable methods of contraception during the study and up to the protocol defined EOS.
EXCLUSION CRITERIA FOR THE EXTENSION TREATMENT PERIOD	There are no exclusion criteria for the Extension Treatment Period. However: • Study drug specific dose-reduction, interruption, or premature discontinuation criteria remain in force for the duration of the study. These are described in Section 5.1.10. • Forbidden concomitant therapies remain in force for the duration of the study. These are described in Section 5.3.5.
STUDY TREATMENTS	**Investigational treatment (study drug): ponesimod** Ponesimod is supplied as its free base, in oral film-coated tablets at doses of 2, 3, 4, 5, 6, 7, 8, 9, 10, and 20 mg. One tablet of ponesimod at any dose will be taken orally once daily. **Core Treatment Period** For this dose-escalation study, subjects will receive three treatment courses, with each treatment course studying one of the following ponesimod daily doses: 5, 10, and 20 mg.

	A 6 day up-titration scheme will be implemented from Day 1 to Day 6 using a titration blister wallet, to reduce ponesimod first-dose effects. On-site subject monitoring will be required at enrollment on Day 1 [see Section 5.1.7]. A 4-day up-titration scheme will be implemented from Day 29 to Day 32 to gradually transition from the 5 mg to the 10 mg daily dose. The subject will have the dose escalated from 10 to 20 mg on Day 57 (without gradual up-titration). The first day of the 4-day up-titration (Day 29) and the Day 57 dose escalation do not require on-site monitoring. Criteria to permit dose increases at Day 29 and Day 57 Subjects may have daily doses up-titrated from 5 mg to 10 mg, starting on Day 29, and dose escalated from 10 mg to 20 mg on Day 57, if the following are true: a) Subject has not met the study-specific criteria for interruption, dose reduction, or premature discontinuation of study treatment, described in Section 5.1.10. b) Subject does not have an ongoing grade 2 adverse event at least possibly related to study drug. c) Subject took ponesimod dose the day prior to the day of up-titration or dose-escalation. d) Investigator has reviewed and approved of the results of the Day 29 and/or Day 57 pre-dose assessments specified in Table 1. **Extension Treatment Period** Subjects will receive their last tolerated ponesimod dose (prior to EOT1) for 96 weeks, including up-titration. **Study drug re-initiation after interruption (Core and Extension Treatment Periods)** See Section 5.1.8 for guidance on re-initiation of ponesimod in the event of study drug interruption of any duration.

	Systemic glucocorticoids (Core Treatment Period only) Glucocorticoid dosing should not be increased or decreased during the course of the study, with the following exceptions: • The investigator may see reason to initiate or increase the dose of systemic glucocorticoid to treat chronic GVHD flare or another condition. In this case, the investigator should consult with the sponsor prior to initiation or dose increase and the reason for dose increase should be documented. The subject may continue on ponesimod. The prednisone-equivalent dose should never exceed 1 mg/kg/day. • Systemic glucocorticoid dosing may be lowered to avoid or prevent short- and long-term glucocorticoid toxicity. For subjects on longer term glucocorticoid therapy, it is recommended that the dose reduction rate does not exceed 10% of the dose per week. Glucocorticoid dosing may be increased following reduction, if medically indicated. • Systemic glucocorticoid dosing is not subject to restrictions during the Extension Treatment Period. **Mandatory systemic IS other than ponesimod or systemic glucocorticoids (Core Treatment Period only)** Systemic IS dosing (mg daily dose) should not be increased above baseline dose during the course of the study, with the following exception: • Systemic IS blood or serum level is below the therapeutic range that was defined for the subject at the time of entry into the study. The dose should be increased to restore blood or serum levels to within the defined therapeutic range. (IS that are not monitored with blood or serum level monitoring may never be increased above baseline dose.) Systemic IS dosing (mg daily dose) <u>should not be lowered during the course of the study</u>, with the following exceptions: • Adverse event (AE) or intolerance due to the systemic IS. The dose should be sufficiently lowered or discontinued, per investigator judgment.

	• Systemic IS blood or serum level is above the therapeutic range that was defined for the subject at the time of entry into the study. The dose should be lowered to restore blood or serum levels to within the defined therapeutic range. Systemic IS dosing is not subject to restrictions during the Extension Treatment Period. **Topical calcineurin inhibitors or glucocorticoids (Core Treatment Period only)** • The sponsor recommends not starting or increasing dosage of topical calcineurin inhibitors (CNI) or glucocorticoid therapy during the course of the core study. • Topical CNI or glucocorticoid therapy dosing or area of application should not be decreased during the course of the core study, unless there is an AE or intolerance due to the topical drug. The dose should then be sufficiently lowered or discontinued, per investigator judgment. • Topical CNI or glucocorticoid dosing is not subject to restrictions during the Extension Treatment Period.
CONCOMITANT THERAPY	**Mandatory concomitant therapy (Core Treatment Period only)** Systemic glucocorticoids AND/OR one of the following systemic agents: CsA, TAC, MMF, MPS, EVL, SRL, or MTX. **Allowed concomitant therapy (Core and Extension Treatment Periods)** • Administration of intravenous (i.v.) atropine in the event of symptomatic bradycardia • Topical glucocorticoid • Topical CNI • Oral budesonide • QT-prolonging drugs with known risk of Torsades de Pointes should be used with caution, since ponesimod

	may potentially enhance their effect on QT interval (list of drugs and guidance are provided in Appendix 3) • Short-acting ß$_2$ agonists for respiratory symptoms and/or reduced pulmonary function during ponesimod treatment • Vaccination with non-live vaccines • Other treatments considered necessary for the subject's benefit and not categorized as forbidden concomitant medications **Forbidden concomitant therapy (Core and Extension Treatment Periods)** • β-blockers, diltiazem, verapamil, digoxin, digitoxin, or any other anti-arrhythmic or HR-lowering systemic therapy (a non-exhaustive list of drugs provided in Appendix 4) • IS or immunomodulatory treatments other than those prescribed per protocol • Mesenchymal stem cell therapy • Retinoids • Thoracoabdominal irradiation • Extracorporeal photopheresis • Vaccination with live vaccines • Any other investigational drug other than ponesimod.
PHARMACOKINETIC AND PHARMACODYNAMIC ENDPOINTS	**<u>Core Treatment Period Endpoints</u>** **Pharmacokinetic (PK) evaluations** • Trough concentrations of ponesimod at Day 1, Weeks 4, 8, 12, 16, and 20 (all samples pre-dose), and Week 24 • Ponesimod concentration 3 hours post-dose at Day 1 and Week 12 **Pharmacodynamic (PD) evaluations** <u>Primary PD endpoint</u> • Change in peripheral absolute lymphocyte count from baseline to Week 4, Week 8 and Week 12

	The primary endpoint assesses intra-subject dose response during the first 12 weeks of treatment. Other PD endpoints • Peripheral absolute blood lymphocyte count change from baseline (pre-dose on Day 1) to Weeks 4, 8, 12, 16, 20, 24, and FU1, and change from pre-dose Week 12 to 3 hours post-dose Week 12. • Peripheral absolute lymphocyte count reversibility from EOT1 to FU1 expressed as absolute change and percent change from baseline **PK/PD relationship** The PK and selected efficacy and safety variables will be correlated with the PD (peripheral absolute lymphocyte count and magnitude of reduction of lymphocyte count). If deemed appropriate, the PK will also be correlated with selected safety variables. **Extension Treatment Period Endpoints** The same endpoints, except for PK, will be assessed in the Extension Treatment Period as were assessed in the Core Treatment Period, however adjusted for the corresponding visit schedule.
SAFETY ENDPOINTS	**Core Treatment Period Endpoints** The treatment-emergent period is defined as the time from first study drug intake up to 30 days (inclusive) after last study drug intake. **Overall safety endpoints** • Treatment-emergent AEs, serious adverse events, and AEs of special interest [see Appendix 5] • AEs leading to premature discontinuation of study drug • Deaths **Peripheral absolute lymphocyte count** • Treatment-emergent absolute lymphocyte count $< 0.2 \times 10^9$/L (< 200 cells/mm^3)

	Cardiac rate and rhythm safety endpoints
	• Treatment-emergent morphological ECG abnormalities (as defined by the ECG provider)
	• Change in 12-lead ECG variables (HR, PR, QRS, QT, QT corrected for HR on the basis of Bazett's formula [QTcB], QT corrected for HR on the basis of Fridericia's formula [QTcF]) from pre-dose to selected post-dose assessments (1 h, 2 h, 3 h, 4 h) on Day 1 and on day(s) of re-initiation of study drug
	• Notable abnormalities for selected 12-lead ECG variables (HR, PR, QT, QTc) at the 3-hour post-dose assessment on Day 1, pre-dose Weeks 4, 8, and 12 and Week 24 (notable abnormalities definition in Appendix 6)
	• Cardiac safety events will include:
	  • Treatment-emergent QTc > 450 ms (male), > 470 ms (female), > 500 ms (male), and > 520 ms (female)
	  • Treatment-emergent QTc increase from baseline > 30 ms, > 60 ms
	  • Other treatment-emergent abnormalities observed by 12-lead ECG
	  • Treatment-emergent (serious) cardiac AEs of special interest
	Pulmonary function safety endpoints
	• Treatment-emergent decrease of FEV_1 or FVC > 20% from baseline values
	• Treatment-emergent decrease of percent of predicted FEV_1 or FVC > 20 percentage points from baseline values
	• Change in FEV_1 and FVC from baseline, absolute and % of absolute change to all time points up to FU1
	• Among subjects with a decrease of > 200 mL and > 12% in FEV_1 or FVC, respectively, from baseline to EOT1, reversibility is defined as a decrease of < 200 mL and < 12% in FEV_1 or FVC, respectively, from baseline to last available follow-up

	• Change from baseline to FU1 vs change from baseline to EOT1 in FEV_1 or FVC (absolute and % of predicted) • Change in lung diffusion capacity as assessed by diffusing capacity of lung for carbon monoxide (DL_{CO}), expressed in absolute change and % of predicted value from baseline to all time points up to FU1 • Change from baseline to FU1 vs change from baseline to EOT1 in DL_{CO} (absolute and % of predicted) • (Serious) pulmonary AEs of special interest • Withdrawal due to pulmonary reasons/AE **Other safety endpoints** • Treatment-emergent notable blood pressure abnormalities [definition in Appendix 6] • Treatment-emergent notable laboratory abnormalities [definition in Appendix 6] **<u>Extension Treatment Period Endpoints</u>** The same endpoints will assessed in the Extension Treatment Period as were assessed in the Core Treatment Period, however adjusted for the corresponding visit schedule.
EFFICACY ENDPOINTS	**<u>Core Treatment Period Endpoints</u>** **NIH response endpoints** • Achievement of a partial or complete overall response at 24 weeks post-enrollment (per NIH Consensus Development Project response criteria) Definitions for the efficacy endpoint are based on the draft 2014 NIH Consensus Guidelines [see Appendix 7]. Baseline or subsequent organ abnormalities that are not due to chronic GVHD are not evaluable for response (at the organ level). <u>Complete overall response definition</u>: A complete response is defined as resolution of all reversible manifestations due to chronic GVHD in all of the following organs at the Week 24 assessment, resulting in: • Skin: NIH Skin Score of 0 after previous involvement

	• Mouth: NIH Modified Oral Mucositis Score of 0 after previous involvement • Liver: normal ALT, alkaline phosphatase, and TBL after previous elevation of one or more • Upper GI: NIH Upper GI Score of 0 after previous involvement • Lower GI: NIH Lower GI Score of 0 after previous involvement • Esophagus: NIH Esophagus Score of 0 after previous involvement • Lungs: normal FEV_1 absolute value after previous involvement (normalization to $FEV_1 \geq 80\%$ predicted is considered a complete response) • Eyes: NIH Eye Score of 0 after previous involvement • Joint/fascia: Both NIH Joint and Fascia Score of 0 and photographic range of motion (P-ROM) score of 25 after previous involvement by at least one measure • Global: Clinician Overall Severity Score of 0 <u>Partial overall response definition</u>: A partial overall response is defined as improvement in a measure for at least one organ without progression in measures for any other organ. The proposed general guideline for defining partial response in a specific organ requires a change in score from baseline as follows: • Skin: decrease in NIH Skin Score by at least 1 point • Mouth: decrease in NIH Modified Oral Mucositis Score by at least 2 points • Liver: decrease by 50% in ALT, alkaline phosphatase, or TBL • Upper GI: decrease in NIH Upper GI Score by at least 1 point • Lower GI: decrease in NIH Lower GI Score by at least 1 point

	• Esophagus: decrease in NIH Esophagus Score by at least 1 point • Lungs: increase by at least 10% predicted absolute value of FEV_1, as long as initial FEV_1 < 70% predicted • Eyes: decrease in NIH Eye Score by at least 1 point • Joint/fascia: decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 or more points for any site • Global: Clinician Overall Severity Score decreases by 2 or more points on a 0–10 scale The proposed general guideline for defining progression in a specific organ requires a change in score from baseline as follows: • Skin: increase in NIH Skin Score by at least 1 point, except from 0 to 1 • Mouth: increase in NIH Modified Oral Mucositis Score by at least 2 points • Liver: increase by ≥ 2 × ULN for ALT, alkaline phosphatase or TBL • Upper GI: increase in NIH Upper GI Score by at least 1 point, except from 0 to 1 • Lower GI: increase in NIH Lower GI Score by at least 1 point, except from 0 to 1 • Esophagus: increase in NIH Esophagus Score by at least 1 point, except from 0 to 1 • Lungs: decrease by at least 10% absolute value of FEV_1, as long as final FEV_1 < 70% predicted • Eyes: increase in NIH Eye Score by at least 1 point, except from 0 to 1 • Joint/fascia: increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 or more points for any site • Global: Clinician Overall Severity Score increases by 2 or more points on a 0–10 scale <u>Subject responder / non-responder definition</u>

	The endpoint is reached if the subject is considered a partial or complete responder at Week 24. The remaining subjects will be considered as non-responders, this includes subjects with stable disease and subjects with mixed response (defined as complete or partial response in at least one organ accompanied by progression in another organ).
	
	Other exploratory efficacy endpoints
	• Need for rescue therapy for chronic GVHD
	  o Rescue therapy is the addition of any new systemic or topical IS therapy or exceeding baseline dose for any systemic non-steroid IS or exceeding glucocorticoid dose equivalent to prednisone > 1 mg/kg/day
	• Partial or complete organ-specific response for the specific organ manifestation at Week 12 and Week 24 in subjects with a specific organ manifestation of chronic GVHD at study baseline
	  o Affected organs limited to 2014 NIH consensus criteria organs of skin, eyes, mouth, esophagus, upper GI, lower GI, liver, lungs, and joints and fascia
	• Partial or complete overall response at Week 12 post-enrollment
	• Complete response at Week 24
	• Partial or complete overall response at latest evaluable assessment during the core study (Week 12 and 24)
	• Average glucocorticoid daily dose over 24 weeks versus baseline dose
	• Percent glucocorticoid dose at Week 24 versus baseline
	
	<u>Extension Treatment Period Endpoints</u>
	The same endpoints will assessed in the Extension Treatment Period as were assessed in the Core Treatment Period, however adjusted for the corresponding visit schedule.

QUALITY OF LIFE ENDPOINTS	**<u>Core Treatment Period Endpoints</u>**

	• Change from baseline to Week 12 and Week 24 in Lee Symptom Scale for chronic GVHD [Appendix 8] • Change from baseline to Week 12 and Week 24 in each of the subject-reported chronic GVHD symptoms (skin, eyes, mouth and genitals [Appendix 7 – Form B]). • Change from baseline to Week 12 and Week 24 in each of the patient-reported global ratings (Mild-Moderate-Severe Scale, Overall Severity Scale and 7-Point Change Scale [Appendix 7 – Form B]). **Extension Treatment Period Endpoints** The same endpoints will assessed in the Extension Treatment Period as were assessed in the Core Treatment Period, however adjusted for the corresponding visit schedule.
ASSESSMENTS	Refer to the schedule of assessments in Table 1.
STATISTICAL METHODOLOGY	**Analysis sets** Full Analysis set (FAS): The FAS includes all subjects who received at least one dose of study medication. Safety Set (SAF): The safety set is defined like the FAS and will be used for all safety-related outputs. Per-Protocol set (PPS): The per-protocol set is defined as subjects from the FAS without any major protocol deviations. Additional details of the definition of the PPS are described in Section 11.1.3 and in the statistical analysis plan. PD analysis set (PDS): The PD analysis set includes all subjects who received at least 4 weeks of study treatment and have at least one absolute lymphocyte count measurement between the Week 4 visit and Week 12 visit. The PD endpoints of this study will be analyzed based on the PD analysis set. PK analysis set (PKS): The PK analysis set includes all subjects from the safety set who provided at least one blood sample. All PK related data will be analyzed on the PK analysis set.

Extension set (ES): The extension set includes all subjects enrolled in the Extension Treatment Period and who received at least one dose of ponesimod in the Extension Treatment Period.

Primary analysis variable (PD endpoint)

The change in absolute lymphocyte count from baseline to Week 4, Week 8 and Week 12 in the Core Treatment Period is defined as:

- l_d = absolute lymphocyte count for dose d – absolute lymphocyte count at baseline

The change in absolute lymphocyte counts (l_d) is assessed at Week 4 for the 5 mg dose, at Week 8 for 10 mg and at Week 12 for 20 mg in the Core Treatment Period.

Overall testing strategy for the PD endpoint

Null and alternative hypotheses

The null hypothesis is that there is no dose response on the change from baseline in absolute lymphocyte count in the intra-subject dose escalation within the first 12 weeks of treatment and the alternative hypothesis is the existence of any intra-subject dose response within the first 12 weeks of treatment:

H_0: $l_d \geq 0$ for all doses d = 5, 10, 20 mg

vs

H_1: $l_d < 0$ for at least 1 dose d = 5, 10, 20 mg

To meet the objective of demonstrating existence of an intra-subject dose response on the absolute lymphocyte count reduction from baseline in subjects with GVHD, at least one of the null hypotheses must be rejected with a one-sided significance level of 5%. The type-1 error will be controlled via a hierarchical ordering of the tests: pairwise comparisons will be conducted in decreasing dose order. Within-subject t-tests will be performed at each dose level (assuming normally distributed data).

Further t-tests will be performed across dose levels (5 mg vs 10 mg, 5 mg vs 20 mg and 10 mg vs 20 mg). These tests,

	performed at a one-sided significance level of 5%, will be considered as exploratory. In addition an E_{max} model will be fitted for the baseline, Week 4, Week 8 and Week 12 data. The data will be summarized with point-wise and model-based estimates, standard deviation (STD) and 95% confidence-interval on the reduction in absolute lymphocytes from baseline at the examined dose levels. A plot of the estimated dose-response curve with 95% credibility interval limits will be presented along with the observed response at each dose. The primary analysis will be performed on the PD analysis set and a sensitivity analysis will be performed on the FAS. A last observation carried forward approach (using the Week 4 visit or later) will also be performed for subjects with a missing Week 8 or Week 12 assessment, based on the FAS. **Exploratory efficacy endpoints** The FAS is considered to be the main analysis set for the exploratory efficacy endpoints. Some analyses will be repeated on the PPS, if applicable. The exploratory efficacy endpoints will be analyzed descriptively. **Safety endpoints** Safety endpoints will mainly be analyzed descriptively on the safety set. Selected safety outputs might be analyzed by dose level and/or time-point. **Extension endpoints** The ES is considered to be the main analysis set for the safety and efficacy endpoints for the Extension Treatment Period. **Quality of Life endpoints** Analyses are described in Section 11. **PK/PD endpoints** Analyses are described in Section 11.
SAMPLE SIZE ASSUMPTIONS	**Sample size based on PD endpoint** The sample size of this single arm intra-subject dose-escalation study is based on simulations, comparing

	lymphocyte data at baseline to Week 4 data of the estimated 5 mg dose in the Core Treatment Period, using t-tests. Since no studies of subjects receiving ponesimod have been conducted in GVHD, historical data of the Actelion multiple sclerosis and psoriasis programs have been used to determine the sample size. As GVHD subjects are known to have reduced lymphocyte counts, assumptions were adjusted appropriately. Dose-response modeling techniques were applied to support the sample size estimation [details in Section 11]. Based on these simulations 30, subjects will be recruited in order to establish an intra-subject dose response and to collect sufficient safety data. The simulations were performed comparing the change of absolute lymphocyte counts at Week 4 (5 mg dose; mean: 0.85×10^9/L; STD 0.40) vs baseline (mean: 1.2×10^9/L; STD 0.60), applying t-tests with a one-sided alpha-level of 0.05. Based on those assumptions a power of around 85% is reached. As absolute lymphocyte counts are expected to be closest to baseline data for the 5 mg dose, the sample size of 30 subjects is expected to be sufficient for the 10 mg and 20 mg doses as well.
SITE PERSONNEL	To facilitate the performance of efficacy and safety assessments required by the protocol, it is essential that the site personnel have the appropriate medical expertise and that the roles are defined clearly up front. At each center, the study staff will consist of a/an: • Principal investigator; • Cardiac safety assessor (qualified physician evaluating cardiac safety assessments, may be the same person as principal investigator); • Clinical coordinator/study nurse; • Ophthalmologist; • Pulmonologist; • Pulmonary function laboratory technician or expert. It is recommended that the designated personnel remain unchanged throughout the entire course of the study and that

	an adequately trained back-up is designated in case of absence of any of the staff listed above.
STUDY COMMITTEES	**Study Monitoring Committee (SMC)** • The SMC will ensure that the study is properly conducted, monitored, and that data are appropriately analyzed and interpreted. The SMC will review toxicity assessments for each subject. At any time, the SMC may interrupt enrollment or recommend termination of the study for safety reasons. The SMC will recommend the dose of ponesimod for further development in chronic GVHD. • The SMC core comprises at least two medical experts in the field of chronic GVHD and two medical experts from the sponsor (i.e., the project physician, and a drug safety physician with expert knowledge of the safety profile of ponesimod). • Additional permanent attendees of SMC meetings will include the study statistician, the clinical trial scientist and the clinical study coordinator. • The composition and operation of the SMC is described in the SMC charter. **Ophthalmology Safety Board (OSB)** • The OSB will review and evaluate any new or suspected cases of macular edema. • The OSB is composed of two independent ophthalmologists. • The composition and operation of the OSB is described in the OSB charter.
STUDY EXTENSION	**Extension study** Subjects successfully completing the 24 week Core Treatment Period and fulfilling eligibility criteria in Sections 4.6 and 4.7 may enter the 96 week Extension Treatment Period.

Table 1 Visit and assessment schedule

Periods	Name	SCREENING	CORE TREATMENT PERIOD			
			COURSE 1 (up to 5 mg)	COURSE 2 (up to 10 mg)	COURSE 3 (20 mg)	
	Duration	Up to 30 Days	4 weeks	4 Weeks	16 Weeks	
Visits	Number	1	2	3	4	5
	Name	Screening	Enrollment	W4	W8	W12
	Time	Day −30 to −1	Day 1	Week 4	Week 8	Week 12
	Visit window			± 3 days	± 3 days	± 7 days
Informed consent*		X				
Inclusion/exclusion criteria*		X	X Pre-dose			
Demographics*		X				
Medical history*		X				
Chronic GVHD Stage & Score*		X				
Chronic GVHD Activity Assessment, Form A and B*			X Pre-dose			X
Lee Symptom Scale*			X Pre-dose			X
Chest X-ray		X (1)				
Concomitant medications*		X	X	X	X	X
Physical examination*		X				X
Body weight and height*		X	X (weight only)			
Systolic/diastolic blood pressure*		X	X See Section 5.1.7	X (4) pre-dose	X (4) pre-dose	X pre-dose
12-lead ECG (2)**		X	X See Section 5.1.7	X (4) pre-dose	X (4) pre-dose	X pre-dose
Ophthalmological examination		X				X
OCT (3)		X				X
Spirometry*/DL_{CO}*		X	X Pre-dose	X (4) pre-dose	X (4) pre-dose	X pre-dose
Hematology**/Chemistry**/ Urinalysis		X	X pre-dose	X (4) pre-dose /local and central lab	X (4) pre-dose /local and central lab	X pre-dose
Tuberculosis test**		X				
Viral serology**		X				
Additional blood samples for exploratory biomarkers**			X			
Pregnancy test*/** MOC* (5)		X serum**	X serum/urine*	X urine*	X urine*	X urine*
PK and PD** sampling			X See Section 7.2.1	X pre-dose	X pre-dose	X pre-dose & 3 hr post-dose
Study drug dispensing & accountability (6)**			X	X	X	X
AEs & SAEs (7)*		X	X	X	X	X

*Data collected in the eCRF **Electronically transferred to the sponsor

Table 1 Visit and assessment schedule (continued)

Periods	Name	*Continued:* **CORE TREATMENT PERIOD, COURSE 3 (20 mg)**			**UNSCHEDULED** Applies to all periods in Table 1		**FOLLOW -UP PERIOD 1**
	Duration	16 Weeks			Variable		30, 90 days
Visits	Number	6	7	8	R1, R2,…	U1, U2, …	9, 10
	Name	W16	W20	W24 (EOT1)	Re-initiation	Un-scheduled	FU1, FU2 (8)
	Time	Week 16	Week 20	Week 24 (earlier if prematurely discontinued)	Any day between Day 1 and EOT2	Any day between Day 1 and EOS	EOT1+30 & EOT1+90 days
	Visit window	± 7 days	± 7 days	± 7 days	NA	NA	+ 7 days
Chronic GVHD Activity Assessment, Form A and B*				X			X (9)
Lee Symptom Scale*				X			X (9)
Concomitant medications*		X	X	X	X	X	X
Physical examination*				X		Optional	
Body weight and height*				X (weight only)		Weight optional	
Systolic/diastolic blood pressure*		X pre-dose	X pre-dose	X	X See Section 5.1.7	X pre-dose	X (FU1 only)
12-lead ECG (2)**		X pre-dose	X pre-dose	X	X See Section 5.1.7	Optional; pre-dose	X (FU1 only)
Ophthalmological examination				X		Optional	
OCT (3)				X		Optional	
Spirometry*/DL_{CO}*				X		Optional	X (FU1 only)
Hematology**/ Chemistry**/ Urinalysis		X pre-dose	X pre-dose	X	X pre-dose	Optional	X
Additional blood samples for exploratory biomarkers**				X			X (FU1 only)
Pregnancy test*/MOC* (5)		X urine	X urine	X urine	X urine	Optional urine	X urine
PK and PD** sampling		X pre-dose	X pre-dose	X			X (PD only) (FU1 only)
Study drug dispensing & accountability (6)**		X	X	X	X		
AEs & SAEs (7)*		X	X	X	X	X	X

*Data collected in the eCRF **Electronically transferred to the sponsor

Table 1 Visit and assessment schedule (continued)

Periods	Name	EXTENSION TREATMENT PERIOD				FOLLOW-UP PERIOD 2
	Duration	96 Weeks				30 Days
Visits	Number	11	12, 13, 14, 15, 16	17, 18, 19, 20, 21, 22	23	24
	Name	EX-1 (8)	EX-2, 3, 4, 5, 6	EX-7, 8, 9, 10, 11, 12	EX-13	FU3 (EOS) (8)
	Time	EOT1 + 7 days to EOT1 + 90 days (10)	EX-Weeks 4, 8, 12, 16, 20	EX-Weeks 24, 36, 48, 60, 72, 84	EX-Week 96 (EOT2)	EOT2 + 30 days
	Visit window		± 7 days	± 7 days	± 7 days	+ 7 days
Extension Treatment inclusion/exclusion criteria*		X				
Chronic GVHD Activity Assessment, Form A and B*		X	X (Visit EX-4 only)	X	X	
Lee Symptom Scale*		X	X (Visit EX-4 only)	X	X	
Concomitant medications*		X	X	X	X	X
Physical examination*		X	X (Visit EX-4 only)	X	X	
Body weight*		X	X (Visit EX-4 only)	X	X	
Systolic/diastolic blood pressure*		X See Section 5.1.7	X (pre-dose)	X (pre-dose)	X	X
12-lead ECG (2)**		X See Section 5.1.7	X (pre-dose)	X (pre-dose)	X	X
Ophthalmological examination*			X (Visit EX-4 only)		X	
OCT (3)*			X (Visit EX-4 only)		X	
Spirometry*/DL_{CO}*		X pre-dose	X (Visit EX-4 only) pre-dose	X pre-dose	X	X
Hematology**/Chemistry**/ Urinalysis		X pre-dose	X pre-dose	X pre-dose	X	X
Pregnancy test*/MOC* (5)		X urine	X urine	X urine (11)	X urine	X urine
PK and PD** sampling		X (PD only) pre-dose	X (PD only) (Visit EX-4 only) pre-dose	X (PD only) pre-dose	X (PD only)	X (PD only)
Study drug dispensing & accountability (6)**		X	X	X	X	
AEs & SAEs (7)*		X	X	X	X	X

*Data collected in the eCRF **Electronically transferred to the sponsor

Table 1 Visit and assessment schedule (continued)

Table notes

Day 1 (date of first study drug intake) is to be used as the reference date for the purpose of calculating the subsequent visit dates (and time windows).

(1) Any chest X-ray that has been performed within 90 days prior to screening can be used (in this case, no need to repeat chest X-ray at screening).

(2) In the event of a CTCAE grade 2 QTc elevation identified on 12-lead ECG (QTc 481–500 ms), a 12-lead ECG must be repeated 3 hours post dose. The subject is prematurely discontinued if the repeated QTcF > 500 ms.

(3) OCT is performed at indicated visits plus any visit in case of visual symptoms suggestive of macular edema.

(4) Investigator must review all test results prior to permitting subject to start the 4-day up-titration at Visit 3 and/or the dose escalation to 20 mg at Visit 4.

(5) For women of child-bearing potential, the serum pregnancy test at Visit 1 must be performed at least 3 weeks before a urine pregnancy test at Visit 2. A second serum pregnancy may be performed instead of the urine test as early as 7 days after the first serum pregnancy test, and enrollment can begin as soon as the negative result is available. Assess and reinforce continued use of MOC for women of child-bearing potential at every visit.

(6) Subjects record study medication compliance in a diary. Study drug accountability must be performed by the study staff on the day of the visit and recorded on the Study Drug Dispensing and Accountability Log.

(7) All AEs and SAEs that occur after signing the Informed Consent Form and up to 90 days after EOT1 (up to 30 days after EOT1 for prematurely discontinued subjects) and up to 30 days after EOT2 must be reported, as per Sections 10.1.5 and 10.2.2.

(8) FU1 is cancelled if the subject enrolls in Extension Treatment and visit EX-1 occurs the day of, or prior to, the scheduled FU1 visit.

FU2 is cancelled if the subject enrolls in Extension Treatment and visit EX-1 occurs the day of, or prior to, the scheduled FU2 visit.

- If a subject discontinues study drug prematurely during the Core Treatment Period then visit FU1 is the EOS visit.
- If a subject completes the 24 week Core Treatment Period and does not enroll in Extension Treatment, then visit FU2 is the EOS visit.
- If a subject completes the 24 week Core Treatment Period and does enroll in Extension Treatment, then visit FU3 is the EOS visit.

(9) Subjects who prematurely discontinued study drug do not undergo this assessment at FU1.

(10) Subjects may be retreated with ponesimod at least 7 days after EOT1 (treatment course 3) and no later than 90 days after EOT1 if they successfully completed the first 24 weeks of the study and meet eligibility criteria as listed in Sections 4.6 and 4.7.

(11) Monthly urine pregnancy tests must be done at home between quarterly visits EX-7, 8, 9, 10, 11, 12, and 13. Subject will telephone the study site to convey results. See Section 7.3.11.2.

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; DL_{CO} = diffusing capacity of lung for carbon monoxide; ECG = electrocardiogram; eCRF = electronic Case Report Form; EOS = End-of-Study; EOT = End-of-Treatment; FU = follow-up; GVHD = graft versus host disease; MOC = methods of contraception; OCT = optical coherence tomography; PD = pharmacodynamics; PK = pharmacokinetics; QTc = corrected QT interval; QTcF = QT interval corrected according to Fridericia's formula; SAE = serious adverse event

PROTOCOL

1 BACKGROUND

1.1 Chronic graft versus host disease

Chronic graft versus host disease (GVHD) is a pleomorphic syndrome with autoimmune-like features. The disease can affect multiple sites, including the skin and subcutaneous connective tissues, lacrimal and salivary glands, oral mucosa, lungs, esophagus, joints, gastrointestinal (GI) tract and liver [Martin 2011]. Chronic GVHD is the most serious and common long-term complication of allogeneic hematopoietic stem cell transplantation (HSCT), and has a median time to onset of 4 to 6 months after transplantation, although up to 10% of cases may be diagnosed beyond 1 year [Lee 2008].

Chronic GVHD has distinctive signs and symptoms, which include sicca syndrome, obstructive bronchiolitis, and lichenoid or sclerotic skin changes, among others. Chronic GVHD also has signs and symptoms that are shared with acute GVHD, and these include erythematous skin rash, nausea, vomiting, diarrhea, and cholestatic liver disease [Weisdorf 2007].

Risk factors for chronic GVHD include use of a mobilized blood cell graft, a human leukocyte antigen (HLA)-mismatched or unrelated donor, older patient age, and especially a history of acute GVHD. The risk of this disease can be decreased by T-cell depletion from the graft or treatment of the recipient with anti-T-cell antibodies as part of the conditioning regimen prior to transplant [Martin 2011].

Chronic GVHD is a leading cause of late death in HSCT patients; however, at the same time, GVHD is associated with lower leukemia relapse rates. Data are conflicting regarding the correlation of this effect with GVHD severity [Garnett 2013].

1.1.1 Epidemiology

Approximately 8000 allogeneic HSCT are now performed in the USA each year [Pasquini 2013]. Of these, approximately 35% are expected to develop chronic GVHD requiring systemic treatment, with a total incidence of approximately 3000 patients per year [Flowers 2011]. Based on reported rates of survival, recurrent malignancy and withdrawal of immunosuppression after resolution of chronic GVHD [Vigorito 2009], the total prevalence in the USA is estimated at less than 10,000 [NIH Design of Clinical Trials 2014].

1.1.2 Pathogenesis

The pathophysiology of chronic GVHD is complex and involves both autoreactive and alloreactive T and B lymphocytes [Wolff 2011a, Antin 2011]. Several themes have emerged from different studies, which include: a potential role for regulatory T-cell

abnormalities in the development of chronic GVHD; thymic injury and dysfunction from chemotherapy, radiation, and/or acute GVHD leading to loss of self-tolerance; the observed presence of autoantibodies (anti-nuclear, -mitochondrial, -parietal, -smooth muscle, or -parotid) present in some chronic GVHD patients; elevated levels of B-cell activating factor in chronic GVHD patients [Linhares 2013]; and contribution of transforming growth factor and platelet-derived growth factor pathways [Nishimori 2013]. T- and B-cell pathways may present potential targets for treating chronic GVHD [Linhares 2013].

1.1.3 Current treatments

Symptomatic mild chronic GVHD may often be managed with local therapies alone, whereas patients with moderate or severe chronic GVHD are candidates for systemic immunosuppressant (IS) therapy [Jagasia 2015, Filipovich 2005]. Duration of IS therapy is determined by clinical response, with median duration estimated at 2 to 3 years [Stewart 2004].

Currently, there are no approved therapies for chronic GVHD in the USA. However, glucocorticoids, with or without the concomitant administration of calcineurin inhibitors (CNI), are considered standard treatments [Teshima 2009, Linhares 2013], are the most common treatments [Weisdorf 2007], and their use is based on data from randomized trials [Wolff 2011a]. The required intensity and duration of initial treatments for chronic GVHD are not well established [Wolff 2011a].

Generally, the prednisone or methylprednisolone starting daily dose should not exceed 1.0 mg/kg body weight and is followed by tapering over several months [Wolff 2011a]. Glucocorticoid tapering is stopped or the dose is increased with the recurrence or exacerbation of chronic GVHD symptoms [Martin 2009].

CNIs are often co-administered with glucocorticoids as first-line therapy, and may ameliorate steroid-related side effects but are unlikely to provide an additional survival advantage [Koc 2002]. CNIs are worth considering for severe chronic GVHD [Wolff 2011a], and one approach is co-administration of CNIs with glucocorticoids, with CNI doses decreased only after glucocorticoids have been stopped [Martin 2011].

Approximately 50% of patients receiving initial therapy do not have a sustained response. There is no standard second-line therapy, with approximately 40 drugs having been studied in poorly standardized Phase 2 trials or reported in retrospective case analyses [Linhares 2013]. Many of these drugs, while studied as second-line therapy, have been used almost exclusively in combination with glucocorticoids [Wolff 2011a]. Results of a survey on second-line treatment of chronic GVHD indicated that the following agents were frequently used in at least 5 of the 30 responding centers, located in Germany, Austria, and Switzerland: steroids (30/30), cyclosporine (22/30), photopheresis (13/30), mycophenolate

mofetil (13/30), tacrolimus (9/30), mycophenolic acid (8/30), sirolimus (6/30), and pulse dose of steroids (5/30) [Wolff 2011a].

1.1.4 Unmet medical need

Although chronic GVHD has been associated with a reduced risk of recurrent malignancy after HSCT, survival is not improved. Patients with chronic GVHD have an increased risk of infections and a 30–50% risk of mortality during the first 5 years after diagnosis [Martin 2011].

The prognosis of patients with glucocorticoid refractory chronic GVHD appears to be especially poor [Teshima 2009, Wolff 2011a]. There is a lack of agreement on the definition of glucocorticoid refractory [Greinix 2007], although one proposed working definition includes failure to improve after at least 2 months or progression after 1 month of standard glucocorticoid-based IS therapy [Lee 2008]. Another proposed definition consists of the following criteria: (1) progression on prednisone at 1 mg/kg/day for 2 weeks, (2) stable disease on ≥ 0.5 mg/kg/day of prednisone for 4-8 weeks, and (3) inability to taper prednisone below 0.5 mg/kg/day [Wolff 2011a]. Table 2 shows reported response and survival rates for a variety of secondary agents, which were typically studied in patients with glucocorticoid-refractory or -resistant chronic GVHD. Results were highly variable, with large proportions (> 35%) of patients having failed to demonstrate overall response in most studies. Survival ranged from 53% at 1 year to 85% at 2 years. Due to the lack of robust data, and especially in the setting of glucocorticoid-refractory disease, it is recommended that patients are enrolled in clinical trials whenever possible [Garnett 2013].

Table 2 Overall response and survival rates for selected secondary agents

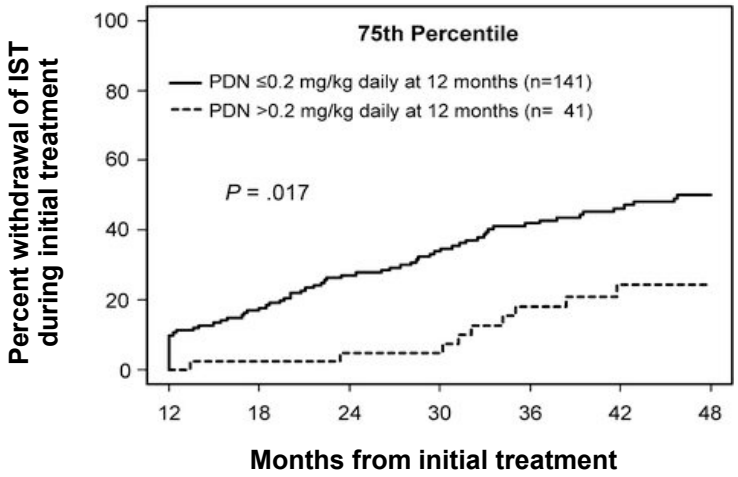
Agent	Published overall response rates*	Survival
Mycophenolate mofetil	46–75% (N=21-26)	85% at 2 years
High-dose corticosteroids	48% (N=56)	88% at 1 year
Extracorporeal photopheresis	61% (N=71)	53% at 1 year
Sirolimus	63% (n=35)	50% at 15 months
2-deoxycoformycin	53% (N=58)	78% at 1 year
Tacrolimus	35% (N=39)	Not reported
Rituximab	65–70% (N=21-38)	76% at 2 years
Thalidomide	20–38% (N=23-80)	41% at 2 years

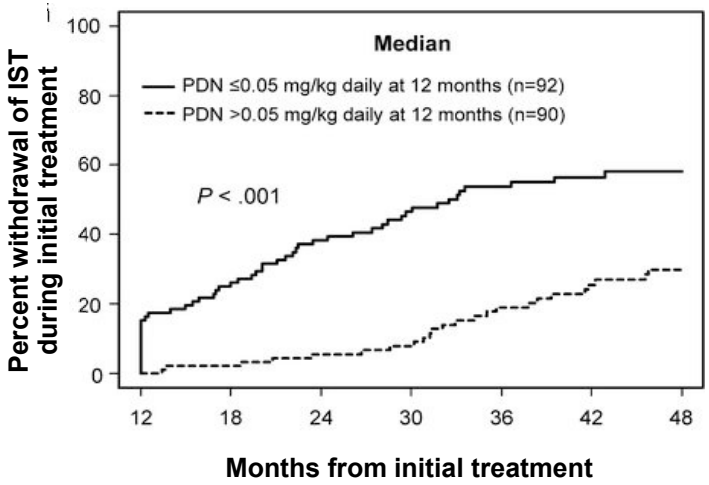
Source: Adapted from Lee 2008. *Definitions of response vary.

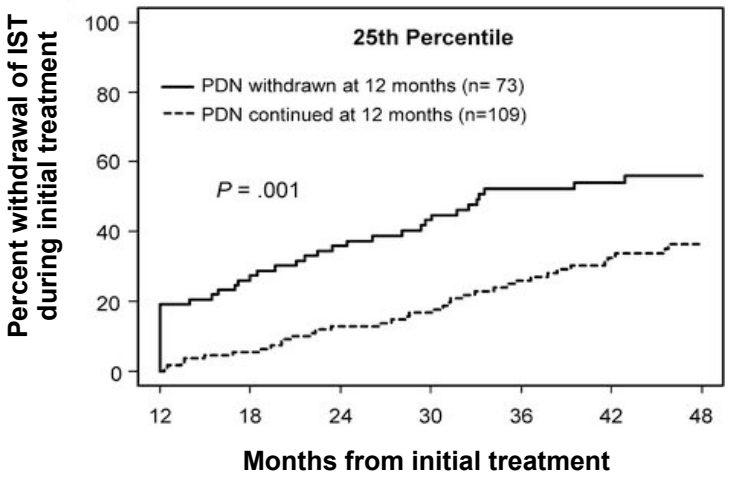
Glucocorticoid-dependent patients likely represent another subgroup with sub-optimal outcomes. Although there are no accepted definitions for glucocorticoid dependence in chronic GVHD, the ongoing University of California Davis study UCDCC#229 utilizes the following: chronic GVHD manifestations requiring a glucocorticoid dose of prednisone > 0.25 mg/kg/day (0.5 mg/kg by mouth every other day) for at least 12 weeks[1]. A recent Fred Hutchinson Cancer Research Center study provides insight into the unmet medical need for these patients. This observational study of 400 consecutive relapse-free subjects who received initial systemic treatment of moderate or severe chronic GVHD was designed to (among various objectives) determine whether the dose of prednisone at 6 or 12 months of treatment is associated with long-term success in withdrawing IS treatment due to resolution of GVHD [Inamoto 2014a]. Data was reported for up to 48 months. For those patients with failure-free survival (FFS) at 12 months, lower glucocorticoid doses were associated with successful withdrawal of all IS treatment [Figure 1]. FFS was defined as the absence of treatment change, NRM, and recurrent malignancy during initial systemic treatment. Furthermore, subsequent overall survival was slightly better among patients taking doses ≤ 0.3 or ≤ 0.2 mg/kg/day at 6 months compared with those taking respectively higher doses.

[1] Retrieved from https://ccresources.ucdmc.ucdavis.edu/csr/ctsu/clinicaltrial/2158/?displayelig=y

Figure 1 Long-term success in withdrawing all IS treatment in patients initially treated with glucocorticoids







Results were analyzed according to prednisone (PDN) doses at 12 months after initial treatment. Withdrawal of all immunosuppressive treatment (IST) after resolution of GVHD among patients without recurrent malignancy was counted during initial treatment among patients initially treated with steroids. Patients with recurrent malignancy or with treatment change before 12 months were excluded.

Source: Adapted from Inamoto Y et al. *Blood* 2014;124:1363-1371

1.2 Sphingosine 1-phosphate receptors

Sphingosine 1-phosphate (S1P) plays a central role in lymphocyte trafficking [Cyster 2005, Brinkmann 2007, Brinkmann 2010, Schwab 2007]. S1P is synthesized and secreted by many cell types, including platelets, erythrocytes, and mast cells, and elicits a variety of physiological responses [Cyster 2005, Alvarez 2007]. Among other effects, lymphocyte egress from primary and secondary lymphoid organs is dependent on the interaction between S1P and the sphingosine 1-phosphate receptor 1 ($S1P_1$). $S1P_1$ agonists block lymphocyte migration out of lymphoid tissue into the lymphatic and vascular circulation, thereby reducing peripheral absolute lymphocyte count and preventing lymphocyte recruitment to sites of inflammation. Following withdrawal of an $S1P_1$ agonist, the functional lymphocytes return to the circulation from their sites of sequestration. Other functions that do not rely on homing mechanisms, such as antibody generation by B lymphocytes, first-line immunological protection by granulocytes and monocytes, and antigen-dependent T cell activation and expansion, are not affected by this mechanism [Pinschewer 2000].

S1P itself induces pleiotropic effects, which are mediated by a family of five G protein-coupled receptors, $S1P_1$-$S1P_5$, located on endothelial cells, vascular and cardiac smooth muscle cells, and cardiac myocytes [Alvarez 2007, Brinkmann 2007, Brinkmann 2010]. The first S1P receptor modulator, fingolimod (FTY720, Gilenya®), which has been approved by the FDA and the EMA for the treatment of MS, is not selective for $S1P_1$, but interacts also with $S1P_3$, $S1P_4$, and $S1P_5$ [Brinkmann 2007, Brinkmann 2010].

1.2.1 S1P and GVHD: preclinical evidence

Fingolimod, a non-selective S1P receptor modulator, has shown benefit in experimental acute GVHD in mice [Kim 2003, Katakoka 2005] and rats [Masabuchi 1996, Song 2006]. Due to the limited availability of bona fide chronic GVHD models in rodents [Chu 2008], a paucity of literature exists on the use of $S1P_1$ modulators.

One report documented the benefit of using fingolimod in both prevention and treatment in a sclerodermatous model of chronic GVHD in mice. Fingolimod treatment led to a significant decrease of body weight loss and inhibited skin and lung fibrosis. Best effects were observed when treatment with fingolimod was initiated at day 0 of disease induction [Huu 2013].

Multiple mechanisms have been described to explain the efficacy of fingolimod in chronic GVHD. Most importantly, fingolimod inhibited the infiltration of T- cells and other mononuclear cells into the skin (the major organ studied in this report) but also normalization of PTEN, MMP-1 and p-Smad-3 expression (gene products involved in fibrosis [Nho 2006, Gu 2007]) in skin. Also, mRNA expression of cytokines/chemokines

were reduced and the number of regulatory myeloid and lymphoid cells increased after treatment with fingolimod [Huu 2013].

1.3 Ponesimod, selective modulator of $S1P_1$

Ponesimod, an iminothiazolidinone derivative, is an orally active, selective modulator of $S1P_1$ that induces a rapid, dose-dependent, and reversible reduction in peripheral absolute lymphocyte count by blocking the egress of lymphocytes from lymphoid organs. T- and B-cells are most sensitive to ponesimod-mediated sequestration. In contrast, monocytes, natural killer (NK) cell, and neutrophil counts are not reduced by ponesimod. The effect of ponesimod on circulating effector T-cells represents a promising therapeutic approach for diseases in which activated T-cells play a critical role.

More detailed information can be found in the Investigator's Brochure [Ponesimod IB].

1.3.1 Nonclinical studies

The main findings in the nonclinical studies conducted with ponesimod are:

- Ponesimod causes a rapid and substantial reduction in circulating lymphocytes in rats and dogs, which is also rapidly and fully reversible. The effect correlates well with the plasma concentration of ponesimod.
- Studies with ponesimod in animal models of T-cell-mediated diseases, such as MS, rheumatoid arthritis, type 1 diabetes and skin hypersensitivity, consistently indicated a therapeutic potential of ponesimod at oral doses that lower peripheral blood lymphocyte counts.
- Ponesimod shows an oral bioavailability of 35–74%, low clearance, and a tissue distribution greater than total body water in rats and dogs. Plasma protein binding is high (≥ 98.9%) in rats, dogs, and humans.
- Based on available nonclinical data, the potential for drug-drug interactions (DDI) is limited.
- The metabolism of ponesimod is comparable in rats, dogs, and humans. The main metabolite, ACT-338375 (M13), is present in plasma of mice, rats, and dogs at levels similar to or higher than steady-state exposures in humans at 40 mg/day.
- The main targets for ponesimod-related toxicity after treatment of up to 4 weeks were the lungs (mice, rats, and dogs) and the nervous system (clinical signs, dogs only). After 13, 26, and 52 weeks of treatment, the heart and skin were identified as additional target organs in dogs. No-observed-adverse-effect levels were established for all toxicologically relevant targets in rats, mice, and dogs after 4, 13, 26, and 52 weeks of treatment, and resulting safety margins are considered acceptable.

- Embryo-fetal toxicity studies in rats and rabbits indicated that ponesimod has embryotoxic and teratogenic potential. In rat fertility studies, ponesimod had no effects on female and male fertility and did not produce any testicular morphologic changes.

Ponesimod has not been studied in nonclinical models of chronic GVHD, and no such studies are currently planned, due to the limited availability of models, alternative S1P class nonclinical data in acute and chronic GVHD [see Section 1.2.1], and extensive ponesimod safety and efficacy data obtained in both nonclinical studies and Phase 1 and Phase 2 studies in patients with autoimmune diseases. However, relevant to chronic GVHD, and in addition to the effect on circulating lymphocyte reduction, a decrease of local cytokines and chemokines has been demonstrated using ponesimod in animal models for skin inflammation and arthritis [Piali 2011]. Relative increases of regulatory T- and B-cells were also observed using ponesimod in a model of diabetes [You 2013] and in Phase 1 studies for ponesimod [D'Ambrosio 2015]. Ponesimod has also been demonstrated to inhibit the increase of IgA titers in a mouse model of lupus (data on file).

More detailed information can be found in the Investigator's Brochure [Ponesimod IB].

1.3.2 Clinical studies

Overall, more than 1000 subjects were exposed to ponesimod in the completed Phase 1 or Phase 2 clinical studies: 330 healthy male and female subjects, 24 subjects with hepatic impairment, and 16 subjects with renal impairment were exposed to single doses of ponesimod up to 75 mg and multiple doses up to 100 mg for up to 22 days; 304 subjects with moderate-to-severe chronic plaque psoriasis were exposed to ponesimod up to 40 mg once daily (o.d.) for up to 28 weeks, and 435 subjects with relapsing-remitting multiple sclerosis (RRMS) were exposed to ponesimod up to 40 mg o.d. for up to 4 years.

1.3.2.1 Clinical pharmacology

The pharmacokinetic (PK) profile of ponesimod is characterized by low variability. The terminal elimination half-life is about 32 h. There is approximately two-fold accumulation of the drug with repeated daily oral dosing, and steady state is achieved within 4–5 days. There is a good correlation between the plasma concentration of ponesimod and the peripheral blood absolute lymphocyte count. Food, age, race or sex do not appear to relevantly affect the PK and pharmacodynamics (PD) of ponesimod. The PK DDI potential of ponesimod is judged to be low based on current nonclinical and clinical data.

More detailed information can be found in the Investigator's Brochure [Ponesimod IB].

1.3.2.2 Pharmacodynamics in humans

Oral administration of ponesimod dose dependently reduces the circulating lymphocyte count in humans. The maximum reduction from baseline of approximately 65–80% is achieved after a single dose of ≥ 50 mg, or at steady-state, at 40 mg o.d. The nadir in

lymphocyte count is attained within 6–10 h following a given single dose. There is no evidence of tachyphylaxis of lymphocyte reduction. Peripheral blood counts of both T- and B-cells are reduced by ponesimod, while NK cells and neutrophils are not reduced. Food, race and/or gender do not appear to relevantly affect the PD of ponesimod. Upon discontinuation of ponesimod, the lymphocyte count generally returns to within the normal range within 1 week.

The magnitude of lymphocyte-count reductions seen with ponesimod in subjects with MS were consistent with observations made after treatments of short duration in healthy subjects. In the Phase 2 dose-finding study AC-058B201 with subjects with RRMS, at Week 24, the mean reductions from baseline in lymphocyte count were 49.8%, 65.3% and 68.6% in the ponesimod 10 mg, 20 mg, and 40 mg groups, respectively, compared to a mean increase of 3.3% in the placebo group. Lymphocyte count remained stable on treatment and returned to baseline levels within 1 week following ponesimod treatment discontinuation.

More detailed information can be found in the Investigator's Brochure [Ponesimod IB].

1.3.2.3 Efficacy in humans

Efficacy results are available for ponesimod in moderate-to-severe psoriasis and in RRMS.

Study AC-058A200 was a randomized placebo-controlled study, and the primary objective was to demonstrate the efficacy of 20 mg ponesimod o.d. on mean Psoriasis Area and Severity Index (PASI) at Week 6 in plaque psoriasis subjects. Although PASI improved, the primary endpoint was not achieved. PASI improved in both ponesimod and placebo groups up to Week 4; thereafter, the rate of decrease appeared more pronounced in ponesimod groups.

Study AC-058A201 was a randomized placebo-controlled study, and the primary objective was to demonstrate the efficacy of 20 and 40 mg ponesimod versus placebo at 16 weeks. There was a highly significant effect of both 20 and 40 mg doses over placebo in subjects achieving a 75% reduction in PASI score (primary analysis) and in Physician's Global Assessment of 'Clear' or 'Almost clear' at Week 16.

Study AC-058B201 was a randomized, placebo-controlled Phase 2b study, in which efficacy, safety, and tolerability of 10, 20, or 40 mg ponesimod administered for 24 weeks were investigated in subjects with RRMS. Treatment with ponesimod at all tested doses was associated with a statistically significant decrease in the cumulative number of new T1 gadolinium-enhanced lesions at Weeks 12, 16, 20, and 24 (primary endpoint) compared to placebo. The observed effect was dose dependent, reaching a risk reduction versus placebo of 77% ($p < 0.0001$), 83% ($p < 0.0001$) and 43% ($p < 0.05$) in the 40, 20, and 10 mg groups, respectively, versus placebo. The study was not powered to detect a significant

effect of ponesimod on clinical endpoints like aggregate annualized relapse rate (ARR) or time to first confirmed relapse. Treatment with ponesimod was associated with a reduction in the aggregate ARR up to Week 24. The ARR reduction in the 40 mg dose group was 52% (0.251 versus 0.525 for placebo; nominal $p < 0.05$), compared with 21% and 37% in the 20 mg and 10 mg groups, respectively. Treatment with ponesimod was associated with an increase in time to first confirmed relapse on treatment. The hazard ratio for subjects treated with 40 mg ponesimod was 0.42 (95% confidence interval [CI] 0.20–0.87, $p = 0.0189$). In the 20 mg and 10 mg groups, the hazard ratio was 0.79 (95% CI 0.43, 1.45) and 0.64 (95% CI 0.33, 1.22), respectively.

Study AC-058B202 is a parallel-group, blinded extension to study AC-058B201. Subjects who completed 24 weeks of treatment with ponesimod in the core study were offered to continue treatment with ponesimod. Subjects who completed 24 weeks of treatment with placebo were randomized in a 1:1:1 ratio to either 10, 20 or 40 mg ponesimod daily. The results from an interim analysis of study AC-058B201/B202 with cut-off date of 31 October 2013 have shown sustained low rates of magnetic resonance imaging and clinical disease activity with dose-dependent effects on relapse rate and disability accumulation.

More detailed information can be found in the Investigator's Brochure [Ponesimod IB].

1.3.2.4 Safety and tolerability

Clinical studies to date have identified transient changes in heart rate (HR) and atrioventricular (AV) conduction as the most prominent safety-related signal with ponesimod. Oral doses of ponesimod resulted in dose-dependent sinus rate reductions in all treated subjects; the changes were transient, with a nadir at approximately 1.5–2.5 hours post-dose, and resolved largely within 6–10 hours after dosing. In some subjects, these HR reductions were accompanied by a transient effect on AV conduction with prolongation of the PR interval on the electrocardiogram (ECG) and, occasionally, second degree AV-block. The effects on HR and AV conduction diminish with repeated administration of ponesimod, indicating desensitization. To minimize the first-dose effects on HR and AV conduction, a dose up-titration regimen was successfully tested and is implemented in current clinical trials.

Difficulty in inspiration (dyspnea) and related pulmonary function test (PFT) changes have also been detected in humans. Mild transient dyspnea/cough was noted frequently 2–6 h after an oral dose of 40 mg or higher. Symptoms resolved spontaneously upon discontinuation of treatment with ponesimod. Dose-dependent decreases from baseline in forced expiratory volume in 1 second ($FEV_{1)}$ were observed in the ponesimod groups. These decreases were established within the first few weeks, remained stable thereafter (including over long-term treatment), and were fully reversible following treatment discontinuation.

Elevations of aspartate transaminase (AST) and/or alanine aminotransferase (ALT) without any bilirubin increase have been noted with ponesimod; they have been reversible upon discontinuation of dosing. The changes were asymptomatic.

Individual cases of macular edema associated with changes in visual acuity have been observed in subjects treated with ponesimod. These events resolved upon discontinuation of ponesimod.

Nonclinical safety testing of ponesimod indicates an embryotoxic and teratogenic potential. Pregnant or lactating women are excluded from clinical trials, and women of child-bearing potential (WOCBP) must use reliable methods of contraception (MOC) and must not become pregnant during a clinical study and for at least 30 days after study drug discontinuation. A hormonal contraceptive is allowed as one of the required MOC, as the PK profile of hormonal contraceptives has been shown not to be substantially altered in the presence of ponesimod.

More detailed information can be found in the Investigator's Brochure [Ponesimod IB].

1.4 Rationale and purpose of the study

The central role of S1P in lymphocyte trafficking and the ability of an S1P receptor modulator to reduce the availability of circulating lymphocytes suggests a promising therapeutic approach for numerous immune system diseases [see Section 1.2].

The rationale for the study of ponesimod in the treatment of chronic GVHD is based on inhibition of T- and B-cell infiltration, reduction of local pro-inflammatory cytokines, relative increases of regulatory T-cells and possibly the reduction of antibody titers. Parts of these pathways were assessed in a model of sclerodermatous chronic GVHD using the non-selective $S1P_1$ modulator fingolimod. Ponesimod has also demonstrated efficacy and a consistent safety profile in plaque psoriasis and RRMS, two conditions where lymphocytes are considered central to pathophysiology [see Section 1.3].

The purpose of this Phase 2 study is to explore dose response, safety and efficacy of ponesimod at 5, 10, and 20 mg daily doses in subjects with moderate or severe chronic GVHD who are glucocorticoid refractory, dependent, or intolerant and inadequately responding to the most recent line of therapy.

2 STUDY OBJECTIVES

2.1 Main objectives

- To investigate the dose response in peripheral absolute lymphocyte count reduction with ponesimod in subjects with chronic GVHD
- To investigate the safety and tolerability of ponesimod in subjects with chronic GVHD

2.2 Exploratory objectives

- To investigate the efficacy of ponesimod in subjects with chronic GVHD

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This is a Phase 2 prospective, multi-center, open-label, intra-subject dose-escalation study. The study is designed to investigate the biological activity, safety, tolerability, and PK of ponesimod in subjects with symptomatic moderate or severe chronic GVHD inadequately responding to first- or second-line therapy.

Approximately 30 subjects will be enrolled to receive ponesimod in escalating doses of 5, 10 and 20 mg over the Core Treatment Period of 24 weeks. The study will be conducted at approximately 10 sites in the USA. Enrollment will proceed until the required number of subjects has been reached. Any subject in screening at the time of enrollment of the 30th subject may continue to enroll. Recruitment will be competitive across sites. Actelion may replace sites with no subject enrollment.

Subjects completing the initial 24 weeks of the study will have the option to restart ponesimod for an extension treatment course of 96 weeks, should their chronic GVHD progress within a defined timeframe after stopping ponesimod at Week 24 of the study.

3.2 Study periods

3.2.1 Screening Period

This period starts up to 30 days prior to the day of enrollment and includes the screening visit and all baseline assessments occurring before the time of enrollment (Visit 1 and Visit 2 pre-dose).

3.2.2 Core Treatment Period

The Core Treatment Period starts at enrollment, which occurs at the time of first study drug intake, and continues until the end of treatment at Week 24. Visits during the treatment period will consist of an enrollment visit (Day 1) and visits at Weeks 4, 8, 12, 16, 20, and 24.

The End-of-Treatment 1 (EOT1) visit will take place at Week 24 (Visit 8) or earlier in case of premature discontinuation of study drug. In all cases, the EOT1 visit should take place not later than 7 days after the last dose of study drug.

Subjects who complete EOT1 will be subsequently treated according to local standard of care at the investigator’s discretion.

3.2.3 Core Safety Follow-up Period / Follow-up Period 1

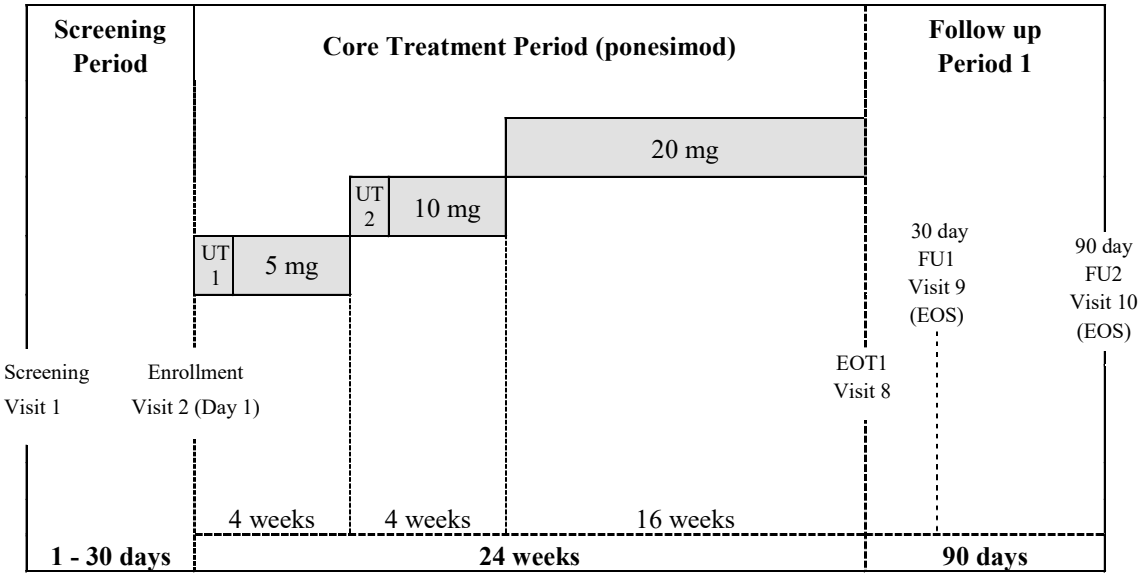
All subjects will enter the core safety follow-up period after EOT1 (Follow-up period 1), which will last for either 30 or 90 days.

The follow-up period for subjects who were prematurely discontinued lasts for 30 days after the last dose of study drug and ends with the 30-day follow-up 1 (FU1) visit. This is the End-of-Study (EOS) visit for these subjects. WOCBP must continue to use acceptable MOC during this 30-day period.

The follow-up period for subjects who were not prematurely discontinued lasts for 90 days after the last dose of study drug, and consists of the 30-day FU1 site visit and the 90-day follow-up 2 (FU2) visit, which is also the EOS visit. If the subject starts the study drug (and thus enters the Extension Treatment Period) prior to or on the day of scheduled FU1 and/or FU2, then one or both of these visits are cancelled. WOCBP must continue to use acceptable MOC during this 90-day period.

The study periods are depicted in Figure 2.

Figure 2 Study periods: Screening through Follow-up Period 1



EOT = End-of-Treatment; EOS = End-of-Study; FU = follow-up; UT 1 = 6-day up-titration; UT 2 = 4-day up-titration.

3.2.4 Extension Treatment Period

Subjects who completed the 24 weeks of study treatment (i.e., who were not prematurely discontinued from ponesimod) and whose chronic GVHD progressed after EOT1 may be restarted on study drug at least 7 days after EOT1 and no later than 90 days after EOT1.

The Extension Treatment Period starts the day ponesimod is started, on visit EX-1 (Visit 11) and can continue for up to 96 weeks. Visits during the Extension Treatment Period will consist of visit EX-1 and visits at EX-Weeks 4, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, and 96.

The End-of-Treatment 2 (EOT2) visit will take place at EX-Week 96, EX-13 (Visit 23) or earlier in case of premature discontinuation of study drug. In all cases, the EOT2 visit should take place not later than 7 days after the last dose of study drug.

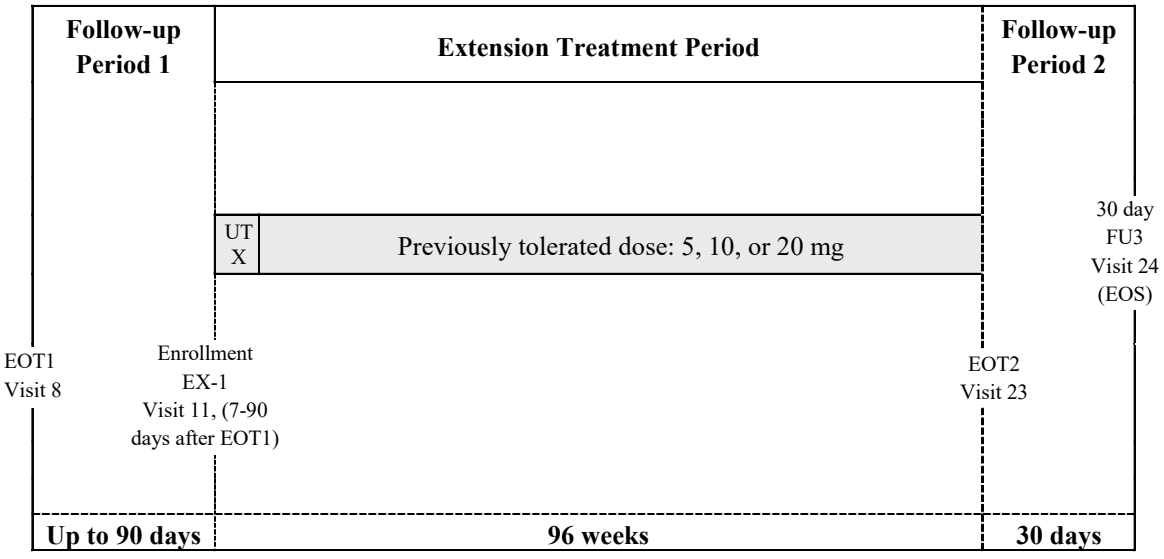
Subjects completing the EOT2 will be subsequently treated according to local standard of care at the investigator's discretion.

3.2.5 Extension Safety Follow-up Period (Follow-up Period 2)

All subjects will enter the safety follow-up period after EOT2 (Follow-up Period 2), which will last for 30 days after the last dose of study drug and end with the 30-day follow-up 3 (FU3) site visit (Visit 24). This visit is the EOS visit for these subjects. WOCBP must continue to use acceptable MOC during this 30-day period.

The study periods are depicted in Figure 3.

Figure 3 Study periods: Follow-up Period 1 through Follow-up Period 2



EOT1, 2 = End-of-Treatment 1, 2; EOS = End-of-Study; FU = follow-up; UTX = 6 or 14 day up-titration.

3.3 Study design rationale

Ponesimod has demonstrated efficacy, safety, and tolerability at 10, 20, and 40 mg daily doses in RRMS and moderate-to-severe chronic plaque psoriasis. Furthermore, the magnitude of lymphocyte count reductions seen with ponesimod in RRMS subjects treated

over 2 years and psoriasis subjects treated for up to 28 weeks were consistent with observations made after short-term treatment in healthy subjects [Ponesimod IB, section 5.2.2].

Unique to chronic GVHD, and in contrast to other immune diseases, is the event of HSCT and subsequent immune system reconstitution. Most conditioning protocols destroy the patient's immune system completely. After transplantation, donor monocytes are the first cells to engraft, followed by granulocytes, platelets, and NK cells. Clinical engraftment depends on achieving a sustained granulocyte count > 0.5 G/L and typically occurs 10 to 25 days after HSCT. The number of most leucocyte subsets normalize quickly afterwards. However, transfer of the donor's immunity is poor and T- and B-cell responses are incomplete for a long period after HSCT [Storek 2008]. Lymphocytes, the target of ponesimod, may have a markedly different homeostasis in chronic GVHD versus other studied diseases.

In order to safely conduct the first study of ponesimod in chronic GVHD, an open-label dose-escalation trial is proposed. Ponesimod effects on lymphocyte count will be established at the lower doses of 5 mg and 10 mg daily, prior to final dose escalation to 20 mg. This study seeks to expose subjects to the lower doses for an adequate time to establish the magnitude of dose response prior to allowing dose increases. Based on previous experience, maximal lymphocyte reduction occurs approximately 2 to 3 weeks after dose initiation, including up-titration [Ponesimod IB, section 5.2]; consequently, a one-month exposure duration (including up-titration) is assigned to the 5 mg and 10 mg daily doses each. Lymphocyte count will also be assessed 4 weeks after the final dose escalation to 20 mg to assess dose response and ensure subject safety.

Each chronic GVHD subject may have achieved different stages of immune reconstitution and lymphocyte homeostasis based on numerous variables, including time from transplant, conditioning regimen, age, and so on. Therefore, an intra-subject dose-escalation study is expected to provide the most meaningful results regarding ponesimod effects on lymphocyte count reduction in a study of modest sample size.

Ponesimod will be given over 24 weeks, 16 weeks of which are at the 20 mg daily dose. This timeframe will permit further evaluation of safety, including infections and ponesimod effects on lung function. Frequent monitoring, with 4-week intervals between visits and testing at minimum, will serve to ensure safety.

Efficacy will also be assessed. It is believed that improvement for many symptoms of chronic GVHD could be evident within the first four weeks of therapy [NIH Design of Clinical Trials 2014]; however, a response at 24 weeks is more meaningful. Currently, no standardized, validated global response measure has been developed for studies testing products for treatment of chronic GVHD

[NIH Design of Clinical Trials 2014]. Nevertheless, categorical criteria should be defined for response for each organ affected by GVHD, even if they have not been validated. Criteria for overall response should be unambiguous [Martin 2011]. This study employs updated draft NIH 2014 response criteria [NIH Therapeutic Response 2014], which were originally developed in 2005 [Pavletic 2006]. These criteria are based on international expert opinion.

The study will require stable administration of background IS therapy, including glucocorticoids. The following are exceptions: (1) glucocorticoid dose reductions will be permitted to ameliorate safety concerns related to prolonged steroid exposure; (2) glucocorticoid dose increases (or initiation) will be permitted to treat chronic GVHD flare or another condition; however, the sponsor will need to be notified prior to a dose increase (or initiation). Stable administration of study drug and other concomitant IS agents facilitates the interpretation of study results in chronic GVHD [Martin 2011].

Subjects successfully completing the initial 24 week treatment period (i.e., subjects not prematurely discontinued from study drug) are followed for 90 days after stopping study drug. Should subject's chronic GVHD progress after stopping ponesimod, they may restart ponesimod 7 to 90 days later. The rationale for the timeframe to restart is based on the following data:

- Previous experience in humans shows that lymphocyte counts recover within 7 days of stopping ponesimod [Ponesimod IB, section 1.4]. (It would be difficult to attribute progression of chronic GVHD to cessation of ponesimod's effect during the first 7 days after stopping, and difficult to justify restarting ponesimod in that period for that reason).

- Previous experience in chronic plaque psoriasis patients suggests that the proportion of patients with relapse of psoriasis approaches a plateau within 12 weeks after cessation of ponesimod [figure 2 in Vaclavkova 2014].

Subjects may be retreated with ponesimod for 96 weeks. There is limited data to support a rationale for duration of therapy of an investigational agent in responders. However, resolution of chronic GVHD is known to occur slowly, with many patients requiring several years of immunosuppressive therapy [Martin 2009].

The 96 week Extension Treatment portion of the study will thus continue to make study drug available for subjects who were previously shown to benefit from ponesimod. This extended treatment period will also provide longer term safety, tolerability and efficacy data. In contrast to the initial 24 week treatment period, investigators will have greater flexibility in administering allowed concomitant background immunosuppressant therapy.

3.4 Site personnel and their roles

It is recommended that the designated personnel remain unchanged throughout the entire course of the study and that an adequately trained back-up be designated in case of absence of any of the staff listed below.

At each site, the study staff will consist of:

- A principal investigator
- A cardiac safety assessor
- A clinical coordinator/study nurse (if required)
- An ophthalmologist
- A pulmonologist
- A pulmonary function laboratory technician or expert

3.4.1 Principal investigator and sub-investigator

The principal investigator is responsible for the overall conduct of the study at the site. It is her/his responsibility to explain the study and all its aspects to the subject and obtain her/his informed consent. The principal investigator will be responsible for subject clinical care and management, e.g., eligibility evaluation, supervision of study drug administration, monitoring of safety (including recording and treating of adverse events (AEs), physical examination, and routine laboratory results) and concomitant medications. The principal investigator may delegate duties to a sub-investigator but remains responsible for the overall conduct of the study at his/her site. The principal investigator and sub-investigator must be physicians experienced in treating chronic GVHD patients.

The principal investigator or sub-investigator will assess efficacy via the chronic GVHD Activity Assessment [Appendix 7] according to the protocol schedule.

3.4.2 Cardiac safety assessor

The cardiac safety assessor must be a physician adequately trained and experienced in cardiology. He/she must be qualified and equipped to provide emergency treatment in cases of acute cardiac events. While the exams themselves may be performed by a delegate (e.g., study nurse), their review and interpretation must be performed by the physician. The investigator may perform this role if qualified.

He/she is responsible for conducting all blood pressure (BP) and ECG assessments requested by the protocol during the study, including the close monitoring of the subject during the first 4 hours and up to 12 hours following study drug intake at Visit 2 (Day 1). He/she will independently assess eligibility for discharge or continued subject management on Visit 2 and on visits for re-initiation of study drug where post-dose monitoring will be required.

He/she will support the principal investigator in making a decision on eligibility of the subject prior to enrollment, and on providing adequate treatment in cases of cardiac events.

Significant findings, which in view of the cardiac safety assessor meet the definition of an AE, must be reported to the principal investigator and recorded on the Adverse Event page of the electronic Case Report Form (eCRF).

Any cardiac events of potential clinical concern must be assessed by the cardiac safety assessor for seriousness, and reported accordingly.

3.4.3 Clinical coordinator / study nurse

A clinical coordinator / study nurse may be required to assist the principal investigator / sub-investigator in all aspects of subject management. He/she will be responsible for scheduling visits and assessments as planned in the study protocol, recording concomitant medications, maintaining source documentation, and transcription of data into the eCRF. He/she will instruct the subjects on study drug administration, and collect, process, and send all blood and urine samples to the central laboratory. Additionally, he/she may be responsible for coordinating the conduct of PFTs, ophthalmological and cardiac examination, and the appropriate administration of the Patient-Reported Outcomes instruments. In the absence of a clinical coordinator / study nurse, the above tasks will be performed by the principal investigator or a sub-investigator.

3.4.4 Ophthalmologist

The ophthalmologist will review and interpret the ophthalmological examinations and optical coherence tomography (OCT) assessments as scheduled in the study protocol. In the event of suspected clinically significant findings (e.g., macular edema), unscheduled ophthalmology and OCT examination should be performed by the ophthalmologist, and the investigator will be notified for reporting of an AE. In the event of findings observed at any visit during the study, the ophthalmologist will conduct further examination, as per local standard practice, to rule out or confirm the diagnosis.

3.4.5 Pulmonary function laboratory technician or expert

The PFTs must be performed by experienced staff, such as a pulmonary function technician or expert according to the American Thoracic Society (ATS) / European Respiratory Society (ERS) guidelines [Miller 2005a] and study protocol schedule, in an established PFT unit.

3.4.6 Pulmonologist

A pulmonologist (or a physician adequately trained in pulmonology), will review PFT and diffusing capacity of lung for carbon monoxide (DL_{CO}) results. If clinically significant alterations in PFTs or DL_{CO} variables indicating a pulmonary condition that could result in increased risk for the subject are observed, he/she may be prematurely discontinued from

ponesimod at the discretion of the investigator. In the event of findings observed at any visit during the study, the pulmonologist will conduct further examination, as per local standard practice, to rule out or confirm the diagnosis.

3.5 Study Committees

3.5.1 Study Monitoring Committee

A Study Monitoring Committee (SMC), with a core comprising at least two medical experts in the field of chronic GVHD and two medical experts from the sponsor (i.e., the clinical project physician, and a drug safety physician with expert knowledge of the safety profile of ponesimod) will review toxicity assessments of each subject. At any time, the SMC may interrupt enrollment or recommend termination of the study for safety reasons. Additional permanent attendees of SMC meetings will include the clinical trial statistician, the clinical trial scientist and the clinical study coordinator. The SMC, governed by a charter, will ensure that the study is properly conducted, monitored, and that data are appropriately analyzed and interpreted. The SMC will recommend the dose of ponesimod for further development in chronic GVHD.

3.5.2 Ophthalmology Safety Board

An Ophthalmology Safety Board (OSB) composed of two independent ophthalmologists will review and evaluate any new or suspected case of macular edema. The composition and operation of the OSB is described in the OSB charter.

4 SUBJECT POPULATION

4.1 Subject population description

This study will enroll male and female subjects aged 18 to 70 with chronic GVHD. Subjects will need a change of systemic IS therapy, in the opinion of the investigator. The need for a change will be based on the following: (1) subjects must have symptomatic moderate or severe chronic GVHD; (2) subjects must be glucocorticoid refractory, dependent, or intolerant; and (3) subjects must have inadequate response to their current systemic IS therapy according to the investigator's judgment. The background IS therapy will be limited to commonly prescribed systemic first- and second-line therapies: glucocorticoids and/or one of the following: cyclosporine, tacrolimus, mycophenolate mofetil, mycophenolate sodium, everolimus, sirolimus, or methotrexate.

Subjects with specified clinically significant medical conditions cannot enter the study. These include active or uncontrolled infections, new or recurrent malignancy, serious cardiac, pulmonary, or renal disease, and uncontrolled diabetes, among others. Subjects with Karnofsky Performance Score < 60 are excluded.

Subjects receiving IS other than allowed background therapy and specified rate and rhythm altering drugs, such as β-blockers, verapamil or digoxin, cannot enter the study.

Eligible subjects must be able and willing to give informed consent for participation in the clinical study.

4.2 Rationale for the selection of the study population

The study seeks to enroll chronic GVHD patients with high unmet need, which is established at several levels.

Firstly, subjects must be symptomatic and have at least moderate severity chronic GVHD. Systemic therapy is typically indicated for chronic GVHD of at least moderate severity [Jagasia 2015].

Secondly, subjects should be glucocorticoid refractory, dependent, or intolerant. Glucocorticoids are standard first-line therapy for chronic GVHD, and it may be inappropriate to study ponesimod, initially, in subjects who could potentially benefit from glucocorticoids; however, approximately 50% of chronic GVHD patients do not have a sustained response to standard initial therapy, and the prognosis for patients considered to be glucocorticoid refractory or dependent is suboptimal [see Sections 1.1.3 and 1.1.4].

Finally, subjects should be inadequately responding to their current therapy. Since chronic GVHD may take several weeks to respond to a new course of therapy, it could be inappropriate to start ponesimod shortly after the current course was initiated, or if subjects are improving on the current course. Therefore, investigators may enroll subjects in this ponesimod study if they judge subjects' chronic GVHD to have progressed despite four weeks of the current course, or chronic GVHD to have not improved despite eight weeks of the current course. These criteria should be applied to first, second, or a subsequent line of current therapy, and have been adapted from general recommendations for indications for secondary treatment [Martin 2009].

With the exception of bronchiolitis obliterans syndrome (BOS), this study does not exclude any chronic GVHD manifestations from the patient population. However, due to safety considerations in this initial Phase 2 study, subjects with liver enzyme values, pulmonary function values, platelet counts, and other laboratory measures exceeding defined thresholds are excluded from enrollment. Thus, in addition to BOS, subjects with severe liver manifestations will not enter this study.

4.3 Inclusion criteria

For inclusion into the study, all of the following inclusion criteria must be fulfilled. No waivers of any of the criteria for any subject are allowed:

1. Signed informed consent prior to initiation of any study-mandated procedure.

2. Males and females aged 18 to 70 years.
3. Recipients of allogeneic HSCT diagnosed with chronic GVHD.
4. Currently receiving systemic IS therapy at enrollment, with no dose changes in the 14 days prior to enrollment, consisting of systemic glucocorticoids AND/OR one of the following systemic agents: cyclosporine (CsA), tacrolimus (TAC), mycophenolate mofetil (MMF), mycophenolate sodium (MPS), everolimus (EVL), sirolimus (SRL), or methotrexate (MTX).
5. Subject needs a change of current systemic IS therapy, in the opinion of the investigator, based on all of the following conditions:
    a. Symptomatic moderate or severe chronic GVHD per NIH global severity scoring assessed at screening [see Appendix 2 for NIH global severity scoring form].
    b. Glucocorticoid refractory, dependent, or intolerant status at screening [see Appendix 1 for guidance].
    c. Evidence of GVHD progression at enrollment despite ≥ 4 weeks current systemic IS therapy, OR without evidence of GVHD improvement at enrollment despite ≥ 8 weeks current systemic IS therapy. Current systemic IS therapy must be the same as in inclusion criterion 4 [see Appendix 1 for guidance].
6. Chronic GVHD manifestations involve at least one of the following organs: skin, mouth, eyes, joints and fascia, esophagus, upper or lower GI tract. The qualifying manifestation should have an NIH chronic GVHD activity assessment score of at least 1 at enrollment [see Form A, Appendix 7].
7. WOCBP, as defined in Section 4.3.1, must have a negative serum pregnancy test at screening and a negative urine or serum pregnancy test prior to enrollment, and must agree to undertake urine pregnancy tests every 4 weeks during the study and up to the protocol defined EOS.
8. WOCBP must agree to use acceptable MOC during the study and up to the protocol defined EOS.

4.3.1 Women of child-bearing potential

A woman is considered to be of child-bearing potential unless she meets at least one of the following criteria:

- Previous bilateral salpingo-oophorectomy or hysterectomy
- Premature ovarian failure confirmed by a specialist
- XY genotype, Turner syndrome, uterine agenesis
- Postmenopausal, defined as 12 consecutive months with no menses without an alternative medical cause (ICH M3 definition)

WOCBP participating in the study must agree to use one of the following reliable MOC from the screening visit and up to the protocol defined EOS:

- Two MOC, one from Group 1 and one from Group 2, defined as follows:
    - Group 1: Oral, implantable, transdermal or injectable hormonal contraceptives or intrauterine devices. If a hormonal contraceptive is chosen from this group, it must be taken for at least 1 month prior to enrollment
    - Group 2: Female or male condoms, diaphragm or cervical cap

OR

- True abstinence from intercourse with a male partner only when this is in line with the preferred lifestyle of the subject

OR

- Permanent female sterilization (tubal occlusion/ligation at least 6 weeks prior to screening)

OR

- Sterilization of the male partner with documented post-vasectomy confirmation of the absence of sperm in the ejaculate

4.4 Exclusion criteria

Subjects must not fulfill any of the following exclusion criteria. It is not permitted to waive any of the criteria for any subject:

Cardiovascular

1. Resting HR < 50 bpm measured by 12-lead ECG at enrollment (prior to study drug administration).
2. Myocardial infarction within 24 weeks prior to screening or ongoing unstable ischemic heart disease.
3. Cardiac failure (NYHA class III or IV) or any severe cardiac disease at time of screening.
4. History or presence of valvular heart disease associated with symptoms or hemodynamic change.
5. History or presence of cardiac rhythm disorders (e.g., sino-atrial heart block, symptomatic bradycardia, atrial flutter or atrial fibrillation, ventricular arrhythmias, cardiac arrest).

6. Presence of an increased QT corrected for HR on the basis of Fridericia's formula (QTcF) interval > 470 ms (females), > 450 ms (males) measured by 12-lead ECG at screening or pre-dose on Day 1.
7. History of syncope associated with cardiac disorders.
8. Systemic arterial hypertension not controlled by medication as judged by the investigator.

Hematologic

9. Hemoglobin (Hb) < 8.0 g/dL or need for red blood cell transfusion at screening.
10. Absolute neutrophil count < 1.5×10^9/L (< 1500 cells/mm^3) at screening.
11. Absolute lymphocyte count < 0.5×10^9/L (< 500 cells/mm^3) at screening.
12. Platelet count < 50×10^9/L (< 50,000 cells/mm^3) or need for platelet transfusion at screening.

Hepatic

13. ALT and/or AST ≥ 3.0-fold the upper limit of normal (ULN) at screening.
14. Total bilirubin (TBL) > 1.5-fold ULN (unless in the context of known Gilbert's Syndrome) at screening.
15. Known chronic liver or biliary disease that is not due to chronic GVHD.

Infection and infection risk

16. Active or uncontrolled bacterial, viral, or fungal infection (except onychomycosis and dermatomycosis); positive hepatitis B surface antigen or hepatitis C antibody tests at screening.
17. Cytomegalovirus (CMV) disease, including CMV pneumonia, CMV retinitis, and CMV gastroenteritis and/or subjects meeting institutional criteria for systemic therapy for CMV reactivation. (Subjects with positive CMV serology and/or CMV reactivation are not excluded if they do not have CMV disease and do not require systemic therapy.)
18. Active or latent tuberculosis (TB), as assessed by chest X-ray (CXR) performed at screening or within 90 days prior to screening, and interferon gamma release assay (QuantiFERON-TB-Gold®) at screening, except if there is documentation that the subject has received adequate treatment for TB previously.
19. Congenital or acquired severe immunodeficiency or known human immunodeficiency virus (HIV) or positive HIV testing at screening.

Malignancy

20. New or recurrent malignancy or minimal residual disease.

Metabolic

21. Type 1 or 2 diabetes that is poorly controlled according to investigator judgment or diabetes complicated with organ involvement such as nephropathy or retinopathy.

Ophthalmologic

22. Presence of macular edema.

Pregnancy and breastfeeding

23. Breastfeeding, pregnant women or women planning to become pregnant during the study.

Pulmonary

24. Subjects with a clinically significant pulmonary condition including asthma and chronic obstructive pulmonary disease (COPD) that is insufficiently controlled according to investigator judgment.
25. Subjects with diagnosed BOS.
26. Subjects with any hospitalization due to a clinically significant pulmonary condition including asthma or COPD exacerbation within 24 weeks prior to screening (with the exception of a fully resolved pulmonary infection).
27. Subjects with abnormal PFTs: FEV_1 < 60% of predicted normal value or FEV_1/forced vital capacity (FVC) ratio < 0.7 at screening.

Renal

28. Severe renal insufficiency defined as a calculated creatinine clearance < 30 mL/min/1.73 m^2 (Cockroft-Gault) at screening.

Treatments

29. Systemic glucocorticoids at prednisone-equivalent dose > 1.0 mg/kg/day at screening.
30. Treatment within 15 days prior to enrollment with:
    - Azathioprine
    - β-blockers, diltiazem, verapamil, digoxin, digitoxin or any anti-arrhythmic or HR-lowering systemic therapy (a non-exhaustive list of drugs provided in Appendix 4)
    - CsA, TAC, MMF, MPS, EVL, SRL (with the exception of any therapy serving as a mandatory concomitant therapy, as per inclusion criterion 4 and Section 5.2).
    - Extracorporeal photopheresis
    - Isotretinoin

- Thalidomide

31. Treatment within 30 days prior to enrollment with:
    - Acitretin
    - Cyclophosphamide
    - Etanercept
    - Imatinib
    - Vaccination with live vaccines
32. Treatment within 45 days prior to enrollment with:
    - Pulse methylprednisolone
    - MTX (with the exception if MTX serves as a mandatory concomitant therapy, as per inclusion criterion 4 and Section 5.2).
33. Treatment within 60 days prior to enrollment with:
    - Basiliximab
34. Treatment within 24 weeks prior to enrollment with:
    - Anti-lymphocyte globulin (ALG)
    - Anti-thymocyte globulin (ATG)
    - Belimumab
    - Mesenchymal stem cell therapy
    - Ofatumumab
    - Pentostatin
    - Rituximab
35. Treatment within 36 weeks prior to enrollment with:
    - Hydroxychloroquine
36. Treatment within 48 weeks prior to enrollment with:
    - Alemtuzumab
    - Clofazamine
37. Treatment with any IS or immunomodulatory drug or technology not identified in items 30 to 37, unless discussed with the sponsor to determine appropriate washout. Chemotherapy and radiation for conditioning treatment leading up to the stem cell transplant and growth factors are exempt and do not have to be discussed with the sponsor.

Other Categories

38. Karnofsky Performance Score (KPS) < 60%.
39. Known history of clinically significant drug or alcohol abuse.
40. Known allergy to any of the ponesimod formulation excipients.
41. Any other clinically relevant medical or surgical condition, which, in the opinion of the investigator, would put the subject at risk by participating in the study.
42. Subjects unlikely to comply with protocol, e.g., uncooperative attitude, inability to return for follow-up visits, or known likelihood of not completing the study including mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study.

4.5 Medical history

Relevant medical history, as defined below, must be recorded in the eCRF:

- Chronic medical conditions at any time in the past.
- Cardiac, cardiovascular, pulmonary, immune, hepatic, and eye conditions at any time in the past.
- New, significant acute medical conditions in the past 12 months prior to the study start.
- Smoking status

HSCT and GVHD history, as defined below, must be recorded in the eCRF including:

- Diagnosis leading to HSCT (acute myelogenous leukemia, acute lymphoblastic leukemia, aplastic anemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, hodgkin's lymphoma, multiple myeloma, myelodysplastic syndrome, myeloproliferative disorder, non-hodgkins lymphoma, other cancer, other non-malignant disease).
- Date of HSCT
- HSCT-conditioning regimen (myeloablative, non-myeloablative, reduced-intensity, none)
- HSCT-conditioning agents (ALG, ATG [for ALG, ATG, specify source: horse, rabbit, other]; busulphan, oral; busulphan, i.v.; campath; carmustine; cyclophosphamide; cytarabine/AraC; etoposide; fludarabine; melphalan ≤ 140 mg/m^2; melphalan > 140 mg/m^2; total body irradiation ≤ 500cGy single dose / ≤ 800cGy fractionated; total body irradiation > 500cGy single dose / > 800cGy fractionated; no conditioning; other)
- HSCT source (bone marrow, mobilized peripheral blood stem cells, cord blood, double cord)

- Allogeneic donor type (syngeneic; HLA-identical sibling; HLA-matched other relative; HLA-mismatched relative – 1 antigen mismatched [haplo-identical (yes, no)]; HLA-mismatched relative – ≥ 2 mismatched [haplo-identical (yes, no)]; matched unrelated donor; mismatched unrelated donor).
- For double cord only, second donor type (syngeneic; HLA-identical sibling; HLA-matched other relative; HLA-mismatched relative – 1 antigen mismatched [haplo-identical (yes, no)]; HLA-mismatched relative – ≥ 2 mismatched [haplo-identical (yes, no)]; matched unrelated donor; mismatched unrelated donor).
- Donor gender (male, female; choose two genders if double cord: male/female, male/male, female/female).
- Date of onset and resolution of acute GVHD.
- Acute GVHD diagnosis based on evidence from a biopsy (yes, no).
- Maximum overall grade of acute GVHD: I, II, III, or IV.
- Maximum severity of skin involvement, acute GVHD
    - No skin acute GVHD / rash not attributable to acute GVHD
    - Stage 0 – no rash
    - Stage 1 – maculopapular rash, < 25% of body surface
    - Stage 2 – maculopapular rash, 25–50% of body surface
    - Stage 3 – generalized erythroderma
    - Stage 4 – generalized erythroderma with bullae formation and desquamation
- Maximum severity of lower gastrointestinal tract, acute GVHD
    - No lower GI acute GVHD / diarrhea not attributable to acute GVHD
    - Stage 0 – no diarrhea
    - Stage 0 – diarrhea ≤ 500 mL/day
    - Stage 1 – diarrhea > 500 but ≤ 1000 mL/day
    - Stage 2 – diarrhea > 1000 but ≤ 1500 mL/day
    - Stage 3 – diarrhea > 1500 mL/day
    - Stage 4 – severe abdominal pain, with or without ileus
- Maximum severity of upper gastrointestinal tract, acute GVHD

  - No upper GI acute GVHD / persistent nausea or vomiting not attributable to acute GVHD
  - Stage 0 – no persistent nausea or vomiting
  - Stage 1 – persistent nausea or vomiting
- Maximum severity of liver involvement, acute GVHD
  - No liver acute GVHD / bilirubin level not attributable to acute GVHD
  - Stage 0 – bilirubin < 2.0 mg/dL
  - Stage 1 – bilirubin 2.0–3.0 mg/dL
  - Stage 2 – bilirubin 3.1–6.0 mg/dL
  - Stage 3 – bilirubin 6.1–15.0 mg/dL
  - Stage 4 – bilirubin > 15.0 mg/dL
- Other clinical involvement, acute GVHD (lung, other, none).
- Current and past acute GVHD treatments (ALG, ATG [for ALG, ATG, specify source: horse, rabbit, other]; glucocorticoids, systemic; glucocorticoids, topical; CsA; extra-corporeal photopheresis; tacrolimus [TAC]; anti-CD25 [zenapax, daclizumab, anti-Tac]; campath; etanercept; infliximab; other *in vivo* monoclonal antibody; *in vivo* immunotoxin; MTX; MMF; MPS; SRL; EVL; ursodiol; other agent).
- Date of onset of chronic GVHD
- Onset of chronic GVHD was:
  - Progressive (acute GVHD progressed directly to chronic GVHD)
  - Interrupted (acute GVHD resolved, then chronic GVHD developed)
  - *De novo* (acute GVHD never developed)
  - Chronic GVHD flare (symptoms reactivated within 30 days of drug tapering or discontinuation)
- Platelet count at diagnosis of chronic GVHD (expressed as $\times 10^9$/L)
- KPS at time of diagnosis of chronic GVHD.
- Diagnosis was based on: histologic evidence / biopsy proven; clinical evidence; both; unknown.
- Current and past chronic GVHD treatments (ALG, ATG [for ALG, ATG, specify source: horse, rabbit, other]; azathioprine; glucocorticoids, systemic; glucocorticoids, topical; CsA; extra-corporeal photopheresis; etretinate; TAC; hydroxychloroquine;

anti-CD25 [zenapax, daclizumab, anti-Tac]; campath; etanercept; infliximab; other *in vivo* monoclonal antibody; clofazimine; MMF; MPS; psoralen and ultraviolet A; SRL; EVL; thalidomide; ursodiol; other agent).

Concomitant baseline therapies, as defined in Section 5.3, will be recorded in the eCRF.

4.6 Extension Treatment Period inclusion criteria

For inclusion into the Extension Treatment Period of the study, all of the following inclusion criteria must be fulfilled. No waivers of any of the criteria for any subject are allowed:

1. Signed informed consent prior to initiation of any study-mandated procedure.
2. Subject has completed the 24 weeks of treatment of the Core Treatment Period and the EOT1 visit.
3. Subject has experienced disease progression 7 to 90 days after EOT1 visit, versus EOT1 chronic GVHD activity assessment, for at least one previously involved organ. Progression is per NIH Consensus Development Project response criteria and is defined in Section 6.3.2.
4. WOCBP, as defined in Section 4.3.1, must have a negative urine pregnancy test at enrollment visit EX-1, and at all prior visits, and must agree to undertake monthly scheduled urine pregnancy tests during the study and up to the protocol defined EOS.
5. WOCBP must agree to use acceptable MOC during the study and up to the protocol defined EOS.

4.7 Extension Treatment Period exclusion criteria

There are no exclusion criteria for the Extension Treatment Period. However:

- Study drug specific dose-reduction, interruption, or premature discontinuation criteria remain in force for the duration of the study. These are described in Section 5.1.10.
- Forbidden concomitant therapies remain in force for the duration of the study. These are described in Section 5.3.5.

5 TREATMENTS

5.1 Study treatment

The study treatment is the investigational drug ponesimod, administered during the Core and Extension Treatment Periods of the study.

In the Core Treatment Period, study treatment consists of a 5 mg ponesimod treatment period (from Days 1 to 28 including up-titration), 10 mg ponesimod treatment period (from Days 29 to 56 including up-titration) and a 20 mg treatment period (from Days 57 to day before EOT1).

In the Extension Treatment Period, study treatment consists of the subject's last tolerated dose administered throughout the Extension Treatment Period. The dose is either 5 mg, 10 mg, or 20 mg. The Extension Treatment Period is 96 weeks long, including up-titration, and starts with the enrollment visit EX-1 and ends with the EOT2 visit.

5.1.1 Investigational treatment: description and rationale

Ponesimod is supplied as its free base, in oral film-coated tablets at the doses of 2, 3, 4, 5, 6, 7, 8, 9, 10, and 20 mg. One tablet of ponesimod at any dose will be taken orally o.d.

Core Treatment Period

For this dose-escalation study, subjects will receive three treatment courses, with each treatment course studying one of the following ponesimod daily doses: 5, 10, and 20 mg.

This is the first clinical trial of ponesimod in subjects with chronic GVHD, and will assess PK, PD, safety and efficacy of 5, 10 and 20 mg of ponesimod. Initially, subjects enrolling in the study will be treated for 4 weeks with 5 mg ponesimod (6-day up-titration, 22 days at 5 mg), followed by treatment for 4 weeks with 10 mg of ponesimod (4-day up-titration, 24 days at 10 mg). For the remaining 16 weeks of the study the subjects will be treated with 20 mg ponesimod.

From past clinical trial experience, 20 mg ponesimod has displayed an optimal benefit-risk balance in subjects with MS and psoriasis. For these reasons, 20 mg has been chosen as the maximum dose to be studied in this clinical trial.

Extension Treatment Period

Subjects who completed the Core Treatment Period (i.e., not prematurely discontinued from study drug) may enroll in the Extension Treatment Period should their chronic GVHD worsen after stopping study drug at Week 24/EOT1 visit (as per eligibility criteria in Sections 4.6 and 4.7). Subjects will be up-titrated to their last tolerated ponesimod dose (prior to EOT1) and will receive ponesimod for 96 weeks, including up-titration.

5.1.2 Study treatment administration

5.1.2.1 Subject study treatment diary

Core Treatment Period

Subjects will be given a device to record every time ponesimod is taken. Details of the diary and instructions for completing it will be provided to the investigator. Site personnel will instruct the subject on how to complete the diary prior to administration of the first dose of study medication on Day 1 (Visit 2).

Extension Treatment Period

Subjects will be given instructions on proper use of ponesimod (no device will be provided).

5.1.2.2 Titration

Core Treatment Period

A 6-day up-titration will occur during study Days 1–6 using a titration blister wallet, to reduce ponesimod first-dose effects. On-site subject monitoring will be required at enrollment on Day 1 [see Section 5.1.7]. A 4-day up-titration will occur during study Days 29–32 to gradually transition from the 5 mg to the 10 mg daily dose. The subject will have the dose escalated from 10 to 20 mg on Day 57 (without gradual up-titration). The first day of the 4-day up-titration (Day 29) and the Day 57 dose escalation do not require on-site monitoring. [See Table 3].

Table 3 Up-titration and dose-escalation schedule: Core Treatment Period

Treatment Course		Study Day	Ponesimod Daily Dose
1	6-day up-titration	1 (Enrollment)	2 mg *(first dose given on-site with monitoring)*
		2	2 mg
		3 and 4	3 mg
		5 and 6	4 mg
	5 mg daily	7 to 28	5 mg
2	4-day up-titration	29 (Week 4)	6 mg
		30	7 mg
		31	8 mg
		32	9 mg
	10 mg daily	33 to 56	10 mg
3	Dose escalation to 20 mg	57 (Week 8)	20 mg
	20 mg daily	58 to day before EOT1 (Week 24)	20 mg

EOT1 = End-of-Treatment for the Core Treatment Period

Extension Treatment Period

A 6- or 14-day up-titration will occur starting at Visit EX-1 using a titration blister wallet, to reduce ponesimod first-dose effects. On-site subject monitoring will be required at enrollment at Visit EX-1 [see Section 5.1.7]. The choice of the 6- or 14-day up-titration will depend on the targeted dose: 5 mg, 10 mg, or 20 mg. The targeted dose is the subject's previously tolerated ponesimod dose just prior to EOT1. [See Table 4].

Table 4 Up-titration schedule: Extension Treatment Period

- The following up-titration scheme using a titration blister wallet is applied if the ponesimod 5 mg dose is targeted.

6 day up-titration scheme		
Day(s)	**Ponesimod Daily Dose**	**Given at site with monitoring**
1 (Visit EX-1)	2 mg	Yes
2	2 mg	No
3 and 4	3 mg	No
5 and 6	4 mg	No
7 to EOT2	5 mg	No

- The following up-titration scheme using a titration blister wallet is applied if the ponesimod 10 mg dose is targeted.

14 day up-titration scheme		
Day(s)	**Ponesimod Daily Dose**	**Given at site with monitoring**
1 (Visit EX-1)	2 mg	Yes
2	2 mg	No
3 and 4	3 mg	No
5 and 6	4 mg	No
7	5 mg	No
8	6 mg	No
9	7 mg	No
10	8 mg	No
11	9 mg	No
12, 13, and 14	10 mg	No
15 to EOT2	10 mg	No

- The following up-titration scheme using a titration blister wallet is applied if the ponesimod 20 mg dose is targeted.

14 day up-titration scheme		
Day(s)	**Ponesimod Daily Dose**	**Given at site with monitoring**
1 (Visit EX-1)	2 mg	Yes

2	2 mg	No
3 and 4	3 mg	No
5 and 6	4 mg	No
7	5 mg	No
8	6 mg	No
9	7 mg	No
10	8 mg	No
11	9 mg	No
12, 13, and 14	10 mg	No
15 to EOT2	20 mg	No

Core and Extension Treatment Periods

Study drug dose up-titration, other than described above, is prohibited. Study drug dose reduction is permitted under some circumstances [see Section 5.1.10].

One tablet will be taken orally o.d., preferably in the morning, with or without food, and preferably at approximately the same time each day. The tablet will be swallowed as a whole. The last administration date and time of study drug before a visit and the administration date and time of study drug on the days of visits will be recorded in the eCRF.

5.1.2.3 Criteria to permit dose increases at Day 29 and Day 57 (Core Treatment Period)

Subjects may have daily doses up-titrated from 5 mg to 10 mg started on Day 29, or dose escalated from 10 mg to 20 mg on Day 57, if the following is true:

a) Subject has not met the study-specific criteria for interruption, dose reduction, or premature discontinuation of study treatment, described in Section 5.1.10.
b) Subject does not have an ongoing grade 2 adverse event at least possibly related to study drug.
c) Subject took the correct scheduled study drug dose the day prior to the day of up-titration or dose escalation.
d) Investigator has reviewed and approved of the results of the Day 29 and/or Day 57 pre-dose assessments specified in Table 1.

5.1.2.4 Maintenance of ponesimod dose (Core and Extension Treatment Periods)

One tablet of study drug will be taken orally o.d., preferably in the morning, either before, with or after breakfast. It is preferable that the tablet be taken each day at approximately

the same time. The tablet will be swallowed as a whole. During the Core Treatment Period only, the date and time of each study drug administration will be recorded by the subject in a diary.

On the day of the study visits, study drug must be administered only after the completion of the scheduled pre-dose safety assessments (systolic BP [SBP] and diastolic BP [DBP], ECGs, PFTs, laboratory tests) and PK sampling.

5.1.3 Blinding

Not applicable.

5.1.4 Study treatment supply

Manufacture, labeling, packaging and supply of study treatments will be conducted according to Good Manufacturing Practice, Good Clinical Practice (GCP) and any local or national regulatory requirements.

All treatment supplies are to be used only in accordance with this protocol and not for any other purpose.

5.1.4.1 Study treatment packaging and labeling

5.1.4.1.1 Study treatment packaging

Study treatment is provided as film-coated tablets and supplied in the following childproof bottles and childproof blister wallets:

- 6-day up-titration wallet containing two 2 mg tablets; two 3 mg tablets; two 4 mg tablets.
- 4-day up-titration wallet containing: one 6 mg tablet; one 7 mg tablet; one 8 mg tablet; one 9 mg tablet.
- 14 day up-titration wallet containing: two 2 mg tablets; two 3 mg tablets; two 4 mg tablets; one 5 mg tablet; one 6 mg tablet; one 7 mg tablet; one 8 mg tablet; one 9 mg tablet; three 10 mg tablets.
- 5 mg maintenance bottle containing thirty-six 5 mg tablets.
- 10 mg maintenance bottle containing thirty-six 10 mg tablets.
- 20 mg maintenance bottle containing thirty-six 20 mg tablets.

5.1.4.1.2 Study treatment labeling

Study treatment is labeled to comply with the applicable laws and regulations.

5.1.4.2 Study treatment distribution and storage

Treatment supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the medication labels. Ponesimod must not be stored above 25 °C (recommended storage is 15–25 °C).

5.1.4.3 Study treatment dispensing

The subjects will receive sufficient study treatment to cover the period up to the next scheduled visit. Subjects are asked to return all used, partially used and unused study treatment blister wallets and/or bottles at each protocol-scheduled visit. An accurate record of the date and amount of study treatment dispensed to each subject must be available for inspection at any time.

5.1.4.4 Study treatment return and destruction

On an ongoing basis and/or on termination of the study, the monitor will collect used and unused bottles or blister wallets, which will be sent to the warehouse, where Actelion or a deputy will check treatment reconciliation.

5.1.5 Drug accountability and compliance

5.1.5.1 Drug accountability

Records of study drug dispensed and returned, dosages administered, and intervals between visits are kept during the study. Study treatment accountability must be performed by the study staff on the day of the visit and before providing further study treatment, in order to ensure that the subject is compliant with study requirements. Study treatment accountability is checked by the monitor during site visits and at the end of the study.

5.1.5.2 Drug compliance

Core Treatment Period

Subjects' compliance with study drug intake will be monitored using a diary. On each day, the subjects will be asked to enter the date, time, number of tablets taken, and the unique bottle or blister wallet identifying number from which the tablets were taken from. In addition, during the up-titration, the position of the well on the blister wallet will be recorded in order to monitor that study drug tablets were taken in the correct sequence [see Section 5.1.2.1].

The study drug accountability performed by the site at each visit [see Section 5.1.5.1] will be used to crosscheck the subject's compliance as indicated in the diary. Identified discrepancies will be reconciled by the site. Subjects will be asked to explain the observed discrepancies. Interruptions with known dates will be recorded accordingly in the study drug log [see Section 5.1.6]. Study drug intake requirement will be re-explained to the subject each time an interruption is observed.

Extension Treatment Period

The study drug accountability performed by the site at each visit [see Section 5.1.5.1] will allow to assess the subject compliance. Interruptions with known dates will be recorded accordingly in the study drug log [see Section 5.1.6]. Study drug intake requirements will be re-explained to the subject each time an interruption is observed.

5.1.6 Ponesimod dose adjustments and interruptions

Ponesimod up-titration, other than described in Section 5.1.2, is prohibited. Ponesimod dose reduction is permitted under some circumstances [see Section 5.1.10].

Ponesimod interruption should be avoided. If ponesimod intake is interrupted by the subject for any reason, he/she must immediately inform the investigator.

Ponesimod may be temporarily interrupted in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons. Study-specific criteria for interruption of ponesimod are described in Section 5.1.10.

Detailed guidance on how to re-initiate ponesimod in the event of drug interruption is provided in Section 5.1.8.

Ponesimod dose adjustments / interruptions must be recorded in the eCRF.

5.1.7 Cardiac monitoring for ponesimod initiation and re-initiation requiring re-uptitration

Subjects must undergo cardiac monitoring at the site on Day 1 (Visit 2 - ponesimod initiation) and EX-1 (Visit 11 - ponesimod treatment initiation in the extension).

Subjects must also undergo cardiac monitoring at the site on the first day of any ponesimod re-initiation requiring up-titration.

Cardiac monitoring is overseen by the cardiac safety assessor and consists of the following:

- Pre-dose: 12-lead ECG; systolic/diastolic BP measurement.
- Hourly post-dose, starting 1 hour post-dose: 12-lead ECG; systolic/diastolic BP measurement. ECG and BP are recorded hourly until the subject is discharged from monitoring.
- Discharge from monitoring at least 4 hours post-dose, as per “Discharge from Cardiac Monitoring Criteria” below.

Discharge from Cardiac Monitoring Criteria

After the collection of the 12-lead ECG and systolic/diastolic BP measurement at 4 hours post-dose and up to 12 hours post-dose, the subject may be discharged from the clinic and continue on ponesimod as soon as all of the following are met:

- ECG-derived resting HR > 45 bpm on the last ECG. If ECG-derived resting HR < 50 bpm on the last ECG, then HR at last ECG must be higher than at least one HR recorded on any prior post-dose ECG.
- SBP > 90 mmHg.
- QTcF < 481 ms on the last ECG.
- Increase in QTcF on the last ECG versus pre-dose ECG must be < 60 ms.
- No persisting significant ECG abnormality (e.g., QT prolongation, AV block second degree or higher) or ongoing AE requiring continued hospitalization or prohibiting study continuation as an outpatient.

Should the subject not meet the criteria for discharge at 12 hours post-dose, he/she must be discontinued from ponesimod. Subjects who are discontinued may be discharged from the monitored setting only after the following criteria are met:

- Vital signs return to near baseline values.
- No persisting ECG abnormality (e.g., AV block second degree or higher).
- No ongoing AE requiring continued hospitalization.
- Absence of any other medical indication to remain in the monitoring setting.

5.1.8 Procedures for re-initiation of ponesimod in the event of interruption

Under no circumstances should a subject take more than one tablet per day.

Terminology

- Interruption: a day or the days where subject did not take a prescribed ponesimod dose.
- Re-initiation: the day a ponesimod dose is taken following an interruption.
- Re-initiation with up-titration: Re-initiation of a gradually increasing ponesimod dose regimen that reaches a target dose over several days. Not all re-initiations include up-titrations.

If ponesimod intake is interrupted by the subject for any reason, the subject must immediately inform the investigator. The investigator and subject must adhere to the mandatory procedures described here regarding re-initiation.

Mandatory procedures for the following five interruption scenarios:

<u>Scenario 1:</u> Subject missed taking 1 to 3 consecutive doses, with first dose missed on study Day 2–6. (Scenario 1 applies to Core Treatment Period only.)

- Ponesimod must be re-initiated within 3 days of last missed dose, otherwise ponesimod is prematurely discontinued.
- The following up-titration scheme using a titration blister wallet needs to be applied:

6 day up-titration scheme		
Re-initiation Day	**Ponesimod Daily Dose**	**Given at site with monitoring**
1	2 mg	Yes
2	2 mg	No
3 and 4	3 mg	No
5 and 6	4 mg	No
7, 8, …	5 mg	No

- Re-initiation with up-titration for scenario 1 is allowed only once during the study, otherwise ponesimod is prematurely discontinued.

<u>Scenario 2:</u> Subject missed taking ≥ 4 consecutive doses, with first dose missed during study Days 2–56. (Scenario 2 applies to Core Treatment Period only.)

- Subjects may only be re-initiated on ponesimod as per protocol and per investigator judgment, and according to the up-titration schemes in Scenario 4 below. Subsequent dose escalation from 5 mg to 10 mg or from 10 mg to 20 mg, whichever is relevant, is prohibited.

<u>Scenario 3:</u> Subject missed taking 1 to 3 consecutive doses any time after study Day 6. (Scenario 3 applies to both Core and Extension Treatment Periods.)

- Dosing should be re-initiated at the same dose as the dose taken prior to ponesimod interruption, **with the following exceptions (exceptions apply to the Core Treatment Period only):**
  i. If the interruption occurs during Core Treatment Period Days 29–32 (up-titration to 10 mg), the missed dose(s) is/are taken to complete remaining doses in the titration blister wallet
  ii. If the interruption includes Core Treatment Period Day 57 (dose-escalation to 20 mg), the 10 mg dose is restarted, and a clinic visit is scheduled to conduct required assessments (e.g., ECG) prior to dose escalation to 20 mg
- Ponesimod intake may be re-initiated by the subject at home.
- Subjects must be instructed to contact the investigator immediately if they experience any symptoms of bradycardia (e.g., dizziness, vertigo, syncope).

<u>Scenario 4:</u> Subject missed taking ≥ 4 consecutive doses during study Days 57–148 (Core Treatment Period) or at any time during the Extension Treatment Period.

- The following up-titration scheme using a titration blister wallet is applied if the ponesimod 5 mg dose is targeted. Ponesimod must be re-initiated within 10 days of last missed dose, otherwise ponesimod is prematurely discontinued (discontinuation applies to Core Treatment Period only).

6 day up-titration scheme		
Re-initiation Day	**Ponesimod Daily Dose**	**Given at site with monitoring**
1	2 mg	Yes
2	2 mg	No
3 and 4	3 mg	No
5 and 6	4 mg	No
7 to EOT1, 2	5 mg	No

- The following up-titration scheme using a titration blister wallet is applied if the ponesimod 10 mg dose is targeted. Ponesimod must be re-initiated within 10 days of last missed dose, otherwise ponesimod is prematurely discontinued (discontinuation applies to Core Treatment Period only).

14 day up-titration scheme		
Re-initiation Day	**Ponesimod Daily Dose**	**Given at site with monitoring**
1	2 mg	Yes
2	2 mg	No
3 and 4	3 mg	No
5 and 6	4 mg	No
7	5 mg	No
8	6 mg	No
9	7 mg	No
10	8 mg	No
11	9 mg	No
12, 13, and 14	10 mg	No
Day 15 to EOT1, 2	10 mg	No

- The following up-titration scheme using a titration blister wallet is applied if the ponesimod 20 mg dose is targeted. Ponesimod must be re-initiated within 10 days of last missed dose, otherwise ponesimod is prematurely discontinued (discontinuation applies to Core Treatment Period only).

14 day up-titration scheme		
Re-initiation Day	**Ponesimod Daily Dose**	**Given at site with monitoring**
1	2 mg	Yes
2	2 mg	No
3 and 4	3 mg	No
5 and 6	4 mg	No
7	5 mg	No
8	6 mg	No
9	7 mg	No
10	8 mg	No
11	9 mg	No
12, 13, and 14	10 mg	No
Day 15 to EOT1, 2	20 mg	No

- Re-initiation with up-titration for scenario 4 is allowed only once during the Core Treatment Period, otherwise ponesimod is prematurely discontinued.
- Re-initiation with up-titration for scenario 4 may be permitted more than once during the Extension Treatment Period if it is in the best interest of the subject. The investigator should discuss with Actelion.

Scenario 5:
Subject missed taking ≥ 4 consecutive doses during study Days 149–167.

- Ponesimod is prematurely discontinued and an EOT1 visit is conducted.

5.1.9 Premature discontinuation of ponesimod

The decision to prematurely discontinue study treatment may be made by the subject, the investigator or Actelion.

A subject has the right to prematurely discontinue study treatment at any time by withdrawal from treatment only or by withdrawal from treatment and any further participation in the study.

The investigator should discontinue study treatment for a given subject if, on balance, he/she believes that continued administration would be contrary to the best interests of the subject.

Premature discontinuation of study treatment may also result from a decision by Actelion, e.g., in case of premature termination or suspension of the study [see Section 9.3].

The main reason and whether discontinuation of study treatment is the decision of the subject, the investigator or Actelion must be documented in the eCRF.

A subject who prematurely discontinues study treatment is NOT considered as withdrawn from the study and will be followed up until the end of the safety follow-up period (30 days after study drug discontinuation), provided that the subject's consent for this limited participation in the study has not been withdrawn.

A subject who prematurely discontinues study treatment and withdraws consent to participate in any further study assessments is considered withdrawn from the study. Subjects who die or are lost to follow-up are also considered as withdrawn from the study. Withdrawal from the study and follow-up medical care of subjects withdrawn from the study is described in Sections 9.2 and 9.4, respectively.

5.1.10 Specific dose-reduction, interruption, or premature discontinuation criteria

Ponesimod should be prematurely discontinued before initiating rescue IS therapy or other forbidden medications during the Core Treatment Period. Ponesimod should also be prematurely discontinued before initiating forbidden medications during the Extension Treatment Period. See Section 5.3.5.

Ponesimod-specific dose reduction, interruption, or premature discontinuation criteria are presented for a variety of conditions and scenarios grouped according to the following organ systems. These criteria apply during both the Core and Extension Treatment Periods:

(1) Cardiovascular
(2) Hematologic
(3) Hepatobiliary
(4) Immune/infection

(5) Ocular
(6) Reproductive/pregnancy
(7) Respiratory

5.1.10.1 Cardiovascular

Ponesimod must be discontinued if any of the following are true at any time:

1) The following are observed and also documented by ECG at any time during the study:
   a) HR < 40 bpm, or
   b) HR < 60 bpm is sustained for at least 1 hour and is associated with symptoms of bradycardia (e.g., syncope, dizziness, or vertigo), or
   c) QTcF > 500 ms is observed at any time throughout the study.
2) The subject does not meet the criteria for discharge from hospital on Day 1, EX-1 or on the first day of re-initiation of ponesimod following drug interruptions after 12 h post-dose monitoring.
3) The subject needs to receive systemic chronic treatment with β-blockers, diltiazem, verapamil, digoxin, digitoxin, or any other anti-arrhythmic or HR-lowering therapy (non-exhaustive list of drugs provided in Appendix 4).
4) Subject experiences *de novo* or worsening of pre-existing hypertension that cannot be adequately controlled by medications.

Continuous ECG monitoring is recommended for subjects who meet ponesimod discontinuation criteria related to bradycardia or other arrhythmias. Subjects who are prematurely discontinued may be discharged from the monitored setting only after the following criteria are met:

Mandatory discharge from the clinic/hospital criteria for subjects discontinued due to bradycardia or other arrhythmias:

- Vital signs return to near baseline values.
- No persisting ECG abnormality (e.g., AV block second degree or higher).
- No ongoing AE requiring continued hospitalization.
- Absence of any other medical indication to remain in the monitoring setting.

At Visits 3, 4, 5, 6 and 7 (Weeks 4, 8, 12, 16 and 20) in the Core Treatment Period and Visits EX-2, EX-3, EX-4, EX-5, EX-6, EX-7, EX-8, EX-9, EX-10, EX-11, and EX-12 (Extension Weeks 4, 8, 12, 16, 20, 24, 36, 48, 60, 72, and 84) in the Extension Treatment Period, 12-lead ECG measurements are collected pre-dose. In the event of a grade 2 QTc elevation, a repeat 12-lead ECG must be collected 3 hours post-dose. If QTcF > 500 ms, the subject is prematurely discontinued from the study. In addition, a PK sample must be collected within 20 minutes after the 3 hour post-dose ECG.

Any clinically relevant finding found after ponesimod initiation and during the follow-up period and meeting the definition of an AE will be recorded accordingly in the eCRF.

5.1.10.2 Hematologic

Ponesimod must be prematurely discontinued for any of the following laboratory findings at any time:

- Confirmed neutrophil count < 0.5×10^9/L (< 500 cells/mm^3).
- Confirmed absolute lymphocyte count < 0.1×10^9/L (< 100 cells/mm^3), and subject is receiving ponesimod 5 mg daily or less.

Ponesimod must be prematurely discontinued or, alternatively, the dosage must be reduced (dose reduction) for the following laboratory finding at any time:

- Confirmed absolute lymphocyte count < 0.1×10^9/L (< 100 cells/mm^3), and subject is receiving ponesimod 10 mg or 20 mg.

Confirmation will be done as follows:
Whenever a neutrophil count < 0.5×10^9/L (< 500 cells/mm^3) or an absolute lymphocyte count < 0.1×10^9/L (< 100 cells/mm^3) is recorded by the central laboratory, an alert will be sent to the principal investigator and the sponsor. The site will immediately contact the subject and ask her/him to return to the site within 48 hours at the latest to repeat the test at trough level (pre-dose) by the central laboratory (unless the clinical situation mandates immediate local testing). If the repeat test confirms a neutrophil count < 0.5×10^9/L (< 500 cells/mm^3) or an absolute lymphocyte count < 0.1×10^9/L (< 100 cells/mm^3), then ponesimod must be discontinued or dose reduced according to the criteria above.

Monitoring for prematurely discontinued subjects
Neutrophil or lymphocyte counts must be monitored at least once a week by the local laboratory until the neutrophil count has returned to ≥ 80% of the baseline value or the absolute lymphocyte count has returned to ≥ 0.5×10^9/L (≥ 500 cells/mm^3) or ≥ 80% of the baseline value. Any clinically relevant finding found after ponesimod initiation and

during the follow-up period and meeting the definition of an AE will be recorded accordingly in the eCRF.

Dose reduction and monitoring
For those subjects qualifying for dose reduction, the previously tolerated dose is immediately instituted without dose interruption. For subjects currently on ponesimod 10 mg, the 5 mg dose is restarted. For subjects on 20 mg, the 10 mg dose is restarted. Subjects remain on the lower dose for the remainder of the study, with no further dose-escalation. Lymphocyte counts are repeated at the next scheduled study visit after dose-reduction (or earlier per investigator judgment), and **if the absolute lymphocyte count remains < 0.1 × 10^9/L (< 100 cells/mm^3) ponesimod is discontinued.** Hematologic monitoring for prematurely discontinued subjects is continued as per above.

5.1.10.3 Hepatobiliary

In case of abnormal liver tests or signs and symptoms suggestive of drug-induced liver injury, subjects will be closely observed, liver tests will be repeated, and ponesimod may need to be prematurely discontinued or interrupted.

The central laboratory will send alerts to the principal investigator and the sponsor whenever any of the following hepatobiliary laboratory abnormalities are recorded during the study:

- ≥ Grade 2 elevation ALT (> 3 × ULN)
- ≥ Grade 2 elevation AST (> 3 × ULN)
- ≥ Grade 2 elevation blood bilirubin (same as TBL) (> 1.5 × ULN)

The site will immediately contact the subject and ask him/her to return to the site within 72 hours, at the latest, to repeat the test by the central laboratory (unless the clinical situation mandates immediate local testing). An inquiry should be made about symptoms.

Should repeat testing confirm continuing abnormality, the following will apply:

Ponesimod must be prematurely discontinued for any of the following:

- Grade 4 ALT or AST elevation (> 20.0 × ULN).
- Grade 4 blood bilirubin (same as TBL) elevation (> 10.0 × ULN).
- Grade 2 or higher ALT or AST elevation (> 3 × ULN) and (TBL > 2 × ULN or international normalized ratio [INR] > 1.5; corresponds to Hy's Law).
- Grade 2 or higher ALT or AST elevation (> 3 × ULN) with the appearance of: fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
- Grade 3 or higher ALT or AST elevation (> 5.0 × ULN) during study Days 2–56 or study Days 149–168.
- Grade 3 or higher TBL elevation (> 3.0 × ULN) during study Days 2–56 or study Days 149–168.
- Grade 3 or higher ALT or AST elevation (> 5.0 × ULN) and subject is taking ponesimod 5 mg.
- Grade 3 or higher TBL elevation (> 3.0 × ULN) and subject is taking ponesimod 5 mg.

Please see box "Monitoring for all subjects with confirmed ≥ grade 2 AST, ALT, or TBL elevations".

Ponesimod is interrupted for any of the following:

- Grade 3 ALT or AST elevation (> 5.0–20.0 × ULN) during study Days 57–148 or during the Extension Treatment Period.
- Grade 3 TBL elevation (> 3.0–10.0 × ULN) during study Days 57–148 or during the Extension Treatment Period.

Procedure for interruption

- Interrupt ponesimod for at least 7 days.
- Perform a re-test of AST, ALT, TBL within 7 days.
- If elevated values do not return to baseline levels within 7 days following treatment interruption, **ponesimod is prematurely discontinued. Please see box "Monitoring for all subjects with confirmed ≥ grade 2 AST, ALT, or TBL elevations".**
- If elevated values return to baseline levels within 7 days following treatment interruption, **ponesimod is re-initiated with up-titration.**

Procedure for re-initiation with up-titration

- Re-initiation occurs 8–10 days after ponesimod was interrupted.
- The previously tolerated dose is targeted at re-initiation with up-titration. For subjects on ponesimod 10 mg at the time of interruption, the 5 mg dose is targeted. For subjects on 20 mg at the time of interruption, the 10 mg dose is targeted. Subjects remain on the lower dose for the remainder of the study, with no further dose-escalation.
- **Re-initiation and up-titration should be conducted in accordance with Section 5.1.8, scenario 4.**

Perform a re-test of AST, ALT, TBL at 5–7 and 10–12 days following re-initiation, and monthly thereafter. Recurrence of ≥ grade 3 AST, ALT, TBL results in premature discontinuation with follow-up monitoring.

Please see box "Monitoring for all subjects with confirmed ≥ grade 2 AST, ALT, or TBL elevations".

Monitoring for all subjects with confirmed ≥ grade 2 AST, ALT, or TBL elevations

- Monitoring continues even after ponesimod discontinuation or interruption.
- AST, ALT, and TBL are re-tested weekly, and more frequently if indicated, until laboratory abnormalities are no longer regarded as clinically relevant.
- Follow-up monitoring, including more frequent visits, is provided until signs and symptoms have resolved or until medically indicated.
- Further diagnostic work-up/consultation with a hepatologist or other specialist should be considered according to local practice and the clinical situation.

Any clinically relevant finding found after ponesimod initiation and during the follow-up period and meeting the definition of an AE will be recorded in the eCRF.

5.1.10.4 Immune/infection

Subjects must be prematurely discontinued from ponesimod at any time during the study in the event of an infection requiring discontinuation of treatment per investigator judgment.

In the event of an infection, the subject should be treated as clinically indicated and, if medically appropriate, study drug discontinued at the discretion of the investigator. In case of study drug discontinuation, adequate treatment needs to be provided, and the subject must be monitored until complete resolution of the infection.

If the infection resolves and the benefit/risk balance is considered acceptable for the subject to resume study treatment, ponesimod may be re-initiated at the discretion of the investigator. See Section 5.1.8 for re-initiation procedures.

Given ponesimod effects on lymphocytes, heightened vigilance is required for opportunistic infections, with particular attention to be paid to viral infections. However, investigators and physicians following subjects should also be alert to potential systemic infections caused by fungi and bacteria.

Table 5 highlights opportunistic infections common in patients at least 30 days following HSCT (and relevant for the patient population in this study).

Table 5 Common opportunistic infections in patients at least 30 days post-HSCT

Stage	Infections
Post-engraftment: approximately 30 to 100 days post-transplant	• Herpes viruses, especially CMV (Note: CMV causes pneumonia, hepatitis, and colitis and potentiates superinfection with opportunistic pathogens, particularly among patients with active GVHD) • *Pneumocystis carinii* • *Aspergillus*
Late phase: approximately 100 days post-transplant	• CMV • VZV • EBV-related post-transplant lymphoproliferative disease • CRV • Encapsulated bacteria (e.g., *H. influenzae* and *S. pneumoniae*).

Adapted from: CDC 2000
CMV = cytomegalovirus; CRV = community-acquired respiratory viruses; EBV = Epstein-Barr virus; GVHD = graft versus host disease; VZV = varicella zoster virus

If an opportunistic infection should occur despite appropriate and tailored infection prophylaxis and if, in the judgment of the investigator, the opportunistic infection does not respond as expected to anti-infectives, the subject must discontinue ponesimod and must be referred to an expert in infectious diseases for further examination and treatment.

The Centers for Disease Control and Prevention (CDC) recommendations for infection prophylaxis and immunizations for chronic GVHD patients can be obtained at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm. Suggested prophylaxis [as adapted from Martin 2009] appears in Table 6.

Table 6 Suggested infection prophylaxis in chronic GVHD

Infection or Risk Scenario	Prophylaxis (Comment)
Pneumocystis pneumonia and encapsulated bacterial infections	Antibiotic prophylaxis is strongly recommended for all patients until 6 months after resolution of chronic GVHD and discontinuation of all systemic IS treatment.
Pneumococci and *haemophilus influenzae B*	Vaccination with conjugate pneumococcal vaccine at 1 year after HSCT is strongly recommended. (Comment: chronic GVHD impairs splenic clearance of encapsulated organisms. Response to unconjugated vaccines is poor in patients at 1 year after HSCT).
Recurrent bacterial infections in patients with serum immunoglobulin G concentrations < 400 mg/dL or deficiencies of IgG2 or IgG4	Intravenous administration of gamma globulin may be indicated.
Patients who are at risk of CMV infection	Virologic surveillance of blood and pre-emptive antiviral therapy should be instituted whenever surveillance tests become positive, before the onset of overt CMV disease. (Comment: if feasible, CMV-seronegative recipients with CMV-seronegative donors should receive screened or leukocyte-depleted blood products).
MMR, and other infections prevented with live virus vaccines	Patients should not be given live virus vaccines such as MMR until at least 1 year after resolution of chronic GVHD and withdrawal of all IS treatment.
VZV	Long-term administration of valacyclovir or acyclovir is recommended to prevent reactivation of VZV in patients previously infected with this virus. The safety and efficacy of VZV vaccination after resolution of chronic GVHD has not yet been determined.
Patients on glucocorticoid treatment: glucocorticoid treatment increases the risk of fungal infections	Prophylactic administration of fluconazole can prevent certain types of candida infections, but this agent is not effective for prevention of invasive mold infections. (Comment: clinical trials will be needed to determine whether newer agents such as itraconazole, voriconazole, or posaconazole can prevent invasive mold infections during glucocorticoid treatment for patients with chronic GVHD).

Adapted from: [Martin 2009]
CMV = cytomegalovirus; GVHD = graft versus host disease; HSCT = hematopoietic stem cell transplantation; IS = immunosuppressant; MMR = measles, mumps, rubella; VZV = varicella zoster virus.

Particular vigilance is required for rare and unusual neurological symptoms, as their recognition is crucial for the early diagnosis of neurotropic herpes virus infections and progressive multifocal leucoencephalopathy (PML), caused by reactivation of John Cunningham virus. Neurological warning signs for PML include major changes in vision, unusual eye movements, loss of balance or coordination, disorientation, and confusion. As there is no known treatment for PML, rapid recognition is essential. Several cases of PML have been reported in patients with GVHD [Focosi 2007].

The thorough physical examination and blood tests on the routine visits should focus on any potential sign of skin, mucosal surface, GI tract, liver, hematological, or other abnormality and organ dysfunction suggesting a potential opportunistic infection.

Subjects should be advised to be pro-active and alert in reporting any unusual neurological symptoms and any signs and symptoms indicative of systemic infections, such as fever, malaise and fatigue [Kappos 2011].

5.1.10.5 Ocular

In the event of suspected clinically significant findings (e.g., macular edema), an unscheduled ophthalmology and OCT examination should be performed. The OSB will receive all information related to suspected cases of macular edema and will perform central review of OCT results and subject data. In the case of macular edema confirmed by the local ophthalmologist, the subject must be discontinued from study drug and will be managed and followed-up until resolution or until medically indicated. Any clinically relevant finding found after study drug initiation and during the follow-up period and meeting the definition of an AE will be recorded accordingly in the eCRF.

5.1.10.6 Reproductive/pregnancy

If a subject becomes pregnant while on ponesimod, ponesimod must be discontinued. Female subjects participating in the study and wishing to become pregnant during the study must discontinue ponesimod.

5.1.10.7 Respiratory

Subjects experiencing new or worsening persistent respiratory symptoms must be carefully evaluated. Lung infections are common in chronic GVHD, and should be suspected, especially in case of fever and cough. BOS is an uncommon and serious condition in chronic GVHD and is associated with irreversible pulmonary function decline which does not respond to bronchodilators. Ponesimod can cause pulmonary function decline which is reversible upon cessation of drug and which is also reversible with bronchodilators.

Lung function testing, including spirometry, is assessed frequently in this study. **Investigators may conduct unscheduled spirometry at any time, and should do so particularly in case of unexplained respiratory symptoms.** Spirometry results may

require a subsequent bronchodilator challenge, the results of which may lead to premature ponesimod discontinuation and further diagnostic work up to exclude/diagnose BOS or other lung disease.

Bronchodilator challenge is required if all of the following spirometry parameters are met at any time:

- > 10% decrease from the study baseline FEV_1, and
- FEV_1 < 60% predicted, and
- $FEV_1/FVC < 0.7$

Further dose escalation is prohibited once these parameters have been met.

Bronchodilator challenge

Subjects undergo bronchodilator challenge to help distinguish pulmonary function decline due to ponesimod from potential BOS or other causes.

Procedure for bronchodilator challenge

- An initial PFT assessment is performed.
- Then, four separate inhalations (puffs) of 100 µg salbutamol/albuterol are administered using a spacer device.
- A second PFT assessment must be performed 30 minutes (± 15 minutes) after administration of salbutamol/albuterol.

Ponesimod may be continued, without interruption, if all of the following parameters are met following bronchodilator challenge:

- $FEV_1 \geq 60\%$ predicted, and
- $FEV_1/FVC \geq 0.7$, and
- $FEV_1 \leq 10\%$ decrease from study baseline and
- Subjects on 5 mg are not experiencing respiratory symptoms (this parameter does not apply to subjects on 10 or 20 mg).

For continuing subjects, refer to the box: "CONTINUATION (after successful bronchodilator challenge)".

If these parameters are not met, ponesimod must be prematurely discontinued and further assessment is required; refer to the box: "PREMATURE DISCONTINUATION (after failing bronchodilator challenge)".

CONTINUATION (after successful bronchodilator challenge)

Generally, subjects are continued on ponesimod at the current dose, and no further dose escalation is allowed. If following a successful bronchodilator challenge, the conditions for performing the bronchodilator challenge are met again, a new bronchodilator challenge is recommended but not required and may be performed at the discretion of the investigator.

For those subjects on ponesimod 10 mg or 20 mg, immediate dose reduction to 5 mg or 10 mg may be considered by the investigator if subjects have respiratory symptoms. Dose escalation is not allowed after dose reduction in this study.

For subjects continuing ponesimod, spirometry testing is conducted at all subsequent scheduled visits. In case of a recurrent 10% decline versus study baseline in FEV_1, or continuing or worsening respiratory symptoms following dose reduction, subjects must be prematurely discontinued.

PREMATURE DISCONTINUATION (after failing bronchodilator challenge)

If the subject fails the bronchodilator challenge, ponesimod as the cause of lung function decline is still not ruled out. Ponesimod effects on lung function reverse rapidly within a few days following cessation of drug intake. Therefore, a rapid and robust improvement in lung function is required to help confirm ponesimod induced lung function decline and simultaneously help exclude BOS (which is not reversible).

Spirometry must be conducted 7 to 10 days following premature discontinuation.

Pulmonary function decline is very likely due to ponesimod, and BOS is unlikely if:

- FEV_1 assessed 7 to 10 days post premature discontinuation returns to baseline FEV_1.

All prematurely discontinued subjects need follow-up monitoring and evaluation. See box: "MONITORING AND WORK-UP for prematurely discontinued subjects".

MONITORING AND WORK-UP for prematurely discontinued subjects

In all cases of premature discontinuation, monitoring must be provided until respiratory AEs have resolved and changes in pulmonary function are no longer regarded as clinically relevant, or until medically indicated.

Further diagnostic work-up and consultation with a pulmonologist or other specialist is required and should be in accordance with local practice if PFT abnormalities or respiratory symptoms persist.

The current recommended work-up for BOS includes PFT testing and expiratory computed tomography (CT). Because a new diagnostic technique for BOS termed parametric response mapping is currently under investigation, a high resolution (helical) CT of inspiration and expiration is encouraged if available. This technique will permit visual representation of lung affected by obstructive disease (BOS) versus lung tissue with normal aeration or restrictive disease, and may become a valuable measure in the future [Jagasia 2015].

Use of short-acting β_2 agonist for subjects continuing on ponesimod

Subjects experiencing respiratory symptoms or reduced pulmonary function during the course of the treatment with ponesimod and fulfilling criteria to continue study medication may be prescribed short-acting β_2 agonist (to be used on an 'as needed' basis / 'PRN' use), at the investigator's discretion.

For all subjects: any clinically relevant finding found after signing of informed consent and during the follow-up period and meeting the definition of an adverse event will be recorded accordingly in the eCRF.

5.2 Mandatory concomitant chronic GVHD treatment (Core Treatment Period only)

Section 5.2 applies only to the Core Treatment Period.

5.2.1 Immunosuppressant treatments other than ponesimod

Along with the study drug ponesimod, subjects must be treated with **s**ystemic glucocorticoids AND/OR one of the following systemic agents: CsA, TAC, MMF, MPS, EVL, SRL, or MTX.

5.2.2 Modifications to IS treatments

Mandatory and allowed (e.g., topical IS) IS therapies make up the subject's background chronic GVHD IS therapy during the study. The dose and frequency of these medications should be kept constant during the study.

Systemic glucocorticoids

Glucocorticoid dosing should not be increased or decreased during the course of the study, with the following exceptions:

- The investigator may see reason to initiate or increase the dose of systemic glucocorticoid to treat chronic GVHD flare or another condition. In this case, the investigator should consult with the sponsor prior to initiation or dose increase and the

reason for dose increase should be documented. The subject may continue on ponesimod. The prednisone equivalent dose should never exceed 1 mg/kg/day.

- Systemic glucocorticoid dosing may be lowered to avoid or prevent short- and long-term glucocorticoid toxicity. For subjects on longer term glucocorticoid therapy, it is recommended that the dose reduction rate does not exceed 10% of dose per week. Glucocorticoid dosing may be increased following reduction, if medically indicated.
- Systemic glucocorticoid dosing is not subject to restrictions during the Extension Treatment Period.

Mandatory systemic IS other than ponesimod or systemic glucocorticoids

Systemic IS dosing (mg daily dose) should not be increased above baseline dose during the course of the study, with the following exception:

- Systemic IS blood or serum level is below the therapeutic range that was defined for the subject at the time of entry into the study. The dose should be increased to restore blood or serum levels to within the defined therapeutic range. (ISs that are not monitored with blood or serum level monitoring may never be increased above baseline dose.)

Systemic IS dosing (mg daily dose) should not be lowered during the course of the study, with the following exceptions:

- AE or intolerance due to the systemic IS. The dose should be sufficiently lowered or discontinued, per investigator judgment.
- Systemic IS blood or serum level is above the therapeutic range that was defined for the subject at the time of entry into the study. The dose should be lowered to restore blood or serum levels to within the defined therapeutic range.

Topical CNIs or glucocorticoids

- The sponsor recommends not starting or increasing dosage of topical CNI or topical glucocorticoid therapy during the course of the core study.
- Topical CNIs or glucocorticoid therapy dosing or area of application should not be decreased during the course of the core study, unless there is an AE or intolerance due to the topical drug. The dose should then be sufficiently lowered or discontinued, per investigator judgment.

5.3 Previous and concomitant therapy

Section 5.3 applies to both Core and Extension Treatment Periods.

5.3.1 Definitions

A previous therapy is any treatment for which the end date is prior to the start of study (i.e., signing of initial informed consent).

All therapy that is study-concomitant (i.e., ongoing or initiated after signing of informed consent, and initiated before EOS visit) must be captured in the eCRF.

5.3.2 Reporting of previous HSCT and GVHD therapies

Previous HSCT and GVHD therapies will be collected as part of HSCT and GVHD history [see Section 4.5].

5.3.3 Reporting of concomitant therapy in the eCRF

The use of all study-concomitant therapy (including contraceptives and traditional or alternative medicines, i.e., plant-, animal-, or mineral-based medicines) will be recorded in the eCRF. The generic name, start/end dates of administration (as well as whether it was ongoing at start of treatment and/or EOS), route, dose, frequency, and indication will be recorded in the eCRF.

5.3.4 Allowed concomitant therapy

- Administration of i.v. atropine in the event of symptomatic bradycardia
- Topical glucocorticoid
- Topical CNI
- Oral budesonide
- QT-prolonging drugs with known risk of Torsades de Pointes should be used with caution since ponesimod may potentially enhance their effect on QT interval (list of drugs and guidance are provided in Appendix 3)
- Short-acting ß2 agonists for respiratory symptoms and/or reduced pulmonary function during ponesimod treatment
- Vaccination with non-live vaccines (***Note:*** although nonclinical data indicate no significant impairment of antibody response to immunization, no clinical data is currently available on vaccination efficacy under ponesimod treatment, therefore it is suggested that all planned/indicated vaccinations are completed more than 30 days before the start of treatment and, in case of vaccination during the study, titer control is recommended.)
- Other treatments considered necessary for the subject's benefit and not categorized as prohibited concomitant medications

5.3.5 Forbidden concomitant therapy

- IS or immunomodulatory treatments other than those prescribed per protocol
- Retinoids
- Thoracoabdominal irradiation
- Mesenchymal stem cell therapy

- Extracorporeal photopheresis
- Vaccination with live vaccines
- β-blockers, diltiazem, verapamil, digoxin, digitoxin or any other anti-arrhythmic or HR-lowering systemic therapy (a non-exhaustive list of drugs provided in Appendix 4)
- Any other investigational drug

6 STUDY ENDPOINTS

This section describes the Core Treatment Period endpoints only. Similar endpoints will be assessed for the Extension Treatment Period, however adjusted for the corresponding visit schedule.

6.1 Pharmacokinetic and pharmacodynamic endpoints

6.1.1 Pharmacokinetic evaluations

- Trough concentrations (C_{trough}) concentrations of ponesimod at Day 1, and Weeks 4, 8, 12, 16, and 20 (all samples pre-dose), and Week 24
- Ponesimod concentration 3 hours post-dose at Day 1 and Week 12

6.1.2 Pharmacodynamic evaluations

Primary PD endpoint

- Change in peripheral absolute lymphocyte count from baseline to Week 4, Week 8 and Week 12

The primary endpoint assesses intra-subject dose response during the first 12 weeks of treatment.

Other PD endpoints

- Peripheral absolute blood lymphocyte count change from baseline (pre-dose on Day 1) to Weeks 4, 8, 12, 16, 20, 24, and FU1, and change from pre-dose Week 12 to 3 hours post-dose Week 12.
- Peripheral absolute lymphocyte count reversibility from EOT1 to FU1 expressed as absolute change and percent change from baseline

6.1.3 PK/PD relationship

The PK and selected efficacy and safety variables will be correlated with the PD (peripheral absolute lymphocyte count and magnitude of reduction of lymphocyte count). If deemed appropriate, the PK will also be correlated with selected safety variables.

6.2 Safety endpoints

The treatment-emergent period is defined as the time from first study drug intake up to 30 days (inclusive) after last study drug intake.

6.2.1 Overall safety endpoints

- Treatment-emergent AEs, serious adverse events (SAEs), and AEs of special interest [see Appendix 5]
- AEs leading to premature discontinuation of study drug
- Deaths

6.2.2 Absolute lymphocyte count

- Treatment-emergent absolute lymphocyte count $< 0.2 \times 10^9$/L (< 200 cells/mm^3)

6.2.3 Cardiac rate and rhythm safety endpoints

- Treatment-emergent morphological ECG abnormalities (as defined by the ECG provider)
- Change in 12-lead ECG variables (HR, PR, QRS, QT, QT corrected for HR on the basis of Bazett's formula [QTcB], QT corrected for HR on the basis of Fridericia's formula [QTcF]) from pre-dose to selected post-dose assessments (1 h, 2 h, 3 h, 4 h) on Day 1 and on day of re-initiation of study drug.
- Notable abnormalities for selected 12-lead ECG variables (HR, PR, QT, QTc) at 3 hours post-dose assessment on Day 1, pre-dose on Weeks 4, 8, and 12, and Week 24 (notable abnormalities definition in Appendix 6).
- Cardiac safety events will include:
    - Treatment-emergent QTc > 450 ms (male), > 470 ms (female), > 500 ms (male), and > 520 ms (female)
    - Treatment-emergent QTc increase from baseline > 30 ms, > 60 ms
    - Other treatment-emergent abnormalities observed by 12-lead ECG
    - Treatment-emergent (serious) cardiac AEs of special interest.

6.2.4 Pulmonary function safety endpoints

- Treatment-emergent decrease of FEV_1 or FVC > 20% from baseline values
- Treatment-emergent decrease of percent of predicted FEV_1 or FVC > 20 percentage points from baseline values
- Change in FEV_1 and FVC from baseline, absolute and % of absolute change to all time points up to FU1

- Among subjects with a decrease of > 200 mL and > 12% in FEV_1 or FVC from baseline to EOT1, reversibility is defined as a decrease of < 200 mL or < 12% in FEV_1 or FVC, respectively, from baseline to last available follow-up
- Change from baseline to FU1 vs change from baseline to EOT1 in FEV_1 or FVC (absolute and % of predicted)
- Change in lung diffusion capacity as assessed by the DL_{CO}, expressed in absolute change and % of predicted value from baseline to all time points up to FU1
- Change from baseline to FU1 vs change from baseline to EOT in DL_{CO} (absolute and % of predicted)
- (Serious) pulmonary AEs of special interest
- Withdrawal due to pulmonary reasons/AE

6.2.5 Other safety endpoints

- Treatment-emergent notable BP abnormalities [definition in Appendix 6]
- Treatment-emergent notable laboratory abnormalities [definition in Appendix 6]

6.3 Efficacy endpoints (exploratory)

The main efficacy endpoint is:

- Achievement of a partial or complete overall response at 24 weeks post-enrollment

Definitions for the efficacy endpoint are based on the draft 2014 NIH Consensus Development Project response criteria [NIH Therapeutic Response 2014]. Baseline or subsequent organ abnormalities that are not due to chronic GVHD are not evaluable for response (at the organ level).

6.3.1 Complete overall response definition

A complete overall response is defined as resolution of all reversible manifestations due to chronic GVHD in the following organs at the Week 24 assessment, resulting in:

- Skin: NIH Skin Score of 0 after previous involvement
- Mouth: NIH Modified Oral Mucositis Score of 0 after previous involvement
- Liver: normal ALT, alkaline phosphatase, and TBL after previous elevation of one or more
- Upper GI: NIH Upper GI Score of 0 after previous involvement
- Lower GI: NIH Lower GI Score of 0 after previous involvement
- Esophagus: NIH Esophagus Score of 0 after previous involvement
- Lungs: normal FEV_1 absolute value after previous involvement (normalization to FEV_1 $\geq$ 80% predicted is considered a complete response)

- Eyes: NIH Eye Score of 0 after previous involvement
- Joint/fascia: Both NIH Joint and Fascia Score of 0 and photographic range of motion (P-ROM) score of 25 after previous involvement by at least one measure
- Global: Clinician Overall Severity Score of 0

6.3.2 Partial overall response definition

A partial overall response is defined as improvement in a measure for at least one organ without increase in measures for any other organ. A subject is considered as a partial responder at the Week 24 assessment, if there is a change of clinical benefit from baseline in at least one of the organs assessed (skin, mouth, liver, upper and lower GI, esophagus, lung, eye, and joint/fascia) and no progression in any other organ (stable NIH scores compared to baseline).

The proposed general guideline for defining partial response in a specific organ requires a change in score from baseline as follows:

- Skin: decrease in NIH Skin Score by at least 1 point
- Mouth: decrease in NIH Modified Oral Mucositis Score by at least 2 points
- Liver: decrease by 50% in ALT, alkaline phosphatase, or TBL
- Upper GI: decrease in NIH Upper GI Score by at least 1 point
- Lower GI: decrease in NIH Lower GI Score by at least 1 point
- Esophagus: decrease in NIH Esophagus Score by at least 1 point
- Lungs: increase by at least 10% predicted absolute value of FEV_1, as long as initial $FEV_1 < 70\%$ predicted
- Eyes: decrease in NIH Eye Score by at least 1 point
- Joint/fascia: decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 or more points for any site
- Global: Clinician Overall Severity Score decreases by 2 or more points on a 0–10 scale

The proposed general guideline for defining progression in a specific organ requires a change in score from baseline as follows:

- Skin: increase in NIH Skin Score by at least 1 point, except from 0 to 1
- Mouth: increase in NIH Modified Oral Mucositis Score by at least 2 points
- Liver: increase by $\geq 2 \times$ ULN for ALT, alkaline phosphatase or TBL
- Upper GI: increase in NIH Upper GI Score by at least 1 point, except from 0 to 1
- Lower GI: increase in NIH Lower GI Score by at least 1 point, except from 0 to 1

- Esophagus: increase in NIH Esophagus Score by at least 1 point, except from 0 to 1
- Lungs: decrease by at least 10% absolute value of FEV_1, as long as final $FEV_1 < 70\%$ predicted
- Eyes: increase in NIH Eye Score by at least 1 point, except from 0 to 1
- Joint/fascia: increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 or more points for any site
- Global: Clinician Overall Severity Score increases by 2 or more points on a 0–10 scale

6.3.3 Subject responder / non-responder definition

The endpoint is reached if the subject is considered a partial or complete responder at Week 24. The remaining subjects will be considered as non-responders, this includes subjects with stable disease and subjects with mixed response (defined as complete or partial response in at least one organ accompanied by progression in another organ).

In case of deviations from the planned schedule of prednisone treatment (with the exception of prednisone exceeding 1 mg/kg/day), the subject will still be eligible for the primary analysis.

6.3.4 Other efficacy endpoints

Other efficacy endpoints include:

- Need for rescue therapy for chronic GVHD
    - Rescue therapy is the addition of any new systemic or topical IS therapy, or exceeding baseline dose for any non-steroid IS, or exceeding glucocorticoid dose equivalent to prednisone > 1 mg/kg/day
- Partial or complete organ-specific response for the specific organ manifestation at Week 12 and Week 24 in subjects with a specific organ manifestation of chronic GVHD at study baseline
    - Affected organs limited to 2014 NIH consensus criteria organs of skin, eyes, mouth, esophagus, upper GI, lower GI, liver, lungs, and joints and fascia
- Partial or complete overall response at 12 weeks post-enrollment
- Complete response at Week 24
- Partial or complete overall response at latest evaluable assessment during the core study (Week 12 and Week 24)
- Average glucocorticoid daily dose over 24 weeks versus baseline dose
- Percent glucocorticoid dose at Week 24 versus baseline

6.4 Quality of life endpoints

- Change from baseline to Week 12 and Week 24 in Lee Symptom Scale for chronic GVHD [Appendix 8]
- Change from baseline to Week 12 and Week 24 in each of the patient-reported chronic GVHD symptoms (skin, eyes, mouth and genitals [Appendix 7 – Form B])
- Change from baseline to Week 12 and Week 24 in each of the patient-reported global ratings (Mild-Moderate-Severe Scale, Overall Severity Scale and 7-Point Change Scale [Appendix 7 – Form B])

7 STUDY ASSESSMENTS

All study assessments are performed by a qualified study staff member: medical, nursing, or specialist technical staff, and are recorded in the source and eCRF, unless otherwise specified. Study assessments performed during unscheduled visits will also be recorded in the eCRF.

If the principal investigator delegates any study procedure/assessment for a subject, e.g., ECG, blood sampling etc., to an external facility, he/she should inform Actelion to whom these tasks are delegated. The set-up and oversight will be agreed upon with Actelion. The supervision of any external facilities remains under the responsibility of the principal investigator.

Calibration or service certificates for the following devices used to perform study assessments must be available prior to the enrollment of the first subject:

- Temperature measurement devices for study medication storage area and lab sample storage (i.e., freezer)
- Spirometer; in addition, a copy of the calibrations check (syringe check) of the day of measurement must be stored and a log of calibration check results must be maintained at the site [see Section 7.3.3].
- OCT
- DL_{CO} gas analyzer; in addition, a copy of the calibrations check of the day of a test must be stored, and a log of calibration results must be maintained at the site. In addition, frequent testing involving the same healthy subject control (biological quality check) or a DL_{CO} simulator will ensure continuous monitoring of the gas analyzer measurement accuracy over time [see Section 7.3.4].
- ECGs
- BP monitoring device

7.1 Screening/baseline assessments

7.1.1 Informed consent (screening visit)

Prior to performing any study-specific procedures or assessments at Visit 1 (screening) or Visit 11 (Extension Treatment Period – Visit EX-1), the subject must provide written informed consent to participate in the study. If the signing of informed consent and performance of the first study-specific procedures or assessments take place on the same day, it must be clear from the source documents that informed consent was obtained prior to any study-specific procedures being performed. If a study-specific procedure or assessment has been performed as part of routine care of the subject and the results are available prior to the subject's signing of informed consent, such procedure or assessment may be used to assess eligibility and does not have to be repeated. In such cases, it must be clear from the source document when and for which reason the assessment was done prior to the signing of the informed consent.

It is the responsibility of the investigator to explain the study in all its aspects to the subject and obtain her/his informed consent. The informed consent process will be documented in the investigator site file. The language used in the oral and written information about the trial, including the informed consent form (ICF), will be provided in a language that is fully understandable to the subject.

For subjects who provide informed consent but are subsequently not enrolled into the study, the reasons for not being enrolled will be recorded in the eCRF.

7.1.2 Baseline demographics and disease characteristics

Baseline demographics (sex, age, ethnicity, body weight, and height) are to be recorded in the eCRF at Visit 1. Complete, clinically relevant medical history and current conditions are to be documented in the eCRF, as well as smoking status and disease characteristics including the date of first chronic GVHD symptoms, date of chronic GVHD diagnosis [see Section 4.5], and chronic GVHD stage and score [Appendix 2]. Complications or symptoms associated with chronic GVHD within the last 24 months prior to the study will be collected in the medical history of the eCRF.

7.1.3 Study-concomitant therapies

All study-concomitant therapy (including contraceptives and traditional and alternative medicines, i.e., plant-, animal-, or mineral-based medicines) taken by the subject from the signing of informed consent until the end of their participation in the study (i.e., EOS) will be recorded in the Concomitant Therapies pages of the eCRF. This includes all ongoing therapies and those initiated or stopped during this period. The corresponding generic name, indication, route, dose, dates of initiation and discontinuation will be recorded.

7.2 Pharmacokinetic and pharmacodynamic assessments

These assessments are done to investigate PK and PD effects of ponesimod.

7.2.1 Pharmacokinetic assessments

7.2.1.1 Timing for sampling

PK samples will be collected during this study for all subjects, in order to provide information about study drug exposure in the target population.

At Visit 2 (Day 1), blood samples are collected pre-dose and then hourly (+/−20 minutes) post-dose, at the same time ECG measurements are taken, for a minimum of 4 and up to a maximum of 12 collections, depending on the number of ECG measurements taken. The ECG assessment schedule for Visit 2 (Day 1) is described in Sections 7.3.1 and 5.1.7. Placement of a peripheral venous catheter may facilitate these frequent blood collections.

Blood samples will also be collected pre-dose at Visits 3, 4, 5, 6, and 7 (Weeks 4, 8, 12, 16, and 20) and Visit 8 (EOT1). PK samples will also be drawn 3 hours (+/−20 minutes) post-dose at Visit 5 (Week 12).

7.2.1.2 Procedures for sampling

Up to 3 mL of blood must be collected in tubes containing ethylenediaminetetraacetic acid (EDTA). Immediately following collection of the required blood volume, the tubes must be slowly tilted backwards and forwards (no shaking) to bring the anti-coagulant into solution, and immediately cooled on ice. Within 30 minutes of collection, the tubes must be centrifuged at approximately 1500 g for 10 minutes at 2 to 8 °C. When a centrifuge that can be cooled is not available, the blood samples and the bucket of the centrifuge must be cooled on ice prior to centrifugation. The plasma must be transferred into one labeled opaque polypropylene tube to avoid carry-over of erythrocytes. All samples must be stored in an upright position at –25 °C (freezer settings: intended temperature –25 °C; upper limit –20 °C). The exact time of withdrawal of the blood sample must be entered in the eCRF, as well as the status of the subject (fed or fasted), and the time of last previous study drug intake. Blood samples for PK analysis must be drawn prior to study drug intake on the day of the visit (Visits 2, 3, 4, 5, 6, 7). Additional PK samples are drawn hourly post-dose at Visit 2. One additional PK sample is drawn 3 h post-dose at Visit 5.

To prevent degradation of ponesimod in the plasma samples, exposure to light should be minimized. After centrifugation, plasma samples should be kept in the dark.

7.2.1.3 Labeling and shipment

Details of the collection, labeling and shipment of the samples can be found in the laboratory manual provided to the investigator. The tubes and labels for the samples will be provided to the investigator and/or staff by the central laboratory.

7.2.1.4 Bioanalysis

The concentration of ponesimod in plasma will be determined by a validated liquid chromatography-tandem mass spectrometry assay by Actelion, Preclinical Pharmacokinetics and Metabolism. The lower limit of quantification is 1 ng/mL.

Concentrations will be calculated by interpolation from a calibration curve. Quality control samples will be analyzed throughout the study. Their measured concentrations will be used to determine between-run and overall precision and accuracy of the analyses.

The samples will be destroyed upon signature of the Clinical Study Report.

7.2.2 Pharmacodynamic assessments

The PD marker is absolute lymphocyte counts, which will be measured as part of the hematology tests [see Section 7.3.11]. An additional PD sample will be collected at Visit 5, 3 hours (+/−20 minutes) post-dose.

7.3 Safety assessments

The definitions, reporting and follow-up of AEs, SAEs and potential pregnancies are described in Section 10.

7.3.1 12-lead ECG

A standard 12-lead ECG will be recorded at all scheduled study visits (except FU2 – Visit 10) with the subject in a fully rested supine position after the subject has been allowed to rest for a minimum of 5 minutes prior to the measurement.

At Visit 2 (Day 1), Visit 11 (EX-1) and at visits for re-initiation of study drug where post-dose monitoring will be required, the 12-lead ECG monitoring will be performed under the responsibility of the cardiac safety assessor who will also evaluate and interpret these assessments. At all other visits, it will be performed either under the responsibility of the cardiac safety assessor or the investigator.

The following variables will be evaluated: HR (bpm), PR (ms), QRS (ms), QT (ms), QTc (ms), and any ECG findings. QTC (ms) will be calculated according to Bazett's and Fridericia's formula (QTcB = QT/(RR) ½ and QTcF = QT/(RR) ⅓, respectively).

Before study drug administration (pre-dose) at Visit 2 (Day 1) and Visit 11 (EX-1), the cardiac safety assessor must provide the ECG results and interpretation to the principal investigator and support her/him, if requested, to make a final decision on the subject's eligibility according to the inclusion/exclusion criteria. At Visit 2 (Day 1) and Visit 11 (EX-1), the pre-dose ECG must be performed prior to enrollment and the exclusion criterion of HR < 50 bpm checked.

During the Core and Extension Treatment Periods, ECGs must be performed at pre-dose. In case of need of concomitant treatment with a QT-prolonging drug with known risk of Torsades de Pointes, additional ECGs will be performed according to the guidance provided in Appendix 3.

At Visit 2 (Day 1), Visit 11 (EX-1) and on the day of re-initiation of study drug [see Section 5.1.8], ECGs must be performed at pre-dose and hourly thereafter for a minimum of 4 hours and up to 12 h post-dose. Subjects may be discharged from the hospital if they meet the discharge criteria before 12 h post-dose but no sooner than 4 h post-dose [see Section 5.1.7]. If the subject does not meet the defined discharge criteria at 12 hours post-dose, the cardiac safety assessor notifies the principal investigator and the subject is prematurely discontinued from ponesimod but will be kept in the hospital for observation, and additional ECG measurements will be performed until changes in ECG variables are no longer clinically relevant (i.e., discharge criteria are met [see Section 5.1.7]), or until medically indicated.

At Visit 2 (Day 1), Visit 11 (EX-1), and on the day of re-initiation of study drug where post-dose monitoring is required, significant findings – which in view of the cardiac safety assessor meet the definition of an AE and are resolved at the time of discharge of the subject – must be recorded directly on an Adverse Event page of the eCRF. All other significant findings, on Day 1, EX-1 or on the day of re-initiation of study drug where post-dose monitoring is required, that are unresolved at the time of discharge of the subject or with an onset on any other day (which in her/his view meet the definition of an AE) must be reported to the principal investigator who will record these events on the Adverse Event page of the eCRF. (The investigator may perform the function of the cardiac safety assessor if qualified, as per Section 3.4.2.)

At Visits 3, 4, 5, 6 and 7 (Weeks 4, 8, 12, 16 and 20) in the Core Treatment Period and Visits EX-2, EX-3, EX-4, EX-5, EX-6, EX-7, EX-8, EX-9, EX-10, EX-11, and EX-12 (Extension Weeks 4, 8, 12, 16, 20, 24, 36, 48, 60, 72, and 84) in the Extension Treatment Period, 12-lead ECG measurements are collected pre-dose. In the event of a grade 2 QTc elevation, a repeat 12-lead ECG must be collected 3 hours post-dose. If QTcF > 500 ms, the subject is prematurely discontinued from the study as stated in Section 5.1.10.1. In addition, a PK sample must be collected within 20 minutes after the 3 hour post-dose ECG.

Digital 12-lead ECG devices will be provided to each site by the central ECG reader for the duration of the study. Digital ECG recording must be performed for all subjects according to the study protocol schedule. The data records will be sent to the evaluation center for central reading.

Details will be provided in the ECG laboratory manual.

7.3.2 Blood pressure

BP measurements include SBP and DBP.

BP monitoring will be performed using the same type of device throughout the study on the same arm with the subject in a fully rested supine position after the subject has been allowed to rest for a minimum of 5 minutes prior to the measurement.

At each pre-dose assessment, SBP and DBP will each be measured twice. The two obtained measurements (i.e., two SBP measurements and two DBP measurements) and the position and arm used are to be recorded in the eCRF. The means of the two obtained measurements will be calculated by the eCRF.

Post-dose assessments at Visit 2 (Day 1), Visit 11 (EX-1) and at visits for re-initiation of study drug where post-dose monitoring is required will only be measured once at each time point. This single obtained SBP measurement is to be used for determining discharge criteria on Day 1 and Visit 11 and on day of re-initiation of study drug where post-dose monitoring is required.

At Visit 2 (Day 1), Visit 11 (EX-1) and at visits for re-initiation of study drug where post-dose monitoring is required, the assessment of vital signs will be performed under the responsibility of the cardiac safety assessor who will also evaluate and interpret these assessments. At all other visits, it will be performed either under the responsibility of the cardiac safety assessor or investigator.

At Visit 2 (Day 1), Visit 11 (EX-1) and at visits for re-initiation of study drug where post-dose monitoring is required, significant findings – which in view of the cardiac safety assessor meet the definition of an AE and are resolved at the time of discharge of the subject – must be recorded directly on an Adverse Event page of the eCRF. All other significant findings, on Day 1, EX-1 or on the first day of re-initiation of study drug where post-dose monitoring is required, that are unresolved at the time of discharge of the subject or with an onset on any other day (which in her/his view meet the definition of an AE) must be recorded on the Adverse Event page of the eCRF.

BP measurements will be performed at all study visits (except FU2 – Visit 10). At Visit 2 (Day 1), Visit 11 (EX-1) and on days of re-initiation of study drug, where post-dose monitoring is required [see Section 5.1.8], SBP and DBP will be measured at pre-dose, and hourly thereafter for a minimum of 4 hours and up to 12 h post-dose. Subjects may be discharged from the hospital if they meet the discharge criteria before 12 h post-dose but no sooner than 4 h post-dose [see Section 5.1.7]. If the subject does not meet the defined discharge criteria at 12 hours post-dose, the subject will be prematurely discontinued from ponesimod but will be kept in the hospital for observation, and additional BP measurements

will be performed until changes are no longer clinically relevant (i.e., discharge criteria are met [see Section 5.1.7]), or until medically indicated.

7.3.3 Spirometry

Spirometry tests will be performed at visits indicated in Table 1. In addition, unscheduled spirometry will have to be conducted in the event of respiratory symptoms (e.g., dyspnea).

Spirometry at Visit 1 can be performed at any time during the screening period. Spirometry at Visit 2 (Day 1) must be performed within 48 hours of the visit and prior to study drug intake. At Visits 3 and 4 (Week 4 and Week 8), spirometry may be performed up to 3 days prior to the visit date and must be performed prior to study drug intake. At Visit 5 (Week 12), spirometry may be performed up to 7 days prior to the visit date and must be performed prior to study drug intake. At Visits 8 and 23 (EOT1 and EOT2), spirometry may be performed up to 7 days prior to the visit date and no later than 7 days after the discontinuation of study drug. At all other visits indicated in Table 1, spirometry may be performed 7 days prior to or after the visit date. All spirometry assessments must be performed in the morning, preferably between 06:00 and 10:00, at approximately the same time to avoid diurnal variation.

Spirometry testing will consist primarily of assessing FEV_1 and FVC. Further parameters may be explored and/or used for spirometry quality control measures.

Spirometry tests will be conducted according to the ATS/ERS guidelines [Miller 2005a, Miller 2005b, Macintyre 2005]. The pulmonary function facility will ensure that the spirometer is functioning properly and is calibrated according to manufacturer instruction and ATS/ERS guidelines. A copy of the calibrations of the day of a test must be stored as source documents in the subject charts at each subject visit, and a log of calibration results must be maintained at the site.

Spirometry testing will be performed by a PFT technician, respiratory therapist or expert, or an equally experienced person according to the ATS/ERS guidelines [Miller 2005a] (e.g., for US, registered pulmonary function technologist and/or registered respiratory therapist). To the extent logistically feasible, attempts should be made to have the same tester throughout the study for a subject, and this information will be recorded in the eCRF. Back-up testers (PFT technician, respiratory therapist, or expert or an equally qualified person according to the ATS/ERS guidelines [Miller 2005a]) may conduct spirometry if the primary tester is not available. All PFT technicians or other qualified persons participating in the studies will be trained on the specific requirements for the studies and have refreshment on ATS/ERS recommendations before study start and when compliance issues are identified.

Subjects must refrain from taking short-acting ß2 agonists (i.e., salbutamol) for 6 hours and long-acting ß2 agonists for 24 hours prior to spirometry testing. To perform the spirometry test, subjects will be rested for a minimum of 5 minutes prior to start. Sufficient forced expiratory maneuvers (up to a maximum of eight) will be performed to produce a minimum of three technically acceptable and repeatable traces (according to ATS/ERS guideline criteria. The best (largest) FEV_1 and FVC values from the three acceptable and repeatable tests are to be selected by the PFT technician and recorded in the eCRF and will serve for the calculation of % of predicted values and used for the endpoint derivations. These values may come from separate maneuvers. The FEV_1 and FVC measures obtained at Visit 2 (Day 1) and selected as described above will be used as the study baseline.

PFT values that trigger study drug discontinuation are described in Section 5.1.10.7. Clinically relevant findings meeting the definition of an AE (new AE, or worsening of previously existing condition) [see Section 10.1.1] must be recorded on an AE page of the eCRF.

Predicted normal values for FVC and FEV_1 will be used to determine exclusion criteria as well as withdrawal criteria [see Section 5.1.10.7**]**. Predicted normal values will be adjusted for subjects from ethnic groups other than white/Caucasian. The formulas for the calculation of the predicted normal values for FEV_1 and FVC and the ethnic group adjustments used in this study are those of the European Community Coal and Steel [Quanjer 1993].

7.3.4 DL_{CO}

DL_{CO} tests will be performed along with spirometry [Section 7.3.3]. DL_{CO} tests will be assessed by the single breath testing technique. DL_{CO} efforts, up to a maximum of five, will be performed to produce at least two technically acceptable and repeatable traces, according to ATS/ERS guideline criteria [Macintyre 2005]. There must be a minimal interval of at least 4 minutes between each effort performed.

The average of at least two within session DL_{CO} efforts that meet the acceptability criteria are to be reported as the value for this session in the eCRF. If only one acceptable effort is achieved, this value is to be reported for this session in the eCRF. If no acceptable effort is achieved, the effort with the highest inspiratory vital capacity is to be reported in the eCRF. Reported DL_{CO} values will be entered in the eCRF, without any further adjustments.

If clinically significant alterations in DL_{CO} variables indicating a pulmonary condition that could result in increased risk for the subject are observed, he/she may be prematurely discontinued from ponesimod at the discretion of the investigator. Clinically relevant findings meeting the definition of an AE (new AE, or worsening of previously existing condition) [see Section 10.1.1] must be recorded on an AE page of the eCRF.

7.3.5 Chest X-ray

A CXR will be performed at Visit 1 (screening), and assessed by the local radiologist in order to exclude any subject with findings suggestive of active or latent TB. Any CXR that had been performed within 90 days prior to screening can be used; if available, there is no need to repeat CXR at screening.

7.3.6 Test for tuberculosis

An interferon gamma release assay (QuantiFERON-TB-Gold®) will be performed at Visit 1 (screening) to screen for active or latent TB. The test will be analyzed and interpreted at the central laboratory [see Section 7.3.11] and electronically transferred to the sponsor.

Only subjects with a negative test at screening and without CXR findings [see Section 7.3.5] at screening or within the previous 90 days suggestive of active or latent TB can be included in the study. If the test result is positive, subjects must not be included in the study, except if there is documentation that the subject has received adequate treatment for TB previously. If the test result is inconclusive (invalid, indeterminate, or borderline), the test may be repeated once and a negative result must be obtained prior to enrollment in order to include the subject. If the result of the repeated test is again inconclusive (invalid, indeterminate, or borderline), subjects must not be included in the study.

Details on the performance of the test for TB will be provided in the specific central laboratory manual.

7.3.7 Ophthalmological assessments

Ophthalmological assessments will be performed by an ophthalmologist at visits indicated in Table 1. Testing at Visit 1 can be performed at any time during the screening period. Testing at Visits 8 and 23 (EOT1 and EOT2) may be performed up to 7 days prior to the visit date and no later than 7 days after the discontinuation of study drug. Testing at all other visits indicated in Table 1, may be performed 7 days prior to or after the visit date. In addition, unscheduled ophthalmological examination will be done in the event of visual symptoms.

The safety ophthalmological assessment includes previous eye history and ophthalmic condition, any new or current ophthalmological symptoms, assessment of best corrected visual acuity (Early Treatment Diabetic Retinopathy Study charts), measurement of Goldmann applanation tonometry, slitlamp examination of the anterior segment, and dilated indirect funduscopy. While the visual acuity, and measurement of Goldmann applanation tonometry exams themselves may be performed by a delegate (e.g., certified technician, optometrician), the review and interpretation must be performed by the ophthalmologist. Conduct, review, and interpretation of all other ophthalmological exams

must be performed by the ophthalmologist. Fluorescence angiography (if applicable) may be performed by a delegate (e.g., certified technician, optometrician) but always in the presence of the ophthalmologist who will review and interpret the results.

The purpose of the assessment prior to enrollment is to exclude subjects with macular edema or diabetic retinopathy from the study, and to document a baseline assessment. No data will be collected in the eCRF, but clinically relevant findings meeting the definition of an AE (new AE, or worsening of previously existing condition) [see Section 10.1.1] must be recorded on an AE page of the eCRF.

7.3.8 Optical Coherence Tomography

OCT will be assessed at visits indicated in Table 1. Testing at Visit 1 can be performed at any time during the screening period. Testing at Visits 8 and 23 (EOT1 and EOT2) may be performed up to 7 days prior to the visit date and no later than 7 days after the discontinuation of study drug. Testing at all other visits indicated in Table 1, may be performed 7 days prior to or after the visit date. In addition, unscheduled OCT examination will have to be assessed in the event of visual symptoms or findings suggestive of macular edema according to the ophthalmologist. While the OCT exam may be performed by a delegate (e.g., certified technician, optometrician), the review and interpretation must be performed by the ophthalmologist.

The purpose of the assessment prior to enrollment is to exclude subjects with macular edema or diabetic retinopathy from the study, and to document a baseline assessment. The site will use the OCT device available locally and must ensure it is working properly. To the extent that is logistically feasible, the same OCT machine is to be used for each individual subject throughout the study.

No data will be collected in the eCRF, but clinically relevant findings meeting the definition of an AE (new AE, or worsening of previously existing condition) [see Section 10.1.1] must be recorded on an AE page of the eCRF.

The OSB will receive all information related to suspected cases of macular edema and will perform a central review of OCT results and subject data of suspected cases of macular edema.

7.3.9 Weight and height

Body weight will be measured at visits indicated in Table 1. Body height is only measured at Visit 1 (screening). Data will be collected in the eCRF. Measurements will be conducted with subjects wearing clothes but without shoes.

7.3.10 Physical examination

Physical examination is performed at visits indicated in Table 1. Unscheduled physical examination may be performed at any time during the study (Visits U1, U2, …).

Physical examination should be recorded by body system in the eCRF as normal or abnormal. If an abnormality is found, it should be specified on the corresponding eCRF page, describing the signs related to the abnormality (e.g., systolic murmur) not the diagnosis (e.g., mitral valve insufficiency). Clinically relevant findings meeting the definition of an AE (new AE, or worsening of previously existing condition), must be recorded on an AE page of the eCRF.

7.3.11 Laboratory assessments

7.3.11.1 Type of laboratory

A central laboratory (see central laboratory manual for contact details) will be used for all protocol-mandated laboratory tests, including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits. Central laboratory data will be automatically transferred from the central laboratory database to Actelion's clinical database.

Under specific circumstances (e.g., subject lives far away from the site and cannot return for a unscheduled visit during the first 24 weeks), laboratory samples could be drawn in a local laboratory close to where the subject lives and analyzed at the central laboratory. In such circumstances, the local laboratory must be provided with the central laboratory kits, which must be used for blood collection. The blood samples collected locally will be shipped by the local laboratory to the central laboratory for analysis. Local laboratories should be identified prior to enrollment, if possible.

Local laboratory results will be collected in the following situations:

- In case of missing central laboratory values, local laboratory values (if available) for the tests assessed per protocol are to be recorded in the eCRF (together with the corresponding normal ranges), especially local laboratory results related to the diagnostic work-up (i.e., detection, confirmation and/or monitoring) of decrease in lymphocyte, neutrophils, or white blood cell (WBC) count, ALT/AST elevations, serum creatinine increase, or decrease in calculated creatinine clearance. In the event that several local laboratory samples are taken on the same day or if the sample was tested several times, the 'worst' value (e.g., highest value for ALT/AST) should be reported in the eCRF.

- In exceptional cases (e.g., subject is hospitalized in a different hospital from the study center due to a medical emergency) where a local laboratory is used for the collection

and analysis of blood samples, the local laboratory results (with the corresponding normal ranges) will be entered into the clinical database via dedicated eCRF pages.

For these local laboratories, the investigator/delegate will provide Actelion with the name, professional degree and curriculum vitae of the laboratory director, a copy of the laboratory's certification, and the normal ranges for each laboratory test that is evaluated in the study. These laboratory references must be updated whenever necessary.

In case a central laboratory sample is lost, has deteriorated or cannot be analyzed for whatever reason, the investigator will collect an additional sample as soon as possible for repeat analysis if still clinically relevant.

The central laboratory will provide all laboratory results by fax or normal mail to the site.

All laboratory reports must be signed and dated by the principal investigator or delegate within 5 calendar days of receipt and filed with the source documentation. The investigator/delegate must indicate on the laboratory report whether abnormal values are considered clinically relevant or not. Clinically relevant laboratory findings meeting the definition of an AE [see Section 10.1.1] must be reported as an AE or SAE as appropriate [see Section 10], and must be followed until the value returns to within the normal range or is stable, or until the change is no longer clinically relevant. Further laboratory analyses should be performed as indicated and according to the judgment of the investigator.

Details about the collection, sampling, storage, shipment procedures, and reporting of results and abnormal findings can be found in the laboratory manual.

7.3.11.2 Laboratory tests

Blood samples will be drawn before the morning administration of study medication, at visits indicated in Table 1. Urinalysis will be assessed using dipsticks at visits indicated in Table 1.

Hematology

- Red blood cell count
- Total and differential WBC counts (basophils, eosinophils, lymphocytes, monocytes, neutrophils, band forms)
- Platelet count
- Hb
- Hematocrit

Clinical chemistry

- Glucose
- ALT, AST, alkaline phosphatase, TBL, lactate dehydrogenase

- Creatinine
- Calculated creatinine clearance (Cockroft-Gault)
- INR
- Urea
- Uric acid
- Total cholesterol
- Triglycerides
- Sodium, potassium, chloride, calcium
- Total protein, albumin
- C-reactive protein

Virus serology

- Hepatitis B surface antigen, Hepatitis C antibodies, HIV1 and HIV2 antibodies at Visit 1 (screening)

Additional analyses in the event of infections

- A serum sample will be taken at Visit 1 (screening) to be stored at the central laboratory for potential retrospective analyses of viral serology titers in the event of infections (e.g., suspected opportunistic infection) during the study.

Test for TB

- An interferon gamma release assay will be performed at Visit 1 (screening) to screen for active or latent TB [see Section 7.3.6].

Pregnancy test

A serum pregnancy test for WOCBP will be performed at Visit 1 (screening) and if pregnancy is suspected during the study. A urine or a serum pregnancy test will be performed at Visit 2 (Day 1). Urine pregnancy tests will be performed at visits indicated in Table 1. Home urine pregnancy tests will be conducted by the subject at Weeks EX-28, EX-32, EX-40, EX-44, EX-52, EX-56, EX-64, EX-68, EX-76, EX-80, EX-88, and EX-92. The subject will telephone the site and convey the results of the home urine pregnancy test. The site must follow-up with the subject in case results are not received by the site within 7 days of the planned home urine test date.

In order for WOCBP to be enrolled in the study, they must have a confirmed negative serum pregnancy test at Visit 1 (screening) and a second confirmed negative urine or serum pregnancy test prior to enrollment at Visit 2 (Day 1). The two tests must be performed a minimum of 3 weeks or 10 days apart, respectively.

Serum pregnancy testing results data will be automatically transferred from the central laboratory database to Actelion's clinical database. Urine pregnancy testing results will be

recorded in the eCRF. In case of pregnancy, a Pregnancy Form must be completed [see Section 10.3].

Urinalysis

- pH
- Glucose
- Proteins
- Blood
- Leukocytes
- Bilirubin, urobilinogen

Urine dipsticks provided by the central laboratory will be used to perform the urinalysis. The test should be performed and analyzed at the site. The results must be documented in the source documents / subject charts. No data will be collected in the eCRF. Clinically relevant findings meeting the definition of an AE (new AE, or worsening of previously existing condition) [see Section 10.1.1] will be recorded accordingly on an AE page of the eCRF.

7.4 Efficacy assessments

7.4.1 Organ-specific assessments (Chronic GVHD Activity Assessment Form A)

Organ-specific assessments will be performed at visits indicated in Table 1. These must be assessed by the investigator or a qualified delegate [see Section 3.4.1]. Baseline assessments are collected at Visit 2 (Day 1) before study drug is administered to the subject. Baseline or subsequent abnormalities not attributed to chronic GVHD will be recorded as AEs (if new since signing informed consent) but are not included as efficacy assessments. Organ-specific assessments are a part of the Chronic GVHD Activity Assessment eCRF. The Chronic GVHD Activity Assessment source document forms are in Appendix 7.

7.4.1.1 Skin

7.4.1.1.1 NIH Skin Score

This NIH Skin Score is a 4-point scale ranging from 0–3 [NIH Therapeutic Response 2014]. It considers body surface area (BSA) affected and the type of skin involvement (erythema, sclerotic and/or ulceration). It consists of the following four categories of increasing severity: 0 = no symptoms; 1 = ≤ 18% BSA and no sclerosis; 2 = 19–50% BSA and/or any moveable sclerosis; 3 = > 50% BSA and/or any non-moveable sclerosis, impaired mobility, or ulcers.

The evaluator should determine the % BSA by the “Rule of 9s” [see Appendix 9]. This convention separates the skin surface area into multiples of 9, with the genitals

corresponding to 1%; the total is 100%. Each area is described below with the corresponding percentage.

Anatomic structure	BSA
Anterior head	4.5%
Posterior head	4.5%
Anterior torso	18%
Posterior torso	18%
Anterior right leg	9%
Anterior left leg	9%
Posterior right leg	9%
Posterior left leg	9%
Anterior right arm	4.5%
Anterior left arm	4.5%
Posterior right arm	4.5%
Posterior left arm	4.5%
Genitals/perineum	1%

7.4.1.2 Mouth

7.4.1.2.1 NIH Modified Oral Mucositis Score.

The NIH Modified Mucosistis Score is a 13 point scale ranging from 0–12. It measures a) mucosal erythema (color intensity and percent of oral surface area); b) lichen-like (percent of oral surface area); and c) ulcerations (percent of oral surface area) [NIH Therapeutic Response 2014]. The 13-point scale is divided into four groups, roughly corresponding with: none, mild, moderate and severe. The categories are further defined in Form A in Appendix 7.

7.4.1.3 Liver

7.4.1.3.1 Liver tests: ALT, alkaline phosphatase, and TBL

The liver tests used for the organ-specific assessments are ALT, alkaline phosphatase, and total serum bilirubin [Section 7.3.11].

7.4.1.4 Lungs

7.4.1.4.1 PFTs: FEV_1

The FEV_1 is the basis of assessing response in lung. Collection of FEV_1 is further detailed in Section 7.3.3.

7.4.1.4.2 Lung symptoms

Lung symptoms data is collected to generate an NIH lung score, but this score does not form the basis of assessing response when FEV_1 data is available. The NIH lung score is a 4-point scale measuring increasing severity of breathing symptoms [Filipovich 2005, NIH Therapeutic Response 2014]. The investigator assesses symptoms ranging in a score from 0–3: 0 = no symptoms; 1 = mild symptoms (shortness of breath after climbing one flight of steps); 2 = moderate symptoms (shortness of breath after walking on flat ground); 3 = severe symptoms (shortness of breath at rest; requiring oxygen).

7.4.1.5 Eyes

7.4.1.5.1 NIH Eye Score

The NIH Eye Score is a 4-point scale measuring increasing severity of dryness [Filipovich 2005, NIH Therapeutic Response 2014]. The investigator assesses symptoms ranging in a score from 0–3: 0 = no symptoms; 1 = mild dry eye symptoms not affecting activities of daily living (ADL; requiring lubricant eye drops ≤ 3 × per day), 2 = moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 × per day or punctal plugs), without new vision impairment due to keratoconjunctivitis sicca (KCS); 3 = severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain), or unable to work because of ocular symptoms, or loss of vision due to KCS.

7.4.1.6 Joints and fascia

7.4.1.6.1 NIH Joint and Fascia Score

The NIH Joint and Fascia Sore is a 4-point scale measuring increasing severity of symptoms of the joints and fascia including those affecting range of motion, limb tightness and inflammation [Inamoto 2014a, NIH Therapeutic Response 2014]. The investigator assesses symptoms ranging in a score from 0–3: 0 = no symptoms; 1 = mild tightness of arms and legs, normal or mild decrease in range of motion (ROM) and not affecting ADL; 2 = tightness of arms or legs or joint contractures, erythema thought to be due to fasciitis, moderate decrease ROM and mild-to-moderate limitation of ADL; 3 = contractures with significant decrease in ROM, and significant limitation of ADL (unable to tie shoes, button shirts, dress self, etc.)

7.4.1.6.2 Photographic Range of Motion

The P-ROM is a 25-point scale based on predicted range of motion. The scale consists of a series of photographic images capturing ROM separately at the shoulders, elbows, wrists/fingers, and ankles [Inamoto 2014a, NIH Therapeutic Response 2014]. The score is the sum of all four joints, with lower scores indicating a decreased ROM. Shoulders, elbows and wrists/fingers are scored on a scale from 1–7 with 1 = worst ROM and 7 = normal ROM. Ankles are scored on a scale of 1–4 with 1 = worst ROM and 4 = normal ROM.

7.4.1.7 GI tract

Assessment of the GI tract is separated into three categories: upper GI, lower GI and esophagus.

7.4.1.7.1 NIH Upper GI Score

The NIH Upper GI Score is a 4-point scale measuring increasing severity of the upper GI symptoms: early satiety, or anorexia, or nausea and vomiting [NIH Therapeutic Response 2014]. The investigator assesses symptoms ranging in a score from 0–3: 0 = no symptoms; 1 = mild, occasional symptoms, with little reduction in oral intake during the past week; 2 = moderate, intermittent symptoms, with some reduction in oral intake during the past week; 3 = more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week.

7.4.1.7.2 NIH Lower GI Score

The NIH Lower GI Score is a 4 point scale measuring increasing severity of diarrhea [NIH Therapeutic Response 2014]. The investigator assesses symptoms ranging in a score from 0–3: 0 = no loose or liquid stools during the past week; 1 = occasional loose or liquid stools on some days during the past week; 2 = intermittent loose or liquid stools throughout the day, on almost every day of the past week, without requiring intervention to prevent or correct volume depletion; 3 = voluminous diarrhea on almost every day of the past week, requiring intervention to prevent or correct volume depletion.

7.4.1.7.3 NIH Esophagus Score

The NIH Esophagus Score is a 4-point scale measuring increasing severity of esophageal symptoms of dysphagia or odynophagia [NIH Therapeutic Response 2014]. The investigator assesses symptoms ranging in a score from 0–3: 0 = no esophageal symptoms; 1 = occasional dysphagia or odynophagia with solid foods or pills during the past week; 2 = intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week; 3 = dysphagia or odynophagia for almost all oral intake, on almost every day of the past week.

7.4.2 Clinician global reported ratings (Chronic GVHD Activity Assessment Form A)

7.4.2.1 Clinician Overall Severity Scale.

The Clinician Overall Severity Score consists of an 11-point scale [NIH Therapeutic Response 2014]. The investigator rates the severity of the subject's chronic GVHD symptoms on a scale of 0–10 with a score of 0 = chronic GVHD symptoms are not at all severe and a score of 10 = the most severe chronic GVHD symptoms possible.

The Clinician Overall Severity Score will be performed at visits indicated in Table 1. This must be assessed by the investigator or a qualified delegate. Baseline assessments are

collected at Visit 2 (Day 1) before study drug is administered to the subject. The Clinician Overall Severity Score is part of the Chronic GVHD Activity Assessment eCRF. The Chronic GVHD Activity Assessment source document forms are in Appendix 7.

7.4.2.2 Clinician None-Mild-Moderate-Severe Scale

The Clinician None-Mild-Moderate-Severe Scale is a 4-point scale measuring increasing severity of chronic GVHD symptoms [NIH Therapeutic Response 2014]. The investigator assesses symptoms ranging in a score from 0–3: 0 = none; 1 = mild; 2 = moderate; 3 = severe.

The Clinician None-Mild-Moderate-Severe Scale will be performed at visits indicated in Table 1. This must be assessed by the investigator or a qualified delegate. Baseline assessments are collected at Visit 2 (Day 1) before study drug is administered to the subject. The Clinician None-Mild-Moderate-Severe Scale is part of the Chronic GVHD Activity Assessment eCRF. The Chronic GVHD Activity Assessment source document forms are in Appendix 7.

7.4.2.3 Clinician 7-Point Change Scale

The Clinician 7-Point Change Scale is a 7-point scale measuring chronic GVHD changes over time [NIH Therapeutic Response 2014]. The investigator scores changes in subjects' overall chronic GVHD symptoms since the last visit on a scale of 7: +3 = very much better; +2 = moderately better; +1 = a little better; 0 = about the same; –1 = a little worse; –2 = moderately worse; –3 = very much worse. Assessments will occur during Visits 5 and 8. At Visits 5 and 8, the investigator must assess the change in the subject's chronic GVHD symptoms since the last visit (Visits 4 and 7, respectively).

The Clinician 7-Point Change Scale will be performed at visits indicated in Table 1 except for Visit 2 (Day 1). This must be assessed by the investigator or a qualified delegate. No baseline assessments are collected for this parameter. The Clinician 7-Point Change Scale is part of the Chronic GVHD Activity Assessment eCRF. The Chronic GVHD Activity Assessment source document forms are in Appendix 7.

7.5 Quality of Life assessments

7.5.1 Lee Symptom Scale

The Lee Symptom Scale (LSS) is a Quality of Life questionnaire used to assess the burden of chronic GVHD symptoms) [Lee 2002]. It measures many organ-specific symptoms as well as symptoms of fatigue and psychological disorders. Subjects will complete the questionnaire at visits indicated in Table 1.

The LSS instructs the subject to review a list of symptoms and report any that have been bothering him/her in the past month and to what extent. It includes 30 items sorted under

the following categories: skin; eyes and mouth; breathing; eating and digestion; muscles and joints; energy; and mental and emotional. The degree of burden is measured on a 5-point scale from 0–4 (0 – not at all, 1 – slightly, 2 – moderately, 3 – quite a bit, and 4 – extremely).

It is recommended that the LSS is completed prior to any clinical assessments. Subjects should complete the LSS while waiting for their appointment before any interaction with health care providers to avoid any potential bias in their responses.

A sample of the LSS is provided as Appendix 8. Subjects will complete the questionnaire on a validated paper form that will be collected and transcribed in the eCRF.

The LSS does not require a license agreement.

7.5.2 Patient-reported chronic GVHD symptoms (Chronic GVHD Activity Assessment Form B)

7.5.2.1 Skin itching

Subjects will complete an itching symptoms scale at visits indicated in Table 1. The scale requests the subjects to recall their worst itching symptoms in the past 7 days and score it on a scale of 0–10 with 0 = not present and 10 = as bad as you can imagine. The subject-reported skin-itching scale is part of the Chronic GVHD Activity Assessment eCRF. The Chronic GVHD Activity Assessment source document forms are in Appendix 7.

7.5.2.2 Skin and/or joint tightening

Subjects will complete a skin and/or joint tightening symptoms scale at visits indicated in Table 1. The scale requests the subjects to recall their worst skin and/or joint tightening symptoms in the past 7 days and score it on a scale of 0–10 with 0 = not present and 10 = as bad as you can imagine. The subject-reported skin-itching scale is part of the Chronic GVHD Activity Assessment eCRF. The Chronic GVHD Activity Assessment source document forms are in Appendix 7.

7.5.2.3 Mouth sensitivity

Subjects will complete a mouth sensitivity scale at visits indicated in Table 1. The scale requests the subjects to recall their worst mouth sensitivity symptoms in the past 7 days and score it on a scale of 0–10 with 0 = Not present and 10 = As bad as you can imagine. The subject-reported mouth-sensitivity scale is part of the Chronic GVHD Activity Assessment eCRF. The Chronic GVHD Activity Assessment source document forms are in Appendix 7.

7.5.2.4 Genital discomfort

Subjects will complete a genital discomfort scale at visits indicated in Table 1. The scale requests the subjects to recall their worst genital discomfort symptoms in the past 7 days and score it on a scale of 0–10 with 0 = not present and 10 = as bad as you can imagine. The subject-reported genital-discomfort scale is part of the Chronic GVHD Activity Assessment eCRF. The Chronic GVHD Activity Assessment source document forms are in Appendix 7.

7.5.2.5 Eyes

Subjects will complete an eyes symptom scale at visits indicated in Table 1. Subjects are asked to provide the main complaint with regard to their eyes and the associated severity on an 11-point scale ranging from 0–10 with 0 = not at all severe and 10 = most severe. The subject-reported eyes-symptoms scale is part of the Chronic GVHD Activity Assessment eCRF. The Chronic GVHD Activity Assessment source document forms are in Appendix 7.

7.5.3 Patient-reported global ratings (Chronic GVHD Activity Assessment Form B)

7.5.3.1 Patient-Reported Overall Severity Scale

The subject will complete the Patient-Reported Overall Severity Scale at visits indicated in Table 1. Subjects are asked to score how severe their chronic GVHD symptoms are on a scale of 0–10 with 0 = chronic GVHD symptoms not at all severe and 10 = most severe chronic GVHD symptoms possible. The Patient-Reported Overall Severity Scale is part of the Chronic GVHD Activity Assessment eCRF. The Chronic GVHD Activity Assessment source document forms are in Appendix 7.

7.5.3.2 Patient-Reported Mild-Moderate-Severe Scale

The subject will complete the Patient-Reported Mild-Moderate-Severe Scale at visits indicated in Table 1. Subjects are asked to report if they think their overall chronic GVHD is mild, moderate or severe. The Patient-Reported Mild-Moderate-Severe Scale is part of the Chronic GVHD Activity Assessment eCRF. The Chronic GVHD Activity Assessment source document forms are in Appendix 7.

7.5.3.3 Patient-Reported 7-Point Change Scale

The subject will complete the Patient-Reported 7-Point Change Scale at visits indicated in Table 1. Subjects are asked to compare their current chronic GVHD symptoms to one month prior on a scale of 7: +3 = very much better; +2 = moderately better; +1 = a little better; 0 = about the same; –1 = a little worse; –2 = moderately worse; –3 = very much worse. The Patient-Reported 7-Point Change Scale is part of the Chronic GVHD Activity

Assessment eCRF. The Chronic GVHD Activity Assessment source document forms are in Appendix 7.

7.6 Exploratory biomarker assessments

7.6.1 Blood lymphocyte subsets

$S1P_1$ modulators such as ponesimod reduce total lymphocyte counts (T and B lymphocytes) in healthy subjects as a defined PD effect. T- and B-cells consist of different subsets having distinct functions in chronic GVHD disease manifestation and progression. Analysis of specific blood lymphocyte subsets provides a detailed understanding of the ponesimod effect on B and T lymphocyte subsets in a chronic GVHD patient population.

7.6.1.1 Sampling time

Blood samples for lymphocyte subsets will be taken from every subject at visits indicated in Table 1.

7.6.1.2 Sampling procedure

Up to 5 mL of blood is collected.

7.6.1.3 Labeling and shipment

Details of the collection, labeling and shipment of the samples can be found in the laboratory manual provided to the investigator. The tubes and labels for the samples will be provided to the investigator and/or staff by the sponsor or the central laboratory.

7.6.1.4 Bioanalysis

Blood samples will be analyzed by the sponsor following the principles of GCLP. The assays are validated for the purpose of exploration. B- and T-cell subsets are defined by a combination of cell surface markers and are analyzed in four separate panels (panel 1–4). The specified list of surface markers is not exhaustive.

- Panel 1: CD19, CD20, IgD, CD27, CD38, CD45, CXCR3, CD138
- Panel 2: CD3, CD4, CD8, CD45RA, CD25, CD45, CD127, CCR7
- Panel 3: CD3, CD4, CD8, CCR6, CXCR3, CXCR5, CD45, CRTH2
- Panel 4: CD45, CD19, CD10, CD21, CD 27, IgD

7.6.2 Plasma biomarkers

A recent report on biomarkers for chronic GVHD prepared by the NIH Biomarker Working Group identified several candidate biomarkers for the purpose of diagnosis, prognosis/risk stratification and prediction of treatment effect [NIH Biomarkers]. Biomarkers with

sufficient evidence (cohesive findings in > 2 reports) will be investigated in plasma samples using assays validated for the purpose of exploration.

7.6.2.1 Sampling time

Plasma samples will be taken from every subject at visits indicated in Table 1.

7.6.2.2 Sampling procedure

5 mL of blood is collected in vacutainer tubes containing EDTA as anti-coagulant.

7.6.2.3 Labeling and shipment

Details of the collection, labeling and shipment of the samples can be found in the laboratory manual provided to the investigator. The tubes and labels for the samples will be provided to the investigator and/or staff by the central laboratory.

7.6.2.4 Bioanalysis

Plasma samples will be analyzed by the central laboratory. The assays will be validated for the purpose of exploration.

7.6.3 Exploratory biomarker samples

New scientific evidence on biomarkers related to chronic GVHD or $S1P_1$ modulators may trigger new analysis.

Research samples allow investigation of questions related to:

A. Change of biomarker level over 24 weeks in a chronic GVHD patient population

B. Baseline biomarker level in a chronic GVHD patient population

C. Effect of ponesimod on biomarker level in a chronic GVHD patient population

Research samples are collected under the core ICF and can be stored by the sponsor for the duration specified in the core ICF.

7.6.3.1 Sampling time

Blood samples will be taken at visits indicated in Table 1.

7.6.3.2 Sampling procedure

5 mL of blood is collected in vacutainer tubes containing EDTA as anticoagulant.

7.6.3.3 Labeling and shipment

Details of the collection, labeling and shipment of the samples can be found in the laboratory manual provided to the investigator. The tubes and labels for the samples will be provided to the investigator and/or staff by the central laboratory.

7.7 Total blood volume

The total blood volume to be drawn per subject during the Core Treatment Period is described in Table 7.

Table 7 Total blood volume drawn per subject - Core Treatment Period and Follow-up Period 1

Test	Number of tests	Volume per test	Total volume per scheduled study visits
Viral serology at screening	1	5 mL	5 mL
Interferon gamma release assay for tuberculosis at screening	1	3 × 1 mL	3 mL
Serum sample at baseline[1]	1	5 mL	5 mL
Hematology[2]	12	3 mL	36 mL
Blood chemistry[3]	12	7.5 mL	90 mL
Ponesimod pharmacokinetics[4]	12	3 mL	36 mL
Blood lymphocyte subsets	3	5 mL	15 mL
Plasma biomarkers	3	5 mL	15 mL
Exploratory biomarker samples	3	5 mL	15 mL
Total blood volume drawn at scheduled study visits: 220 mL			

1. To be stored at the central laboratory for potential retrospective analyses of viral serology titers in the event of infections.
2. Additional samples may be needed in the event of absolute lymphocytes < 100 cells/µL and in case of a second serum pregnancy test prior to enrollment.
3. Includes serum pregnancy or post-menopausal test at screening, if needed.
4. Additional samples may be needed in the event of additional ECG measurements on Day 1 (Visit 2).

The total blood volume to be drawn per subject during the Extension Treatment Period is described in Table 8.

Table 8 Total blood volume drawn per subject - Extension Treatment Period and Follow-up Period 2

Test	Number of tests	Volume per test	Total volume per scheduled study visits
Hematology[1]	14	3 mL	42 mL
Blood chemistry	14	7.5 mL	105 mL
Total blood volume drawn at scheduled study visits: 147 mL			

1. Additional samples may be needed in the event of total lymphocytes < 100 cells/µL.

8 SCHEDULE OF VISITS AND ASSESSMENTS

A tabulated summary of all visits and assessments described in the following sections is provided in Table 1. The schedule of visit dates should be established at the time of

screening. To the extent possible, subjects will be expected to adhere to the established visit schedule.

The time point for every visit is defined taking as a reference Day 1 (Visit 2), which is the day of enrollment.

When scheduling the different assessments for a subject visit, the following should be taken into account:

- The subject must come to the clinic before the morning administration of study drug, when applicable.
- At Visit 2 (Day 1), Visit 11 (EX-1) and on the days of re-initiation of study drug (if applicable), the assessments during the visits will be divided into two parts: before (pre-dose) and after (post-dose) the administration of ponesimod, which will be taken at the site on the day of visits.
- At other visits, ECGs, SBP/DBP, PFTs, blood drawings for hematology and blood chemistry, along with all other assessments, are to be performed pre-dose.
- Pre-dose PK samplings are to be done at Visits 2 (Day 1), 3 (Week 4), 4 (Week 8), 5 (Week 12), 6 (Week 16) and 7 (Week 20). Additional samples are drawn post-dose at Visits 2 (Day 1) and 5 (Week 12). At Visit 2, post-dose sampling must be drawn hourly at approximately the same time as post-dose ECGs are performed (as per Section 7.2.1.1). At Visit 5, the sample is collected 3 hours post-dose. A PK sample is also collected at EOT1, Visit 8 (Week 24); no study drug is taken at this visit.
- Resting time:
  - When the subject is to go to another department within the hospital for a specific test, sufficient time should be allowed for the subject to rest prior to the examination.
  - Sufficient time between blood drawing and cardiac assessments (i.e., ECGs and/or BP measurement) is to be allowed.
- Preferably, questionnaires will be completed by the subject in the morning prior to any other protocol assessment and prior to any other discussion with the investigator. Subjects will provide responses to the questionnaires while waiting for their appointment. Questionnaires should be completed prior to any discussion with the investigator in the following order:
  - Patient-reported chronic GVHD symptoms and patient-reported overall ratings (Chronic GVHD Activity Assessments Patient self-report Form B, [Appendix 7])
  - LSS

To ensure compliance, at each visit the study personnel must remind WOCBP to use the MOC defined for this study. The reminders must be documented in the eCRF.

It is permitted to re-screen subjects once if the reason for non-eligibility was transient (e.g., abnormal laboratory test, insufficient wash-out period of a forbidden medication), provided that documented authorization has been received from Actelion. All pre-enrollment assessments should then be repeated at the time of re-screening (with the exception of CXR).

Unscheduled visits may be performed at any time during the study. Depending on the reason for the unscheduled visit (e.g., re-initiation of study drug, AE, central laboratory re-test, etc.), appropriate assessments may be required or may be performed based on the judgment of the investigator and must be recorded in the eCRF. After an unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule.

8.1 Screening period

The screening period must take place within 30 days prior to enrollment and include the Visit 1 (screening) and the pre-dose assessments of Visit 2 (Day 1).

The start of screening occurs on the day the first screening assessment was performed (i.e., signature of informed consent).

8.1.1 Visit 1 (screening)

Visit 1 will be performed from 30 days to 1 day prior to enrollment. The Visit 1 date is defined as the date of the first assessment performed for the study (i.e., informed consent signature). During this visit, subject informed consent will be obtained, and assessments required for the determination of subject eligibility will be performed. These assessments may generally be performed on separate days within the screening period.

Visit 1 includes:

- After discussing the study with the investigator and after agreeing to study participation by signing the ICF, subjects will be assigned a subject number by the interactive response technology (IRT) provider. For any subject, it is the responsibility of the investigator to obtain written informed consent (subject's signature) prior to performing any protocol-mandated assessment. However, assessments performed as part of the routine care of the subject may be used to assess eligibility. The subject number will identify the subject throughout the study. In case of re-screening [see Section 8], the subject number assigned during the first screening procedure will be retained.
- Review of chronic GVHD diagnosis and assess stage and score per 2014 NIH consensus criteria [Appendix 2]
- Recording of demographics, medical history, smoking status, and disease characteristics

- Recording of previous and concomitant medications [see Section 5.2]
- SBP/DBP
- Body weight and height
- Physical examination
- Spirometry (under the responsibility of the pulmonologist)
- DL_{CO} (under the responsibility of the pulmonologist)
- Ophthalmological examination (under the responsibility of the ophthalmologist)
- OCT (under the responsibility of the ophthalmologist)
- Hematology, blood chemistry, serum pregnancy test for WOCBP and exploratory biomarker assessments (blood lymphocyte subsets, plasma biomarkers, exploratory biomarker samples)
- TB test
- Viral serology
- Urinalysis
- 12-lead ECG
- CXR (any CXR performed within 90 days prior to screening can be used). In case of rescreening, CXR does not need to be repeated.
- Recording of AEs/SAEs: all AEs/SAEs occurring after signing of the ICF are to be reported in the eCRF and on an SAE form, if applicable.

The investigator must check inclusion/exclusion criteria. The subject must meet all eligibility criteria to be enrolled into the study. Eligibility will be assessed again at Visit 2 before the subject is enrolled and receives study drug. The reasons for screening failure are documented in the eCRF (screening information is collected for all screen failure subjects).

8.1.2 Visit 2 Enrollment Day 1 (pre-dose)

The assessments during this visit will be divided into two parts: before (pre-dose) and after (post-dose) the administration of ponesimod. During this visit, the inclusion and exclusion criteria will be confirmed and baseline assessments will be performed and recorded.

For WOCBP, the urine or serum pregnancy test at Visit 2 must be performed at least 21 days or 7 days, respectively, after the serum pregnancy test performed at Visit 1.

All Visit 2 pre-dose assessments are mandatory and must be performed within the allowed time window (described in Section 8.1.2.1). These same assessments may concurrently also serve as the Visit 1 screening assessment, if the screening assessment was not previously performed.

8.1.2.1 Visit 2 – Day 1 – pre-dose assessments

The investigator must check all inclusion/exclusion criteria. Pre-dose assessments include:

Assessments performed within 48 hours prior to study drug administration (pre-dose)

- Spirometry (under the responsibility of the pulmonologist)
- DL_{CO} (under the responsibility of the pulmonologist)
- Body weight
- Chronic GVHD Activity Assessments – physician-assessed [Appendix 7 – Form A]
- Administer Chronic GVHD Activity Assessment – Patient self-report [Appendix 7 – Form B]
- Administer LSS (subject completes the questionnaire after patient self-report but prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)
- Hematology and blood chemistry
- Urine or serum pregnancy test for WOCBP (must be at least 21 days and at least 7 days after Visit 1 serum pregnancy, respectively)

Assessments performed on the morning of study drug administration (pre-dose)

- PK/PD samples
- Recording of change in previous and concomitant medications since Visit 1 [see Section 5.2]
- SBP/DBP (under the responsibility of the cardiac safety assessor)
- 12-lead ECG (under the responsibility of the cardiac safety assessor)
- Recording of MOC (for WOCBP only)
- Recording of AEs/SAEs: all AEs/SAEs occurring after signing of the ICF are to be reported in the eCRF and on an SAE form, if applicable.

8.2 Core Treatment Period

The Core Treatment Period consists of Visits 2 (first study drug administration) to 8 (Enrollment – Day 1, Week 4, and every 4 weeks thereafter until EOT1 / Week 24).

8.2.1 Visit 2 – Enrollment Day 1 (post-dose)

Visit 2 corresponds to the start of the treatment period (Day 1 of the study). The ECGs (pre- and post-dose), BP (pre- and post-dose), and first dose administration must be performed on the same day and define the date of the visit. This date should preferably correspond to the date of enrollment in the IRT system.

8.2.1.1 Visit 2 - Day 1 - Enrollment and post-dose assessment

If eligible, the subject should be enrolled in the study, and take the first dose of study drug. The subject must be monitored for up to 12 h post-dose. Starting at 4 hours post-dose, the cardiac safety assessor must check whether the subject fulfills the hospital discharge

criteria [see Section 5.1.7]. Subjects may be discharged from the hospital if they meet the discharge criteria before 12 h post-dose but no sooner than 4 h post-dose [see Section 5.1.7].

Visit 2 enrollment and post-dose assessment includes:

- After confirmation of eligibility (i.e., verification of all entry criteria) by the investigator:
  - Enrollment via IRT to obtain study treatment kit number
  - Dispensing of study treatment
- SBP/DBP hourly for up to 12 h post-dose with a minimum of 4 h post-dose (under the responsibility of the cardiac safety assessor)
- 12-lead ECG hourly for up to 12 h post-dose with a minimum of 4 h post-dose (under the responsibility of the cardiac safety assessor)
- PK sampling hourly for up to 12 h post-dose with a minimum of 4 samples taken.
- Recording of AEs and SAEs. (Note: On Day 1, significant findings, which in the view of the cardiac safety assessor meet the definition of an AE and are resolved at the time of discharge of the subject, must be reported to the principal investigator and recorded directly on the Adverse Event page of the eCRF.)
- Remind WOCBP to use the MOC defined for this study. The reminders must be documented in the hospital chart and the eCRF.
- Schedule an appointment for next visit and instruct subject to:
  - bring back any blister wallets
  - not take study treatment on the day of study visit prior to coming to the site

Subjects will need to gradually up-titrate from 2 mg to 5 mg during Days 1 to 7. As there is no site visit planned until Week 4, subjects will be instructed on how to perform the gradual up-titration during Visit 2.

The subject will be instructed to contact the site if he/she has any questions or problems.

8.2.2 Visit 3 – Week 4

The visit window for this visit is ± 3 days. The date of drug dispensing, preferably corresponding to the date of registration of the visit in the IRT system, defines the date of the visit. Hematology, blood chemistry, urinalysis, spirometry, DL_{CO} and pregnancy tests may be performed up to 3 days prior to this visit date. The visits include:

- Recording of changes in concomitant medications
- Assessing the MOC and recording in the eCRF (for WOCBP only)
- SBP/DBP (pre-dose)

- 12-lead ECG pre-dose
- Hematology, blood chemistry (pre-dose, local and central labs)
- PK sampling (pre-dose)
- PD sampling (pre-dose)
- Urinalysis
- Urine pregnancy test for WOCBP
- Spirometry (pre-dose; under the responsibility of the pulmonologist)
- DL_{CO} (pre-dose; under the responsibility of the pulmonologist)
- Recording of AEs and SAEs
- Study medication accountability and compliance review
- IRT call and study drug dispensing
- Remind WOCBP to use the MOC defined for this study. The reminders must be documented in the hospital chart.
- Schedule an appointment for next visit and instruct subject to:
    - bring back any blister wallets
    - not take study treatment on the day of study visit prior to coming to the site.

8.2.3 Visit 4 – Week 8

The visit window for this visit is ± 3 days. The date of drug dispensing, preferably corresponding to the date of registration of the visit in the IRT system, defines the date of the visit. Hematology, blood chemistry, urinalysis, spirometry, DL_{CO} and pregnancy tests may be performed up to 3 days prior to this visit date. The visits include:

- Recording of changes in concomitant medications
- Assessing the MOC and recording in the eCRF (for WOCBP only)
- SBP/DBP (pre-dose)
- 12-lead ECG (pre-dose)
- Hematology, blood chemistry (pre-dose, local and central labs)
- PK sampling (pre-dose)
- PD sample (pre-dose)
- Urinalysis
- Urine pregnancy test for WOCBP
- Spirometry (pre-dose; under the responsibility of the pulmonologist)
- DL_{CO} (pre-dose; under the responsibility of the pulmonologist)
- Recording of AEs and SAEs
- Study medication accountability and compliance review

- IRT call and study drug dispensing
- Remind WOCBP to use the MOC defined for this study. The reminders must be documented in the hospital chart.
- Schedule an appointment for next visit and instruct subject to:
  - bring back any blister wallets
  - not take study treatment on the day of study visit prior to coming to the site

8.2.4 Visit 5 – Week 12

The visit window for this visit is ± 7 days. The date of drug dispensing, preferably corresponding to the date of registration of the visit in the IRT system defines the date of the visit. Spirometry, DL_{CO}, OCT, ophthalmological examination, hematology, blood chemistry, urinalysis, spirometry, DL_{CO} and pregnancy tests may be performed up to 7 days prior to or after this visit date. The visits include:

- Administer Chronic GVHD Activity Assessment - Patient self-report [Appendix 7 – Form B]
- Administer LSS (subject completes the questionnaire after patient self-report but prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)
- Recording of changes in concomitant medications
- Assessing the MOC and recording in the eCRF (for WOCBP only)
- SBP/DBP (pre-dose)
- 12-lead ECG (pre-dose)
- Physical examination
- Spirometry (pre-dose; under the responsibility of the pulmonologist)
- DL_{CO} (pre-dose; under the responsibility of the pulmonologist)
- OCT (under the responsibility of the ophthalmologist)
- Ophthalmological examination (under the responsibility of the ophthalmologist)
- Hematology, blood chemistry (pre-dose)
- PK sampling (pre-dose and 3 hours post-dose)
- PD sampling (pre-dose and 3 hours post-dose)
- Urinalysis
- Urine pregnancy test for WOCBP
- Chronic GVHD Activity Assessments – physician-assessed [Appendix 7 – Form A]
- Recording of AEs and SAEs
- Study medication accountability and compliance review

- IRT call and study drug dispensing
- Remind WOCBP to use the MOC defined for this study. The reminders must be documented in the hospital chart.
- Schedule an appointment for next visit and instruct subject to:
    - bring back any bottles or blister wallets
    - not take study treatment on the day of study visit prior to coming to the site

8.2.5 Visits 6 and 7 - Weeks 16 and 20

The visit window for these visits is ± 7 days. The date of drug dispensing, preferably corresponding to the date of registration of the visit in the IRT system defines the date of the visit. Hematology, blood chemistry, urinalysis and pregnancy tests may be performed up to 7 days prior to or after this visit date. The visits include:

- Recording of changes in concomitant medications
- Assessing and recording of MOC (for WOCBP)
- SBP/DBP (pre-dose)
- 12-lead ECG (pre-dose)
- Hematology, blood chemistry (pre-dose)
- PK sampling (pre-dose)
- PD sampling (pre-dose)
- Urinalysis
- Urine pregnancy test for WOCBP (if applicable)
- Recording of AEs and SAEs
- Study medication accountability and compliance review
- IRT call and study drug dispensing
- Remind WOCBP to use the MOC defined for this study. The reminders must be documented in the hospital chart.
- Schedule an appointment for next visit and instruct subject to:
    - bring back any bottles or blister wallets
    - not take study treatment on the day of study visit prior to coming to the site

8.2.6 Visit 8 – EOT1 Visit

The EOT1 visit will take place at Week 24 (± 7 days) or earlier in case of premature discontinuation of study drug. In all cases, the EOT1 visit must take place 1 to 3 days after the last dose of study drug. It is strongly preferred that the EOT1 visit takes place 1 day after the last dose of study drug. Spirometry, DL_{CO}, hematology, blood chemistry, urinalysis and pregnancy tests should be performed 1 to 3 days after the last dose of study drug and do not need to be performed on the same day as the EOT1 visit. OCT and the

ophthalmological examination may be performed up to 7 days after the last dose of study drug.

The visit includes:

- Administer Chronic GVHD Activity Assessment – Patient self-report [Appendix 7 – Form B]
- Administer LSS (subject completes the questionnaire after patient self-report but prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)
- Chronic GVHD Activity Assessments - physician assessed [Appendix 7 – Form A]
- Recording of changes in concomitant medications
- Assessing and recording of MOC (for WOCBP only)
- SBP/DBP
- 12-lead ECG
- Body weight
- Physical examination
- Spirometry (under the responsibility of the pulmonologist)
- DL_{CO} (under the responsibility of the pulmonologist)
- OCT (under the responsibility of the ophthalmologist)
- Ophthalmological examination (under the responsibility of the ophthalmologist)
- Hematology, blood chemistry, PK/PD and exploratory biomarker assessments (blood lymphocyte subsets, plasma biomarkers, exploratory biomarker samples)
- Urinalysis
- Urine pregnancy test for WOCBP (if applicable)
- Recording of AEs and SAEs
- Study medication accountability and compliance review
- IRT call
- Remind WOCBP to use the MOC defined for this study. The reminders must be documented in the hospital chart.
- Schedule an appointment for next visit.

8.3 Core Safety Follow-up Period / Follow-up Period 1

The Follow-up Period 1 consists of the 30-day (+7 day window) post-core treatment safety follow-up visit (FU1) and the 90-day (+7 day window) post-core treatment safety follow-up visit (FU2).

The EOS visit occurs:

- At visit FU1 if a subject discontinues study drug prematurely during the Core Treatment Period.

- At FU2 if the subject does not prematurely discontinue study drug during the Core Treatment Period.

For subjects who completed the 24 week Core Treatment Period: if such a subject enters the Extension Treatment Period prior to or on the same day of a scheduled FU1 and/or FU2 visit, then the respective FU1 and/or FU2 visits are cancelled. If these visits are cancelled then EOS occurs only after the subject completes the Extension Safety Follow-up Period [Section 8.4.5].

8.3.1 Visit 9 - 30-day post-Core Treatment Safety Follow-up visit 1 (FU1)

The FU1 visit includes:

- Administer Chronic GVHD Activity Assessment – Patient self-report [Appendix 7 – Form B]
- Administer LSS (subject completes the questionnaire after patient self-report but prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)
- Chronic GVHD Activity Assessments - physician assessed [Appendix 7 – Form A]
- Recording of changes in concomitant medications
- SBP/DBP
- 12-lead ECG
- Spirometry (under the responsibility of the pulmonologist)
- DL_{CO} (under the responsibility of the pulmonologist)
- Hematology, blood chemistry, PD and exploratory biomarker assessments (blood lymphocyte subsets, plasma biomarkers, exploratory biomarker samples)
- Urinalysis
- Urine pregnancy test for WOCBP (if applicable)
- Recording of AEs and SAEs
- Schedule an appointment for next visit and instruct subject to:

8.3.2 Visit 10 - 90-day post-treatment Safety Follow-up visit 2 (FU2)

The FU2 visit includes:

- Administer Chronic GVHD Activity Assessment – Patient self-report [Appendix 7 – Form B]
- Administer LSS (subject completes the questionnaire after patient self-report but prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)
- Chronic GVHD Activity Assessments - physician assessed [Appendix 7 – Form A]
- Recording of changes in concomitant medications
- Hematology, blood chemistry

- Urinalysis
- Urine pregnancy test for WOCBP (if applicable)
- Recording of AEs and SAEs

8.4 Extension Treatment Period

Subjects eligible for the retreatment extension may restart ponesimod at the earliest 7 days after Visit 8 (EOT1). Restarting ponesimod requires an up-titration to the maximum tolerated dose the subject received during the Core Treatment Period (same dose as at EOT1). At the first retreatment extension visit, the subject must be monitored for up to 12 h post-dose. Starting at 4 h post-dose, the cardiac safety assessor must check whether the subject fulfills the cardiac monitoring discharge criteria [see Section 5.1.7]. Subjects may be discharged from the cardiac monitoring setting if they meet the discharge criteria before 12 h post-dose but no sooner than 4 h post-dose [see Section 5.1.7].

8.4.1 Visit 11 (EX-1)

Assessments performed within 48 hours prior to study drug administration (pre-dose)

- Spirometry (under the responsibility of the pulmonologist)
- DL_{CO} (under the responsibility of the pulmonologist)
- Body weight
- Physical examination
- Chronic GVHD Activity Assessments – physician-assessed [Appendix 7 – Form A]
- Administer Chronic GVHD Activity Assessment – Patient self-report [Appendix 7 – Form B]
- Administer LSS (subject completes the questionnaire after patient self-report but prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)
- Hematology and blood chemistry

Assessments performed on the morning of study drug administration (pre-dose)

- PD samples
- Recording of change in previous and concomitant medications since FU visit of the Core Treatment Period (FU1 or FU2)
- Urine pregnancy test for WOCBP (if applicable)
- SBP/DBP (under the responsibility of the cardiac safety assessor)
- 12-lead ECG (under the responsibility of the cardiac safety assessor)
- Recording of MOC (for WOCBP only)
- Recording of AEs/SAEs

Dosing and assessments performed post-dose

- After confirmation of eligibility (i.e., verification of all entry criteria) by the investigator:
    - IRT to obtain study treatment kit number
    - Dispensing of study treatment
- SBP/DBP hourly for up to 12 h post-dose with a minimum of 4 h post-dose (under the responsibility of the cardiac safety assessor)
- 12-lead ECG hourly for up to 12 h post-dose with a minimum of 4 h post-dose (under the responsibility of the cardiac safety assessor)
- Recording of AEs and SAEs. (Note: On Day EX-1, significant findings, which in the view of the cardiac safety assessor meet the definition of an AE and are resolved at the time of discharge of the subject, must be reported to the principal investigator and recorded directly on an Adverse Event page of the eCRF.)
- Remind WOCBP to use the MOC defined for this study. The reminders must be documented in the hospital chart and the eCRF.
- Schedule an appointment for next visit and instruct subject to:
    - bring back any blister wallets
    - not take study treatment on the day of study visit prior to coming to the site

Subjects will need to gradually up-titrate to their previously tolerated dose within EX- Days 1 to 14.

The subject will be instructed to contact the site if he/she has any questions or problems.

8.4.2 Visits 12, 13, 15, and 16 (EX-2, EX-3, EX-5, and EX-6), Extension Weeks 4, 8, 16, and 20

The visit window for these visits is +/– 7 days.

- Recording of changes in concomitant medications
- Assessing and recording of MOC (for WOCBP only)
- SBP/DBP (pre-dose)
- 12-lead ECG (pre-dose)
- Hematology, blood chemistry
- Urinalysis
- Urine pregnancy test for WOCBP (if applicable)
- Recording of AEs and SAEs
- Study medication accountability and compliance review
- IRT call and study drug dispensing
- Remind WOCBP to use the MOC defined for this study. The reminders must be documented in the hospital chart.
- Schedule an appointment for next visit and instruct subject to:

- bring back any bottles or blister wallets
- not take study treatment on the day of study visit prior to coming to the site

8.4.3 Visits 14, 17, 18, 19, 20, 21, and 22 (EX-4, EX-7, EX-8, EX-9, EX-10, EX-11, and EX-12), Extension Weeks 12, 24, 36, 48, 60, 72, and 84

The visit window for these visits is +/– 7 days.

- Administer Chronic GVHD Activity Assessment – Patient self-report [Appendix 7 – Form B]
- Administer LSS (subject completes the questionnaire after patient self-report but prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)
- Chronic GVHD Activity Assessments - physician assessed [Appendix 7 – Form A]
- Recording of changes in concomitant medications
- SBP/DBP (pre-dose)
- 12-lead ECG (pre-dose)
- Assessing and recording of MOC (for WOCBP only)
- Body weight
- Physical examination
- Spirometry (pre-dose; under the responsibility of the pulmonologist)
- DL_{CO} (pre-dose; under the responsibility of the pulmonologist)
- OCT, visit EX-4 only (under the responsibility of the ophthalmologist)
- Ophthalmological examination, visit EX-4 only (under the responsibility of the ophthalmologist)
- Hematology, blood chemistry (pre-dose)
- PD sampling (pre-dose)
- Urinalysis
- Urine pregnancy test for WOCBP (if applicable)
- Recording of AEs and SAEs
- Study medication accountability and compliance review
- IRT call and study drug dispensing
- Remind WOCBP to use the MOC defined for this study. The reminders must be documented in the hospital chart
- Schedule an appointment for next visit and instruct subject to:
  - bring back any bottles or blister wallets
  - not take study treatment on the day of study visit prior to coming to the site

8.4.4 Visit 23 (EX-13, EOT2) Extension Week 96

The EOT2 visit will take place at Week 96 (± 7 days) or earlier in case of premature discontinuation of study drug. In all cases, the EOT2 visit must take place within 3 days after the last dose of study drug. It is strongly preferred that the EOT2 visit takes place 1 day after the last dose of study drug. Spirometry, DL_{CO}, hematology, blood chemistry, urinalysis and pregnancy tests should be performed within 3 days after the last dose of study drug and do not need to be performed on the same day as the EOT2 visit. OCT and the ophthalmological examination may be performed up to 7 days after the last dose of study drug.

The visit includes:

- Administer Chronic GVHD Activity Assessment – Patient self-report [Appendix 7 – Form B]
- Administer LSS (subject completes the questionnaire after patient self-report but prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)
- Chronic GVHD Activity Assessments - physician assessed [Appendix 7 – Form A]
- Recording of changes in concomitant medications
- SBP/DBP
- 12-lead ECG
- Assessing and recording of MOC (for WOCBP only)
- Body weight
- Physical examination
- Spirometry (under the responsibility of the pulmonologist)
- DL_{CO} (under the responsibility of the pulmonologist)
- OCT (under the responsibility of the ophthalmologist)
- Ophthalmological examination (under the responsibility of the ophthalmologist)
- Hematology, blood chemistry
- PD sampling
- Urinalysis
- Urine pregnancy test for WOCBP (if applicable)
- Recording of AEs and SAEs
- Study medication accountability and compliance review
- IRT call
- Remind WOCBP to use the MOC defined for this study. The reminders must be documented in the hospital chart
- Schedule an appointment for next visit and instruct subject to:

8.4.5 Extension Safety Follow-up Period (Follow-up Period 2)

Subjects enrolled in the Extension Treatment Period will be followed for 30 days after the last dose of study drug. The safety follow-up 3 visit (FU3) occurs 30 days (+7 day window) after the last dose of study drug. This is the EOS visit.

The FU3 visit includes:

- Recording of changes in concomitant medications
- Assessing and recording of MOC (for WOCBP only)
- SBP/DBP
- 12-lead ECG
- Spirometry (under the responsibility of the pulmonologist)
- DL_{CO} (under the responsibility of the pulmonologist)
- Hematology, blood chemistry
- PD sampling
- Urinalysis
- Urine pregnancy test for WOCBP (if applicable)
- Recording of AEs and SAEs

8.5 Unscheduled visits

An unscheduled site visit may be performed at any time during the study (between scheduled visits), as necessary, based on the investigator's discretion. These visits include (but are not limited to) those performed due to safety (e.g., occurrence of an AE, laboratory abnormalities), administration of study drug (e.g., re-initiation of study drug requiring up-titration, return of unused study medication, need to initiate treatment with a QT-prolonging drug), and/or other health-related issues.

The date of the visit and the reason for such visits as well as any data related to study assessments performed at unscheduled visits will be recorded in the eCRF.

8.5.1 Visits for re-initiation of study drug

As described in detail in Section 5.1.8, subjects may need to be monitored at the study site when re-initiating study drug following a study drug treatment interruption.

The following assessments/procedures need to be done during the re-initiation visit:

- Recording of changes in concomitant medications
- Assessing and recording of MOC (for WOCBP only)
- Hematology, blood chemistry (pre-dose)
- SBP/DBP (pre-dose)

- SBP/DBP hourly for up to 12 h post-dose (under the responsibility of the cardiac safety assessor) with a minimum of 4 h post-dose.
- 12-lead ECG (pre-dose)
- 12-lead ECG hourly for up to 12 h post-dose (under the responsibility of the cardiac safety assessor) with a minimum of 4 h post-dose.
- Urine pregnancy test for WOCBP (if applicable)
- IRT call and study drug dispensing
- The discharge criteria will be applied as described for Day 1. Subjects may be discharged from the hospital if they meet the discharge criteria before 12 h post-dose but no sooner than 4 h post-dose [see Section 5.1.7]
- Recording of AEs and SAEs.

The date of visit and any data related to study assessments performed during this visit (12-lead ECGs, SBP/DBP) will be reported on the specific eCRF pages for unscheduled visit for re-initiation requiring up-titration of study drug.

These visits for the cardiac monitoring of the subjects when re-initiating study drug are additional unscheduled visits. The regular scheduled study visits must be resumed according to the original visit and assessment schedule. If the visit occurs at the same time as a regular visit, all non-redundant regular visit assessments have to be performed as well.

8.5.2 Unscheduled visits for reasons other than re-initiation of study drug

Unscheduled visits may be performed at any time during the study for reasons other than re-initiation of study drug. Depending on the reason for the unscheduled visit (e.g., loss of efficacy, AE, etc.), appropriate assessments may be performed based on the judgment of the investigator and must be recorded in the eCRF. After an unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule.

Unscheduled visit assessments may include:

- Assessment of concomitant medications
- Assessment of MOC (for WOCBP only)
- PFTs
- SBP/DBP (pre-dose)
- 12-lead ECGs (e.g., in case of need of concomitant treatment with a QT prolonging drug with known risk of Torsades de Pointes [see Appendix 3], pre-dose).
- Ophthalmological examination
- OCT (e.g., presence of visual symptoms suggestive of macular edema)
- Spirometry (under the responsibility of the pulmonologist)

- DL_{CO} (under the responsibility of the pulmonologist)
- Physical examination
- Measurement of body weight
- Complete laboratory tests including: hematology, blood chemistry, urinalysis, or serum pregnancy test (for WOCBP only)
- Assessment of AEs and SAEs
- Return of study drug blisters and unused medication and dispensing of new blisters, if appropriate.

Additional unscheduled spirometry will have to be conducted in the event of respiratory symptoms (e.g., dyspnea) during the course of the study. Administration of inhaled short-acting $ß_2$ agonists (e.g., albuterol/salbutamol) for symptom relief may be performed at the discretion of the investigator. Administration of short-acting $ß_2$ agonists will be collected in the eCRF.

If any of the laboratory parameters listed in Section 7.3.11.2 need to be analyzed, this must be done at the central laboratory, except in case of emergency; if it has been done at a local laboratory, results must be recorded in the eCRF [see Section 7.3.11]).

9 STUDY COMPLETION AND POST-STUDY TREATMENT/MEDICAL CARE

9.1 Study completion

For an individual subject, EOS is reached when treatment and post-treatment safety follow-up periods have been completed.

The reason(s) for discontinuing the study along with, if applicable, who made the decision (subject, investigator or Actelion) must be recorded in the eCRF.

EOS on a study level occurs at the time all subjects have completed their EOS visits, as described above.

9.2 Premature withdrawal from study

Subjects may voluntarily withdraw from the study for any reason at any time. Subjects are considered withdrawn if they state an intention to withdraw further participation in all components of the study, die or are lost to follow-up for any other reason. The investigator may withdraw a subject from the study (without regard to the subject's consent) if, on balance, they believe that continued participation in the study would be contrary to the best interests of the subject. Withdrawal from the study may also result from a decision by Actelion for any reason, including premature termination or suspension of the study [see Section 9.3].

Subjects are considered as lost to follow-up if all reasonable attempts by the investigator to communicate with the individual fail. The site must take preventive measures to avoid a subject being lost to follow-up (e.g., document different ways of contact such as telephone number, home address, e-mail address, person to be contacted in case the subject cannot be reached). If the subject cannot be reached, the site must make a reasonable effort to contact the subject, document all attempts and enter the loss of follow-up information into the eCRF. The following methods must be used: at least three telephone calls must be placed to the last available telephone number and one registered letter must be sent by post to the last available home address. Additional methods may be acceptable if they are compliant with local rules/regulations (e.g., site staff visit to the subject's home), respecting the subject's right to privacy. If the subject is still unreachable after all contact attempts listed above, he/she will be considered to be lost to follow-up.

If premature withdrawal occurs for any reason, the reason for premature withdrawal from the study, along with who made the decision (subject, investigator or Actelion) must be recorded in the eCRF.

If, for whatever reason (except death or loss-to-follow-up), a subject was withdrawn from the study, the investigator should make efforts to conduct a last visit/contact to assess the safety and well-being of the subject, collect unused study drug and discuss follow-up medical care. The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as described in Section 9.4.

9.3 Premature termination or suspension of the study

Actelion reserves the right to terminate the study at any time globally or locally. Investigators can terminate the participation of their site in the study at any time.

If a study is prematurely suspended or terminated, Actelion will promptly inform the investigators, the IRBs/IECs and health authorities, as appropriate, and provide the reasons for the suspension or termination.

If the study is suspended or prematurely terminated for any reason, the investigator in agreement with Actelion must promptly inform all enrolled subjects and ensure their appropriate treatment and follow-up, as described in Section 9.2 for subjects prematurely withdrawn from the study. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subjects' interests.

In addition, if the investigator suspends or terminates a study without prior agreement from Actelion, the investigator must promptly inform Actelion and the IRB/IEC, and provide both with a detailed written explanation of the termination or suspension.

If the IRB/IEC suspends or terminates its approval/favorable opinion of a study, the investigator must promptly notify Actelion and provide a detailed written explanation of the termination or suspension.

9.4 Medical care of subjects after study completion / withdrawal from study

After the subject's study completion or premature withdrawal from the study, whichever applies, the investigator/delegate will explain to subjects what treatment(s)/medical care is necessary and available according to local regulations.

10 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

10.1 Adverse events

10.1.1 Definitions of adverse events

An AE is any adverse change, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease that occurs in a subject during the course of the study (beginning with signing of the ICF), whether or not considered by the investigator as related to study treatment.

A treatment-emergent AE is any AE temporally associated with the use of study treatment (from study treatment initiation until 30 days[2] after study treatment discontinuation) whether or not considered by the investigator as related to study treatment.

AEs include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at study start that worsen following the start of the study.
- Abnormal assessments, e.g., change on physical examination or ECG findings if they represent a clinically significant finding that was not present at study start or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at study start or worsened during the

[2] *Should cover at least 5 elimination half-lives, if more than 30 days.*

course of the study or led to dose reduction, interruption or premature discontinuation of study treatment.

Overdose, misuse and abuse of the study treatment should be reported as an AE and, in addition, study treatment errors must be documented in the study drug log of the eCRF.

10.1.2 Intensity of adverse events

The severity of AEs will be classified according to the common terminology criteria for adverse events (CTCAE) version 4.03 (June 2010) [NCI 2010]. Grades 1 through 5 refer to the severity of the AE, which are based on general guidelines described below. Not all grades are appropriate for each AE. Therefore, the CTCAE may list some AEs with less than five options for grade selection.

If the intensity/seriousness of an AE worsens during the course of the study, a new AE eCRF page must be completed. The onset date of this new AE corresponds to the date of worsening. If the AE lessens in intensity/seriousness, no change in the severity is required.

The five grades of severity are defined as follows:

- **Grade 1**

Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. The event may be noticeable to the subject. It does not influence daily activities, and usually does not require intervention.

- **Grade 2**

Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living that refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.

- **Grade 3**

Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living that refer to bathing, dressing and undressing, feeding self, using the toilet, taking medication, and not bedridden.

- **Grade 4**

Life-threatening consequences; urgent intervention indicated.

- **Grade 5**

Death related to AE.

An AE of grade 1–3 may or may not be serious [see Section 10.1.1]. These grading terms are used to describe the severity of a specific event. Medical judgment should be used on

a case-by-case basis. Any AE reported with a toxicity level of grade 4 or grade 5 indicates a level of seriousness that must be reported as an SAE [refer to Section 10.1.2 for definitions of SAEs].

Seriousness, rather than severity assessment, determines the regulatory reporting obligations.

10.1.3 Relationship to study treatment

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study treatment and reported as either related or unrelated. The determination of the likelihood that the study drug caused the AE will be provided by an investigator who is a qualified physician.

10.1.4 Adverse events associated to study design or protocol-mandated procedures

An AE is defined as related to study design or protocol-mandated procedures if it appears to have a reasonable possibility of a causal relationship to either the study design or to protocol-mandated procedures. Examples include discontinuation of a subject's previous treatment during a washout period leading to exacerbation of the underlying disease.

10.1.5 Reporting of adverse events

10.1.5.1 Subjects prematurely discontinued from the Core Treatment Period

All AEs occurring after study start (i.e., signing of informed consent) and up to 30 days after study treatment discontinuation must be recorded on specific AE pages of the eCRF.

10.1.5.2 Subjects not prematurely discontinued from the Core Treatment Period and not entering the Extension Treatment Period

All AEs occurring after study start (i.e., signing of informed consent) and up to 90 days after study treatment discontinuation must be recorded on specific AE pages of the eCRF.

10.1.5.3 All Subjects entering the Extension Treatment Period

All AEs occurring on or after study start (i.e., signing of informed consent) and up to 30 days after study treatment discontinuation must be recorded on specific AE pages of the eCRF.

10.1.6 Follow-up of adverse events

AEs still ongoing more than 30 days after study treatment discontinuation must be followed up until they are no longer considered clinically relevant.

10.2 Serious adverse events

10.2.1 Definitions of serious adverse events

10.2.1.1 Serious adverse events

An SAE is defined by the ICH guidelines as any AE fulfilling at least one of the following criteria:

- Fatal.
- Life-threatening: 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 that hypothetically might have caused death had it been more severe.
- Requiring inpatient hospitalization, or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs when – based upon appropriate medical judgment – they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for hospitalization are exempted from being reported:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalization for pre-planned (i.e., planned prior to signing informed consent) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris.

However, complications that occur during hospitalization are AEs or SAEs (for example if a complication prolongs hospitalization).

10.2.1.2 Serious adverse events associated with the study design or protocol-mandated procedures

An SAE is defined as related to study design or protocol-mandated procedures if it appears to have a reasonable possibility of a causal relationship to either the study design or to protocol-mandated procedures. Examples include discontinuation of a subject's previous treatment during a washout period leading to exacerbation of the underlying disease or a complication of an invasive procedure that is specifically required by the protocol.

10.2.2 Reporting of serious adverse events

10.2.2.1 During screening period

All SAEs that occur after study start (i.e., signing of informed consent) must be reported (whether considered associated or not associated with study design or study-mandated procedures).

These SAEs must be reported on an SAE form and also in the eCRF.

10.2.2.2 During Core Treatment Period and Extension Treatment Period

All SAEs, regardless of investigator-attributed causal relationship, must be reported.

These SAEs must be reported on an SAE form and also on the AE pages in the eCRF.

10.2.2.3 During the follow-up period for subjects prematurely discontinued from the Core Treatment Period

All SAEs, regardless of investigator-attributed causal relationship, which occur during the follow-up period up to 30 days after study treatment discontinuation must be reported on AE pages in the eCRF and on an SAE form.

10.2.2.4 During follow-up period for subjects not prematurely discontinued from the Core Treatment Period and not entering the Extension Treatment Period

All SAEs, regardless of investigator-attributed causal relationship, which occur during the follow-up period up to 90 days after study treatment discontinuation must be reported on AE pages in the eCRF and on an SAE form.

10.2.2.5 During follow-up period for all subjects entering the Extension Treatment Period

All SAEs, regardless of investigator-attributed causal relationship, which occur during the follow-up period up to 30 days after study treatment discontinuation must be reported on AE pages in the eCRF and on an SAE form.

10.2.3 Follow-up of serious adverse events

SAEs still ongoing at the EOS visit must be followed up until resolution or stabilization, or until the event outcome is provided, e.g., death.

10.2.4 After the follow-up period

New SAEs occurring after the follow-up period must be reported to the Actelion drug safety department within 24 hours of the investigator's knowledge of the event, **only** if considered causally related to previous exposure to the study treatment by the investigator.

10.2.5 Reporting procedures

All SAEs must be reported by the investigator to the Actelion drug safety department within 24 hours of the investigator's first knowledge of the event.

All SAEs must be recorded on an SAE form, irrespective of the study treatment received by the subject, and whether or not this event is considered by the investigator to be related to study treatment.

The SAE forms must be faxed to the Actelion drug safety department (contact details are provided on the SAE form). The investigator must complete the SAE form in English and must assess the causal relationship of the event to study treatment.

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The Actelion drug safety department may contact the investigator to obtain further information.

If the subject is hospitalized in a hospital other than the study site, it is the investigator's responsibility to contact this hospital to obtain all SAE-relevant information and documentation.

The reference safety document to assess expectedness of a suspect serious adverse reaction and reported by the sponsor to health authorities, ECs/IRBs and investigators is the reference safety information section of the Investigator's Brochure [Ponesimod IB].

The SAEs listed below are commonly seen with the underlying disease and are therefore expected to occur in this subject population. These SAEs will be treated as "disease-related" and expected (unless fatal) and will therefore not require expedited reporting to health authorities, IRBs/IECs, and investigators. However, these events will be monitored during the study by the sponsor and by the Study Monitoring Committee:

- Relapses of the underlying leukemia and complications.

10.3 Pregnancy

If a woman becomes pregnant while on study treatment, study treatment must be discontinued. The investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

10.3.1 Reporting of pregnancy

Irrespective of the treatment received by the subject, any pregnancy occurring during the study including during the 30 days following study treatment discontinuation must be reported within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the Actelion Pregnancy form, which is faxed to the Actelion drug safety department (see contact details provided on the Actelion Pregnancy form), and on an AE page in the eCRF.

Male contraception
Nonclinical studies have shown no evidence of an effect on male reproductive organs during the administration of ponesimod. It is considered very unlikely that a significant dose of ponesimod would be delivered to the female by seminal transfer and the potential risk of harm to a human fetus is considered to be very small, based on the high safety margins of 1730 to 1920 for estimated exposure to ponesimod potentially achieved in human females via seminal fluid transfer. Therefore, there is no specific recommendation for male contraception. (**Note:** For allowed concomitant therapies during this trial that require male contraception, the respective method of contraception must be applied.)

10.3.2 Follow-up of pregnancy

Any pregnancy must be followed to its conclusion and its outcome must be reported to the Actelion drug safety department.

Any AE associated with the pregnancy occurring during the follow-up period after study drug discontinuation must be reported on separate AE pages in the eCRF. Any SAE occurring during pregnancy must be reported on an SAE form as described in Section 10.3.1.

10.4 Study safety monitoring

Clinical study safety information (AEs, SAEs, laboratory values, ECGs, vital signs, and project-specific labs/examinations as required) is monitored and reviewed on a continuous basis by the Actelion clinical team (in charge of ensuring subjects' safety as well as data quality) by periodically monitoring clinical studies' activities from protocol conception to database closure. In addition, an SMC is monitoring safety data [see Section 3.5].

11 STATISTICAL METHODS

All statistical analyses will be conducted by Actelion or by designated contract research organizations supervised by Actelion.

The Statistical Analysis Plan (SAP) will be approved prior to database lock for the final analyses. The SAP provides the full details of all analyses, data displays, and algorithms to be used for data derivations.

All data will be listed, and endpoints will be summarized by appropriate descriptive statistics (tables or figures), typically including:

- Number of non-missing observations, number of missing observations, mean, standard deviation (STD), median, Q1, Q3, minimum and maximum for continuous endpoints;
- Number of non-missing observations, number of missing observations and frequency with percentage per category (percentages based on the number of non-missing observations) for categorical endpoints;
- Number of subjects at risk, cumulative number of events, cumulative number of censored observations and Kaplan-Meier estimates of the survival function for time-to-event endpoints.

Absolute changes from baseline are defined as: post-baseline value minus baseline value, i.e., a positive sign indicates an increase as compared to baseline.

A percentage (relative) change from baseline is defined as the absolute change from baseline divided by the baseline value (if the baseline value not equal 0) multiplied by 100.

11.1 Analysis sets

11.1.1 Screened analysis set

This analysis set includes all subjects who were screened and received a subject number.

11.1.2 Full analysis set

The Full analysis set (FAS) includes all subjects who received at least one dose of study medication.

11.1.3 Per-protocol set

The Per-protocol set (PPS) is defined as subjects from the FAS without any major protocol deviations. The most important protocol deviations include:

- Subject failing to reach the Week 24 assessment, i.e., by discontinuing treatment early or for any other reason than lack of efficacy or death
- Subject withdrawing consent before the Week 24 assessment

- Subjects not adhering to the treatment regimen (mandatory concomitant medication, up-titration, study drug)
- Subject receiving prohibited concomitant therapy
- Start of any other IS systemic therapies during the course of the trial

Additional details of the definition of the PPS will be described in the SAP.

11.1.4 Safety set

The Safety set (SAF) is defined like the FAS.

11.1.5 PD analysis set

The PD analysis set (PDS) includes all subjects who received at least 4 weeks of study treatment and have an absolute lymphocyte count measurement at baseline and at least one measurement between the Week 4 visit and Week 12 visit.

11.1.6 PK analysis set

The PK analysis set (PKS) includes all subjects from the SAF, who provided at least one blood sample.

11.1.7 Extension set

The extension set (ES) includes all subjects enrolled in the Extension Treatment Period who received at least one dose of ponesimod in the Extension Treatment Period.

11.1.8 Usage of the analysis sets

The primary analysis is based on the PD variable and will be performed on the PDS (main analysis) and on the FAS as well. Sensitivity analyses of the primary analysis will be performed based on the PDS and FAS.

All Safety variables will be analyzed using the SAF.

Exploratory efficacy variables will be analyzed using both FAS and PPS, as applicable. Details will be provided in the SAP.

Quality of Life endpoints will be analyzed based on the FAS.

PK evaluations will be analyzed using the PKS, and PD evaluations (other than primary PD variable) will be analyzed based on the PDS.

All safety and efficacy endpoints in the Extension Treatment Period will be analyzed on the ES.

11.2 Variables

11.2.1 Primary PD variable

The change in absolute lymphocyte count from baseline to Week 4, Week 8 and Week 12 in the Core Treatment Period is defined as:

- l_d = Absolute lymphocyte count for dose d – absolute lymphocyte count at baseline

The change in absolute lymphocyte counts (l_d) is assessed at Week 4 for the 5 mg dose, at Week 8 for 10 mg and at Week 12 for 20 mg in the Core Treatment Period.

11.2.2 Safety variables

The following safety endpoints/variables will be analyzed. The SAP will summarize these analyses in more detail. Safety endpoints will be analyzed from first study drug intake up to 30 days (inclusive) after last study drug intake.

Overall safety endpoints

- Treatment-emergent AEs, SAEs, and AEs of special interest
- AEs leading to premature discontinuation of study drug
- Deaths

Absolute lymphocyte count

- Treatment-emergent absolute lymphocyte count $< 0.2 \times 10^9$/L (< 200 cells/mm^3)

Cardiac rate and rhythm safety endpoints

- Treatment-emergent morphological ECG abnormalities
- Change in 12-lead ECG variables (HR, PR, QRS, QT, QTcB, QTcF) from pre-dose to selected post-dose assessments (1h, 2h, 3h, 4h) on Day 1 and on day(s) of re-initiation of study drug
- Notable abnormalities for selected 12-lead ECG variables (HR, PR, QT, QTc) at 3 h post-dose assessment on Day 1 and pre-dose on Weeks 4, 8, 12, and 24 (notable abnormalities definition in Appendix 6)
- Cardiac safety events will include:
    - Treatment-emergent QTc > 450 ms (male), > 470 ms (female), > 500 ms (male), and > 520 ms (female)
    - Treatment-emergent QTc increase from baseline > 30 ms, > 60 ms
    - Other treatment-emergent abnormalities observed by 12-lead ECG
    - Treatment-emergent (serious) cardiac AEs of special interest.

Pulmonary function safety endpoints

- Treatment-emergent decrease of FEV_1 or FVC > 20% from baseline values
- Treatment-emergent decrease of percent of predicted FEV_1 or FVC > 20% from baseline values
- Change in FEV_1 and FVC from baseline, absolute and % of absolute change to all visits up to FU1
- Among subjects with a decrease of > 200 mL and > 12% in FEV_1 or FVC, respectively, from baseline to EOT1, reversibility defined as a decrease of < 200 mL and < 12% in FEV_1 or FVC, respectively, from baseline to last available follow-up
- Change from baseline to FU1 vs change from baseline to EOT1, in FEV_1 or FVC (absolute and % of predicted)
- Change in lung diffusion capacity as assessed by DL_{CO} expressed in absolute change and % of predicted value from baseline to all time points up to FU1
- Change from baseline to FU1 vs change from baseline to EOT1 in DL_{CO} (absolute and % of predicted)
- (Serious) pulmonary AEs of special interest
- Withdrawal due to pulmonary reasons/AE

Other safety endpoints

- Treatment-emergent notable BP abnormalities [definition in Appendix 6].
- Treatment-emergent notable laboratory abnormalities [definition in Appendix 6].

11.2.3 Exploratory efficacy variables

The exploratory endpoints are defined as follows:

- Achievement of a partial or complete overall response at 24 weeks post enrollment (per NIH Consensus Development Project response criteria)

Definitions for the efficacy endpoint are based on the draft 2014 NIH Consensus Guidelines [see Appendix 7].

Baseline or subsequent organ abnormalities that are not due to chronic GVHD are not evaluable for response (at the organ level).

Complete overall response definition:

A complete response is defined as resolution of all reversible manifestations due to chronic GVHD in the following organs at the Week 24 assessment, resulting in:

- Skin: NIH Skin Score of 0 after previous involvement
- Mouth: NIH Modified Oral Mucositis Score of 0 after previous involvement

- Liver: normal ALT, alkaline phosphatase, and TBL after previous elevation of one or more
- Upper GI: NIH Upper GI Score of 0 after previous involvement
- Lower GI: NIH Lower GI Score of 0 after previous involvement
- Esophagus: NIH Esophagus Score of 0 after previous involvement
- Lungs: normal FEV_1 absolute value after previous involvement (normalization to $FEV_1 \geq 80\%$ predicted is considered a complete response)
- Eyes: NIH Eye Score of 0 after previous involvement
- Joint/fascia: Both NIH Joint and Fascia Score of 0 and photographic range of motion (P-ROM) score of 25 after previous involvement by at least one measure
- Global: Clinician Overall Severity Score of 0

Partial overall response definition:

A partial overall response is defined as improvement in a measure for at least one organ without progression in measures for any other organ. The proposed general guideline for defining partial response in a specific organ requires a change in score from baseline as follows:

- Skin: decrease in NIH Skin Score by at least 1 point
- Mouth: decrease in Modified Oral Mucositis Score by at least 2 points
- Liver: decrease by 50% in ALT, alkaline phosphatase, or TBL
- Upper GI: decrease in NIH Upper GI Score by at least 1 point
- Lower GI: decrease in NIH Lower GI Score by at least 1 point
- Esophagus: decrease in NIH Esophagus Score by at least 1 point
- Lungs: increase by at least 10% predicted absolute value of FEV_1, as long as initial $FEV_1 < 70\%$ predicted
- Eyes: decrease in NIH Eye Score by at least 1 point
- Joint/fascia: decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 or more points for any site
- Global: Clinician Overall Severity Score decreases by 2 or more points on a 0–10 scale

The proposed general guideline for defining progression in a specific organ requires a change in score from baseline as follows:

- Skin: increase in NIH Skin Score by at least 1 point, except from 0 to 1
- Mouth: increase in Modified Oral Mucositis Score by at least 2 points

- Liver: increase by ≥ 2 × ULN for ALT, alkaline phosphatase or TBL
- Upper GI: increase in NIH Upper GI Score by at least 1 point, except from 0 to 1
- Lower GI: increase in NIH Lower GI Score by at least 1 point, except from 0 to 1
- Esophagus: increase in NIH Esophagus Score by at least 1 point, except from 0 to 1
- Lungs: decrease by at least 10% absolute value of FEV_1, as long as final FEV_1 < 70% predicted
- Eyes: increase in NIH Eye Score by at least 1 point, except from 0 to 1
- Joint/fascia: increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 or more points for any site
- Global: Clinician Overall Severity Score increases by 2 or more points on a 0–10 scale

The endpoint is reached if the subject is considered a partial or complete responder at Week 24. The remaining subjects will be considered as non-responders, this includes subjects with stable disease and subjects with mixed response (defined as complete or partial response in at least one organ accompanied by progression in another organ). Patients who discontinue the study prior to the Week 24 assessment are considered non-responders.

- Need for rescue therapy for chronic GVHD
    - Rescue therapy is the addition of any new systemic or topical IS therapy or exceeding baseline dose for any non-steroid IS or exceeding glucocorticoid dose equivalent to prednisone > 1 mg/kg/day

This exploratory endpoint is defined as a binary endpoint. Subjects will be considered as responders in case no rescue therapy is administered; subjects will be considered as non-responders in case subjects received a rescue therapy during the treatment phase for at least one day. Every effort will be made to collect the concomitant medications data with complete start dates in order to make sure the endpoint is derived correctly. Patients who discontinue the study prior to the Week 24 assessment are considered non-responders.

- Partial or complete organ-specific response for the specific organ manifestation at Week 12 and Week 24 in subjects with a specific organ manifestation of chronic GVHD
    - Affected organs limited to 2014 NIH consensus criteria organs of skin, eyes, mouth, esophagus, upper GI, lower GI, liver, lungs, and joints and fascia

This endpoint is a binary sub-endpoint of the first exploratory endpoint (see above), split by organ. The endpoint will be derived in the same way as described above but at an organ level. The endpoint will be evaluated independently at the Week 12 and Week 24 assessment. Only organs with reversible manifestations will be included in the analysis.

Only subjects with manifestations at baseline or subjects developing manifestations during the study at the corresponding organ will be included in the analyses of the sub-endpoints. Patients who discontinue the study prior to the Week 24 assessment are considered non-responders.

- Partial or complete overall response at Week 12

This binary endpoint is defined like the first exploratory endpoint (see above) but at the Week 12 assessment.

- Complete response at 24 weeks

A responder of this binary endpoint is defined as reaching a complete response at the Week 24 assessment. A non-responder is defined as reaching a partial or mixed response or no response (stable disease or progression) at the Week 24 assessment or dropping out of the study prior to the Week 24 assessment.

- Partial or complete overall response at latest evaluable assessment during the core study (Week 12 and Week 24)

- Average glucocorticoid daily dose over 24 weeks versus baseline dose

The average dose is defined as the sum of all doses of glucocorticoid received, adjusted by the time in days.

- Percent glucocorticoid dose at Week 24 versus baseline.

This exploratory endpoint is defined as the percentage of the glucocorticoid dose received at the Week 24 assessment compared to the dose received at baseline.

11.2.4 Other variables

Quality of Life endpoints

The Quality of Life endpoints are defined in Section 6.4.

- Change from baseline to Week 12 and Week 24 in LSS for chronic GVHD [Appendix 8]
- Change from baseline to Week 12 and Week 24 in each of the subject-reported chronic GVHD symptoms (skin, eyes, mouth and genitals [Appendix 7 – Form B]).
- Change from baseline to Week 12 and Week 24 in each of the subject-reported global ratings (Mild-Moderate-Severe Scale, Overall Severity Scale and 7-Point Change Scale [Appendix 7 – Form B]).

PK evaluations

- C_{trough} concentrations of ponesimod at Day 1, and Weeks 4, 8, 12, 16, and 20 (all samples pre-dose), and Week 24
- Ponesimod concentration 3 hours post-dose at Day 1 and Week 12

PD evaluations

- Peripheral absolute blood lymphocyte count change from baseline (pre-dose on Day 1) to Weeks 4, 8, 12, 16, 20, 24, and FU1, and change from pre-dose Week 12 to 3 hours post-dose Week 12.
- Peripheral absolute lymphocyte count reversibility from EOT1 to FU1 all expressed in absolute change and percent change from baseline

PK/PD relationship

- The PK and selected efficacy and safety variables will be correlated with the PD (peripheral absolute lymphocyte count and magnitude of reduction of lymphocyte count). If deemed appropriate, the PK will also be correlated with selected safety variables.

11.2.5 Variables in Extension Treatment Period

Variables in the Extension Treatment Period will be defined in the same way as defined in the treatment and follow-up periods of the Core Treatment Period and will be fully described in the SAP. As the Extension Treatment Period exceeds the Core Treatment Period by 72 weeks the time points of analysis will be adapted appropriately for all relevant endpoints. The visit EX-1 (Visit 11) will be considered as the baseline visit in the Extension Treatment Period.

11.2.6 Overall testing strategy of the PD variable

The primary analysis of this study is based on the absolute lymphocyte counts at pre-specified time points. Hypotheses are setup to establish a within-subject dose response at baseline vs the Week 4 (5 mg), Week 8 (10 mg) and Week 12 (20 mg) assessments in the Core Treatment Period.

11.2.7 Analysis of the primary PD variable(s)

11.2.7.1 Hypotheses and statistical model

The null hypothesis is that there is no dose response on the change from baseline in absolute lymphocyte counts l_d in the intra-subject dose escalation within the first 12 weeks of

treatment, and the alternative hypothesis is the existence of any intra-subject dose response within the first 12 weeks of treatment:

H_0: $l_d \geq 0$ for all doses d = 5, 10, 20 mg

vs

H_1: $l_d < 0$ for at least 1 dose d = 5, 10, 20 mg

11.2.7.2 Handling of missing data

As the PDS includes all subjects who received at least 4 weeks of study treatment with at least one valid lymphocyte measurement on or after the Week 4 assessment, all available data at the visits of interest (Week 4, Week 8 and Week 12) will be included in the analysis. Thus, data of subjects with one, two or three post-baseline measurements at the predefined time points will contribute to the dose-response analysis. Every effort will be made to collect lymphocyte data, as complete as possible, for every subject at every visit. Last observation carried forward (LOCF) will be used as a sensitivity analysis as described below.

11.2.7.3 Main analysis of the primary PD variable (primary analysis)

To meet the objective of demonstrating existence of an intra-subject dose response on the absolute lymphocyte count reduction from baseline in subjects with GVHD, at least one null hypothesis must be rejected with a one-sided significance level of 5%. The type-1 error will be controlled via a hierarchical ordering of the tests: pairwise comparisons will be conducted in decreasing dose order. Within-subject t-tests will be performed at each dose level (assuming normally distributed data).

In addition, an E_{max} model will be fitted for the baseline, Week 4, Week 8 and Week 12 data. The data will be summarized with point-wise and model-based estimates, standard deviation and 95% CIs on the reduction in absolute lymphocyte counts from baseline at the examined dose levels. A plot of the estimated dose-response curve with 95% credibility interval limits will be presented along with the observed response at each dose.

The primary analysis will be performed on the PD analysis set and conducted after the last patient has completed the Follow-Up 1 visit in the Core Treatment Period.

11.2.7.4 Supportive/sensitivity analyses

A sensitivity analysis of the primary analysis will be performed on the FAS (in case the FAS does not contain the same number of subjects as the PDS).

Further t-tests will be performed across dose levels (5 mg vs 10 mg, 5 mg vs 20 mg and 10 mg vs 20 mg). These tests, performed at a one-sided significance level of 5%, will be

considered as exploratory. These pairwise comparisons will be performed on the FAS and PDS.

An LOCF approach (using the Week 4 visit or later) will be performed for subjects with a missing Week 8 or Week 12 assessment, based on the FAS.

The dose-response modeling will be repeated using the Week 4, Week 8 and Week 24 assessment (instead of the Week 12 assessment), based on the PDS.

11.2.7.5 Subgroup analyses

No subgroup analyses are planned due to small sample size.

11.2.8 Analysis of the efficacy variables

The analyses of all exploratory endpoints will be based on the PPS and FAS, if applicable. The following binary endpoints will be summarized descriptively as described in Section 11:

- Achievement of a partial or complete overall response at 24 weeks (per NIH Consensus Development Project response criteria)
- Need for rescue therapy for chronic GVHD
- Partial or complete organ-specific response for the specific organ manifestation at Week 12 and Week 24 in subjects with a specific organ manifestation of chronic GVHD
- Partial or complete overall response at Week 12
- Complete response at Week 24
- Partial or complete overall response at latest evaluable assessment during the core study (Week 12 and Week 24)

The remaining two exposure-related, continuous endpoints will be analyzed based on summary statistics as described in Section 11:

- Average glucocorticoid daily dose over 24 weeks versus baseline dose
- Percent glucocorticoid dose at Week 24 versus baseline

11.2.9 Analysis of the efficacy variables during the Extension Treatment Period

The analyses of all exploratory endpoints will be based on the ES.

All efficacy variables will be summarized descriptively, by visit, based on the ES. If subject numbers drop below a certain threshold only listings will be provided. No statistical tests will be applied to any of these endpoints.

The endpoint "Achievement of a partial or complete overall response at 24 weeks (per NIH Consensus Development Project response criteria)" will be analyzed at Week 24 and Week 96 in the Extension Treatment Period and selected other time points.

The endpoint "Need for rescue therapy for chronic GVHD" will be analyzed throughout 96 weeks of treatment or up to premature discontinuation.

The endpoint "Partial or complete organ-specific response for the specific organ manifestation at Week 12 and Week 24 in subjects with a specific organ manifestation of chronic GVHD" will be assessed at Weeks 12, 24, and 96 in the Extension Treatment Period and selected other time points.

The endpoint "Partial or complete overall response at Week 12" will also be analyzed at Week 12 in the Extension Treatment Period.

The endpoint "Complete response at Week 24" will be assessed at Week 24 and Week 96 in the Extension Treatment Period and selected other time points.

The endpoint "Partial or complete overall response at latest evaluable assessment during the study" will be extended to the whole Extension Treatment Period.

The exposure related endpoints will be analyzed based on summary statistics. Both endpoints "Percent glucocorticoid dose at Week 24 versus baseline" and "Average glucocorticoid daily dose over 24 weeks versus baseline dose" will be analyzed at the end of treatment visit (EOT2) in the Extension Treatment Period, and compared to the baseline visit of the Extension Treatment Period (Visit EX-1).

If there are not enough subjects in the ES population, only listings will be provided.

11.2.10Analysis of the safety variable(s)

All safety analyses will be conducted on data up to 30 days (inclusive) after last study drug intake for the Core Treatment Period and for the Extension Treatment Period. All AEs will be coded using the latest version of MedDRA available at the time of database closure.

11.2.10.1 Adverse Events

11.2.10.1.1 Treatment-emergent AEs, SAEs, and AEs of special interest

Treatment-emergent AEs and SAEs will be tabulated by system organ class (SOC) and preferred terms within each SOC: the number and percentage of subjects who experienced at least one (S)AE, at least one (S)AE within each SOC and at least one S(AE) within each preferred term will be displayed. (S)AEs will also be summarized by decreasing frequency of preferred term. (S)AEs will also be tabulated by maximum intensity.

AEs of special interest will be summarized in the same way as stated above.

Treatment-emergent AEs and SAEs and AEs of special interest will be analyzed for the Extension Treatment Period as described above.

11.2.10.1.2 AEs leading to premature discontinuation of study drug

(S)AEs leading to premature discontinuation of study drug will be summarized in a similar manner as described above.

(S)AEs leading to premature discontinuation of study drug will be summarized for the Extension Treatment Period as described above.

11.2.10.1.3 Deaths

Fatal SAEs occurring any time after the start of treatment will be summarized in a similar manner as described above. Fatal SAEs will also be summarized for the Extension Treatment Period.

11.2.10.2 Absolute lymphocyte count

Data of subjects with treatment-emergent absolute lymphocyte count $< 0.2 \times 10^9$/L (< 200 cells/mm^3) will be summarized descriptively for the Core Treatment Period and for the Extension Treatment Period.

11.2.10.3 Cardiac Safety

11.2.10.3.1 Treatment-emergent morphological ECG abnormalities (as defined by the ECG provider)

Treatment-emergent morphological ECG abnormalities will be summarized descriptively for the Core Treatment Period and for the Extension Treatment Period.

11.2.10.3.2 12-lead ECG assessments

Descriptive summary statistics, by time and visit, will be provided for observed treatment-emergent values and absolute changes from baseline in numeric 12-lead ECG values (HR, PR, QRS, QT, QTcB and QTcF). Data will be summarized from pre-dose to the post-dose assessments at 1 h, 2 h, 3 h and 4 h on Day 1. 12-lead ECG data will also be summarized for the Extension Treatment Period.

11.2.10.3.3 Notable abnormalities for selected 12-lead ECG variables

Notable abnormalities for selected 12-lead ECG variables (HR, PR, QT, QTcF) will be summarized for all data at the 3-hour post dose assessments on Day 1 and pre-dose at Weeks 4, 8, 12, and 24. Notable abnormalities will also be summarized for the Extension Treatment Period.

11.2.10.3.4 Cardiac safety events

Cardiac safety events will include:

- Treatment-emergent QTc > 450 ms (male), > 470 ms (female), > 500 ms (male), and > 520 ms (female)
- Treatment-emergent QTc increase from baseline > 30 ms, > 60 ms
- Other treatment-emergent abnormalities observed by 12-lead ECG
- Treatment-emergent (serious) cardiac AEs of special interest.

Cardiac safety events will be summarized descriptively for the Core Treatment Period and for the Extension Treatment Period.

11.2.10.4 Pulmonary safety

11.2.10.4.1 PFT

Descriptive summary statistics by visit will be provided for observed treatment-emergent values and changes from baseline by visit in FEV_1, FVC and FEV_1/FVC ratio (all expressed in absolute change, % change and % change of percent predicted value).

The number and proportions of treatment-emergent decreases of FEV_1 or FVC and percent predicted FEV_1 or FVC > 20% from baseline up to Week 24 will be summarized.

Reversibility of pulmonary parameters will be analyzed at the last available follow-up visit. The analysis will summarize subjects still showing a decrease of > 200 mL in FEV_1 and FVC or a change in FEV_1 and FVC of > 12% from baseline at the follow-up visit among subjects with a decrease of > 200 mL or > 12% in FEV_1 or FVC from baseline to EOT1.

The mean (and 95% CIs) change from baseline to FU1 and from baseline to EOT1 in FEV_1 or FVC (absolute and % predicted) will be summarized and plotted. A scatter plot will display the change from baseline to EOT1 versus the change from baseline to FU1 on an individual subject level.

PFT data will be analyzed in a similar manner during the Extension Treatment Period.

11.2.10.4.2 Lung diffusion capacity (DL_{CO})

Descriptive summary statistics and changes from baseline by visit will be provided for observed treatment-emergent values and changes from baseline (expressed in absolute change and % of predicted value) in DL_{CO}. In addition the DL_{CO} change from baseline to FU1 versus change from baseline to EOT1, expressed in absolute change and percent of predicted values change, will be summarized. DL_{CO} data will be analyzed in a similar manner during the Extension Treatment Period.

11.2.10.4.3 Pulmonary safety events

Pulmonary safety events will include:

- Treatment-emergent decrease of FEV_1 or FVC > 20% from baseline values

- (Serious) pulmonary AEs of special interest
- Withdrawal due to pulmonary reasons/AE

Pulmonary safety events will be summarized descriptively for the Core Treatment Period and for the Extension Treatment Period.

11.2.10.5 Vital signs

Descriptive summary statistics by visit will be provided for observed treatment-emergent values and absolute changes from baseline in HR, BP and body weight.

Treatment-emergent notable BP abnormalities will also be summarized. Vital signs data will be analyzed for the Core Treatment Period and for the Extension Treatment Period.

11.2.10.6 Laboratory

11.2.10.6.1 Laboratory tests

For the Core Treatment Period, descriptive summary statistics by visit will be provided for observed treatment-emergent values and absolute and percent changes from baseline for laboratory tests (hematology, blood chemistry, urinalysis). Data will be displayed in SI units whenever possible and graphical approaches will be applied.

Laboratory data will be analyzed in a similar manner for the Extension Treatment Period.

11.2.10.6.2 Laboratory safety events

Laboratory safety events will include:

- Treatment-emergent laboratory test abnormalities based on normal ranges of the central laboratory, project-specific ranges and CTCAE [CTCAE 2010]
- Treatment-emergent laboratory test abnormalities based on FDA Guidance for Drug Induced Liver Injury [FDA 2009] (for ALT/AST/TBIL)
- Absolute lymphocyte count reversibility after EOT, expressed in absolute change and percent change from baseline.

Laboratory safety events will be summarized descriptively for the Core Treatment Period and for the Extension Treatment Period.

11.2.10.7 Ocular safety

Ocular safety events will include:

- Treatment-emergent ocular AEs of specific interest

Ocular safety events will also be summarized for the Extension Treatment Period.

11.2.11Analysis of (other) variable(s)

11.2.11.1 Quality of Life endpoints

Quality of life endpoints will be summarized for the Core Treatment Period and for the Extension Treatment Period.

11.2.11.1.1 Lee Symptom Scale for chronic GVHD

Absolute values and changes from baseline of the LSS for chronic GVHD will be summarized descriptively in the PPS and FAS by visit.

11.2.11.1.2 Patient-reported chronic GVHD symptoms scale and patient-reported global ratings scale

Absolute values and changes from baseline of both scales will be summarized descriptively in the PPS and FAS by visit.

11.2.11.2 PK analysis

C_{trough} (pre-dose) plasma concentrations of ponesimod on Day 1 and Weeks 4, 8, 12, 16, 20 (all samples pre-dose), and Week 24, and plasma concentrations of ponesimod at 3 h post-dose at Day 1 and Week 12, will be analyzed by descriptive statistics, including arithmetic mean, standard deviation, minimum, maximum, and median.

11.2.11.3 PD analysis

For the Core Treatment Period, peripheral absolute lymphocyte counts at each visit assessment and changes from baseline will be analyzed by descriptive statistics, including arithmetic mean, standard deviation, minimum, maximum, and median.

Peripheral absolute lymphocyte count reversibility from EOT1 to FU1 will be summarized and plotted.

PD analyses will be repeated in the Extension Treatment Period.

11.2.11.4 PK/PD relationship

Selected efficacy and safety variables will be correlated with the PD (peripheral absolute lymphocyte count and magnitude of reduction of lymphocyte count). If deemed appropriate, the PK will also be correlated with selected safety variables.

11.3 Interim analyses

There is no interim analysis planned for this study.

11.4 Sample size

The sample size of this single-arm intra-subject dose-escalation study is based on simulations, comparing lymphocyte data at baseline to Week 4 data of the estimated 5 mg dose, using t-tests.

11.4.1 Sample size for primary endpoint

Based on these simulations, 30 subjects will be recruited in order to establish an intra-subject dose response and to collect sufficient safety data. The simulations were performed, comparing the change of absolute lymphocyte counts at Week 4 (5 mg dose; mean: 0.85×10^9/L; STD 0.40) vs baseline (mean: 1.2×10^9/L; STD 0.60), applying t-tests with a one-sided alpha-level of 0.05. Based on those assumptions a power of around 85% is reached. As absolute lymphocyte counts are expected to be closest to baseline data for the 5 mg dose, the sample size of 30 subjects is expected to be sufficient for the 10 mg and 20 mg doses, as well. Even in case of a 25% dropout rate, assuming 23 subjects reaching the Week 12 assessment, there should be enough subjects in the study to establish a dose response (Power of approximately 75% at 5 mg dose).

Since no studies of subjects receiving ponesimod have been conducted in chronic GVHD, historical data of the Actelion MS and psoriasis programs have been used to determine the sample size. As chronic GVHD subjects are known to have reduced lymphocyte counts, assumptions were adjusted appropriately. Dose-response modeling techniques were applied to support the sample size estimation [details in Section 11.4.2].

11.4.2 Sample size assumptions

Dose-response modeling

Dose-response modeling was performed, applying MCP-Mod techniques [Bretz 2005] on the historical lymphocyte data from MS studies (AC-058B201 core and AC-058B202 extension study; doses studied were placebo, 10 mg, 20 mg, and 40 mg), in order to establish a dose response at the chronic GVHD study-specific visits (Week 4, Week 8 and Week 12) and to estimate a mean lymphocyte value for the 5 mg dose that is administered up to Week 4 in the chronic GVHD study. Data of the MS program seemed to be the most appropriate choice for the sample size calculations, as data, doses and length of studies reflect the chronic GVHD study setup. The MCP-Mod estimate of the 5 mg dose was included in the sample size simulations of the PD endpoint (details below), adjusted for lower lymphocyte levels of subjects with chronic GVHD.

Four doses (10 mg, 20 mg, 40 mg and placebo) were included in the dose-response model, based on all available baseline placebo data of the AC-058B201 study, Week 8 data of the 10 mg dose (AC-058B201/B202) and Week 12 data of the 20 and 40 mg doses (AC-058B201/B202), selecting data according to the dose-escalation and assessment schedule of the chronic GVHD study. A candidate set of models was tested (including linear, E_{max},

sigmoid E_{max} and logistic dose-response curve), and a highly significant dose response was established for the candidate models mentioned above (trend-test value of $T > 30$, $p< 0.0001$), with the E_{max} and sigmoid E_{max} being the optimal models, depending on the choice of the input parameters. The derived mean lymphocyte estimates for the 5 mg dose were around 1.4×10^9/L (estimates similar for different linear E_{max} and sigmoid E_{max} models and for different data selections, including AC-058B201 core phase data and pooled AC-058B201/B202 data). Mean absolute lymphocyte counts for other doses were estimated from historical data (mean absolute lymphocyte count of 10 mg at Week 8: 1.0×10^9/L [STD: 0.39]; 20 mg at Week 12: 0.65×10^9/L [STD: 0.28]; baseline: 2.0×10^9/L [STD: 0.69] at the specific time points).

Assuming chronic GVHD subjects enter the study with a reduced absolute lymphocyte count of at least 40%, mean estimates were adjusted proportionally, i.e., a mean baseline absolute lymphocyte count of 1.2×10^9/L (STD 0.6), a count of 0.85×10^9/L (STD 0.4) for the 5 mg dose, a count of 0.6×10^9/L (STD 0.35) for the 10 mg dose and a count of 0.4×10^9/L (STD 0.25) for the 20 mg dose.

Pairwise comparisons of dose levels

Simulations were carried out using the assumptions described above, in order to assess the power of t-tests of the absolute lymphocyte counts of the 5 mg dose versus baseline, based on a lymphocyte reduction of 40% compared to MS data (including drop out analysis):

Analysis	No. Patients	Alpha (1-sided)	Lymph. Reduction compared to MS data	Mean Lymph. Count Placebo	Mean Lymph. Count Pon. 5 mg	STD	Power
Primary Sample Size	30	0.05	40%	1.20	0.85	0.6/0.4	85%
Drop-Out Sample Size	23	0.05	40%	1.20	0.85	0.6/0.4	75%

Assuming an absolute lymphocyte count reduction of 40% (mean of 1.2×10^9/L (STD 0.6) at baseline and a mean of 0.85×10^9/L (STD 0.4) for the 5 mg dose), results in a sample of 30 subjects, based on a 1-sided alpha level of 5% and a Power of approximately 85%. If up to 25% of the subjects drop out during the Core Treatment Period, the Power reduces to 75%.

Further simulations showed that with 30 subjects included in the study, all doses could be clearly distinguished from each other (minimal power of > approximately 84% from comparison of 5 mg versus 10 mg at one-sided alpha of 5%, based on an absolute lymphocyte count reduction of 40% as compared to MS data and STD of 0.6/0.4).

11.4.3 Sample size re-estimation

Not applicable.

12 DATA HANDLING

12.1 Data collection

The investigator/delegate is responsible to ensure the accuracy, completeness, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of the data. Data reported in the eCRF derived from source documents must be consistent with the source documents.

eCRF data will be captured via electronic data capture (using the Rave system provided by Medidata Solutions, Inc., a web-based tool). The investigator and site staff will be trained to enter and edit the data via a secure network, with secure access features (username, password and identification – an electronic password system). A complete electronic audit trail will be maintained. The investigator/delegate will approve the data (i.e., confirm the accuracy of the data recorded) using an electronic signature (ref. to 21 CFR Part 11).

Subject screening and enrollment data will be completed for all subjects (i.e., eligible and non-eligible) through the IRT system and eCRF.

For each subject enrolled, regardless of study treatment initiation, an eCRF must be completed and signed by the investigator/delegate. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be recorded in the eCRF.

12.2 Maintenance of data confidentiality

The investigator/delegate must ensure that data confidentiality is maintained. On eCRFs or other documents submitted to Actelion, subjects must be identified only by number and never by name or initials, hospital numbers or any other identifier. The investigator/delegate must keep a subject identification code list at the site, showing the enrollment number, the subject's name, date of birth and address or any other locally accepted identifiers. Documents identifying the subjects (e.g., signed ICFs) must not be sent to Actelion and must be kept in strict confidence by the investigator/delegate.

12.3 Database management and quality control

eCRFs will be used for all subjects. The investigator will have access to the site eCRF data until the database is locked. Thereafter, they will have read-only access. The eCRF must be kept current to reflect subject status at any time point during the course of the study.

While entering the data, the investigator/delegate will be instantly alerted to data queries by validated programmed checks. Additional data review will be performed by Actelion

on an ongoing basis to look for unexpected patterns in data and study monitoring. If discrepant data are detected, a query specifying the problem and requesting clarification will be issued and visible to the investigator/delegate via the eCRF. All electronic queries visible in the system either require a data correction (when applicable) and a response from the investigator/delegate to clarify the queried data directly in the eCRF, or simply a data correction in the eCRF. The investigator/delegate must, on request, supply Actelion with any required background data from the study documentation or clinical records. This is particularly important when errors in data transcription are suspected. In the case of health authority queries, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

This process will continue until database closure.

Study drug accountability and compliance, laboratory samples, PK samples, and ECGs will be processed centrally through their respective central laboratory/provider, and the results will be sent electronically to Actelion. If local laboratory date is obtained as may be required per-protocol in certain instances, it must be entered in the eCRF by the site.

After the database has been declared complete and accurate, the database will be closed. Any changes to the database after that time may only be made as described in the appropriate standard operating procedure (SOP). After database closure, the investigator will receive the eCRF of the subjects from his/her site (including all data changes made) on electronic media or as a paper copy.

13 PROCEDURES AND GOOD CLINICAL PRACTICE

13.1 Ethics and Good Clinical Practice

Actelion and the investigators will ensure that the study is conducted in full compliance with ICH-GCP guidelines, the principles of the "Declaration of Helsinki" and with the laws and regulations of the country in which the research is conducted.

13.2 Independent Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document provided to the subject (such as Subject Information Leaflet used to obtain informed consent) to an Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Approval from the committee must be obtained before starting the study, and must be documented in a dated letter to the investigator, clearly identifying the study, the documents reviewed, and the date of approval.

Modifications made to the protocol after receipt of the approval must also be submitted as amendments by the investigator to the IRB/IEC in accordance with local procedures and regulations [see Section 13.6].

A list of members participating in the IRB/IEC meetings must be provided, including the names, qualifications and functions of these members. If that is not possible, the attempts made to obtain this information along with an explanation as to why it cannot be obtained or disclosed must be documented in the study documentation. If a study staff member was present during a meeting, it must be clear that this person did not vote.

13.3 Informed consent

It is the responsibility of the investigator/delegate to obtain informed consent according to ICH-GCP guidelines and local regulations from each individual participating in this study and/or legal representative. The investigator/delegate must explain to subjects that they are completely free to refuse to enter the study, or to withdraw from it at any time for any reason.

The ICF will be provided in the country local language(s).

Site staff authorized to participate to the consent process and/or to obtain consent from the subject and/or legal representative will be listed on an Actelion Delegation of Authority form. A study physician must always be involved in the consent process.

The subject and/or legal representative must sign, personally date and time (if appropriate) the ICF before any study-related procedures (i.e., any procedures required by the protocol) begin. The ICF must also be signed, personally dated and timed (if appropriate) by the authorized site staff listed on Actelion Delegation of Authority form.

A copy of the signed and dated ICF is given to the subject and/or legal representative; the original is filed in the site documentation.

The informed consent process must be fully documented in the subject's medical records, including study reference, subject number, date/time (if applicable) when the subject was first introduced to Actelion clinical study, date/time (if applicable) of consent, who participated in the consent discussion, who consented the subject and any additional person present during the consent process (e.g., subject family member), copy of the signed ICF given to the subject / legal representative.

In the case that the site would like to recruit a subject who would be considered as vulnerable (e.g., subject cannot read or write, does not speak or understand the ICF language), additional measures must be implemented in order to ensure subject rights are respected and the consent obtained is legally valid. Actelion, the regulatory authorities (if applicable) and the IRB/IEC must be informed prior to the recruitment. The consent process (e.g., involvement of an impartial witness) must be fully described, submitted to, and approved by the IRB/IEC, according to procedures and before subjects are recruited.

13.4 Compensation to subjects and investigators

Actelion provides insurance in order to indemnify (with both legal and financial coverage) the investigator/site against claims arising from the study, except for claims that arise from malpractice and/or negligence.

The compensation of the subject in the event of study-related injuries will comply with applicable regulations.

13.5 Protocol adherence/compliance

The investigator must conduct the study in compliance with the approved version of the protocol and must not implement any deviation/change from the protocol, except when the change involves only logistical or administrative aspects (e.g., change in telephone number), or in case it would be necessary to eliminate an immediate hazard to the subject.

If a protocol deviation occurs, the investigator/delegate will inform Actelion or its representative in a timely manner. The investigator/delegate must document and explain any deviation from the approved protocol. IRB/IEC and regulatory authorities must be informed, according to their requirements, but no later than 15 calendar days after the event.

13.6 Protocol amendments

Any change to the protocol can only be made through a written protocol amendment. A protocol amendment must be submitted to the IRB/IEC and regulatory authorities, according to their requirements.

13.7 Essential documents and retention of documents

The investigator/delegate must maintain adequate records necessary for the reconstruction and evaluation of the study. A number of attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records are accurate, legible, contemporaneous, original (or certified copy), attributable, complete, consistent, enduring and available when needed.

These records are to be classified into two different categories of documents: investigator's file, and subject clinical source documents.

These records must be kept by the investigator for as long as is necessary to comply with Actelion's requirements (e.g., as specified in the clinical study agreement), and national and/or international regulations, whichever would be the longest period. If the investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements, respecting the data confidentiality, must be made between the investigator and Actelion to store these documents outside the site so that they can be retrieved in case of a regulatory inspection. No study document should be destroyed

without prior written approval from Actelion. Should the investigator wish to assign the study records to another party or move them to another location, Actelion must be notified in advance.

If the site is using an electronic/computerized system to store subject medical records, it can be used for the purpose of the clinical study if it is validated (as per 21 CFR Part 11 or equivalent standard) and if the monitor has been provided personal and restricted access to study subjects only, to verify consistency between electronic source data and the eCRF during monitoring visits.

If the site is using an electronic/computerized system to store subject medical records but it could not be confirmed that the system is validated or if the monitor could not be provided access to the system, the site is requested to print the complete set of source data needed for verification by the monitor. The print-outs must be numbered, stapled together with a coversheet, signed and dated by the investigator/delegate to confirm that these certified copies are exact copies having the same information as the original subject's data. The printouts will be considered as the official clinical study records.

In order to verify that the process the site uses to prepare certified copies is reliable, the monitor must be able to observe this process and confirm that the comparison of the source documents and the certified copy did not reveal inconsistencies. The monitor does not need to verify this process for all data of all subjects but at least for some of them (e.g., first subject; regular check during the study of critical data like inclusion/exclusion criteria, endpoints for some subjects) as per Actelion's instructions. If it were not possible for the monitor to observe this process, it would not be possible to rely on the site's certified copies and therefore the site cannot be selected for the clinical study. The printouts should be filed either with the subject medical records or with the subject's eCRF.

13.8 Monitoring

Prior to study start, a site initiation visit (SIV) will be performed after the required essential study documents are approved by Actelion. The study treatment will be shipped to the site upon approval of the required essential documents.

The principal investigator must ensure that all site personnel involved in the study will be present during the SIV and will dedicate enough time to it. Site Information Technology support should also be available during the initiation visit.

The SIV must be completed before the site can start the screening of study subjects. Following the SIV, a copy of the completed initiation visit report and follow-up letter will be provided to the principal investigator and filed in the investigator site file (ISF).

During the study, the monitor will contact and visit the investigational site regularly and, on request, must be permitted to have access to trial facilities and all source documents

needed to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered in the eCRFs and other protocol-related documents. Actelion monitoring standards require full verification that informed consent has been provided, and verification of adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main efficacy, safety and tolerability endpoints. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study-specific monitoring plan. The frequency of the monitoring visits will be based on subject recruitment rate and critical data collection times.

The investigator/sub-investigator must ensure that the eCRF is completed after a subject's visit to the site and that all requested subject files (e.g., ICFs, medical notes/charts, other documentation verifying the activities conducted for the study) are available for review by the monitor. The required site personnel must be available during monitoring visits and allow adequate time to meet with the monitor to discuss study related issues.

The investigator agrees to cooperate with the monitor(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the subject is hospitalized or dies in a hospital other than the study site, the investigator is responsible for contacting that hospital in order to document the SAE, in accordance with local regulations.

A close-out visit will be performed for any initiated site and when there are no more active subjects and after all study data have been accepted by medical review and all follow-up issues have been resolved. In case a site does not enroll any subjects, the close-out visit may be performed prior to study database closure at the discretion of Actelion.

13.9 Investigator site file

Each site will be provided with an ISF prior to the initiation visit. It will contain all the essential documents that are required to always be up-to-date and filed at site as per ICH-GCP section 8.

The ISF will include a table of contents listing the essential documents. All study-related documentation must be maintained in the ISF.

In some cases, exceptions can be discussed with the monitor regarding the filing of the study documents outside the ISF. It should be clearly documented where each document is filed. This note to file should be present in the specific tab of the document in the ISF.

The ISF must be stored in a secure and access-restricted area during and after the study. It must be kept by the site for as long as needed to comply with any applicable rules and regulations, ICH-GCP as well as instructions from Actelion. If the site needs to transfer the ISF to another location and/or if site facility can no longer store the ISF, the principal investigator must inform Actelion immediately.

If the principal investigator will change, or if the site will relocate, the monitor must be notified as soon as possible.

13.10 Audit

Actelion's Global Quality Management representatives may audit the investigator site (during the study or after its completion). The purpose of this visit will be to determine the investigator's adherence to ICH-GCP, the protocol, and applicable regulations; adherence to Actelion's requirements (e.g., SOPs) will also be verified. Prior to initiating this audit, the investigator will be contacted by Actelion to arrange a time for the audit.

The investigator and staff must cooperate with the auditor(s) and allow access to all study documentation (e.g., subject records) and facilities.

13.11 Inspections

Health authorities and/or IRB/IEC may also wish to conduct an inspection of Actelion's clinical study (during the study or after its completion).

Should an inspection be requested by a health authority and/or IRB/IEC, the investigator must inform Actelion immediately, (usually via the monitor) that such a request has been made.

The investigator and staff must cooperate with inspector(s) and allow access to all study documentation (e.g., subject records) and study facilities.

13.12 Reporting of study results and publication

Study results will be documented in a clinical study report that will be signed by Actelion representatives and the coordinating investigator (or principal investigator for single-center studies).

The coordinating investigator and the Steering Committee, if any, will have the opportunity to review the analysis of the data and to discuss the interpretation of the study results with Actelion prior to publication.

Actelion will post results from its clinical studies on Actelion's Clinical Trial Register, and on external/national registries, as required by law.

Actelion's Policy on Disclosure of Clinical Research Information can be found at:
http://www.actelion.com/documents/corporate/policies_charters/policy_clinical-research-information.pdf

In accordance with the Good Publication Practices and ethical practice, the results of the study will be submitted for publication in a peer-reviewed journal. Study results can be submitted for presentation at a congress before publication in a peer-reviewed journal.

Authorship will be determined in accordance with the International Committee of Journal Editors criteria, and be based on:

- Substantial contributions to: the conception or design of the study, or the acquisition, analysis or interpretation of data; and
- Drafting of the publication or critical review for important intellectual content; and
- Providing final approval of the version to be published; and
- 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.

The list of authors of any publication of study results may include representatives of Actelion, and will be determined by mutual agreement.

Any study-related publication written independently by investigators must be submitted to Actelion for review at least 30 days prior to submission for publication or presentation. Upon review, Actelion may provide comments and may also request alterations and/or deletions for the sole purpose of protecting its confidential information and/or patent rights. Neither the institution nor the investigator should permit publication during such a review period.

Actelion's Policy on Scientific Publications can be found at:
http://www.actelion.com/documents/corporate/policies_charters/policy_scientific-publications.pdf

14 REFERENCES

[Alvarez 2007] Alvarez SE, Milstien S, Spiegel S. Autocrine and paracrine roles of sphingosine-1-phosphate. Trends Endocrinol Metab 2007;18:300–7.

[Antin 2011] Antin, J. H. T-Cell Depletion in Gvhd: Less Is More? Blood 117, no. 23(2011):6061-2.

[Bretz 2005] Bretz F, Pinheiro JC, Branson M; Combining Multiple Comparisons and Modeling Techniques in Dose-Response Studies; Biometrics 2005;61:738-748.

[Brinkmann 2007] Brinkmann V. Sphingosine 1-phosphate receptors in health and disease: Mechanistic insights from gene deletion studies and reverse pharmacology. Pharmacol Ther 2007;9(11):883-897.

[Brinkmann 2010] Brinkmann V, Billich A, Baumruker T, et al. Fingolimod (FTY720): discovery and development of an oral drug to treat multiple sclerosis. Nat Rev Drug Discov 2010;115:84–105.

[CDC 2000] Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm, accessed 16 December 2014.

[Chu 2008] Chu, Y.W. and R.E. Gress, Murine models of chronic graft-versus-host disease: insights and unresolved issues. Biol Blood Marrow Transplant, 2008.14(4):p.365-78.

[CTCAE 2010] Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010); U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES; National Institutes of Health; National Cancer Institute; available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf, accessed 16 December 2014.

[Cyster 2005] Cyster JG. Chemokines, sphingosine-1-phosphate, and cell migration in secondary lymphoid organs. Annu Rev Immunol 2005;23:127–59.

[D'Ambrosio 2015] D'Ambrosio D, Steinmann J, Brossard P, Dingemanse J. Differential effects of ponesimod, a selective $S1P_1$ receptor modulator, on blood-circulating human T cell subpopulations. Immunopharmacology And Immunotoxicology 2015 Feb; 37(1):103-9.

[D'Ambrosio 2016] D'Ambrosio D, Freedman MS, Prinz J. Ponesimod, a selective $S1P_1$ receptor modulator: a potential treatment for multiple sclerosis and other immune-mediated diseases. Ther Adv Chronic Dis. 2016 Jan; 7(1):18-33.

[Dignan 2014] Dignan FL, Aguilar S, Scarisbrick JJ, Shaw BE, Potter MN, Cavenagh J. Impact of extracorporeal photopheresis on skin scores and quality of life in patients with steroid-refractory chronic GVHD. Bone Marrow Transplantation 2014,49(5):704-8.

[FDA 2009] Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation; available at: http://www.fda.gov/downloads/Drugs/.../ Guidances/UCM174090.pdf, accessed 12 June 2014.

[Filipovich 2005] Filipovich, A. H., D. Weisdorf, S. Pavletic, G. Socie, J. R. Wingard, S. et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-Versus-Host Disease: I. Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant 11, 12(2005):945-56.

[Fingolimod] Fingolimod (NDA 22-527) Background Package; FDA/CDER/Peripheral and Central Nervous system Drugs Advisory Committee Meeting; available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022527Orig1s000medr. pdf, accessed 16 December 2014.

[Flowers 2011] Flowers MED, Inamoto Y, Carpenter PA, et al. Comparative analysis of risk factors for acute and for chronic graft-versus-host disease according to National Institute of Health consensus criteria. Blood. 2011;117(11):3214-9.

[Focosi 2007] Focosi D, Kast RE, Maggi F, et al. Central nervous system graft-versus-host disease: consider progressive multifocal leukoencephalopathy among the differential diagnoses. Bone Marrow Transplant 2007; 40:1095-6.

[Francis 2010] Francis G, Collins W, Burtin P. Fingolimod (NDA 22-527) Briefing Document prepared by Novartis Pharmaceuticals for the Peripheral and Central Nervous System Drugs Advisory Committee Meeting 10 June 2010. Downloaded on 6 June 2011 from http://www.fda.gov/downloads/AdvisoryCommittees/ CommitteesMeetingMaterials/Drugs/.

[Francis 2014] Francis G, Kappos L, O'Connor P, Collins W, Tang D, Mercier F, et al. Temporal profile of lymphocyte counts and relationship with infections with fingolimod therapy. Mult Scler. 2014 Apr; 20(4):471-80.

[Garnett 2013] Garnett C, Pavlů J. Treament and management of graft-versus-host disease: improving response and survival. Ther Adv Hematol 2013. 4:366-378.

[Greinix 2007] Greinix HT, Antin JH. Salvage therapy in chronic graft versus host disease. In: Vogelsang GB, Pavletic SZ ed. Chronic Graft versus Host Disease: interdisciplinary management. Cambridge, 134-45.

[Gu 2007] Gu, L., et al., Effect of TGF-beta/Smad signaling pathway on lung myofibroblast differentiation. Acta Pharmacol Sin, 2007. 28(3): 382-91.

[Huu 2013] Huu, D.L., et al., FTY720 ameliorates murine sclerodermatous chronic graft-versus-host disease by promoting expansion of splenic regulatory cells and inhibiting immune cell infiltration into skin. Arthritis Rheum, 2013. 65(6):1624-35.

[Inamoto 2014a] Inamoto, Y., J. Pidala, X. Chai, B. F. Kurland, D. Weisdorf, et al. Assessment of Joint and Fascia Manifestations in Chronic Graft-Versus-Host Disease. Arthritis Rheumatol 66,4(2014):1044-52.

[Inamoto 2014b] Inamoto Y, Flowers MED, Sandmaier BM, et al. Failure-free survival after systemic treatment of chronic graft-versus-host-disease. Blood. 2014;124:1363-71.

[Jagasia 2015] Jagasia MH, Greinix HT, Arora M. et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant. 2015 Mar; 21(3):389-401.

[Kappos 2011] Kappos L, Bates D, Edan G, et al. Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. Lancet Neurol. 2011;10:745-58

[Kappos 2015] Kappos L, Mehling M, Arroyo R, Izquierdo G, Selmaj K, Curovic-Perisic V, et al. Randomized trial of vaccination in fingolimod-treated patients with multiple sclerosis. Neurology. 2015 Mar 3;84(9):872-9.

[Katakoka 2005] Kataoka, H., et al., Immunosuppressive activity of FTY720, sphingosine 1-phosphate receptor agonist: II. Effect of FTY720 and FTY720-phosphate on host-versus-graft and graft-versus-host reaction in mice. Transplant Proc. 2005;37(1): p.107-9.

[Kim 2003] Kim YM, Sachs T, Asavaroengchai W, et al. Graft-versus-host disease can be separated from graft-versus-lymphoma effects by control of lymphocyte trafficking with FTY720. J Clin Invest 2003. 111:659-69.

[Kim 2015] Kim HT, Armand P, Frederick D, Andler E, Cutler C, Koreth J, et al. Absolute lymphocyte count recovery after allogeneic hematopoietic stem cell transplantation predicts clinical outcome. Biol Blood Marrow Transplant. 2015 May; 21(5):873-80.

[Koc 2002] Koc S, Leisenring W, Flowers M, et al. Therapy for chronic graft versus host disease: a randomized trial comparing cyclosporine plus prednisolone versus prednisolone alone. Blood 2002. 100: 48-51.

[Lee 2002] Lee, Sk, E. F. Cook, R. Soiffer and J. H. Antin. Development and Validation of a Scale to Measure Symptoms of Chronic Graft-Versus-Host Disease. Biol Blood Marrow Transplant 8, no. 8 (2002): 444-52.

[Lee 2008] Lee SJ, Flowers MED. Recognizing and managing chronic graft-versus-host-disease. Hematology Am Soc Hematol Educ Program 2008;134-140

[Lee 2015] Lee SJ, Wolff D, Kitko C, Koreth J, Inamoto Y, Jagasia M, et al. Measuring Therapeutic Response in Chronic Graft-versus-Host Disease. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. The 2014 Response CriteriaWorking Group Report. Biol Blood Marrow Transplant. 2015; 21(6):984-99.

[Linhares 2013] Linhares YLP, Pavletic S, Gale RP. Chronic GVHD: Where are we? Where do we want to be? Will immunomodulatory drugs help? Bone Marrow Transplantation 2013; 48:203-209.

[Macintyre 2005] Macintyre N, Crapo RO, Viegi G, et al. ATS/ERS Task Force. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005 Oct;26(4):720-35.

[Marras 2004] Marras TK, Chan CK, Lipton JH, Messner HA, Szalai JP, Laupacis A. Long-term pulmonary function abnormalities and survival after allogeneic marrow transplantation. Bone Marrow Transplantation 2004 Mar: 33 (5):509–17.

[Martin 2009] Martin PJ, Gilman AL. Front line treatment of chronic graft versus host disease. In: Vogelsang GB, Pavletic SZ ed. Chronic Graft versus Host Disease: interdisciplinary management. Cambridge, pp. 124-133.

[Martin 2011] Martin PJ, Inamoto Y, Carpenter PA, et al. Treatment of chronic graft-versus-host disease: past, present and future. Korean J Hematol 2011.46:153-163.

[Masabuchi 1996] Masubuchi, Y., et al., FTY720, a novel immunosuppressant, possessing unique mechanisms. IV. Prevention of graft versus host reactions in rats. Transplant Proc, 1996;28(2):1064-5.

[Mehling 2011] Mehling M, Johnson T, Antel J, Kappos L, Bar-Or A. Clinical immunology of the sphingosine 1-phosphate receptor modulator fingolimod (FTY720) in multiple sclerosis. Neurology. 2011 Feb 22;76:S20–7.

[Miller 2005a] Miller MR, Crapo R, Hankinson J, et al,; ATS/ERS Task Force. General considerations for lung function testing. Eur Respir J. 2005 Jul;26(1):153-61. Review.

[Miller 2005b] Miller MR, Hankinson J, Brusasco V, et al; ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J. 2005 Aug;26(2):319-38.

[NCI 2010] National Cancer Institute, June 2010. Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, U.S. Department of Health and Human Services.

[Nho 2006] Nho, R.S., et al., PTEN regulates fibroblast elimination during collagen matrix contraction. J Biol Chem, 2006. 281(44): p. 33291-301.

[NIH Biomarkers] Biomarkers for chronic graft versus host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-Versus-Host Disease: III Biomarker Working Group Report, available at: http://ncifrederick.cancer.gov/events/GvHD/Biomarker.pdf

[NIH Design of Clinical Trials 2014] National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: VI. Design of Clinical Trials Working Group Report; available at: http://ncifrederick.cancer.gov/events/GvHD/ClinicalTrialsWorkingGroupReport.pdf, accessed 16 December 2014.

[NIH Therapeutic Response 2014] 2014 NIH chronic GVHD Consensus Conference, Response Criteria Working Group documents, in press, personal communication by Dr Steven Pavletic.

[Nishimori 2013] Nishimori, H., Y. Maeda and M. Tanimoto. Chronic Graft-Versus-Host Disease: Disease Biology and Novel Therapeutic Strategies. Acta Med Okayama. 2013;67(1):1-8.

[Pai 2014] Pai CS, Chen M, Mirsoian A, et al. Treatment of chronic graft-versus-host disease with bortezomib. Blood. 2014;124:1677-88.

[Pasquini 2013] Pasquini MC, Wang Z. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR Summary Slides, 2013. Available at: http://www.cibmtr.org, accessed 16 December 2014.

[Pavletic 2006] Pavletic SZ, Martin P, Lee SJ, et al. Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group report. Biol Blood Marrow Transplant 2006; 12:252-66.

[Piali 2011] Piali, L, et al., The selective sphingosine 1-phosphate receptor 1 agonist ponesimod protects against lymphocyte-mediated tissue inflammation. J Pharmacol Exp Ther, 2011; 337(2):p.547-56.

[Pinschewer 2000] Pinschewer DD, Ochsenbein AF, Odermatt B, et al. FTY720 immunosuppression impairs effector T cell peripheral homing without affecting induction, expansion, and memory. J Immunol 2000;164:5761–70.

[Ponesimod IB] Ponesimod $S1P_1$ receptor agonist. Investigator's Brochure, Version 10 Amendment 1, July 2015.

[Quanjer 1993] Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 1993;16:5–40.

[Schwab 2007] Schwab SR, Cyster JG. Finding a way out: lymphocyte egress from lymphoid organs. Nat Immunol 2007;8:1295–301.

[Song 2006] Song, J, et al., Inhibition of donor-derived T cells trafficking into target organs by FTY720 during acute graft-versus-host disease in small bowel transplantation. Clin Exp Immunol, 2006; 146(1):85-92.

[Stewart 2004] Stewart B, Storer B, Storek J, et al. Duration of immunosuppressive treatment for chronic graft-versus-host-disease. Blood 2004; 104:3501-3506.

[Storek 2008] Reconstitution of the immune system after hematopoietic stem cell transplantation in humans. Semin Immunopathol. 2008 Dec;30(4):425-37.

[Teshima 2009] Teshima T, Nagafuji K, Henzan H, et al. Rituximab for the treatment of corticoisteroid-refractory chronic graft-versus-host disease. Int J Hematol 2009;90:253-60.

[Vaclavkova 2014] Vaclavkova A, Chimenti S, Arenberger P, et al. Oral ponesimod in patients with chronic plaque psoriasis: a randomised, double-blind, placebo-controlled Phase 2 trial. Lancet. 2014;384:2036–45.

[Vigorito 2009] Vigorito AC, Campregher PV, Storer BE, et al. Evaluation of NIH consensus criteria for classification of late acute and chronic GVHD. Blood. 2009;114(3):702-708.

[Weisdorf 2007] Weisdorf D. GVHD - the nuts and bolts. Hematology Am Soc Hematol Educ Program 2007;62-67.

[Wolff 2011a] Wolff D, Bertz H, Greinix H, et al. The treatment of chronic graft-versus-host disease. Dtsch Arztebl Int 2011;108:732-740.

[Wolff 2011b] Wolff D., Schleuning M, von Harsdorf S, et al. Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease. Biol Blood Marrow Transplant. 2011;17:1-17.

[Woosley 2016] Woosley, RL, Romero, KA. QTdrugs List, 2016, AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755
Available from: www.crediblemeds.org

[Yamamoto 2014] Yamamoto W, Ogusa E, Matsumoto K, Maruta A, Ishigatsubo Y, Kanamori H. Lymphocyte recovery on day 100 after allogeneic hematopoietic stem cell transplant predicts non-relapse mortality in patients with acute leukemia or myelodysplastic syndrome. Leuk Lymphoma. 2014 May; 55(5):1113-8.

[You 2013] You, S, et al., Therapeutic use of a selective $S1P_1$ receptor modulator ponesimod in autoimmune diabetes. PLoS One, 2013. 8(10): p. e77296.

15 APPENDICES

Appendix 1 Additional subject eligibility guidance

The following guidance should be applied by investigators in assessing the eligibility for subjects for enrollment in this study, with respect to inclusion criteria 5b and 5c.

Inclusion criterion 5b
The investigator must determine subject to be glucocorticoid refractory, dependent, or intolerant at screening.
Guidance
Systemic glucocorticoids are established first-line therapy for chronic GVHD. This study will not include subjects who could benefit from standard use of glucocorticoids. Therefore, a glucocorticoid refractory, dependent, or intolerant status must exist for all eligible subjects. **Currently, there are no uniformly accepted definitions for these states in chronic GVHD.** The investigator should consider the following definitions in his or her assessment of the subject's prior experience with glucocorticoids: **Refractory to or dependent on glucocorticoids** • Progression on prednisone-equivalent steroid dose at 1 mg/kg/day for 2 weeks • Stable disease on prednisone-equivalent steroid dose at ≥ 0.5 mg/kg/day for 4–8 weeks • Inability to taper below prednisone-equivalent steroid dose of 0.5 mg/kg/day • Treatment with prednisone-equivalent steroid dose of > 0.25 mg/kg/day received for ≥ 12 weeks **Sources:** [Wolff 2011b, Pai 2014, Inamoto 2014b] **Intolerant to glucocorticoids** • Subjects have a glucocorticoid intolerance that required a dose reduction. Intolerance includes the development of severe side effects due to glucocorticoid use, such as poorly controlled hypertension or diabetes, active peptic ulcer disease, myopathy, psychiatric derangements, significant bone loss, or systemic fungal infection.

Inclusion criterion 5c
Subjects have evidence of GVHD progression at enrollment despite ≥ 4 weeks current systemic IS therapy, OR are without evidence of GVHD improvement at enrollment despite ≥ 8 weeks current systemic IS therapy. Current systemic IS therapy must be same as in inclusion criterion 4.
Guidance
This study seeks to avoid enrolling subjects who are improving on their current systemic IS therapy or who have not received an adequate duration of therapy to demonstrate response. • Lack of response (progression or no improvement) to the current systemic IS therapy, determined at enrollment, will need to be documented in the eCRF. Investigators should consider the 2014 NIH response criteria checklist [see Appendix 7] when comparing chronic GVHD disease activity at enrollment versus previous chronic GVHD activity. Reason for lack of response has to be documented in the medical record and eCRF at the time of enrollment. Subjects with indications of overall partial or complete response are not eligible. • For the purposes of this study, current systemic IS therapy is systemic glucocorticoids AND/OR one of the following systemic agents: CsA, TAC, MMF, MPS, EVL, SRL, or MTX. These agents are present at enrollment and will be continued during the study. It is not required that these agents were initiated at the same time, or that dosing was always constant. It is required that the agents were given together over the minimum duration (4 or 8 weeks)* leading up to enrollment, and that there were no dose changes in the 14 days prior to enrollment. • Other agents (e.g., cyclophosphamide, rituximab) may have been initiated and stopped in the past; however, these are not considered to be part of the current systemic IS therapy, and specific washout periods prior to enrollment must be achieved to permit eligibility. These agents and washout periods are described in the exclusion criteria. **Source** *Duration and response requirements adapted from Martin 2009.

Appendix 2 Chronic GVHD Stage and Score forms

All forms in Appendix 2 are NIH Consensus Development Criteria [Jagasia 2015].

AC-058C202

SITE NO: _____ SUBJECT NO: _____ VISIT NO: _____ DATE: _____

FORM 1: NIH GLOBAL SEVERITY OF CHRONIC GHVD

Please check one severity only (mild, moderate, or severe)

Please check all justifications which apply for severity level selected

Form 1 entries must be based on the assessment entered in Forms 2 and 3.

Severity	Justification
☐ **Subject has mild chronic GVHD**	☐ 1 or 2 Organs involved with no more than score 1 *plus* Lung score 0.
☐ **Subject has moderate chronic GVHD**	☐ 3 or More organs involved with no more than score 1 ☐ At least 1 organ (not lung) with a score of 2 ☐ Lung score 1
☐ **Subject has severe chronic GVHD**	☐ At least 1 organ with a score of 3 ☐ 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).

Investigator's signature _____

Appendix 2 Chronic GVHD Stage and Score forms (cont'd)

Organ Scoring Chronic GVHD Form

STUDY: AC-058C202

SITE NO: _____ **SUBJECT NO:** _____ **VISIT NO:** _____ **DATE:** _____

FORM 2: ORGAN SCORING OF CHRONIC GVHD

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS**	☐ Asymptomatic and fully active (KPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (KPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (KPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (KPS < 60%)
SKIN† SCORE %BSA ☐	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA

GVHD features to be Scored by HAS:
Check all that apply:
☐ Maculopapular rash/erythema
☐ Lichen planus-like features
☐ Sclerotic features
☐ Papulosquamous lesions of ichthyosis
☐ Keratosis pilaris-like GVHD

SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration

Other skin GVHD features (NOT scored by BSA)
Check all that apply:
☐ Hyperpigmentation
☐ Hypopigmentation
☐ Poikiloderma
☐ Severe or generalized pruritus
☐ Hair involvement
☐ Nail involvement

☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify) :* _____

MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake.	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake

☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____

Organ scoring of chronic GVHD. KPS: Karnofsky Performance Status; BSA: body surface area; ADL: activities of daily living; LFTs: liver function tests; AP: alkaline phosphatase; ALT: alanine aminotransferase; NUL: normal upper limit; "Weight loss within 3 months". †Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous feature scales. When a discrepancy exists between the percentage of total body surface (BSA), score and the skin feature score, OR if superficial sclerotic features are present (Score 2),but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring. †To be completed by specialist or trained medical providers (see **Supplemental figure).** "Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

Investigator's signature _____

Appendix 2 Chronic GVHD Stage and Score forms (cont'd)

Organ Scoring Chronic GVHD Form (continued)

STUDY: AC-058C202

SITE NO: _____ **SUBJECT NO:** _____ **VISIT NO:** _____ **DATE:** _____

FORM 2 Continued: ORGAN SCORING OF CHRONIC GVHD

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* □ **Yes** □ **No** □ **Not examined**	□ No symptoms	□ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	□ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eyedrops > 3x per day or punctal plugs). **WITHOUT** new vision impairment due to KCS.	□ Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS.
□ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				
GI Tract ***Check all that apply:*** □ Esophageal web/proximal stricture or ring □ Dysphagia □ Anorexia □ Nausea □ Vomiting □ Diarrhea □ Weight loss ≥ 5%* □ Failure to thrive	□ No symptoms	□ Symptoms without significant weight loss*(<5%)	□ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living.	□ Symptoms associated with significant weight loss*>15%, requires nutritional supplement for most calorie need **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living.
□ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				
Liver	□ Normal total bilirubin and ALT or AP < 3 x ULN	□ Normal total bilirubin with ALT ≥ 3 to 5 x ULN or AP ≥ 3 x ULN	□ Elevated total bilirubin but ≤ 3 mg/dL or ALT > 5 ULN	□ Elevated total bilirubin > 3mg/dL
□ *Abnormality present but explained entirely by non-GVHD documented cause (specify) :* _____				
Lungs** **Symptom Score:**	□ No symptoms	□ Mild symptoms (shortness of breath after climbing one flight of steps)	□ Moderate symptoms (shortness of breath (after walking on flat ground)	□ Severe symptoms (shortness of breath at rest, requiring 0_2)
Lung Score: **% FEV1** ☐	□ **FEV1 ≥ 80%**	□ **FEV1 60-79%**	□ **FEV1 40-59%**	□ **FEV1 ≤ 39%**

Pulmonary function tests □ Not performed
□ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____

Investigator's signature _____

Appendix 2 Chronic GVHD Stage and Score forms (cont'd)

Organ Scoring Chronic GVHD Form (continued)

AC-058C202

SITE NO: _____ SUBJECT NO: _____ VISIT NO: _____ DATE: _____

FORM 2 Continued: ORGAN SCORING OF CHRONIC GVHD

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
Joints and Fascia **P-ROM Score:** *(see below)* Shoulder (1-7) ____ Elbow (1-7) ____ Wrist/Finger (1-7) ____ Ankle (1-4) ____	□ No symptoms	□ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL.	□ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL.	□ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self, etc)

□ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____

Genital Tract
(See Supplemental figure) □ Not examined

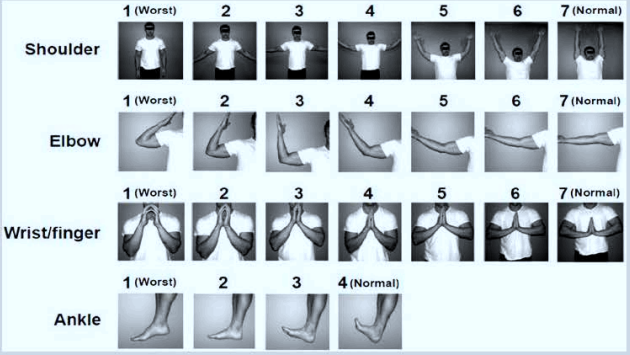
If examined, please enter the score in FORM 3 (next page)

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a Score to severity (0-3) based on functional impact where applicable none -0, mild -1, moderate -2, severe -3

□ Ascites (serositis) ____
□ Pericardial Effusion ____
□ Pleural Effusion(s) ____
□ Nephrotic syndrome ____
□ Myasthenia Gravis ____
□ Peripheral Neuropathy ____
□ Polymyositis ____
□ Weight loss >5% without GI symptoms ____
□ Eosinophilia > 500/ul ____
□ Platelets < 100,000/ ul ____
□ Others (specify)

Overall GVHD Severity *(Opinion of the evaluator)* □ **No GVHD** □ **Mild** □ **Moderate** □ **Severe**

Photographic Range of Motion (PROM)



Investigator's signature _____

Appendix 2 Chronic GVHD Stage and Score forms (cont'd)

Genital Tract Chronic GVHD Assessment Scoring Form

AC-058C202

SITE NO: _____ **SUBJECT NO:** _____ **VISIT NO:** _____ **DATE:** _____

FORM 3: SUPPLEMENTAL FIGURE-GENTIAL TRACT CHRONIC GVHD ASSESSMENT & SCORING FORM

SCORE 0	SCORE 1	SCORE 2	SCORE 3
Genital Tract ***Check:*** ☐ Male ☐ Female	☐No signs	☐ Mild signs and females with or without discomfort on exam	☐ Moderate signs and may have symptoms* with discomfort on exam	☐ Severe signs with or without symptoms*

Currently sexually active: ☐ Yes ☐ No

Check all signs that apply:

- ☐ Lichen planus-like features
- ☐ Lichen sclerosis-like features
- ☐ Vaginal scarring (female)
- ☐ Clitoral/labial agglutination (female)
- ☐ Labial resorption (female)
- ☐ Erosions
- ☐ Fissures
- ☐ Ulcers
- ☐ Phimosis (male)
- ☐ Urethral meatus scarring/ stenosis (male)

☐ *Abnormality present but NOT thought to represent GVHD (specify cause):*_____
☐ *Abnormality thought to represent GVHD PLUS other causes(specify cause):*_____

**Genital symptoms are not specific to cGVHD and can represent premature gonadal failure or genital tract infection.*

If a gynecologist is unavailable, external examination may be performed to determine "discomfort on exam" as follows:

a) Spread the labia majora to inspect the vulva for the above signs. Touch the vestibular gland openings (Skene's and Bartholin's), labia minora and majora gently with a Q-tip. Vulvar pain elicited by the gentle touch of a Q-tip is classified as discomfort on examination. Palpate the vaginal walls with a single digit to detect bands, shortening, narrowing or other signs of vaginal scarring.
b) If the woman is sexually active, determine whether Q-tip palpation or gentle palpation of scarred ridges elicits pain similar to that which the woman experiences during intercourse.

Female genitalia: Severity of signs:
1) Mild (any of the following); erythema on vulvar mucosal surfaces, vulvar lichen-planus or vulvar lichen-sclerosis.
2) Moderate (any of the following); erosive inflammatory changes of the vulvar mucosa, fissures in vulvar folds
3) Severe (any of the following); labial fusion, clitoral hood agglutination, fibrinous vaginal adhesions, circumferential fibrous vaginal banding, vaginal shortening, synechia, dense sclerotic changes, and complete vaginal stenosis.

Male genitalia: Diagnostic features include lichen planus-like or lichen sclerosis-like features and phymosis or urethral scarring or stenosis. Severity of signs:
1) Mild: lichen planus-like feature;
2) Moderate: lichen sclerosus-like feature or moderate erythema;
3) Severe: phimosis or urethral/meatal scarring.

Biopsy obtained: ☐ **Yes** ☐ **No; Site Biopsied:** _____ **; GVHD confirmed by histology:** ☐ **Yes** ☐ **No**

Investigator's signature _____

Appendix 3 Guidance for initiating or dose increasing QT-prolonging drugs with known risk of Torsades de Pointes

QT-prolonging medications with known risk of Torsades de Pointes (e.g., azithromycin, citalopram, clarithromycin, erythromycin, escitalopram, moxifloxacin,…) should be administered with caution since ponesimod may potentially enhance their effect on QT interval. A list of QT-prolonging medications with known risk of Torsades de Pointes is published by AZCERT http://crediblemeds.org/ [Woosley 2016]. The investigator should also take into account other relevant risk factors such as hypokalaemia when considering treatment with a QT-prolonging drug. If treatment with such drugs is considered necessary, the principal investigator should always discuss with the cardiac safety assessor the appropriateness of combining such drugs with ponesimod and may interrupt or prematurely discontinue study drug. If the principal investigator determines in the best interest of the subject to concomitantly administer a QT-prolonging drug with known risk of Torsades de Pointes and ponesimod, the following recommendations must be adhered to:

a) for a need to start treatment or to increase the dose of a QT-prolonging drug with known risk of Torsades de Pointes during up-titration, treatment with study drug must be interrupted.

- Study drug can only be re-initiated [see Section 5.1.8] after the QT-prolonging drug has been stopped or once the QT-prolonging drug has reached the steady-state
    - Once the QT-prolonging drug has reached the steady-state and prior to re-initiation of study drug, the QTcF interval obtained pre-dose on the day of the planned re-initiation must be ≤ 450 ms for males or ≤ 470 ms for females;
    - Following re-initiation of study drug, at next visit (scheduled or unscheduled occurring after completion of the up-titration), perform ECG measurements pre-dose.

Appendix 3 Guidance for initiating or dose increasing QT-prolonging drugs with known risk of Torsades de Pointes (cont'd)

b) for a need to start treatment or to increase the dose of a QT prolonging drug with known risk of Torsades de Pointes during the study, during any maintenance dosing of 5, 10 or 20 mg ponesimod.

- At visit (scheduled or unscheduled) prior to initiation or dose increase of QT prolonging drug with known risk of TsdP, perform ECGs measurements pre-dose.
    - If prior to initiation or dose increase of QT prolonging drug with known risk of TsdP, the QTcF interval is > 450 ms for males or > 470 ms for females, treatment with study drug must be interrupted.
- At next visit (scheduled or unscheduled occurring once the QT prolonging drug has reached the steady-state (approximately after 5 half-lives of the QT prolonging drug)) following initiation or dose increase of QT prolonging drug with known risk of TsdP, perform ECGs measurements pre-dose.

Appendix 4 Prohibited anti-arrhythmic or HR-lowering drugs

The following anti-arrhythmic and HR-lowering drugs (systemic administration) are prohibited during the study [see Section 5.3.5, *Forbidden concomitant therapies*]:

- Adenosine
- Acetobulol
- Ajmaline
- Amiodarone
- Aprinidine
- Atenolol
- Azimilide
- Bepridil
- Betaxolol
- Bisiprolol
- Bretylium
- Bunaftine
- Carvidiol
- Cibenzoline
- Disopyramide
- Dofetilide
- Dronedarone
- Encainide
- Esmolol
- Flecainide
- Ibutilide
- Ivabradine
- Lidocaine
- Lorajmine
- Lorcainide
- Metoprolol
- Mexiletine
- Morcizine
- Nadolol
- Phenytoin
- Pilocarpine
- Prajmaline
- Procainamide
- Propafenone
- Propranolol
- Quinidine
- Sotalol
- Sparteine
- Tedisamil
- Timolol
- Tocainide
- Vernakalant

If, in the judgment of the investigator, it is in the best interests of the subject to receive any of the drugs listed above, study drug must be premature discontinued. This list is not exhaustive, other anti-arrhythmic or HR-lowering drugs are also prohibited. In case of doubt, please discuss with sponsor the use of any potential anti-arrhythmic or HR-lowering drug.

Appendix 5 Adverse events of special interest

AEs of special interest include the anticipated risks of treatment with ponesimod or the known class effects and will address the following safety areas:

- Effect on HR and rhythm related AEs (including adverse events related to hypotension)
- Cardiovascular related AEs
- Hypertension related AEs
- Stroke related AEs
- Seizure related AEs
- Hepatobiliary disorders / liver enzyme abnormality related AEs
- Pulmonary related AEs
- Macular edema related AEs
- Infection related AEs
- Herpetic infections related AEs
- Skin malignancy related AEs
- Non-skin malignancy related AEs

A list of AEs of special interest (MedDRA preferred terms) will be defined in the SAP.

Appendix 6 Abnormalities for ECG, blood pressure and laboratory variables

ECG and blood pressure abnormalities

Notable abnormalities for ECG and blood pressure that are related to the potential effects of ponesimod will address the following variables:

- Morphological ECG findings (defined as any abnormal finding not present prior to start of treatment).
- HR outliers (bpm), based on ECG
- PR interval (ms)
- QT/QTc interval (ms), based on Bazett's or Fridericia's formula)
- Blood pressure (mmHg)

The definition of the abnormal values to be reported will be described in the SAP.

Laboratory abnormalities

Table 9 describes currently implemented thresholds for definition of project specific marked laboratory abnormalities and alerts for the different parameters analyzed in the ponesimod studies. These definitions are generally based on guidance from *OTH-00005 - Definition of Marked Abnormalities in laboratory data.*

For parameters for which no definition of marked abnormalities was defined in [OTH-000005_v07_14 Oct 2014], threshold values have been defined according to the CTCAE v4.03 grading (generally: flagged "HH" or "LL" for ≥ grade 2 and "HHH" or "LLL" for grade 3 or 4) when available [CTCAE 2010]. Marked abnormalities resulting in a GVHD trial-specific alert are also identified in Table 9.

Given the pharmacodynamic effects of ponesimod, specific definitions are given for lymphocytes and White Blood Cell count (WBC). Finally, clinical rationale (likelihood of risk or consequences) or consistency with fingolimod [Fingolimod], a compound in the same class of S1P receptor modulators was used for other parameters when appropriate.

These project-specific definitions may be subject to change, and may be complemented by definitions provided by the central laboratory. In case of discrepancy between project-specific and central laboratory definitions, the definitions in Table 9 should be followed unless clearly justified.

Appendix 6 Abnormalities for ECG, blood pressure and laboratory variables (cont'd)

Table 9 Definition of notable laboratory abnormalities for ponesimod

Parameter	LL	LLL	HH	HHH
Hemoglobin (g/L)	< 100	< 80	Increase in > 20 g/L above ULN or above baseline (if baseline is above ULN)	Increase in > 40 g/L above ULN or above baseline (if baseline is above ULN)
MCH (pg/Cell)	ND*	ND	ND	ND
MCV (fL)	ND	ND	ND	ND
Hematocrit (L/L)	< 0.28 (female) < 0.32 (male)	< 0.20	> 0.55 (female) > 0.60 (male)	> 0.65
Platelet count (10^9 /L)	< 75	< 50	> 600	> 999
WBC count (10^9 /L)	ND	< 1.9	> 20.0	> 100.0
Lymphocyte (10^9 /L)	ND	< 0.1 **< 0.2 TRIAL ALERT****	> 4.0	≥ 8.0
Neutrophils (10^9 /L)	< 1.5	< 1.0 **< 0.5 TRIAL ALERT**	ND	ND
Eosinophils (10^9 /L)	ND	ND	> 5.0	ND
Monocytes (10^9 /L)	ND	ND	ND	ND
Basophils (10^9 /L)	ND	ND	ND	ND
Polymorphonuclear leucocyte/Band cells (%)	ND	ND	> 90%	> 95%
AST (U/L)	ND	ND	≥ 3 × ULN **≥ 3 × ULN TRIAL ALERT**	≥ 5 × ULN **≥ 5 × ULN TRIAL ALERT**

Parameter	LL	LLL	HH	HHH
ALT (U/L)	ND	ND	≥ 3 × ULN **≥ 3 × ULN TRIAL ALERT**	≥ 5 × ULN **≥ 5 × ULN TRIAL ALERT**
Total bilirubin (umol/L)	ND	ND	**> 1.5 × ULN TRIAL ALERT** ≥ 2 × ULN	**≥ 2 × ULN combined with ALT or AST ≥ 3 × ULN: TRIAL ALERT** **> 3 × ULN TRIAL ALERT** ≥ 5 × ULN
Alkaline Phosphatase (U/L)	ND	ND	> 2.5 × ULN	> 5 × ULN
INR	ND	ND	≥ 1.5 × ULN OR ≥ 1.5 × baseline if on anticoagulation	≥ 2.5 × ULN ≥ 2.5 × baseline if on anticoagulation **≥ 1.5 × ULN combine with ALT or AST ≥ 3 × ULN: TRIAL ALERT**
Lactate dehydrogenase	ND	ND	ND	ND
Creatinine (umol/L)	ND	ND	> 1.5 × ULN or > 1.5 × baseline	> 3 ULN or > 3 × baseline
Creatinine clearance (mL/min/1.73 m^2)	ND	ND	ND	ND
Urea (mmol/L)	ND	ND	> 2.5 ULN	> 5 ULN
Albumin (g/L)	< 30	< 20	ND	ND
Protein total (g/L)	ND	ND	ND	ND
C-reactive protein (mg/L)	ND	ND	ND	ND
Glucose (mmol/L)	< 3.0	< 2.2	> 8.9	> 13.9
Potassium (mmol/L)	< 3.2	< 3.0	> 5.5	> 6.0

Parameter	LL	LLL	HH	HHH
Sodium (mmol/L)	ND	< 130	> 150	> 155
Calcium (mmol/L)	< 2.0	< 1.75	> 2.9	> 3.1
Chloride (mmol/L)	ND	ND	ND	ND
Triglyceride (mmol/L)	ND	ND	> 3.42	> 11.4
Cholesterol (mmol/L)	ND	ND	> 7.75	> 12.92

*ND = Not defined; may be complemented by definitions provided by the central laboratory
**ALERT = GVHD trial-specific alert that triggers specific actions in this protocol, including: retest, treatment interruption, and/or premature discontinuation.

Appendix 7 Chronic GVHD Activity Assessment forms

All forms in Appendix 7 are NIH Consensus Development Criteria [Lee 2015].

AC-058C202 SITE NO:_____ SUBJECT NO: _____ VISIT #:_____ DATE: _____

CHRONIC GVHD ACTIVITY ASSESSMENT – CLINICIAN (FORM A)

Health Care Provider Global Ratings: 0=none 1= mild 2=moderate 3=severe	Where would you rate the severity of this patient's chronic GvHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible: 0 1 2 3 4 5 6 7 8 9 10 cGvHD symptoms not at all severe — Most severe cGvHD symptoms possible	Compared to last visit would you say that this patient's cGvHD is +3= Very much better +2= Moderately better +1= A little better 0= About the same -1=A little worse -2=Moderately worse -3=Very much worse

Mouth	Erythema	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
	Lichenoid	None	0	Lichen-like changes (<25%)	1	Lichen-like changes (25-50%)	2	Lichen-like changes (>50%)	3
	Ulcers	None	0			Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
								Total score for all mucosal changes	

☐ Abnormality(ies) present but explained entirely by non-GVHD documented cause (specify):_____

Gastrointestinal-Esophageal
- Dysphagia OR Odynophagia

0= no esophageal symptoms
1=Occasional dysphagia or odynophagia with solid food or pills during the past week
2=Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week
3=Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

Gastrointestinal-Upper GI
- Early satiety OR
- Anorexia OR
- Nausea & Vomiting

0= no symptoms
1=mild, occasional symptoms, with little reduction in oral intake during the past week
2=moderate, intermittent symptoms, with some reduction in oral intake during the past week
3=more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

Gastrointestinal-Lower GI
- Diarrhea

0= no loose or liquid stools during the past week
1= occasional loose or liquid stools, on some days during the past week
*2=intermittent loose or liquid stools throughout the day, on almost every day of the past week, **without requiring** intervention to prevent or correct volume depletion*
*3=voluminous diarrhea on almost every day of the past week, **requiring** intervention to prevent or correct volume depletion*

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

Lungs (Liters and % predicted) • Bronchiolitis Obliterans	FEV1	FVC	Single Breath DLCO (adjusted for hemoglobin)	TLC	RV
				Not applicable	

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

Liver Values	Total serum bilirubin mg/dL	ULN mg/dL	ALT U/L	ULN U/L	Alkaline Phosphatase U/L	ULN U/L
	Values from	**Central Lab**	**Values from**	**Central Lab**	**Values from**	**Central Lab**

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

Baseline Values	Total Distance Walked and time, 2 or 6 Mins: ☐ 2 min ☐ 6 min	Karnofsky score	Platelet Count K/uL	Total WBC K/uL	Eosinophils %
				Values from Central Lab	

Investigator's signature_____

Appendix 7 Chronic GVHD activity assessment forms (cont'd)

AC-058C202 SITE NO:_____ SUBJECT NO: _____ VISIT #:_____ DATE: _____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN (FORM A)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash / erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
☐ **Abnormality present but explained entirely by non-GVHD documented cause (specify):**_____				
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis _____ How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible: 0 1 2 3 4 5 6 7 8 9 10 Symptoms not at all severe — Most severe symptoms possible				
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	☐ Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	☐ Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ **Abnormality present but explained entirely by non-GVHD documented cause (specify):**_____				
EYES	☐ No symptoms symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ **Abnormality present but explained entirely by non-GVHD documented cause (specify):**_____				
LUNGS	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
☐ **Abnormality present but explained entirely by non-GVHD documented cause (specify):**_____				

Investigator's signature_____

Appendix 7 Chronic GVHD activity assessment forms (cont'd)

AC-058C202 SITE NO:_____ SUBJECT NO: _____ VISIT #:_____ DATE: _____

CHRONIC GVHD ACTIVITY ASSESSMENT – CLINICIAN (FORM A)

P-ROM

Shoulder

□ Not Done

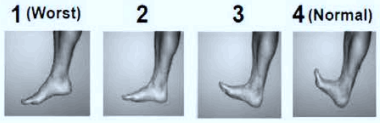
Elbow

□ Not Done

Wrist/finger

□ Not Done

Ankle



□ Not Done

□ **Abnormality present but explained entirely by non-GVHD documented cause (specify):**

_____

Investigator's signature_____

Appendix 7 Chronic GVHD activity assessment forms (cont'd)

AC-058C202 SITE NO:_____ SUBJECT NO: _____ VISIT #:_____ DATE: _____

CHRONIC GVHD ACTIVITY ASSESSMENT – PATIENT SELF REPORT – FORM B

Symptoms Please rate how severe the following symptoms have been in the last seven days. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.	Not Present										As Bad As You Can Imagine
Please check (√)	**0**	1	2	3	4	5	6	7	8	9	10
Your **skin itching** at its WORST?											
Your **skin and/or joint tightening** at their WORST?											
Your **mouth sensitivity** at its WORST?											
Your **genital discomfort** at its WORST? (Women – vagina, vulva, or labia) (Men – penis)											

	What is your main complaint with regard to your eyes?	
	Please rate how severe this symptom is, from **0 (not at all severe) to 10 (most severe):**	0 1 2 3 4 5 6 7 8 9 10

Patient Global Ratings:

1. Overall, do you think that your chronic graft versus host disease is mild, moderate or severe? _____
   1 = mild
   2 = moderate
   3 = severe

2. Please circle the number indicating how severe your chronic graft versus host disease symptoms are, where 0 is cGvHD symptoms that are not at all severe and 10 is the most severe chronic GvHD symptoms possible.

   0 1 2 3 4 5 6 7 8 9 10

   cGvHD symptoms not at all severe — Most severe cGvHD symptoms possible

3. Compared to a month ago, overall would you say that your cGvHD symptoms are: _____
   +3 = Very much better
   +2 = Moderately better
   +1 = A little better
   0 = About the same
   -1 = A little worse
   -2 = Moderately worse
   -3 = Very much worse

Appendix 8 Lee Symptom Scale

AC-058C202 SITE NO:_____ SUBJECT NO: _____ VISIT #:_____ DATE: _____

LEE SYMPTOM SCALE

Please let us know whether you have been bothered by any of the following problems in the past month.

SKIN	Not at all	Slightly	Moderately	Quite a bit	Extremely
a. Abnormal skin color	0	1	2	3	4
b. Rashes	0	1	2	3	4
c. Thickened skin	0	1	2	3	4
d. Sores on skin	0	1	2	3	4
e. Itchy skin	0	1	2	3	4
EYES AND MOUTH	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
f. Dry eyes	0	1	2	3	4
g. Need to use eye drops frequently	0	1	2	3	4
h. Difficulty seeing clearly	0	1	2	3	4
i. Need to avoid certain foods due to mouth pain	0	1	2	3	4
j. Ulcers in mouth	0	1	2	3	4
k. Receiving nutrition from an intravenous line or feeding tube	0	1	2	3	4
BREATHING	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
l. Frequent cough	0	1	2	3	4
m. Colored sputum	0	1	2	3	4
n. Shortness of breath with exercise	0	1	2	3	4
o. Shortness of breath at rest	0	1	2	3	4
p. Need to use oxygen	0	1	2	3	4
EATING AND DIGESTION	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
q. Difficulty swallowing solid foods	0	1	2	3	4
r. Difficulty swallowing liquids	0	1	2	3	4
s. Vomiting	0	1	2	3	4
t. Weight loss	0	1	2	3	4
MUSCLES AND JOINTS	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
u. Joint and muscle aches	0	1	2	3	4
v. Limited joint movement	0	1	2	3	4
w. Muscle cramps	0	1	2	3	4
x. Weak muscles	0	1	2	3	4
ENERGY	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
y. Loss of energy	0	1	2	3	4
z. Need to sleep more/take naps	0	1	2	3	4
aa. Fevers	0	1	2	3	4
MENTAL AND EMOTIONAL	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
bb. Depression	0	1	2	3	4
cc. Anxiety	0	1	2	3	4
dd. Difficulty sleeping	0	1	2	3	4

Appendix 9 Rule of 9s