PROTOCOL 0761-010

Open-Label, Multi-Center, Randomized Study of Anti-CCR4 Monoclonal Antibody KW-0761 (mogamulizumab) Versus Vorinostat in Subjects with Previously Treated Cutaneous T-Cell Lymphoma

REVISED TO INCORPORATE AMENDMENT 10

Protocol Number:	0761-010
Replaces Amendment 9:	20 Apr 2018
Amendment 10:	31 May 2018
Phase:	3
IND Number:	101,843
EudraCT Number:	2012-004766-17
Sponsor:	Kyowa Kirin Pharmaceutical Development, Inc. 212 Carnegie Center, Suite 400 Princeton, NJ 08540 +1 609 919-1100
Study Monitors:	[redacted]
Medical Monitors:	[redacted]

Principal Investigator Signature Page

Protocol Title: Open-Label, Multi-Center, Randomized Study of Anti-CCR4 Monoclonal Antibody KW-0761 (mogamulizumab) Versus Vorinostat in Subjects with Previously Treated Cutaneous T-Cell Lymphoma

Protocol Number: 0761-010, Amendment 10

CONFIDENTIALITY STATEMENT

This protocol contains information that is proprietary to Kyowa Kirin Pharmaceutical Development, Inc. (KKD). This information is being provided to you for the purpose of conducting a clinical trial on behalf of KKD. You may disclose the contents of this protocol to the study personnel under your supervision and to your Institutional Review Board (IRB) or Ethics Committee (EC). As a Clinical Investigator participating in this study you agree to not disclose the contents of this protocol to any other parties (unless such disclosure is required by government regulations or laws) without the prior written permission of KKD.

Any supplemental information (e.g., protocol amendment, Investigator's Brochure) that may accompany this document is also proprietary to KKD and should be handled consistent with the terms stated above.

By my signature below, the Principal Investigator attests that they have read, understood, and agree to abide by all conditions, instructions, and restrictions contained in this protocol (including appendices). The Principal Investigator will not initiate this study without approval from the appropriate IRB or Ethics Committee and understands that any changes in the protocol must be approved in writing by the Sponsor and the IRB or Ethics Committee before they can be implemented, except where necessary to eliminate immediate hazards to the subject.

Principal Investigator:

_____ _____

Printed Name/Signature Date

_____

Institution

_____

Address

Protocol Signature Page

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Date

Summary of Changes in Amendment 10

A new section (Section 7.8) was added to the protocol to specify procedures to be followed for subjects who are ongoing in the study at the time of initial marketing authorization. These procedures should be implemented upon notification by the Sponsor.

1) For subjects who are continuing to receive KW-0761, the Sponsor will continue to supply study drug until KW-0761 becomes commercially available (reimbursable) in the country/region of the study site or until KW-0761 is not approved for marketing for the indication and regimen under study in the country/region of the study site.
2) For all ongoing subjects, i.e., subjects who are continuing to receive KW-0761 or who are in safety or survival follow-up at the time of initial marketing authorization, changes in study procedures and data collection are described.

References to Section 7.8 were added as relevant in other protocol sections.

Other minor updates were made for consistency.

The Sponsor does not consider that these changes impact the overall risk/benefit of this study.

Serious Adverse Event Contact Information

US, Europe, Australia	Japan
Drug Safety Surveillance Phone: +1-609-919-1100 Available 9:00 am-5:00 pm (Eastern time) 2:00 pm-10:00 pm (GMT) US SAE Fax: +1-800-209-2251 UK SAE Fax: +44 808 171 9999 e-mail address: saesource@kyowakirin.com Available 24 hours daily	**Drug Safety Surveillance** SAE Fax: +81-3-6683-7721
After hours Contacts:	
All US, EU, Australian Study Sites: Dmitri O. Grebennik, MD Medical Monitor-KKD Phone: +1-609-902-4703 dmitri.grebennik@kyowakirin.com	**Japanese Study Sites:** Yoshihiro Hara, MD, PhD CMIC Co., Ltd. Tel : +81-80-3341-3861 Fax : +81-3-6683-7721 yoshihiro-hara.kh@cmic.co.jp

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PROTOCOL SYNOPSIS

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Study Location:
United States, Europe, Japan, and Australia

Clinical Phase:
3

Study Period:
Planned enrollment period: 24 months
Planned study period: 36 months

Study Drug:
KW-0761

Comparator Drug:
Vorinostat (ZOLINZA®)

Population Size:
It is anticipated that approximately 317 subjects may be required to enroll in this study in order to achieve the necessary 255 progression-free survival (PFS) events for analysis.

Study Design:
This is an open-label, multi-center randomized, Phase 3 study with 1:1 randomization of study drug, KW-0761 versus the comparator, vorinostat.

Study Population:
This study will enroll subjects with Stage IB, II-A, II-B, III and IV mycosis fungoides (MF) or Sézary syndrome (SS) who have failed at least one prior course of systemic therapy.

Study Objectives:
Primary Objective

- To compare the progression free survival of KW-0761 versus vorinostat for subjects with relapsed or refractory Cutaneous T-Cell Lymphoma (CTCL).

Secondary Objectives

- To compare the overall response rate of KW-0761 versus vorinostat in subjects with relapsed or refractory CTCL;
- To evaluate and compare improvements in Quality of Life (QoL) measurements, Skindex-29, FACT-G, and EQ-5D-3L for subjects receiving KW-0761 versus vorinostat;

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- To evaluate and compare improvements in the Pruritus Evaluation (Likert scale & Itchy QoL) for subjects receiving KW-0761 versus vorinostat;
- To estimate the duration of response for both the KW-0761 and vorinostat arms for those subjects with relapsed or refractory CTCL responding to treatment;
- To determine if subjects who relapse on vorinostat can achieve response upon cross over to treatment with KW-0761;
- To further assess the safety of KW-0761;
- To describe the immunogenicity of KW-0761;

Exploratory Objectives

- To compare the overall survival of KW-0761 versus vorinostat for subjects with relapsed or refractory CTCL.
- To conduct exploratory evaluation of KW-0761 exposure-response relationships.

Inclusion Criteria:

1) Voluntarily signed and dated Institutional Review Board / Ethics Committee approved informed consent form in accordance with regulatory and institutional guidelines. Written informed consent must be obtained prior to performing any study-related procedure;

Age and Sex

2) Males and female subjects ≥ 18 years of age at the Pre-treatment Visit, i.e., at the time that written informed consent is obtained, except in Japan where subjects must be ≥ 20 years of age;

Target Population

3) Histologically confirmed diagnosis of MF or SS;
   a. For SS (defined as meeting T4 plus B2 criteria), where the biopsy of erythrodermic skin may only reveal suggestive but not diagnostic histopathologic features, the diagnosis may be based on either a node biopsy or fulfillment of B2 criteria including a clone in the blood that matches that of the skin.
4) Stage IB, II-A, II-B, III and IV;
5) Subjects who have failed at least one prior course of systemic therapy (e.g., interferon, denileukin diftitox, bexarotene, photopheresis, anti-neoplastic chemotherapy, etc.). Psoralen plus ultraviolet light therapy (PUVA) is not considered to be a systemic therapy;
6) Eastern Cooperative Oncology Group (ECOG) performance status score of ≤ 1;
7) The subject has resolution of all clinically significant toxic effects of prior cancer therapy to Grade ≤ 1 by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0

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(NCI-CTCAE, v.4.0) excluding the specifications required in 8, 9 and 10 below.

8) Adequate hematological function:
   a. absolute neutrophil count (ANC) ≥ 1,500 cells/μL (≥ 1,500/mm^3);
   b. platelets ≥ 100,000 cells/μL; (≥ 100,000/mm^3);
   c. in subjects with known bone marrow involvement, ANC must be ≥ 1,000 cells/μL (≥ 1,000/mm^3) and platelets ≥ 75,000 cells/μL. (≥ 75,000/mm^3).
9) Adequate hepatic function:
   a. bilirubin ≤ 1.5 times the specific institutional upper limit of normal (ULN), except for subjects with Gilbert's syndrome;
   b. aspartate transaminase (AST) and alanine transaminase (ALT) each ≤ 2.5 x ULN or ≤ 5.0 x ULN in the presence of known hepatic involvement by CTCL.
10) Adequate renal function:
   a. serum creatinine ≤ 1.5 x ULN;
   or
   b. calculated creatinine clearance > 50 mL/min using the Cockcroft-Gault formula.
11) Subjects previously treated with anti-CD4 antibody or alemtuzumab are eligible provided their CD4+ cell counts are ≥ 200/mm^3.
12) Subjects with MF and a known history of non-complicated staphylococcus infection/colonization are eligible provided they continue to receive stable doses of prophylactic antibiotics.
13) Women of childbearing potential (WOCBP) must have a negative pregnancy test within 7 days of receiving study medication.
14) WOCBP must agree to use effective contraception, defined as oral contraceptives, double barrier method (condom plus spermicide or diaphragm plus spermicide) or practice true abstinence from sexual intercourse (periodic abstinence, e.g., calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception) during the study and for 3 months after the last dose. WOCBP includes any female who has experienced menarche and who has not undergone successful surgical sterilization or is not postmenopausal (defined as amenorrhea ≥ 12 consecutive months without an alternative medical cause);
15) Male subjects and their female partners of child bearing potential must be willing to use an appropriate method of contraception defined as oral contraceptives, double barrier method (condom plus spermicide or diaphragm plus spermicide) or practice true abstinence from sexual intercourse (periodic abstinence, e.g., calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception) during the study and for 3 months after the last dose.

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NOTE: For subjects continuing to receive study treatment as of protocol Amendment 8, the period of contraceptive use should be extended to 6 months after the last dose of KW-0761.

Exclusion Criteria:

Medical History and Concurrent Diseases

1) Current evidence of large cell transformation (LCT). Subjects with clinical features suggestive of LCT must have a biopsy performed within 4 months prior to Cycle 1 Day 1 to rule out transformed disease. Subjects with a history of LCT but without current aggressive disease and no current evidence of LCT on pathology in skin or lymph nodes would be eligible;
2) Diagnosed with a malignancy in the past 2 years. However, subjects with non-melanoma skin cancers, melanoma in situ, localized cancer of the prostate with current prostate-specific antigen of < 0.1 ng/mL, treated thyroid cancer or cervical carcinoma in situ or ductal/lobular carcinoma in situ of the breast with in the past 2 years may enroll as long as there is no current evidence of disease.
3) Clinical evidence of central nervous system (CNS) metastasis.
4) Psychiatric illness, disability or social situation that would compromise the subject's safety or ability to provide consent, or limit compliance with study requirements.
5) Significant uncontrolled intercurrent illness including, but not limited to:
    a. uncontrolled infection requiring antibiotics;
    b. clinically significant cardiac disease (class III or IV of the New York Heart Association classification);
    c. unstable angina pectoris;
    d. angioplasty, stenting, or myocardial infarction within 6 months;
    e. uncontrolled hypertension (systolic blood pressure (BP) > 160 mm Hg or diastolic BP > 100 mm Hg, found on 2 consecutive measurements separated by a 1-week period) despite 2 anti-hypertensive medications;
    f. clinically significant cardiac arrhythmia; or
    g. uncontrolled diabetes.
6) Known or tests positive for human immunodeficiency virus, human T-cell leukemia virus, hepatitis B or hepatitis C disease.
7) Active herpes simplex or herpes zoster. Subjects on prophylaxis for herpes who started taking medication at least 30 days prior to the Pre-treatment Visit, and have no active signs of active infection, and whose last active infection was more than 6 months ago, may enter the study, and should continue to take the prescribed medication for the duration of the study.
8) Experienced allergic reactions to monoclonal antibodies or other therapeutic proteins.
9) Known active autoimmune disease will be excluded. (For example, Graves' disease; systemic lupus

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erythematosus; rheumatoid arthritis; Crohn's disease; psoriasis).

10) Is pregnant (confirmed by beta human chorionic gonadotrophin [β-HCG]) or lactating.

Prohibited Therapies and/or Medications

11) Prior treatment with KW-0761.
12) Prior treatment with vorinostat. Patients who were exposed to vorinostat for a short time, did not progress while on treatment, and did not have intolerable toxicity but were discontinued for another reason (e.g., comorbidity) may be permitted to enter the study after discussion with the Medical Monitor.
13) Have had any therapy directed against the subject's underlying cancer or any investigational medications within four weeks of randomization (skin directed treatments, including topicals and radiation within 2 weeks of randomization). However, subjects with rapidly progressive malignant disease may be enrolled prior to this period after discussion with the Medical Monitor.
14) Subjects on a stable dose of a low dose systemic corticosteroid (≤ 20 mg prednisone equivalent) for at least 4 weeks prior to the Pre-treatment Visit may continue use although the investigator should attempt to taper the use to the lowest dosage tolerable while on study. Initiation of treatment with systemic corticosteroids or increase in dose while on study is not permitted except to treat an infusion reaction (see Section 5.2.1.7). Subjects may receive intra-articular corticosteroid injections, intraocular corticosteroid drops, inhalation or nasal corticosteroids and replacement doses of systemic corticosteroids as needed.
15) Subjects on a stable dose of medium or low potency topical corticosteroids for at least 4 weeks prior to the Pre-treatment Visit may continue use at the same dose, although the investigator should attempt to taper the use to the lowest dosage tolerable while on study. Initiation of treatment with topical corticosteroids while on study is not permitted except to treat an acute rash.
16) History of allogeneic transplant.
17) Autologous hematopoietic stem cell transplant within 90 days of the Pre-treatment Visit.
18) Subjects on any immunomodulatory drug for concomitant or intercurrent conditions other than T-cell lymphoma or who have received any of these agents within 4 weeks of treatment, including but not limited to the following, will be excluded: low dose or oral methotrexate; azathioprine; intravenous (iv) immunoglobulin; low dose or oral cyclophosphamide; cyclosporine; mycophenolate; infliximab; etanercept; leflunomide; adalimumab; lenalidomide; abatacept; rituximab; anakinra; interferon-β; IL-2 and natalizumab.

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Methods:
Subjects will be randomized 1:1 to receive either KW-0761 or vorinostat. Treatment will be administered on an outpatient basis. The dose of KW-0761 will be 1.0 mg/kg. The dose of vorinostat will be the recommended dose of 400 mg (once daily with food).

Each treatment cycle is 28 days. Subjects will receive KW-0761 as an iv infusion over at least 1 hour on Days 1, 8, 15 and 22 of the first cycle and on Days 1 and 15 of subsequent cycles. Vorinostat will be administered orally daily beginning on Day 1.

Duration of Treatment
Subjects may remain in the treatment phase up until progressive disease (PD), drug intolerance, or unacceptable toxicity, or until any of the other criteria for study removal are met. If the subject experiences an overall CR, the subject may continue treatment for up to 12 months or until progression, whichever comes first.

Cross-over to Study Drug KW-0761
Subjects who have received at least 2 full treatment cycles and demonstrate progression of disease on treatment with vorinostat at the 8 week (Cycle 2, Day 26-28) assessment, or anytime thereafter, may cross over to treatment with KW-0761 after discussion with Medical Monitor or designee and receipt of approval for cross over from KKD. Investigators should strive to maintain subjects on treatment for at least the 8 week period, adjusting the dose of vorinostat as needed for toxicities in order to allow sufficient time to see effect. In cases where a subject's disease progresses rapidly (i.e., prior to 8 weeks), the Medical Monitor or designee should be contacted and may consider the possibility of early crossover, if appropriate for that subject. All subjects must undergo the full extent of disease evaluations (including computed tomography scanning) to document PD prior to crossover.

Study Procedures for Subjects Continuing Study Treatment at the Time of Primary Efficacy Analysis and for Ongoing Subjects at the Time of Initial Marketing Authorization
For subjects who are continuing to receive study treatment at the time of the primary efficacy analysis, procedures and assessments are described in Section 7.7. Procedures to be followed for subjects who are ongoing in the study (i.e., subjects who are continuing to receive KW-0761 or who are in safety or survival follow-up) at the time of initial marketing authorization are described in Section 7.8.

Replacement of Subjects
Subjects will not be replaced.

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Criteria for Evaluation:
Safety: The safety of KW-0761 and vorinostat will be determined by reported AEs, changes in physical examinations, vital sign measurements, ECGs and laboratory analyses. Safety evaluations will be performed throughout the study.
Efficacy: Efficacy evaluations will be based on response to treatment (partial response [PR] or better), time to PD, duration of overall response, and quality of life.

Statistical Analysis:
The following analysis sets will be used in the study:

- Intent-to-Treat (ITT) Set: Includes all subjects randomized to a therapy and assigned a study number.
- Safety Analysis Set: Includes all subjects who received at least one dose of the assigned study agent (even a partial dose).
- Efficacy Evaluable Set: Includes all subjects who receive the first cycle of treatment and who have baseline and the Day 26-28 on-study assessment for response.
- Pharmacokinetic (PK) Analysis Set: All subjects who provide at least one post-dose KW-0761 concentration measurement will be included in the PK analysis dataset.

Evaluation of the data for this study will consist primarily of data listings and summary displays. Demographic and other baseline characteristic information will be summarized for the ITT Set. All summaries for the Safety Analysis Set will be prepared for each treatment arm. Adverse events will be tabulated by body system, severity, and relation to treatment. Similar presentations will be provided for serious adverse events, AEs leading to withdrawal from study, and AEs leading to death. The tabulation of laboratory parameters will indicate the normal range for each parameter. Each value will be classified as falling above, below, or within the normal range.

Subjects will be evaluated for response in each compartment. Progression-free-survival, overall response, duration of response, and QoL will be analyzed. For any time-to-event endpoints, the date of disease progression will be determined by both the on-site investigator's assessment and by independent review (IR). All efficacy analyses will be conducted on both the ITT and Efficacy Evaluable sets.

The primary comparison of PFS between both arms will be performed on the ITT set based upon the results of the on-site investigator's assessment using a stratified Log-rank test at the one-sided 2.5% significance level. Stratification is done by disease type, either SS or MF, and disease stage, either IB/II or III/ IV. A similar secondary analysis will be performed on the results based on the IR. An IR will review each subject to make a determination regarding progression and the date of progression in each compartment.

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Each analysis will also be conducted for the Efficacy Evaluable Set. PFS, which will be analyzed using Kaplan-Meier survival analysis methods, is defined as the time from the first day of randomization to a treatment arm until documented progression or death.

For PFS events, all deaths will be attributed to progression and, hence, the time to progression will equal the time to death and will be uncensored. Subjects who die without a reported prior progression will still be considered to have progressed on the day of their death. In the event that a randomized subject withdraws from the study for any reason before documented progression, the time from the day of randomization to the last tumor assessment (from any compartment) will be used as a censored time point. For all subjects randomized to a treatment arm but withdrawing prior to first tumor assessment for any reason other than disease progression, the PFS time will be censored at last documented visit.

ORR will be calculated as the proportion of subjects who are responders (complete response, and PR) and the 95% exact confidence interval for response will be calculated.

Since the primary endpoint is PFS, the reference median PFS for vorinostat is assumed to be 169 days. The median PFS for KW-0761 therapy is targeted for 254 days, a 50% improvement over this reference median. The ITT set is used for this primary analysis. The same analysis conducted using the Efficacy Evaluable set is considered secondary.

Under these assumptions, for the ITT population, a total of 255 PFS events will give 90% power. In the event that the study is stopped prior to 255 PFS events are observed, the primary test will be performed at less than 90% power under the current assumptions.

A total sample size of 288 may be necessary for 255 PFS events to occur within the projected 36 months of the trial. A 10% inflation factor is applied to this total (about 29 subjects) to take into account those subjects that may be lost to follow-up prior to documented progression, for a total of 317 enrolled subjects to observe 255 PFS events. If the 255 PFS events are not observed within 36 months from the start of enrollment the study will be stopped at approximately 24 months after the last randomized subject's first dose.

Table 1 Study Procedures: First Treatment Cycle

Procedures	Pre-treatment Visit	First Treatment Cycle				
		D 1	D 8	D 15	D 22	D 26-28[a]
Visit Window	Up to Day -30		±2 days	±2 days	±2 days	+ 2 days
Informed consent	X					
Review of subject eligibility	X					
Medical history	X					
Physical examination[b]	X	X		X		X
ECOG performance status (PS)	X	X		X		X
Vital signs, Weight	X	X[c]	X[c]	X[c]	X[c]	X
ECG	X					
Pregnancy test (within 7 days)	X					
Urinalysis	X					X
Hematology profile	X	X[d]	X[d]	X[d]	X[d]	X
Chemistry profile	X	X[d]	X[d]	X[d]	X[d]	X
Coagulation profile	X	X[d]				
Thyroid function tests (Free T4, TSH)	X					X
Hepatitis B & C, HIV, HTLV-1	X					
Flow Cytometric Analysis	X					X
Blood sample for determination of natural ligands	X					X
Serum sample for KW-0761 concentration assessment[e]		X	X	X	X	X
Saliva sample for genetic analysis		X[f]				
KW-0761 Administration[g]		X	X[h]	X[h]	X[h]	
Vorinostat Administration		X[i]				
Adverse event assessment[j]	X	X	X	X	X	X
Concomitant medication assessment[k]	X	X	X	X	X	X
CT (diagnostic quality)	X					X
Bone marrow aspiration & biopsy[l]	X					X
Skin biopsy for assessment of disease	X[m]					X[n]
Skin biopsy or archival tissue for CCR4 expression[o]	X					
Skin photographs		X				X
Modified Severity Weighted Assessment Tool (mSWAT)		X				X
Pruritus Evaluation (Likert Scale & Itchy QoL)		X				X
Skindex-29 , FACT-G & EQ-5D-3L		X				X
Immunogenicity[p]		X				X
Disease Progression[q]	←					→
Survival status[r]	←					→

Footnotes to Table 1

a: If progression is noted at Day 26-28, visit should take place before initiation of new therapy. In cases where the definition of PD or relapse is met but the clinical impression is questionable, subjects may remain on study until the next evaluation (4 weeks later if questionable finding in skin or blood; 8 weeks later in first year and 16 weeks later after Year 1 if questionable finding in lymph nodes or viscera, with at least stable disease in other compartments) to avoid a subject being removed prematurely from the study. For subjects receiving a subsequent treatment course, procedures performed at this time can also be used to satisfy the Day 1 requirements for the subsequent course, provided they are performed within ± 2 days of next KW-0761 administration. For subjects who will not receive subsequent treatment, this visit will be considered the final treatment visit and subjects should undergo testing/procedures specified for End-of-treatment visit (See Table 3).

b: Complete physical examination including height at Pre-treatment Visit; brief physical examination of pertinent systems at other times. Responses to questions for surveillance of autoimmune type symptoms (See Appendix 4) should be documented at time of physical exam.

c: For subjects receiving KW-0761, vital signs will be checked and recorded prior to the start of each infusion, at the end of each infusion and 1 hour after the completion of the infusion. For subjects taking vorinostat, vital signs can be taken irrespective of dosing. Weight will be checked with vitals.

d: Blood can be drawn 1 day prior to visit, if needed, to ensure results are available. In subjects receiving KW-0761, results must be reviewed prior to infusion. The platelet count must be $\geq 100{,}000 / mm^3$ and the ANC must be $\geq 1{,}500/mm^3$ before a subject can receive study drug.

e: Serum samples will be collected for subjects treated with KW-0761 pre-dose on days indicated (sample collection will still be needed even if dosing is not performed at a visit), as applicable. On Day 1, an additional sample should be obtained from the arm contralateral to that of study drug administration at the end of infusion (10-15 minutes after completion of the infusion) as well. At selected sites, 4 additional samples will be drawn between 6 and 8 hours, and at 24, 48, and 72 - 96 hours after the first infusion on Day 1.

f: Samples to be obtained for subjects assigned to KW-0761 as first assigned therapy only.

g: KW-0761 is to be administered over at least one hour.

h: If the study visit does not occur within ± 2 days of the scheduled visits, KW-0761 should not be administered at the visit and the next dose should be administered at the next timepoint.

i: Vorinostat is administered orally daily beginning on Day 1 with food.

j: If a subject who is receiving KW-0761 develops a skin rash, notify KKD and refer to Section 5.2.1.8 to treat and document the rash.

k: Medication taken within 30 days prior to the first dose of study drug, and at any time after the start of treatment until 30 days after the final study drug administration will be recorded.

l: To be performed in subjects with cytopenia or other clinical suspicions of bone marrow involvement, at the discretion of the investigator.

m: Subjects with clinical features suggestive of LCT must have a biopsy performed within 4 months prior to Cycle 1/Day 1 to rule out transformed disease.

n: Biopsy at the end of the cycle is optional and can be performed at the discretion of the investigator. Analysis of the biopsy will be done by a pathologist at the study site.

o: To be performed for CCR4 expression as determined by IHC. IHC analysis will be performed by central laboratory designated by the Sponsor. The paraffin block or a fresh sample, if the study site is unable to process the tissue on the day obtained, may be submitted. Submission of unstained slides, while not recommended due to stability concerns with the sample, will be accepted. In the event, it is not possible to obtain a skin biopsy, use of an archived sample (taken within 6 months prior to treatment) may be allowed with prior authorization from the Sponsor. For subjects receiving vorinostat who cross over to treatment with KW-0761, investigators are strongly encouraged to perform another biopsy for determination of CCR4 expression prior to treatment with KW-0761.

p: KW-0761 subjects only for determination of anti-KW-0761 antibodies.

q: Subjects who terminate for reasons other than disease progression or their referring physicians will be contacted every 3 months (± 14 days) until documented disease progression or death or initiation of alternative therapy.

r: All subjects or their referring physician will be contacted every 3 months (± 14 days) to ascertain survival status following discontinuation of treatment.

Table 2 Study Procedures: Subsequent Cycles in Year 1

Procedures	Subsequent Cycles 2 through 13[a]			
	D 1	**D 15**	**D 26-28 (Cycles 2, 4, 6, 8, 10, 12)[b]**	**D 26-28 (Cycles 3, 5, 7, 9, 11, 13)[b]**
Visit Window		± 2 days	+ 2 days	+ 2 days
Physical examination[c]	X	X	X	X
ECOG PS	X	X	X	X
Vital signs, Weight	X[d]	X[d]	X	X
ECG				
Urinalysis	X			
Hematology profile	X[e]	X[e]	X	X
Chemistry profile	X[e]	X[e]	X	X
Coagulation profile	X[e]			
Thyroid function tests (Free T4, TSH)				X
Flow Cytometric Analysis[f]			X	X
Blood sample for determination of natural ligands				X
Serum sample for KW-0761 concentration assessment	X[g]	X[g]		
KW-0761 Administration	X[h]	X[h]		
Vorinostat Administration	X[i]			
Adverse event assessment[j]	X	X	X	X
Concomitant medication assessment[k]	X	X	X	X
CT (diagnostic quality)[f]				X
Bone marrow aspiration & biopsy[l]				X
Skin biopsy				X[m]
Skin photographs[f]			X	X
Modified Severity Weighted Assessment Tool (mSWAT)[f]			X	X
Pruritus Evaluation (Likert scale & Itchy QoL)			X	X
Skindex-29, FACT-G & EQ-5D-3L				X
Immunogenicity[n]				X
Disease Progression[o]	←	—	—	→
Survival Status[p]	←	—	—	→

a: Subject may remain in treatment phase up until progressive disease, drug intolerance, or unacceptable toxicity, or until any of the other criteria for removal (See Section 5.5) are met. At each cycle, the Investigator must minimally have reviewed the mSWAT to determine if progression of skin disease has occurred prior to subsequent dosing (see Section 5.2.1.4). For subjects who are continuing to receive study treatment at the time of the primary efficacy analysis, procedures and assessments are described in Section 7.7. Procedures to be followed for subjects who are ongoing in the study at the time of initial marketing authorization are described in Section 7.8.

Footnotes to Table 2 (continued).

b: For subjects receiving a subsequent treatment course, procedures performed at this time can also be used to satisfy the Day 1 requirements for the subsequent course, provided they are performed within ± 2 days of next KW-0761 administration. For subjects who will not receive subsequent treatment, this visit will be considered the final treatment visit and subjects should undergo testing/procedures specified for End-of-treatment visit (See Table 3). If progression is noted at Day 26-28, visit should take place before initiation of new therapy. In cases where the definition of PD or relapse is met but the clinical impression is questionable, subjects may remain on study until the next evaluation (4 weeks later if questionable finding in skin or blood; 8 weeks later in first year and 16 weeks later after Year 1 if questionable finding in lymph nodes or viscera, with at least stable disease in other compartments) to avoid a subject being removed prematurely from the study.

c: Brief physical examination of pertinent systems to be performed during subsequent treatment cycles. Complete physical exam to be performed at End of Treatment visit. Responses to questions for surveillance of autoimmune type symptoms (See Appendix 4) should be documented at time of physical exam.

d: For subjects receiving KW-0761, vital signs will be checked and recorded prior to the start of each infusion, at the end of each infusion and 1 hour after the completion of the infusion. For subjects taking vorinostat, vital signs can be taken irrespective of dosing. Weight will be checked with vitals.

e: Blood can be drawn 1 day prior to visit, if needed, to ensure results are available. In subjects receiving KW-0761, results must be reviewed prior to infusion. The platelet count must be ≥ 100,000 / mm^3 and the ANC must be ≥ 1,500/mm^3 before a subject can receive study drug.

f: If clinical progression is noted at any time prior to the scheduled assessments for efficacy, CT, mSWAT, skin photographs and flow cytometry assessments should be done at that time to fully document disease progression, i.e., Global Composite Response Score. CT must be performed even if previously negative at baseline.

g: Serum samples for PK assessment should be collected for subjects treated with KW-0761 prior to infusion of KW-0761 in Cycles 2 and 3 (sample collection will still be needed even if dosing is not performed at a visit).

h: KW-0761 is to be administered over at least one hour.

i: Vorinostat is administered orally daily beginning on Day 1 with food.

j: If a subject who is receiving KW-0761 develops a skin rash, notify KKD and refer to Section 5.2.1.8 to treat and document the rash.

k: Medication taken at any time after the start of treatment until 30 days after the final study drug administration will be recorded.

l: To be performed in subjects with cytopenia or other clinical suspicions of bone marrow involvement, at the discretion of the investigator. If a bone marrow biopsy was performed at baseline and determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR where blood assessment now meets criteria for B0, a repeat bone marrow biopsy must show no residual disease or the response should be considered a PR only (See Table 7.2.2-1).

m: Biopsies at the end of the cycle and to confirm a CR (See Table 7.2.1-3) are optional and can be performed at the discretion of the investigator. Analysis of these biopsies will be done by a pathologist at the study site.

n: KW-0761 subjects only for determination of anti-KW-0761 antibodies and concentration of KW-0761.

o: Subjects who terminate for reasons other than disease progression or their referring physicians will be contacted every 3 months (± 14 days) until documented disease progression or death or initiation of alternative therapy.

p: All subjects or their referring physician will be contacted every 3 months (± 14 days) to ascertain survival status following discontinuation of treatment.

Table 3 Study Procedures: Subsequent Cycles in Year 2 and Beyond[a]

Procedures	D 1	D 15	D 26-28 (Cycles 14, 16, 18, 20, etc)[b]	D 26-28 (Cycles 15, 17, 19, 21, etc)[b]	D 26-28 Q 16 wks (Cycles 17, 21, etc)	End-of-treatment visit	Follow-up[c]
Visit Window		± 2 days	+ 2 days	+ 2 days	+ 5 days	Within 30 days of last dose	
Physical examination[d]	X	X	X	X		X	
ECOG PS	X	X	X	X		X	
Vital signs, Weight	X[e]	X[e]	X	X		X	
ECG						X	
Urinalysis	X					X	
Hematology profile	X[f]	X[f]	X	X		X	
Chemistry profile	X[f]	X[f]	X	X		X	
Coagulation profile	X[f]						
Thyroid function tests (Free T4, TSH)				X		X	
Flow Cytometric Analysis[g]			X	X			
Blood sample for determination of natural ligands				X			
Serum sample for KW-0761 concentration assessment						X	
KW-0761 Administration	X[h]	X[h]					
Vorinostat Administration	X[i]						
Adverse event assessment[j]	X	X	X	X		X	X[k]
Concomitant medication assessment[l]	X	X	X	X		X	X
CT (diagnostic quality)[g]					X		
Bone marrow aspiration & biopsy[m]				X			
Skin biopsy				X[n]			
Skin photographs[g]			X	X			
Modified Severity Weighted Assessment Tool (mSWAT)[g]			X	X			
Pruritus Evaluation (Likert scale & Itchy QoL)			X	X			

Table 3 Study Procedures: Subsequent Cycles in Year 2 and Beyond[a]

Procedures	D 1	D 15	D 26-28 (Cycles 14, 16, 18, 20, etc)[b]	D 26-28 (Cycles 15, 17, 19, 21, etc)[b]	D 26-28 Q 16 wks (Cycles 17, 21, etc)	End-of-treatment visit	Follow-up[c]
Visit Window		± 2 days	+ 2 days	+ 2 days	+ 5 days	Within 30 days of last dose	
Skindex-29, FACT-G & EQ-5D-3L				X		X	
Immunogenicity[o]						X	
CD4, CD8 (for KW-0761 subjects)						X[p]	X[p]
Disease Progression[q]	◄						►
Survival Status[r]	◄						►

a: Subject may remain in treatment phase up until progressive disease, drug intolerance or unacceptable toxicity, or until any of the other criteria for removal (See Section 5.5) are met. At each cycle, the investigator must minimally have reviewed the mSWAT to determine if progression of skin disease has occurred prior to subsequent dosing (see Section 5.2.1.4). For subjects who are continuing to receive study treatment at the time of the primary efficacy analysis, pending notification by the Sponsor, subjects may be followed according to institutional standard of care for subsequent assessments of treatment efficacy as described in Section 7.7. Procedures to be followed for subjects who are ongoing in the study at the time of initial marketing authorization are described in Section 7.8.

b: For subjects receiving a subsequent treatment course, procedures performed at this time can also be used to satisfy the Day 1 requirements for the subsequent course, provided they are performed within ± 2 days of next KW-0761 administration. For subjects who will not receive subsequent treatment, this visit will be considered the final treatment visit and subjects should undergo testing/procedures specified for End-of-treatment visit. If progression is noted at Day 26-28, visit should take place before initiation of new therapy. In cases where the definition of PD or relapse is met but the clinical impression is questionable, subjects may remain on study until the next evaluation (4 weeks later if questionable finding in skin or blood; 8 weeks later in first year and 16 weeks later after Year 1 if questionable finding in lymph nodes or viscera, with at least stable disease in other compartments) to avoid a subject being removed prematurely from the study.

c: For subjects going off treatment after achieving a CR, refer to Section 7.6 for study procedures and timing.

d: Brief physical examination of pertinent systems to be performed during subsequent treatment cycles. Complete physical exam to be performed at End of Treatment visit. Responses to questions for surveillance of autoimmune type symptoms (See Appendix 4) should be documented at time of physical exam.

e: For subjects receiving KW-0761, vital signs will be checked and recorded prior to the start of each infusion, at the end of each infusion and 1 hour after the completion of the infusion. For subjects taking vorinostat, vital signs can be taken irrespective of dosing. Weight will be checked with vitals.

f: Blood can be drawn 1 day prior to visit, if needed, to ensure results are available. In subjects receiving KW-0761, results must be reviewed prior to infusion. The platelet count must be ≥ 100,000 / mm^3 and the ANC must be ≥ 1,500/mm^3 before a subject can receive study drug.

Table 3 Study Procedures: Subsequent Cycles in Year 2 and Beyond[a]

Procedures	D 1	D 15	D 26-28 (Cycles 14, 16, 18, 20, etc)[b]	D 26-28 (Cycles 15, 17, 19, 21, etc)[b]	D 26-28 Q 16 wks (Cycles 17, 21, etc)	End-of-treatment visit	Follow-up[c]
Visit Window		± 2 days	+ 2 days	+ 2 days	+ 5 days	Within 30 days of last dose	

Footnotes to Table 3 continued.

g: If clinical progression is noted at any time prior to the scheduled assessments for efficacy, CT, mSWAT, skin photographs and flow cytometry assessments should be done at that time to fully document disease progression, i.e., Global Composite Response Score. CT must be performed even if previously negative at baseline.

h: KW-0761 is to be administered over at least one hour.

i: Vorinostat is administered orally daily beginning on Day 1 with food.

j: If a subject who is receiving KW-0761 develops a skin rash, notify KKD and refer to Section 5.2.1.8 to treat and document the rash.

k: Adverse events will be collected every 30 days (± 7 days) for up to 90 days after the last dose of study drug or initiation of alternative therapy. In all subjects who cross over from vorinostat to KW-0761, the causality should be assessed for both drugs for 30 days after vorinostat was stopped (or later if the event is considered to be related to vorinostat).

l: Medication taken at any time after the start of treatment until 30 days after the final study drug administration will be recorded. A medication taken during follow-up will also be recorded if it is used to treat an AE or is temporally associated with an AE and may have a causal relationship.

m: To be performed in subjects with cytopenia or other clinical suspicions of bone marrow involvement, at the discretion of the investigator. If a bone marrow biopsy was performed at baseline and determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR where blood assessment now meets criteria for B0, a repeat bone marrow biopsy must show no residual disease or the response should be considered a PR only (See Table 7.2.2-1)

n: Biopsies at the end of the cycle and to confirm a CR (See Table 7.2.1-3) are optional and can be performed at the discretion of the investigator. Analysis of these biopsies will be done by pathologist at the study site.

o: KW-0761 subjects only for determination of anti-KW-0761 antibodies.

p: If CD4 and CD8 counts are less than 200/mm^3 at the End-of-treatment visit, they will be followed every 3 months (±14 days) until they return to at least 200/mm^3, initiation of alternative therapy or 1 year, whichever comes first. Assessments will be performed at the study site.

q: Subjects who terminate for reasons other than disease progression or their referring physicians will be contacted every 3 months (± 14 days) until documented disease progression or death or initiation of alternative therapy.

r: All subjects or their referring physician will be contacted every 3 months (± 14 days) to ascertain survival status following discontinuation of treatment.

List of Abbreviations

Abbreviations

Ab	antibody
ADCC	antibody dependent cellular cytotoxicity
AE	adverse event
Ag	antigen
ALT	Alanine transaminase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	aspartate transaminase
ATL	adult T-cell leukemia-lymphoma
β-HCG	beta-human chorionic gonadotrophin
BUN	blood urea nitrogen
CBC	complete blood count
CCR4	CC chemokine receptor 4, chemokine (C-C motif) receptor 4
CNS	central nervous system
CR	complete response
CS	clinically significant
CT	computed tomography
CTA	Clinical Trial Authorization
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	cutaneous T-cell lymphoma
CTIVRS	ClinTrak Interactive Voice/Web Response System
DOR	duration of response
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HDAC	histone deacetylase
HEENT	head, eyes, ears, nose and throat
HIV	human immunodeficiency virus
HSCT	hematopoetic stem cell transplantation
HTLV-1	human T-cell lymphotropic virus type-1
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IHC	immunohistochemistry
IND	Investigational New Drug Application

Abbreviations

INR	International Normalized Ratio
IRB	Institutional Review Board
IR	Independent Review/Reviewer
ISCL	International Society of Cutaneous Lymphomas
ITT	Intent-to-Treat
iv	intravenous
KKD	Kyowa Kirin Pharmaceutical Development, Inc.
KW-0761	humanized monoclonal antibody against CCR4
LDH	lactate dehydrogenase
Mab	monoclonal antibody
MDC	macrophage derived chemokine
MedDRA	Medical Dictionary for Regulatory Activities
MF	mycosis fungoides
mSWAT	modified Severity Weighted Assessment Tool
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCS	not clinically significant
NHL	non-Hodgkin's Lymphoma
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	progressive disease
PDF	Portable Document Format
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PS	performance status
PT	prothrombin time
PTCL	peripheral T-cell lymphoma
PTT	partial thromboplastin time
QoL	Quality of Life
SAE	serious adverse event
SD	stable disease
SEER	Surveillance Epidemiology and End Results
SGOT	serum glutamic oxaloacetic-transaminase
SGPT	serum glutamic pyruvic-transaminase
SJS	Stevens-Johnson syndrome
SPD	sum of the product of the diameters
SS	Sézary Syndrome
TARC	thymus- and activation-regulated chemokine
TBSA	total body surface area
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
TTP	time to progression
ULN	upper limit of normal
US	United States

Abbreviations

USCLC	United States Cutaneous Lymphoma Consortium
WHO	World Health Organization
WOCBP	women of childbearing potential

Definition of Terms

pH	hydrogen ion concentration; negative logarithm of hydrogen ion activity
p.r.n.	as needed
QT interval	in electrocardiography, the time from the beginning of the QRS complex to the end of the T wave.
QTc interval	QT interval corrected for heart rate

1 BACKGROUND AND RATIONALE

1.1 Cutaneous T-Cell Lymphomas

[redacted]

1.2 Treatment of Cutaneous T-cell Lymphomas

[redacted]

1.3 Chemokine Receptor 4 and T-Cell Malignancies

[redacted]

[redacted]

[redacted]

1.4 KW-0761 (mogamulizumab)

[redacted]

1.5 Safety and Efficacy of KW-0761

[redacted]

[redacted]

1.6 Vorinostat (ZOLINZA®)

[redacted]

[redacted]

[redacted]

1.7 Rationale

[redacted]

[redacted]

2 OBJECTIVES

2.1 Primary Objectives

The primary objective of this study will be:

- To compare the progression free survival of KW-0761 versus vorinostat for subjects with relapsed or refractory CTCL.

2.2 Secondary Objectives

The secondary objectives will be:

- To compare the overall response rate of KW-0761 versus vorinostat in subjects with relapsed or refractory CTCL;
- To evaluate and compare improvements in QoL measurements, Skindex-29, FACT-G and EQ-5D-3L for subjects receiving KW-0761 versus vorinostat;
- To evaluate and compare improvements in the Pruritus Evaluation (Likert scale & Itchy QoL) for subjects receiving KW-0761 versus vorinostat;
- To estimate the duration of response for both the KW-0761 and vorinostat arms for those subjects with relapsed or refractory CTCL responding to treatment;
- To determine if subjects who relapse on vorinostat can achieve response upon cross over to treatment with KW-0761;
- To further assess the safety of KW-0761;
- To describe the immunogenicity of KW-0761.

2.3 Exploratory Objectives

- To compare the overall survival of KW-0761 versus vorinostat for subjects with relapsed or refractory CTCL;
- To conduct exploratory evaluation of KW-0761 exposure-response relationships.

3 STUDY POPULATION

3.1 Subject Selection

This study will enroll subjects with CTCL who have failed at least one prior course of systemic therapy. This should be adequately documented in the subject's medical record.

3.2 Inclusion Criteria

Subject must meet the following criteria for inclusion in this study:

Signed Written Informed Consent

1) Voluntarily signed and dated Institutional Review Board (IRB)/ Ethics Committee approved informed consent form in accordance with regulatory and institutional guidelines. Written informed consent must be obtained prior to performing any study-related procedure;

Age and Sex

2) Males and female subjects ≥ 18 years of age at the Pre-treatment Visit, i.e., at the time that written informed consent is obtained, except in Japan where subjects must be ≥ 20 years of age;

Target Population

3) Histologically confirmed diagnosis of MF or SS;
   a. For SS (defined as meeting T4 plus B2 criteria), where the biopsy of erythrodermic skin may only reveal suggestive but not diagnostic histopathologic features, the diagnosis may be based on either a node biopsy or fulfillment of B2 criteria including a clone in the blood that matches that of the skin (Olsen, 2011).
4) Stage IB, II-A, II-B, III and IV (Olsen, 2011) (see Appendix 1);
5) Subjects who have failed at least one prior course of systemic therapy (e.g., interferon, denileukin diftitox, bexarotene, photopheresis, anti-neoplastic chemotherapy, etc.). Psoralen plus ultraviolet light therapy (PUVA) is not considered to be a systemic therapy;
6) Eastern Cooperative Oncology Group (ECOG) performance status score (Oken, 1982) of ≤ 1 (see Appendix 2).
7) The subject has resolution of all clinically significant toxic effects of prior cancer therapy to Grade ≤ 1 by the National Cancer Institute Common Terminology

Criteria for Adverse Events, version 4.0 (NCI-CTCAE, v.4.0) excluding the specifications required in 8, 9 and 10 below.

8) Adequate hematological function:
   a. absolute neutrophil count (ANC) ≥ 1,500 cells/μL (≥ 1,500/mm^3);
   b. platelets ≥ 100,000 cells/μL (≥ 100,000/mm^3);
   c. in subjects with known bone marrow involvement, ANC must be ≥ 1,000 cells/μL (≥ 1,000/mm^3) and platelets ≥ 75,000 cells/μL (≥ 75,000/mm^3).
9) Adequate hepatic function:
   a. bilirubin ≤ 1.5 times the specific institutional upper limit of normal (ULN), except for subjects with Gilbert's syndrome;
   b. aspartate transaminase (AST) and alanine transaminase (ALT) each ≤ 2.5 x ULN or ≤ 5.0 x ULN in the presence of known hepatic involvement by CTCL.
10) Adequate renal function:
   a. serum creatinine ≤ 1.5 x ULN

   or

   b. calculated creatinine clearance > 50 mL/min using the Cockcroft-Gault formula.
11) Subjects previously treated with anti-CD4 antibody or alemtuzumab are eligible provided their CD4+ cell counts are ≥ 200/mm^3.
12) Subjects with MF and a known history of non-complicated staphylococcus colonization/infection are eligible provided they continue to receive stable doses of prophylactic antibiotics.
13) Women of childbearing potential (WOCBP) must have a negative pregnancy test within 7 days of receiving study medication.
14) WOCBP must agree to use effective contraception, defined as oral contraceptives, double barrier method (condom plus spermicide or diaphragm plus spermicide) or practice true abstinence from sexual intercourse (periodic abstinence, e.g., calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception) during the study and for 3 months after the last dose. WOCBP includes any female who has experienced menarche and who has not undergone successful surgical sterilization or is not postmenopausal (defined as amenorrhea ≥ 12 consecutive months without an alternative medical cause).
15) Male subjects and their female partners of child bearing potential must be willing to use an appropriate method of contraception defined as oral contraceptives, double barrier method (condom plus spermicide or diaphragm plus spermicide) or practice true abstinence from sexual intercourse (periodic abstinence, e.g., calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception) during the study and for 3 months after the last dose.

NOTE: For subjects continuing to receive study treatment as of protocol Amendment 8, the period of contraceptive use should be extended to 6 months after the last dose of KW-0761.

3.3 Exclusion Criteria

Subjects with any of the following will be excluded from the study:

Medical History and Concurrent Diseases

1) Current evidence of large cell transformation (LCT). Subjects with clinical features suggestive of LCT must have a biopsy performed within 4 months prior to Cycle 1 Day 1 to rule out transformed disease. Subjects with a history of LCT but without current aggressive disease and no current evidence of LCT on pathology in skin or lymph nodes would be eligible.
2) Diagnosed with a malignancy in the past 2 years. However, subjects with non-melanoma skin cancers, melanoma in situ, localized cancer of the prostate with current prostate-specific antigen of < 0.1 ng/mL, treated thyroid cancer or cervical carcinoma in situ or ductal/lobular carcinoma in situ of the breast with in the past 2 years may enroll as long as there is no current evidence of disease.
3) Clinical evidence of central nervous system (CNS) metastasis.
4) Psychiatric illness, disability or social situation that would compromise the subject's safety or ability to provide consent, or limit compliance with study requirements.
5) Significant uncontrolled intercurrent illness including, but not limited to:
    a. uncontrolled infection requiring antibiotics;
    b. clinically significant cardiac disease (class III or IV of the New York Heart Association [NYHA] classification, see Appendix 3);
    c. unstable angina pectoris;
    d. angioplasty, stenting, or myocardial infarction within 6 months;
    e. uncontrolled hypertension (systolic blood pressure (BP) > 160 mm Hg or diastolic BP > 100 mm Hg, found on 2 consecutive measurements separated by a 1-week period) despite 2 anti-hypertensive medications;
    f. clinically significant cardiac arrhythmia or
    g. uncontrolled diabetes.
6) Known or tests positive for human immunodeficiency virus (HIV), human T-cell lymphotropic virus (HTLV-1), hepatitis B or hepatitis C disease.
7) Active herpes simplex or herpes zoster. Subjects on prophylaxis for herpes who started taking medication at least 30 days prior to the Pre-treatment Visit, and have no active signs of active infection, and whose last active infection was more than 6 months ago, may enter the study, and should continue to take the prescribed medication for the duration of the study.
8) Experienced allergic reactions to monoclonal antibodies or other therapeutic proteins.
9) Known active autoimmune disease will be excluded. (For example, Graves' disease; systemic lupus erythematosus; rheumatoid arthritis; Crohn's disease; psoriasis).
10) Is pregnant (confirmed by beta human chorionic gonadotrophin [β-HCG]) or lactating.

Prohibited Therapies and/or Medications

11) Prior treatment with KW-0761.
12) Prior treatment with vorinostat. Patients who were exposed to vorinostat for a short time, did not progress while on treatment, and did not have intolerable toxicity but were discontinued for another reason (e.g., comorbidity) may be permitted to enter the study after discussion with the Medical Monitor.
13) Have had any therapy directed against the subject's underlying cancer or any investigational medications within four weeks of randomization (skin directed treatments, including topicals and radiation within 2 weeks of randomization). However, subjects with rapidly progressive malignant disease may be enrolled prior to this period after discussion with the Medical Monitor.
14) Subjects on a stable dose of a low dose systemic corticosteroid (≤ 20 mg prednisone equivalent) for at least 4 weeks prior to the Pre-treatment Visit may continue use although the investigator should attempt to taper the use to the lowest dosage tolerable while on study. Initiation of treatment with systemic corticosteroids or increase in dose while on study is not permitted except to treat an infusion reaction (see Section 5.2.1.7). Subjects may receive intra-articular corticosteroid injections, intraocular corticosteroid drops, inhalation or nasal corticosteroids and replacement doses of systemic corticosteroids as needed.
15) Subjects on a stable dose of medium or low potency topical corticosteroids for at least 4 weeks prior to the Pre-treatment Visit may continue use at the same dose, although the investigator should attempt to taper the use to the lowest dosage tolerable while on study. Initiation of treatment with topical corticosteroids while on study is not permitted except to treat an acute rash.
16) History of allogeneic transplant.
17) Autologous hematopoietic stem cell transplant within 90 days of the Pre-treatment Visit.
18) Subjects on any immunomodulatory drug for concomitant or intercurrent conditions other than T-cell lymphoma or who have received any of these agents within 4 weeks of treatment, including but not limited to the following, will be excluded: low dose or oral methotrexate; azathioprine; iv immunoglobulin; low dose or oral cyclophosphamide; cyclosporine; mycophenolate; infliximab; etanercept; leflunomide; adalimumab; lenalidomide; abatacept; rituximab; anakinra; interferon-β; IL-2 and natalizumab.

3.4 Eligibility for Cross-over to KW-0761

Subjects who are randomized to the vorinostat arm may cross over to KW-0761 upon progression or in the event of intolerable toxicity (see Section 5.3). Crossover may take place following discussion with the Medical Monitor or designee and receipt of approval for cross over from Kyowa Kirin Pharmaceutical Development, Inc. (KKD). However, they must

continue to fulfill inclusion criteria 6 through 15, and will be excluded if they fulfill the exclusion criteria, except for exclusion criteria 1, 12 and 13 (refer to Section 3.3).

4 INVESTIGATIONAL PLAN

4.1 Overview of Study Design

This is an open-label, multi-center randomized, Phase 3 study with 1:1 randomization of study drug, KW-0761 versus the comparator, vorinostat.

4.2 Number of Subjects

Approximately 317 subjects may enroll in this study over a period of 24 months. The primary analysis will be conducted when 255 total progression-free survival (PFS) events have been observed or 24 months after the last randomized subject's first dose, whichever comes first.

4.3 Investigational Centers

It is anticipated that approximately 75 investigational centers in the US, Europe, Japan and Australia will participate in this study.

5 TREATMENT PLAN

5.1 Assignment to Study

After a subject signs consent, screening numbers should be assigned by the investigator (or designee) using ClinTrak Interactive Voice/Web Response System (CTIVRS). Once assigned, numbers for any screen failures or non-treated, non-evaluable, or discontinued subjects will not be re-used.

A subject who meets all entry criteria will be randomized in a 1:1 ratio to receive KW-0761 or vorinostat. The randomization to treatment groups will be stratified by disease type (MF or SS) and disease stage (IB/II or III/IV). When a subject is determined to be eligible for randomization the investigator (or designee) will contact CTIVRS to obtain the randomization assignment for the subject. If a subject is randomized in error, or a dosing error occurs, KKD (or designee) should be notified as soon as the error is discovered.

5.2 Study Treatments

In this protocol, study treatments are KW-0761 and vorinostat. Subjects will be randomized to the study drug, KW-0761 or comparator, vorinostat, in a 1:1 ratio.

5.2.1 Study Drug: KW-0761 (mogamulizumab)

Treatment can be administered on an outpatient basis. Subjects will receive 1.0 mg/kg of KW-0761 as an iv infusion over at least 1 hour on Days 1, 8, 15, and 22 of the first cycle and on Days 1 and 15 of subsequent cycles. No other investigational or commercial agents or therapies other than the study treatment and those described in Section 5.4.1 may be administered with the intent to treat the subject's malignancy.

5.2.1.1 Premedication Prior to KW-0761 Infusion

It is recommended that subjects be premedicated with acetaminophen or paracetamol orally and diphenhydramine 50 mg iv (or equivalent anti-histamine) before the first KW-0761 infusion. For subjects who experience an infusion related reaction, premedication is recommended prior to every subsequent infusion.

5.2.1.2 Definition of Treatment Cycle

Each treatment cycle is 28 days.

5.2.1.3 Delays in Dosing

During the first treatment cycle, KW-0761 should be administered beginning on Day 1 and within ± 2 days of the other scheduled visits (i.e., Days 8, 15 and 22 during Cycle 1; Day 15 during subsequent cycles). If the study visit does not occur within this visit window, KW-0761 should not be administered at the visit and the next dose should be administered at the next timepoint.

A subject's next cycle should begin within 2 weeks of the completion of the prior cycle. The start of a new cycle may be delayed to allow resolution of treatment-related toxicities or for non-medical reasons (holidays, vacations, etc.). Delay of the start of a new cycle greater than 2 weeks must be discussed with the Medical Monitor or designee.

5.2.1.4 Duration of Treatment

Subjects may remain in the treatment phase up until PD, drug intolerance or unacceptable toxicity, or until any of the other criteria for study removal are met, as defined in Section 5.5. Except in cases of unacceptable toxicity or drug intolerance, every effort should be made to ensure the subject remains in the study until disease progression (See Section 7.2.4, regarding definition of disease progression).

At each cycle, the investigator must minimally have reviewed the modified Severity Weighted Assessment Tool (mSWAT) to determine if progression of skin disease has

occurred prior to subsequent dosing. Ideally, results of flow cytometry and CT assessment, as applicable, should be reviewed at this visit as well. However, it is understood that these results may not be reported for several days and may not be available. Once those results are obtained evidence of progression in all compartments should be determined.

In cases where the definition of PD or relapse is met but the clinical impression is questionable, subjects may remain on study until the next evaluation (4 weeks later if questionable finding in skin or blood; 8 weeks later in first year and 16 weeks later after Year 1 if questionable finding in lymph nodes or viscera, with at least stable disease in other compartments) to avoid a subject being removed prematurely from the study. If PD is confirmed at this subsequent evaluation, subject should be discontinued from treatment. If PD is not confirmed at this subsequent evaluation, the subject may remain on study.

This course of action only applies to cases where the clinical impression is questionable; subjects in frank or obvious PD in any compartment should be discontinued from protocol therapy.

If clinical progression is noted at any time prior to the scheduled assessments for efficacy, the assessments (computed tomography [CT], mSWAT, skin photographs and flow cytometry) should be done at that time to fully document disease progression. CT must be performed even if previously negative at baseline.

If the subject experiences an overall CR, the subject may continue treatment for up to 12 months or until progression, whichever comes first.

For subjects who are continuing to receive study treatment at the time of the primary efficacy analysis, procedures and assessments are described in Section 7.7. Procedures to be followed for subjects who are continuing to receive KW-0761 at the time of initial marketing authorization are described in Section 7.8.

5.2.1.5 Replacement of Subjects

Subjects will not be replaced.

5.2.1.6 Dose Modifications

No dose modifications of the KW-0761 will be permitted in this study.

5.2.1.7 Treatment of Hypersensitivity-Like Reactions

It may be difficult to differentiate an infusion reaction from a true hypersensitivity (i.e., allergic) reaction. If a reaction occurs during infusion of KW-0761, investigators may use the following guidelines to best treat the subject's symptoms:

Grade 1/2:

- Stop the infusion for 15–30 minutes;
- Acetaminophen or paracetamol orally and diphenhydramine 50 mg iv or equivalent anti-histamine may be administered;
- If symptoms abate, re-start the infusion at one-half the previous rate;
- If symptoms do not abate after 30 minutes, discontinue that day's treatment. Additional medical measures, such as administration of corticosteroids (see below) may be considered for reactions that do not abate after 30 minutes.

Grade 3

- Stop the infusion for 15–30 minutes;
- Consider administering the following:
  - Acetaminophen or paracetamol orally;
  - Diphenhydramine 50 mg iv or an equivalent anti-histamine;
  - Dexamethasone 20 mg iv or an equivalent corticosteroid;
  - Albuterol or salbutamol inhaler 2 puffs p.r.n. for bronchospasm or an equivalent bronchodilator;
  - O_2 by nasal cannula.
- Additional agents may be administered per institutional guidelines for the treatment of infusion reactions;
- If symptoms abate, re-start the infusion at one-half the previous rate;
- If symptoms do not abate after 30 minutes, discontinue the subject from the study.

Grade 4

- Administration of the agents specified for a Grade 3 infusion reaction above should be considered.
- Any subject who experiences a Grade 4 infusion reaction is to be discontinued from the study.

If a reaction with severity of Grade 2 or higher occurs upon re-challenge with KW-0761, or if in the opinion of the investigator the reaction represents a true hypersensitivity (i.e., allergic) reaction of Grade 2 or higher, KW-0761 should be stopped and not restarted and the subject should be discontinued from the study.

If an infusion reaction occurs, a serum sample should be obtained and sent to the designated central laboratory for analysis of anti-KW-0761 antibodies. (As of Amendment 10, central laboratory analysis of samples will no longer be performed [see Section 7.8].)

If an infusion reaction occurs, the duration of administration of KW-0761 should be increased to 2 hours for the next 2 infusions. Subsequent infusion duration may be 1 to 2 hours, as tolerated.

For infusion reactions occurring *after* completion of the infusion, administration of the agents specified for a Grade 3 infusion reaction above should be considered, along with any other medical intervention stipulated in institutional guidelines for the treatment of infusion reactions.

Any subject who experiences an infusion reaction requiring the administration of systemic vasopressors or that results in hospitalization (directly due to infusion reaction symptoms) of the subject is to be removed from the study.

5.2.1.8 Treatment Emergent Skin Rash

In the event a subject develops a treatment emergent skin rash, the following measures must be taken to appropriately document the event.

> Patients should be closely monitored for symptoms or signs that suggest SJS or TEN. If they occur, mogamulizumab should be interrupted and treatment should not restart unless SJS or TEN is ruled out and cutaneous reaction has resolved to Grade 1 or less.

Initial Work-up of All Skin Rashes (new and re-challenge)

1) Notify KKD of the skin rash.
2) Photograph the rash. (As of Amendment 8, collection of photographs is no longer required.)
3) If the rash is ≥ Grade 2 or if the affected area cannot be differentiated from a new area of lymphoma, a biopsy must be performed. Biopsy the rash as well as an area of skin unaffected by the rash in order to compare possible drug eruption to background lymphoma involved skin. If the rash is Grade 1 and topical steroids are to be applied, the rash must be biopsied prior to steroid treatment.
4) Confer with Medical Monitor or designee after completion of one week of treatment with topical corticosteroids to assess response to treatment.
5) Forward all results to Medical Monitor and discuss with Medical Monitor or designee a treatment plan and medical follow up.
6) Biopsy should be read by the dermatopathologist at the study center. Additional sample should be sent to the laboratory designated by the Sponsor for central review as well. Specific instructions for sample preparation and handling for central laboratory will be provided in the Laboratory Manual. (As of Amendment 10, central laboratory analysis of samples will no longer be performed [see Section 7.8].)
7) If biopsy indicates that rash is a drug eruption record appropriately as AE/SAE. If biopsy indicates that rash is lymphoma, do not record as an AE.

Rash Treatment Guidelines (after initial work-up):

Grade 1 Rash (drug related or non-drug related)

1) Treatment with KW-0761 may continue.
2) Treat rash with topical corticosteroids as needed.

Grade 2 or above Rash (drug related)

1) Treatment with KW-0761 must be stopped.
2) Treat rash with 2-week course of topical corticosteroids.
3) After 2-week course, re-assess rash per the steps outlined in initial assessment; if resolved completely or to Grade 1, KW-0761 treatment may be resumed. If not resolved, contact the Medical Monitor for further discussion.

Grade 2 or above rash on Re-challenge

1) If rash recurs and becomes a Grade 3, the subject must be discontinued from the trial and the rash work up above must be completed.
2) If the rash recurs at a Grade 2, follow the steps above for Grade 2 Rash.
3) If the rash recurs at Grade 2 or higher for a third time, the rash work up must be performed and the subject must be discontinued from the trial.

Table 5.2.1-1 Guidelines for Treatment of Skin Rash

Rash Grade	Photographs	Biopsy	Medical Monitor or designee Consult	Treatment Regimen	KW-0761	Study Participation
Initial Drug Rash						
1	Yes	Required if topical steroids will be used	Yes	Topical corticosteroids as needed	Continue	Continue
2	Yes	Yes	Yes	2-week topical steroid	Temporarily Stop; re-start if ≤ Grade1 within 2 weeks	If rash does not resolve to ≤ Grade 1 within 2 weeks consult with medical monitor
3[a]	Yes	Yes	Yes	2-week topical steroid	Temporarily Stop: re-start if ≤ Grade 1 within 2 weeks	If rash does not resolve to ≤ Grade 1 within 2 weeks consult with medical monitor
Subsequent Drug Rash/Rechallenge						
1	Yes	Yes	Yes	Topical corticosteroids as needed	Continue	Continue
2	Yes	Yes	Yes	2-week topical steroid	Temporarily Stop: re-start if ≤ Grade 1 within 2 weeks	D/C if rash does not resolve to ≤ Grade 1 within 2 weeks
3	Yes	Yes	Yes	2-week topical steroid	Discontinue	Discontinue

a Patients should be closely monitored for symptoms or signs that suggest SJS or TEN. If they occur, mogamulizumab should be interrupted and treatment should not restart unless SJS or TEN is ruled out and cutaneous reaction has resolved to Grade 1 or less.

Subjects who require systemic steroid therapy to treat a severe skin rash including SJS/TEN should be discontinued from the study.

5.2.2 Study Drug: Vorinostat (ZOLINZA®)

Treatment can be administered on an outpatient basis. Subjects will take 400 mg orally once daily with food.

Vorinostat is approved for marketing in the US, Japan and Australia and is indicated for the treatment of progressive, persistent or recurrent CTCL. Investigators will administer according to the currently approved US prescribing information (e.g. dosage and administration, warnings, precautions, adverse reactions, dose modifications and omissions and storage information). No other investigational or commercial agents or therapies other than the study treatments and those described in Section 5.4.1 may be administered with the intent to treat the subject's malignancy.

5.2.2.1 Definition of Treatment Cycle

Each treatment cycle is 28 days.

5.2.2.2 Delays in Dosing

Refer to Section 5.2.2.5.

5.2.2.3 Duration of Treatment

Subjects may remain in the treatment phase up until PD, drug intolerance or unacceptable toxicity, or until any of the other criteria for study removal are met, as defined in Section 5.5. Except in cases of unacceptable toxicity or drug intolerance, every effort should be made to ensure the subject remains in the study until disease progression (See Section 7.2.4, regarding definition of disease progression).

At each cycle, the investigator must minimally have reviewed the mSWAT to determine if progression of skin disease has occurred prior to subsequent dosing. Ideally, results of flow cytometry and CT assessment, as applicable, should be reviewed at this visit as well. However, it is understood that these results may not be reported for several days and may not be available. Once those results are obtained evidence of progression in all compartments should be determined.

In cases where the definition of PD or relapse is met but the clinical impression is questionable, subjects may remain on study until the next evaluation (4 weeks later if questionable finding in skin or blood; 8 weeks later in first year and 16 weeks later after Year 1 if questionable finding in lymph nodes or viscera, with at least stable disease in other compartments) to avoid a subject being removed prematurely from the study. If PD is confirmed at this subsequent evaluation, subject should be discontinued from treatment. If PD is not confirmed at this subsequent evaluation, the subject may remain on study.

This course of action only applies to cases where the clinical impression is questionable; subjects in frank or obvious PD in any compartment should be discontinued from protocol therapy.

If clinical progression is noted at any time prior to the scheduled assessments for efficacy, the assessments (CT, mSWAT, skin photographs and flow cytometry) should be done at that time to fully document disease progression. CT must be performed even if previously negative at baseline.

If the subject experiences an overall CR, the subject may continue treatment for up to 12 months or until progression, whichever comes first.

For subjects who are continuing to receive study treatment at the time of the primary efficacy analysis, procedures and assessments are described in Section 7.7.

5.2.2.4 Replacement of Subjects

Subjects will not be replaced.

5.2.2.5 Dose Modifications

Management of severe or intolerable adverse reactions may require dose omission, reduction or interruption of vorinostat therapy. Refer to US prescribing information for complete recommendations regarding dose modifications.

5.3 Cross-over to Study Drug KW-0761

Subjects who have received 2 full treatment cycles and demonstrate progression of disease on treatment with vorinostat at the 8 week (Cycle 2, Day 26-28) assessment, or anytime thereafter, may cross over to treatment with KW-0761 after discussion with Medical Monitor or designee and receipt of approval for cross over from KKD. Investigators should strive to maintain subjects on treatment for at least the 8 week period, adjusting the dose of vorinostat as needed for toxicities in order to allow sufficient time to see effect. In cases where a subject's disease progresses rapidly (i.e., prior to 8 weeks), the Medical Monitor or designee should be contacted and may consider the possibility of early crossover, if appropriate for that subject. All subjects must undergo the full extent of disease evaluations (including CT scanning) to document PD prior to crossover.

There must be at least 2 weeks between the last dose of vorinostat and first dose of KW-0761. Subject must continue to meet eligibility criteria outlined in Section 3.4 and all toxicity must have resolved to Grade ≤ 1 or to baseline in order to receive KW-0761. Treatment with KW-0761 should commence with procedures outlined for Day 1 in Table 1 of Study

Procedures for the first treatment cycle. In cases where a subject's disease progresses rapidly, the Medical Monitor or designee should be contacted and may consider initiation of treatment with KW-0761 prior to the 2-week washout period.

For subjects who are unable to tolerate the toxicities associated with vorinostat treatment, dose reduction should be initiated in an attempt to have the subject complete 2 full cycles of treatment. If the subject is unable to tolerate treatment with vorinostat despite attempts at dose reduction and has not had documented disease progression, the subject may receive KW-0761 after consultation with the Medical Monitor or designee and subsequent approval documentation from the Sponsor.

Drug intolerance is defined as:

- A serious AE attributed to the drug;
- ≥ Grade 3 AEs excluding inadequately treated nausea, vomiting and diarrhea and alopecia.

5.4 Concomitant Therapy

Subjects should receive appropriate medical care for all intercurrent medical conditions consistent with community standards of medical care. Subjects are to receive vigorous supportive care for study medication-related toxicities and appropriate palliation for tumor symptoms, such as pain and anorexia.

All concomitant treatments whether for treatment of concurrent medical conditions, toxicity, management of pain, infections or other complications of the malignancy, must be recorded on the relevant electronic case report form (eCRF) page along with the reason for use. Medication taken within 30 days prior to the first dose of study drug, and at any time after the start of treatment until 30 days after the final study drug administration will be recorded. A medication taken during follow-up will also be recorded if it is used to treat an AE or is temporally associated with an AE and may have a causal relationship.

While on study treatment, subjects are not permitted to receive any experimental therapy or anticancer therapy other than the study medication. Any subject requiring other anticancer therapy is to be removed from study treatment.

5.4.1 Permitted Treatment

- Hematopoietic growth factors and erythropoiesis-stimulating agents (based on threshold and target hemoglobin levels in the American Society of Hematology (ASH)/American Society of Clinical Oncology (ASCO) guidelines) (Rizzo, 2010) are allowed, if consistent with regional approved prescribing information, after completing Cycle 1.

- Subjects on a stable dose of a low dose systemic corticosteroid (≤ 20 mg prednisone equivalent) for at least 4 weeks prior to the Pre-treatment Visit may continue use. Subjects may receive intra-articular corticosteroid injections, intraocular corticosteroids drops, inhalation or nasal corticosteroids and replacement doses of systemic corticosteroids as needed.
- Subjects on a stable dose of medium or low potency topical corticosteroids for at least 4 weeks prior to the Pre-treatment Visit may continue use at the same dose, although the investigator should attempt to taper the use to the lowest dosage tolerable while on study.
- Prophylactic treatment for the infectious complications of T-cell lymphoma is permitted at the discretion of the investigator.
- For subjects receiving vorinostat, prolongation of prothrombin time (PT) and International Normalized Ratio (INR) have been observed in subject receiving concomitant therapy with coumarin-derivative anticoagulants, carefully monitor PT and INR in these subjects.
- Influenza vaccination consisting of killed virus or viral particles may be administered to subjects on study. Subjects should not receive an influenza vaccine containing live attenuated virus. It should also be understood that because KW-0761, as well as CTCL, can affect the immune system, immunity to influenza may not be achieved despite vaccination.

5.4.2 Prohibited Treatment

- Initiation of treatment with systemic steroids or increase in dose while on study is not permitted except to treat an infusion reaction (see Section 5.2.1.7). Subjects who require systemic steroid therapy to treat a severe skin rash should be discontinued from the study (see Section 5.2.1.8).
- Initiation of treatment with topical corticosteroids while on study is not permitted except to treat an acute rash.
- Any experimental therapy or anticancer therapy including radiation and phototherapy other than the study medications.
- Any live or live attenuated vaccine.
- Alternative medicines, particularly use of St. John's Wort.
- Immunomodulatory agents such as methotrexate; azathioprine; iv immunoglobulin; cyclophosphamide; cyclosporine; mycophenolate; infliximab; etanercept; leflunomide; adalimumab; lenalidomide; abatacept; rituximab; anakinra; interferon-α; interferon-β; IL-2 and natalizumab.
- Other concurrent HDAC inhibitors including valproic acid.
- Whenever possible, concomitant use of drugs which may cause a prolongation of the QTc interval should be avoided. If such a drug is necessary (e.g., anti-emetics), monitor the QTc interval closely.

5.5 Criteria for Removal from Study

In the absence of a medical contraindication or significant protocol violation, every effort will be made by the Principal Investigator to keep the subject in the study. However, should the subject decide to discontinue treatment, all efforts will be made to complete and report the observations as thoroughly as possible, including a complete final evaluation at the time of the subject's withdrawal with an explanation of why the subject is withdrawing from the study.

Study treatment will be stopped if any of the following events occur:

- Disease progression (as defined in Section 7.2.4);
- An infusion-related reaction (see Section 5.2.1.7);
  - with a severity of ≥ Grade 2 upon re-challenge with KW-0761,
  - with a severity of Grade 3 with symptoms that do not abate after 30 minutes,
  - with a severity of Grade 4,
  - requiring the administration of systemic vasopressors,
  - that results in hospitalization (directly due to infusion reaction symptoms),
- Initiation of treatment with systemic corticosteroids, except when initiated to treat an infusion reaction (see Section 5.2.1.7);
- A true hypersensitivity (i.e., allergic) reaction to KW-0761 with a severity of ≥ Grade 2;
- A rash which recurs and becomes Grade 3 on re-challenge (see Section 5.2.1.8);
- A rash which recurs at Grade 2 or higher for a third time on re-challenge (see Section 5.2.1.8);
- A rash which requires systemic steroid therapy (see Section 5.2.1.8);
- Confirmed SJS/TEN (see Section 5.2.1.8);
- The subject has any clinical AE, laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the subject. The Investigator should make a distinction between AEs that may require only interruption of study medication and those that require discontinuation;
- The subject wishes to withdraw consent from the study in the absence of a medical need to withdraw as determined by the Investigator;
- The Investigator concludes that it is in the best interest of the subject to discontinue study treatment including subjects who have not benefited from treatment;
- Subject is willingly or inadvertently noncompliant in the opinion of the Investigator;
- Administrative reasons determined by the Sponsor; or
- If pregnancy is suspected while the subject is receiving study treatment, the study medication must immediately be withheld until the result of pregnancy testing is known.

If pregnancy is confirmed, the study medication will be permanently discontinued and the subject withdrawn from treatment.

In the case of pregnancy that occurs while the subject is receiving study medication through 6 months after the last dose of study medication, the Investigator must immediately notify the Sponsor of this event and record the pregnancy on the Pregnancy Surveillance Form. The Sponsor must also be notified if a partner of a study subject becomes pregnant while the subject was receiving study medication through 6 months after the last dose of study medication. Reasonable attempts will be made to follow the pregnancy to conclusion in order to obtain information regarding the outcome.

The Investigator must complete all applicable End-of-treatment visit procedures (i.e., safety laboratory parameters, electrocardiogram (ECG), physical examination, vital signs) and eCRF pages for subjects who discontinue treatment, and include the reason for discontinuation of treatment.

6 STUDY PROCEDURES

The key study procedures and the frequency of their occurrences are outlined in the Study Procedures Tables (Table 1, Table 2, and Table 3). Labs, ECG, and physical exams on day of treatment should be obtained prior to study treatment.

For subjects who are continuing to receive study treatment at the time of the primary efficacy analysis, procedures and assessments are described in Section 7.7. Procedures to be followed for subjects who are ongoing in the study (i.e., subjects who are continuing to receive KW-0761 or who are in safety or survival follow-up) at the time of initial marketing authorization are described in Section 7.8.

7 STUDY MEASUREMENTS

Screening evaluations used to determine the subject's study eligibility must be completed within 30 days prior to starting treatment unless otherwise specified.

Written informed consent must be obtained prior to any study-specific procedures.

Results of all screening evaluations must be reviewed by the Investigator or his/her designee to ensure that all eligibility criteria have been satisfied prior to registering the subject with the Sponsor. All pathology reports relevant to confirmation of the diagnosis of CTCL (mycosis fungoides or Sezary syndrome) for all enrolled subjects should be de-identified and provided to the Sponsor. For subjects with SS, this would include results confirming fulfillment of B2 criteria including a clone in the blood that matches that of the skin per Section 3.2.

An End-of-treatment visit must be conducted for all subjects who discontinue from study treatment. This visit must occur within 30 days after the last dose of study medication. All End-of-treatment assessments must be conducted prior to the initiation of new therapy.

7.1 Safety Evaluations

The safety of KW-0761 and vorinostat will be determined by reported AEs, changes in physical examinations, vital sign measurements, ECGs and laboratory analyses. Safety evaluations will be performed throughout the study. All subjects who received at least one dose, including a partial dose, of study drug will be evaluated for safety. The NCI-CTCAE v4.0 system will be used to grade AEs, both clinical and laboratory. AEs will be grouped and tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred terms by system organ class. All subjects will be assessed regularly for potential occurrence of AEs from the time of signing the informed consent until 90 days after the last dose or initiation of alternative therapy whichever comes first. In all subjects who cross over from vorinostat to KW-0761, the causality of any reported AEs should be assessed for both drugs for 30 days after vorinostat was stopped (or later if the event is considered to be related to vorinostat).

7.1.1 Clinical Laboratory Evaluations

Clinical laboratory assessments will be performed at the visits specified in the Study Procedures. A pregnancy test (serum or urine) is to be performed for all women of childbearing potential prior to administration of study medication.

Any clinically important abnormal laboratory values noted at the screening visit will be recorded as medical history. In addition, in order for KKD to collect additional information about clinically important laboratory abnormalities, at minimum, the following laboratory abnormalities should be captured on the non-serious or serious AE pages of the eCRF as appropriate:

- Any laboratory test result that meets the criteria for a SAE;
- Any laboratory abnormality that requires the subject to have study medication discontinued or interrupted;
- Any laboratory abnormality that requires the subject to receive specific corrective therapy.

All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until (1) the value returns to baseline, (2) the value is judged to be clinically acceptable by the Investigator and the Sponsor, or (3) a diagnosis that explains the

abnormal laboratory value is made. When possible, the Investigator should report the clinical rather than the laboratory term (e.g., anemia versus low hemoglobin).

Clinical laboratory assessments will include the following:

Table 7.1.1-1 Clinical Laboratory Assessments

Serum Chemistry	Sodium	Albumin	Calcium
	Potassium	SGPT (ALT)	Phosphorus
	Glucose	SGOT (AST)	Chloride
	Blood urea nitrogen (BUN)	Alkaline phosphatase	Bicarbonate (serum or blood)
	Creatinine	Total bilirubin	Uric acid
	Total protein	Lactate dehydrogenase (LDH)	Magnesium
Thyroid function	T4 (free)		TSH
Coagulation Panel	International normalized ratio (INR)		Partial thromboplastin time (PTT) or Activated Partial thromboplastin time (aPTT)
Hematology	Complete blood count (CBC) and differential	Platelet count	
	Absolute neutrophil count		
T-cell counts	Absolute CD4 count	Absolute CD8 count	
	CD4 and CD8 counts will be reported based on the flow cytometric sample sent to Quest while the subject is on study. On site counts need only be obtained at End-of-treatment visit with appropriate follow up if less than 200/mm^3.		
Urinalysis	routine urinalysis or dipstick measurements and, if clinically indicated, microscopic analysis. Parameters should include:		
	Color	WBC	
	Specific Gravity	RBC or hemoglobin	
	pH	Protein	
	Glucose	Ketones	
Pregnancy Test	A serum or urine pregnancy test will be performed for all women of childbearing potential at screening.		
Virus Testing	hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C antibodies (HC Ab)		
	HIV		
	HTLV-1		

7.1.2 Vital Signs and Body Weight

Vital signs (pulse, respiration rate, temperature, and blood pressure) will be measured, with the subject in the seated position, at the visits specified in the Study Procedures (Table 1, Table 2, and Table 3). Additional vital signs will be obtained if clinically significant signs or symptoms occur.

Weight will be included in vital sign assessments. The subject's height will be measured at the Pre-Treatment visit.

7.1.3 Physical Examination

The Investigator will perform a full physical examination at the Pre-treatment (including height at only this visit) and End-of-treatment visits and brief physical examinations at other visits specified in the Study Procedures (Table 1, Table 2, and Table 3). The full physical examination requires assessment of the following categories: head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, skin, musculoskeletal, extremities, neurological, lymph nodes and 'other.' Brief physical examination consists of examination of pertinent systems, i.e., those in which abnormalities were noted previously as well as those likely to be affected during the course of therapy and those suggested by reported adverse experiences.

Attention should be paid to those body systems referable to possible autoimmune disorders, such as the joints, the eyes, the GI tract as well as signs and symptoms of hypothyroidism. To assist in this surveillance, a list of directed questions and suggested actions is provided in Appendix 4.

ECOG Performance Status (PS) will be assessed at each exam according to the ECOG PS criteria (Appendix 2).

7.1.4 Electrocardiograms

A baseline 12-lead ECG is to be obtained at the Pre-treatment Visit. Follow up ECGs should be performed during the study if clinically indicated and then at the End of Treatment visit.

The Investigator will have the responsibility for evaluating the ECG interpretation in relationship to clinical signs and symptoms and for reaching a medical decision regarding the subject's medical status. If not within normal limits, the ECG findings should be marked "clinically significant" or "not clinically significant" (i.e., "CS" or "NCS") and the ECG should be initialed and dated by the Investigator.

7.1.5 Blood Sample for Determination of Natural Ligands

Blood samples will be drawn to measure the concentration of natural ligands such as CCL17/TARC and CCL22/MDC at the visits specified in the Study Procedures. Analysis of samples will be performed by a central laboratory designated by the Sponsor. Instructions for preparation and shipment of samples will be provided in the Laboratory Manual. (As of

Amendment 10, central laboratory analysis of samples will no longer be performed [see Section 7.8].)

7.1.6 Genomic Sampling (For subjects receiving KW-0761 as first assigned therapy only)

A saliva sample will be collected to obtain baseline germline DNA sample to assess Fc-gamma receptor polymorphisms. Exploratory analysis of the effect of this genetic determinant on safety parameters may be performed.

Analysis will be performed by a central laboratory designated by the Sponsor. Instructions for preparation and shipment of samples will be provided in the Laboratory Manual.

7.1.7 Immunogenicity (For subjects receiving KW-0761)

Serum samples will be drawn for the determination of anti-KW-0761 antibodies and concentration of KW-0761 at the visits specified in the Study Procedures. Analysis of samples will be performed by a central laboratory designated by the Sponsor. Instructions for preparation and shipment of samples will be provided in the Laboratory Manual. (As of Amendment 10, central laboratory analysis of samples will no longer be performed [see Section 7.8].)

7.2 Efficacy Evaluations

Response in skin and blood will be evaluated every 4 weeks during treatment. In the first year of treatment, response in lymph nodes and viscera will be documented at 4 weeks after the start of study treatment (end of Cycle 1) and every 8 weeks thereafter. After the first year, response in the lymph nodes and viscera will be documented every 16 weeks. In the first year of treatment, the global composite response (including skin, blood, lymph nodes and viscera) will be assessed at 4 weeks (end of Cycle 1) and every 8 weeks thereafter (Cycle 3, 5, etc.); after the first year, global composite response will be assessed every 16 weeks (Cycle 17, 21, etc.).

For those subjects who cross over from the vorinostat arm to KW-0761 treatment, response within the second arm of the study will be measured from the first day of dosing with KW-0761. Baseline measurements for this arm are considered to be those taken at the last assessment which documented progression on vorinostat or if repeated, assessment completed closest to and before the first KW-0761 infusion (i.e., mSWAT done on Cycle 1, Day 1 is the new baseline).

Prior to starting study treatment, visual inspection of the skin with photographs and measurements (mSWAT), assessment of CT images and hematological examinations will be done to document extent of disease. Skin disease will be evaluated using a modification of the SWAT (Olsen, 2007; Stevens, 2002). Response for skin will be based on mSWAT scores. In addition, pruritus will be evaluated using a Likert scale and Itchy QoL. Lymph nodes and visceral disease will be evaluated by CT. The response in blood will be assessed by flow cytometry.

The response in all compartments (skin, blood, lymph nodes and viscera, as applicable) and overall response will be assessed, except as otherwise noted, in accordance with the response criteria determined by consensus of the International Society of Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC) and the Cutaneous Lymphoma Task Force of the European Organization for Research and Treatment of Cancer (EORTC) (Olsen, 2011).

If clinical progression is noted at any time prior to the scheduled assessments for efficacy, the assessments (CT, mSWAT, skin photographs and flow cytometry) should be done at that time to fully document disease progression. CT must be performed even if previously negative at baseline.

7.2.1 Evaluation of Skin Disease

7.2.1.1 Skin Biopsy

7.2.1.1.1 CCR4 Expression

A skin biopsy will be taken at baseline for determination of CCR4 expression by IHC. In the event it is not possible to obtain a skin biopsy, use of an archived sample (taken within 6 months prior to treatment) may be allowed with prior authorization from the Sponsor. To determine if vorinostat alters CCR4 expression, investigators are strongly encouraged to obtain an additional skin biopsy for the determination of CCR4 expression, prior to treatment with KW-0761, in subjects who cross over from treatment with vorinostat.

Tissue is typically expected to have been prepared for standard histopathological examination following formalin or other fixation and embedding in paraffin. The paraffin block is to be submitted to a Central Laboratory designated by the Sponsor. If the study site is unable to process the tissue, a fresh sample may be sent to the Central Laboratory on the day obtained. Submission of unstained slides, while not recommended due to stability concerns with the sample, will be accepted. Specific instructions for sample preparation and handling will be provided in the Laboratory Manual.

With the consent of the subject, the remainder of the skin or lymph node biopsy specimens, i.e., the tissue that is left over after the study-specific tests are conducted, will be archived and the remainders of the specimens will be used in the development of an immunohistochemical assay for the semi-quantitative detection of CCR4. All specimens submitted for the purpose of the development of this assay should be managed by the investigator and his/her staff with adequate precautions to ensure subject confidentiality, in accordance with applicable national and/or local laws and regulations on personal data protection.

7.2.1.1.2 Disease Status/Other Biopsy Recommendations

Subjects with clinical features suggestive of LCT must have a biopsy performed within 4 months prior to Cycle 1 Day 1 to rule out transformed disease.

Skin biopsies at the end of the cycle and to confirm a CR are optional and can be performed at the discretion of the investigator. Analysis of these biopsies will be done by the pathologist at the study site.

Additional translational assessments may be performed to further characterize the response in skin on any biopsy samples obtained.

7.2.1.2 Skin Photographs

Cameras will be supplied to the study site by Canfield Scientific, Inc. for use in this study. All involved areas that are representative of the subject's extent of disease, will be selected at baseline and measured and photographed using the digital camera provided by Canfield. In addition, half-body global photos (waist to feet, waist to top of head and sides) will also be obtained. Photos should be taken against a blue backdrop.

Skin photographs should be obtained prior to administration of study drug on Day 1 of the first treatment cycle and then as specified in the Study Procedures tables.

Special care should be taken to shield the subject's identity in accordance with local guidelines on data privacy.

Photos must be labeled with only the subject identification number and initials. Digital photos will then be submitted on an ongoing basis to Canfield Scientific, Inc. for quality review. Canfield Scientific, Inc. will review photographs on an ongoing basis for assessment of image quality and provide feedback to sites to ensure the photographs are appropriately representative of extent of skin disease. (As of Amendment 8, submission of photographs to Canfield Scientific, Inc. is no longer required.)

More detailed instructions regarding photographing of skin lesions will be provided in the Photography User Manual.

7.2.1.3 Modified Severity Weighted Assessment Tool (mSWAT)

Skin lesions and erythema will be evaluated using the mSWAT.

The mSWAT is an objective, quantitative, severity-weighted method to assess the extent of skin lesions. An mSWAT score is derived by measuring each lesion as a percentage of total body surface area (%TBSA) and multiplying it by a severity-weighting factor (1 = patch, 2 = plaque, 4 = tumor). All individual numbers are then added to produce a total score.

Areas of skin involvement identified as patch, plaque, or tumor and erythema are defined in Table 7.2.1-1 and Table 7.2.1-2:

Table 7.2.1-1 Modified Severity Weighted Assessment Tool

Skin Lesion Definitions		
Lesion Type	**Abnormal Skin**	**Erythema**
Patch	Abnormal skin not elevated from normal skin	Flat erythema or erythema with mild infiltration
Plaque	Abnormal skin elevated from normal skin by < 5 mm	Elevated erythema or erythema with moderate infiltration
Tumor	Abnormal skin elevated from normal skin by ≥ 5 mm	Erythema with fissuring, ulceration, or tumor
mSWAT Score Calculation		

Sum of %TBSA from all body regions affected by patches x severity-weighting factor of 1
+ Sum of %TBSA from all body regions affected by plaques x severity-weighting factor of 2
+ Sum of %TBSA from all body regions affected by tumors x severity-weighting factor of 4
= Total mSWAT (maximum score = 400).

Table 7.2.1-2 Modified Severity Weighted Assessment Tool Score

Body region (%BSA)	Patch*	Plaque*	Tumor*
Head (7 %)			
Neck (2%)			
Anterior trunk (13%)			
Arms (8%)			
Forearms (6%)			
Hands (5%)			
Posterior trunk (13%)			
Buttocks (5%)			
Thighs (19%)			
Legs (14%)			
Feet (7%)			
Groin (1%)			
Subtotal of lesion BSA			
Weighting factor	x1	x2	x4
Subtotal lesion BSA x weighting factor			
mSWAT score = summation of each column line above =			

patch = any size lesion without induration or significant elevation above the surrounding uninvolved skin: poikiloderma may be present.
plaque = any size lesion that is elevated or indurated; crusting, ulceration or poikiloderma may be present.
tumor = any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

7.2.1.4 Response Criteria for Skin

Response in skin will be determined by changes in mSWAT score as specified in Table 7.2.1-3. Responses (CR and PR) must be confirmed for a minimum of 4 weeks.

Table 7.2.1-3 Response Criteria for Skin, as assessed by mSWAT scores[a]

Response	Definition
CR	100% clearance of skin lesions[b]
PR	50 to 99% clearance of skin disease from baseline without new tumors (T3) in subjects with T1, T2 or T4 only skin disease
SD	< 25% increase to <50% clearance in skin disease from baseline without new tumors (T3) in subjects with T1, T2 or T4 only skin disease
PD[c]	(1) ≥ 25% increase in skin disease from baseline or (2) New tumors (T3) in subjects with T1, T2 or T4 only skin disease or (3) Loss of response: in those with CR or PR, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse[d]	Any disease recurrence in those with CR

a: Based on mSWAT score.

b: A biopsy of normal appearing skin is unnecessary to assign a CR. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease where otherwise a CR would exist. If histologic features are suspicious or suggestive of MF/SS (see histologic criteria for early MF7), the response should be considered a PR only.

c: Whichever criterion occurs first.

d: For purposes of the study, relapse should be defined as loss of response (as defined for PD) in those with CR, ie, increase of skin score of greater than the sum of nadir plus 50% baseline score. Subjects may remain on treatment until subsequent measurement to confirm progression.

7.2.1.5 Pruritus Evaluation

The extent of pruritus can have a significant impact on the subject's QoL. A Likert scale (Appendix 9) will be completed by each subject to assess their degree of pruritus at the visits specified in the Study Procedures. The Itchy Quality of Life questionnaire (Desai, 2008) (see Appendix 5) will also be completed at these visits to further evaluate the impact of pruritus on their QoL. Medications taken to treat pruritus will be documented.

7.2.2 Evaluation of Blood Disease

7.2.2.1 Flow Cytometric Analysis

A peripheral blood sample will be used to evaluate circulating malignant T-cells and further assess immune cells in the blood.

Samples will be sent to a central laboratory designated by the Sponsor. Specific directions for sample preparation and packaging will be provided in the Laboratory Manual. (As of Amendment 10, central laboratory analysis of samples will no longer be performed [see Section 7.8].)

7.2.2.2 Response Criteria in Blood

In subjects with blood involvement, all blood responses (CR and PR) must be confirmed for a minimum of 4 weeks.

Response criteria are specified in Table 7.2.2-1.

Table 7.2.2-1 Blood Response Criteria[a]

CR[b]	B_0
PR[c]	> 50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain criteria for CR, PR or PD
PD[d]	(1) B_0 to B_2 or (2) > 50% increase from baseline and at least 5,000 neoplastic cells/µL or (3) Loss of response: in those with PR who were originally B_2 at baseline, > 50% increase from nadir and at least 5,000 neoplastic cells/µL
Relapse	Increase of neoplastic blood lymphocytes to ≥ B_1 in those with CR

a: As determined by absolute numbers of neoplastic cells/uL.
b: If a bone marrow biopsy was performed at baseline and determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR where blood assessment now meets criteria for B_0, a repeat bone marrow biopsy must show no residual disease or the response should be considered a PR only.
c: There is no PR in those with B_1 disease at baseline as the difference within the range of neoplastic cells that define B_1 is not considered significant and should not affect determination of global objective response.
d: Whichever occurs first.

7.2.3 Evaluation of Disease in Lymph Nodes and Viscera

7.2.3.1 Baseline Tumor Assessments

The baseline tumor burden will be assessed by CT of the neck, chest, abdomen and pelvis within 30 days prior to the first dose of study drug. The Investigator will identify, prospectively, the lesions to be followed to evaluate the subject's response to therapy. Lymph nodes must be > 15 mm in the long axis (greatest transverse diameter, GTD) or > 10 mm in the short axis if the GTD is > 10 to ≤ 15 mm.

Lymph node biopsies may be performed, at the discretion of the Investigator, to rule out inflammation or to confirm disease. Analysis of these biopsies will be done by the pathologist at the study site.

7.2.3.2 Method of Tumor Response Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at Screening and at reassessment during treatment. Imaging-based evaluation is preferred to evaluation by clinical examination when both

methods have been used to assess the anti-tumor effect of a treatment. Lesions evaluated clinically will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. Contrast enhanced CT will be considered the best currently available and reproducible method to measure target lesions selected for response assessment. For subjects who are allergic to contrast agents, non-contrast CT can be performed. The allergy must be documented on the Medical History eCRF. Ultrasound is not an acceptable method to measure disease. Central review of radiology may be performed to confirm the date of disease progression. Images should be transmitted to the central radiology group as described in the Imaging Manual.

7.2.3.3 Determination of Response in Lymph Nodes and Viscera

The Investigator will make a determination of response based on criteria as specified in Table 7.2.3-1 and Table 7.2.3-2. In subjects with lymph node and/or visceral involvement, responses (CR and PR) must be confirmed for a minimum of 4 weeks.

Table 7.2.3-1 Response in Lymph Nodes[a]

CR	All lymph nodes are now ≤ 15 mm in GTD by the method used to assess lymph nodes at baseline. In addition, lymph nodes that were ≤ 15 mm in GTD and > 10 mm in the short axis at baseline must now be ≤ 10 mm in the short axis.
PR	Cumulative reduction ≥ 50% of the SPD as compared to baseline and no new lymph node (> 15 mm in the GTD or > 10 mm in the short axis if the GTD is > 10 mm to ≤ 15 mm).
SD	Fails to attain the criteria for CR, PR, or PD
PD	Must meet any of the following: (1) ≥ 50% increase in SPD from baseline of lymph nodes, or (2) Loss of response, which is > 50% increase from nadir SPD of lymph nodes in subjects previously assessed as PR, or (3) > 50% increase compared to nadir, but which does not meet the criteria for PR (i.e., up to a 50% reduction compared to baseline), or (4) Any new nodal lesion > 15 mm in the GTD or >10 mm in short axis diameter if the GTD is > 10 mm to ≤ 15 mm)
Relapse	(1) Any new lymph node > 15 mm in GTD or >10 mm in short axis if the GTD is > 10 mm to ≤ 15 mm (2) Recurrence of any lymph node previously selected at baseline, which was previously assessed as a CR, but which has recurred and measures > 15 mm in the GTD or > 10 mm in the short axis if the GTD is > 10 mm to ≤ 15 mm.
Unable to Evaluate	A lymph node present at baseline, but which was not measured or which subsequently became unevaluable, leading to an inability to determine the status of that particular node for the time point in question.

a: Peripheral and central lymph nodes

GTD=greatest transverse diameter; SPD=sum of the products of the diameters

Table 7.2.3-2 Response in Viscera

CR	(1) 100% reduction in the SPD of all lesions selected at baseline. (2) Liver or spleen or any organ considered involved at baseline should be considered normal by imaging. (3) No nodules should be present on any imaging of liver or spleen.
PR	(1) ≥ 50% regression in all splenic or liver nodules, or in measurable disease (SPD) in all organs abnormal at baseline. (2) No increase in the size of liver or spleen consistent with disease progression and no new sites of involvement.
SD	Fails to attain the criteria for CR, PR, or PD
PD	Must meet any of the following: (1) > 50% increase in SPD of organs involved at baseline, or (2) New organ involvement, or (3) Loss of response, which is > 50% increase from nadir in the SPD of previous organ involvement in subjects previously assessed as PR, or (4) > 50% increase compared to nadir, but which does not meet the criteria for PR (i.e., up to a 50% reduction compared to baseline).
Relapse	(1) New organ involvement in subjects previously assessed as CR. (2) Recurrence of any lesion previously selected at baseline, which was previously assessed as a CR, but which has recurred and meets the measurement criteria (≥ 10 mm and/or 2× the reconstruction interval in the GTD).
Unable to Evaluate	An area of visceral disease present at baseline, but which was not measured or which subsequently became unevaluable, leading to an inability to determine the status of that particular area for the time point in question.

GTD=greatest transverse diameter; SPD=sum of the products of the diameters

7.2.4 Global Composite Response Score

Overall response will be based on response in each compartment (skin, blood, lymph nodes and viscera) as specified in Table 7.2.4-1.

Table 7.2.4-1 Global Composite Scoring System

Global Score	Definition	Skin	Nodes	Viscera	Blood
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI		
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD		
		PR	No category has a PD and if any other category involved at baseline, at least one has a CR or PR		
SD	Failure to attain CR, PR or PD	PR	No category has a PD and if any other category involved at baseline, no CR or PR in any		
		SD	CR/NI,PR,SD in any category and no category has a PD		
PD	Progressive disease	PD in any category			
Relapse	Recurrence of disease in prior CR	Relapse in any category			

NI=non-involved

Node, viscera and blood response contributes towards global response only if disease present at baseline, unless defining global PD which is met by new disease in previously uninvolved compartment. However, subjects who meet PD criteria in any compartment, or relapse in blood, lymph nodes or viscera, confirmed at 2 consecutive visits must be discontinued from study treatment due to disease progression/relapse. If subsequent assessment does not confirm PD in any compartment, or relapse in blood, lymph nodes or viscera, subject may continue on treatment. An unconfirmed PD/relapse would not preclude future responses (CR or PR).

If PD is documented in any compartment at any point leading to subject's discontinuation from treatment, the overall global composite score should be completed at that time even if all compartments have not been assessed.

7.2.4.1 Independent Review of Progression

A blinded independent review of response data for each subject will be performed to make a determination regarding progression and the date of progression. The nodal and visceral compartments evaluation will be based upon radiologic data. The independent radiology review of radiographic exams will provide an assessment of tumor response and progression for all subjects. A separate radiology charter will detail the roles and responsibilities of the radiology reviewers and how the reads will be performed. An independent reviewer (IR) will assess PFS based on date of progression or death, whichever comes first. For this assessment

the independent reviewer will be supplied the results of the independent radiology review, the mSWAT score for each subject, as assessed by the investigator, and the results of central flow cytometry in order to assess blood response, and date of death for subjects who died before progression.

Secondarily, the IR will review the date of any objective responses (CR or PR).

7.3 Pharmacokinetics (for subjects receiving KW-0761)

Serum samples will be drawn in subjects who receive KW-0761 (as first assigned therapy or crossover) at the timepoints specified in the Study Procedures Tables (Table 1, Table 2, and Table 3) for determination of KW-0761 concentration, through Cycle 3 and at the End-of-treatment Visit. At selected sites, 4 additional samples will be drawn between 6 and 8 hours, and at 24, 48, and 72 - 96 hours after the first infusion on Day 1/Cycle 1 in approximately 10 subjects, including crossover subjects. Blood samples obtained post-infusion should be obtained from the arm contralateral to that of study drug administration. The exact time of sample draw must be recorded in the eCRF.

All samples will be sent to a central laboratory designated by the Sponsor. Specific directions for sample preparation and packaging will be provided in the Laboratory Manual.

7.4 Quality of Life Assessments

Subjects with CTCL often suffer from the symptoms related to their disease (pain, sleep disturbance, etc.), the social and psychological problems related to sometimes unsightly skin lesions and the burden of living with a chronic disease. In an effort to assess some of these QoL issues, the Skindex-29 (see Appendix 6), FACT-G (see Appendix 7) and EQ-5D-3L (see Appendix 8) will be administered.

7.5 Follow-Up

All subjects will be contacted by telephone every 30 days (± 7 days) up to 90 days after the last dose of study medication or initiation of alternative therapy, whichever comes first, to confirm any new onset AEs or toxicities. If a subject who has received KW-0761 undergoes a stem cell transplant at any time during or after the 90-day follow-up period, AEs/SAEs should be documented from the transplant procedure through 180 days post-transplant.

During follow-up, medications used to treat an AE and those that are temporally associated with the AE and may have a causal relationship will be recorded. In all subjects who cross

over from vorinostat to KW-0761, the causality should be assessed for both drugs for 30 days after vorinostat was stopped (or later if the event is considered to be related to vorinostat).

- After a subject who receives KW-0761 goes off study, if CD4 and CD8 counts are less than 200/mm^3 at the End-of-treatment visit, they will be followed every 3 months (± 14 days) until they return to at least 200/mm^3, initiation of alternative therapy or 1 year, whichever comes first.
- In the absence of disease progression, all subjects or their referring physicians will be contacted every 3 months (± 14 days) until documented disease progression or death, or initiation of alternative therapy.
- All subjects or their referring physician will be contacted every 3 months (± 14 days) to ascertain survival status.
- For all subjects who have received KW-0761, subsequent stem cell transplant information should be recorded in a separate CRF provided by the Sponsor. For subjects who undergo transplant, concomitant medications and AEs/SAEs should be documented through 180 days post-transplant on the CRFs provided.
- All follow up information and attempts to obtain follow up information should be documented in the subject's source record.

7.6 Follow-Up for Subjects Achieving a Complete Response

Those subjects who do not continue treatment after achieving a CR will undergo the following assessments every 8 weeks (± 14 days) for the first 6 months (if CR achieved prior to one year on study) and then every 16 weeks (± 14 days) thereafter until progression:

- Chemistry/Hematology profile;
- Skin photographs;
- mSWAT;
- Pruritus evaluation;
- Blood sample for flow cytometric analysis;
- CT;
- Overall Disease Response;
- Immunogenicity (for subjects receiving KW-0761).

After progression of disease, subjects will be followed as applicable according to the procedures for post-treatment follow-up described in Section 7.5 including collection of transplant information for subjects who have received KW-0761.

7.7 Study Procedures for Subjects Continuing Study Treatment at the Time of Primary Efficacy Analysis

Subjects receiving study treatment at the time of the primary efficacy analysis may continue on study. For these subjects, administration of study drug(s) and data collection should continue as described below. Note: Initiation of disease evaluation assessments per institution/Investigator standard of care should not occur until notification by the Sponsor.

Study Drug Administration

- KW-0761 administration: KW-0761 may continue to be administered according to the protocol (as specified in Section 8.1) on Day 1 and Day 15 of each cycle until PD, drug intolerance or unacceptable toxicity, or until any of the other criteria for study removal are met (as defined in Section 5.5) or until KW-0761 is approved/not approved for marketing for the indication and regimen under study in the geographic region of study.
- Vorinostat treatment will continue to be administered as described in Section 5.2.2. Vorinostat will be supplied by the Sponsor for a period of up to 1 year after the data cutoff for the primary efficacy analysis. During this year all study subjects are eligible to cross over to mogamulizumab as described in Sections 3.4 and 5.3.

Safety: Safety data will continue to be collected as described in the protocol for as long as the subject receives study drug through 90 days after the last dose or initiation of alternative therapy whichever comes first (as described in Section 7.1).

If a subject who has received KW-0761 undergoes a stem cell transplant at any time during or after the 90-day follow-up period, transplant information should be documented as described in Section 7.5 including recording of concomitant medications and AEs/SAEs from the transplant procedure through 180 days post-transplant.

Efficacy: Efficacy data will be collected for 1 year after the time of the primary efficacy analysis. During that 1-year period, pending notification by the Sponsor, Investigators should follow study subjects in accordance with the standard of care at their Institution in order to assess subjects' disease status. Required data collection will be limited to the following (additional data may be collected at the discretion of the Investigator):

- At the time of disease progression or discontinuation from treatment for any other reason, sites are to perform the disease evaluation assessments per institution/Investigator standard of care. The method of assessment of PD, if applicable, should be recorded;
- PRO - Itchy QoL, Skindex-29, EQ-SD-3L, Likert, and FACT-G will be collected every 4 mos. (16 weeks) for as long as the subject receives study drug.

In addition, all subjects or their referring physician will continue to be contacted every 3 months (± 14 days) to ascertain survival status.

7.8 Study Procedures for Subjects Ongoing at the Time of Initial Marketing Authorization

For subjects who are continuing to receive KW-0761 at the time of initial marketing authorization, the Sponsor will supply study drug until KW-0761 becomes commercially available (reimbursable) in the country/region of the study site or until KW-0761 is not approved for marketing for the indication and regimen under study in the country/region of the study site.

Procedures to be followed for all ongoing subjects, i.e., subjects who are continuing to receive KW-0761 or who are in safety or survival follow-up, at the time of initial marketing authorization are described below. These procedures should be implemented upon notification by the Sponsor.

Study Drug Administration

KW-0761 may continue to be administered according to the protocol (as specified in Section 8.1) on Day 1 and Day 15 of each cycle until PD, drug intolerance or unacceptable toxicity, or until any of the other criteria for study removal are met (as defined in Section 5.5) or until KW-0761 becomes commercially available (reimbursable) or is not approved for marketing for the indication and regimen under study in the country/region of the study site. For subjects who experience an overall CR, the subject may continue treatment for up to 12 months (as described in Section 5.2.1.4) or until KW-0761 becomes reimbursable or is not approved.

KW-0761 should continue to be administered as described in Section 8.1.3.

Study Drug Accountability

Drug accountability must be maintained as described in Section 8.1.6.

Efficacy and Safety Assessments

Investigators should follow study subjects in accordance with the standard of care at their Institution with respect to assessments of disease status and safety/tolerability, including the use of local clinical laboratories. There will be no further central laboratory requirements.

Subjects who meet the protocol criteria for progression or relapse in one compartment but are clearly deriving benefit in other compartment(s), may remain on treatment at the discretion of the Investigator.

Survival follow-up will be discontinued for all subjects.

Data Collection

Electronic data capture will be terminated for all subjects at the time of implementation of Amendment 10.

Required data collection will be limited to SAEs and treatment-related AEs. These events will be reported only to the KKD Drug Safety Surveillance Department using the SAE form (see Section 9.4).

8 STUDY AGENTS

8.1 KW-0761 (mogamulizumab)

8.1.1 Description

[redacted]

8.1.2 Preparation of Dose

[redacted]

8.1.3 Study Drug Administration

Subjects will receive KW-0761 as an iv infusion over at least 1 hour for all infusions. Subjects will be observed closely for 1 hour following each administration of KW-0761 for

any potential AEs in an area with resuscitation equipment. Vital signs will be checked and recorded prior to start of infusion, at the end of the infusion and at 1 hour after completion of infusion.

Hematology results should be reviewed before each subsequent dose. Laboratory assessments may be performed the day prior to dosing to ensure results are available prior to dosing. The platelet count must be ≥ 100,000 / mm^3 and the ANC must be ≥ 1,500/mm^3 before a subject can receive study drug. If a scheduled dose cannot be given within the allowed window, the dose should be skipped and the subject should resume dosing with the next scheduled dose assuming the platelet count and ANC are within the parameters described above. If a subject misses 2 consecutive doses, contact the Medical Monitor or designee to determine if the subject should be withdrawn from the trial.

Should a hypersensitivity reaction to KW-0761 occur, the subject must be treated according to the best available medical practices. Subjects should be instructed to report any delayed reactions to the investigator immediately. See Section 5.2.1.7 for additional information regarding the treatment of infusion reactions.

8.1.4 KW-0761 Formulation and Storage

[redacted]

8.1.5 Packaging and Labeling of KW-0761

[redacted] will distribute the study drug to the pharmacies at the study sites in the US. [redacted] will distribute the study drug to the pharmacies at the study sites in Europe and Australia. [redacted] will distribute the study drug to the pharmacies at the study sites in Japan.

8.1.5.1 Labeling

Vial and carton labels will bear the appropriate text as required by each country's regulatory agency requirements.

8.1.6 Drug Accountability

The Principal Investigator and pharmacy at the study site are responsible for maintaining accurate records of the receipt, dispensing, and return of all investigational materials. The Investigator may dispense study drug only to subjects enrolled in the study. Under no circumstance will the Investigator allow study drug to be used other than as directed by the protocol.

The pharmacy designated by the Investigator, must maintain an inventory of drug supplies received, dispensed, and destroyed. All used and unused study drug must be accounted for. When a shipment is received, the Investigator or pharmacist must verify the quantities received and return the acknowledgement to the study monitor or designee. The study drug accountability record includes the identification of the person to whom the drug is dispensed, the lot number on the vial, the date of dispensing, and any returned or unused drug. An account must be given of any discrepancies. This record is in addition to information regarding dose recorded on the eCRF. These records must be readily available for inspection by KKD monitor or designee and are open to FDA or other regulatory authority inspection at any time. Copies of this record will be provided to the sponsor by the Investigator at the conclusion of the study.

8.1.7 Return and Destruction

Upon completion or termination of the study, all unopened vials of KW-0761 must be destroyed at the study site according to local regulations, unless other arrangements have been approved by KKD.

8.2 Vorinostat (ZOLINZA®) Capsules

8.2.1 Description

Vorinostat will be supplied by the Sponsor for a period of up to 1 year after 255 PFS events are observed. Vorinostat is a white to light orange powder. Each 100 mg capsule for oral administration contains 100 mg vorinostat and the following inactive ingredients: microcrystalline cellulose, sodium croscarmellose and magnesium stearate. The capsule shell excipients are titanium dioxide, gelatin and sodium lauryl sulfate. This agent is approved for

marketing in the US, Japan and Australia and is indicated for the treatment of progressive, persistent or recurrent CTCL. Since vorinostat is not approved in the EU, it will be labeled as an investigational drug according to applicable regulations. Investigators will use the supplies provided and will follow the FDA approved US prescribing information (e.g., dosage and administration, warnings, precautions, adverse reactions, dose modifications and omissions and storage information).

8.2.2 Administration

Subjects will receive 400 mg daily of vorinostat orally with food commencing on Day 1.

8.2.3 Vorinostat Adverse Events

The most common AEs (≥ 20%) are diarrhea, fatigue, nausea, thrombocytopenia, anorexia and dysgeusia. Please refer to the US prescribing information for more complete information.

8.2.4 Return and Destruction

Upon completion or termination of the study, all unopened containers of vorinostat must be destroyed at the study site according to local regulations, unless other arrangements have been approved by KKD.

9 ADVERSE EVENT REPORTING IN CLINICAL TRIALS

The Investigator will inquire about AEs at all subject visits by asking the subject a question such as: “How have you been feeling since your last visit?” All AEs, whether observed by the Investigator or reported by the subject, must be collected and recorded on the appropriate AE page of the eCRF and as appropriate on the SAE form (see Section 9.2). (See Section 7.8 for reporting requirements/procedures for subjects who are ongoing in the study (i.e., subjects who are continuing to receive KW-0761 or who are in safety or survival follow-up) at the time of initial marketing authorization).

The collection of AE information commences following the subject’s written Informed Consent to participate in the study. If a subject experiences an AE, the subject will receive appropriate treatment and supportive care as necessary, and the Investigator will continue to follow up until there is a return to the subject’s baseline condition, or until a clinically satisfactory resolution is achieved.

Timely and complete reporting of all AEs assists the Sponsor in identifying any untoward medical occurrence, thereby allowing: (1) protection of safety of study subjects; (2) a greater

understanding of the overall safety profile of the study drug; (3) recognition of dose-related study drug toxicity; (4) appropriate modification of study protocols; (5) improvements in study design or procedures; and (6) adherence to worldwide regulatory requirements. Every effort should be made to enter the AE information in the eCRF within 7 days of when the information becomes available in order to ensure timely reporting to the Sponsor.

9.1 Definitions

9.1.1 Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered an investigational product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

The description of each AE will identify the subject, date of onset, the date of resolution, the severity of the event, the action taken regarding study drug, the outcome of the event, and the relationship of the event to study drug. A medical condition present at screening that has increased in frequency or severity must be recorded on the AE page of the eCRF.

Standard medical terminology should be used to document AEs on the eCRF. The subject's exact description of the event will be recorded in the source documentation. In the case of signs and symptoms, the underlying illness or diagnosis will be recorded as the event when known.

For this study, disease progression will not be considered as an AE. Lymphopenia is the pharmacologic effect of the drug and will also not be considered an AE for this study. Lymphocytes will be monitored and evaluated with the laboratory data.

9.1.2 Adverse Event Severity

All AEs will be graded using CTCAE Version 4.0 as:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

a: Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b: Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
ADL=Activities of Daily Living

For AEs not contained within CTCAE, Version 4.0, the Investigator will assess the severity/grade of an AE according to the five grades above.

9.1.3 Adverse Event Relationship to Study Drug

The relationship of each AE to the study drug will be evaluated using the following guidelines:

Definitely Related

An AE that follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug) and that satisfies any of the following: (1) reappearance of a similar reaction upon re-administration (positive re-challenge); (2) positive results in a drug sensitivity test (skin test, etc.); (3) toxic level of the drug as evidenced by measurement of drug concentrations in blood or other bodily fluid.

Probably Related

An AE that follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug) and for which involvement of factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, can reasonably be excluded. This may also include positive dechallenge (event abates upon discontinuation of the investigational agent).

Possibly Related

An AE that follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug) and for which possible involvement of the drug can be suggested (for example previous similar reports or pharmacologic actions of the drug) although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments may also be responsible.

Unlikely

An AE that, while relationship to the drug cannot be definitively excluded, does not appear to follow a reasonable temporal sequence from administration of the drug or that appears to be reasonably explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

Not Related

An AE that does not follow a reasonable temporal sequence from administration of the drug or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

As of Amendment 10, relationship to study drug will be reported as related/not related per SAE form requirements (see Section 7.8).

9.2 Serious Adverse Events

Any AE that is initially considered serious or becomes serious should be reported on the SAE form.

A SAE is any untoward medical occurrence which:

- Results in death;
- Is immediately life threatening;
  - The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
  - If an event is Grade 4 by CTCAE version 4.0, it does not necessarily meet the definition for life-threatening.
- Requires in-patient hospitalization/admission or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is an important medical event:

- Those events that may not be immediately life-threatening or result in death or hospitalization but based upon appropriate medical and scientific judgment may jeopardize the subject or may require intervention to prevent one of the serious outcomes listed above. Examples include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; development of drug dependency or drug abuse.

All AEs, whether non-serious or serious, must be recorded on the AE page of the eCRF. In addition, any AE that is initially considered serious or becomes serious must be reported on the SAE form. The SAE information entered on the eCRF must be consistent with the information entered on the SAE form.

Serious adverse events require expeditious handling to comply with regulatory requirements. Any SAE occurring in a clinical study subject must be reported to the Sponsor or designee within 24 hours of the Investigator having knowledge of the SAE.

The Investigator or other qualified individual at the investigative site must complete the SAE form and fax it to the Sponsor or designee. All telephone communication regarding an SAE must be followed by a written report. In addition, SAE reports may require subsequent notification of the IRB and/or Ethics Committee (EC), if appropriate.

The Investigator is obligated to immediately report to the Sponsor or designee any SAE occurring at any time after the subject signs the Informed Consent Form and within 90 days after the last dose of study drug or initiation of alternative therapy whichever comes first, independent of the circumstances or suspected cause. In all subjects who cross over from vorinostat to KW-0761, the causality should be assessed for both drugs for 30 days after vorinostat was stopped (or later if the event is considered to be related to vorinostat). In addition, the Investigator must promptly report to the Sponsor any SAE occurring at any other time after completion of the study if a causal relationship to study drug is suspected. For all SAEs, the Investigator is obligated to pursue and provide information as requested by the Sponsor in addition to that requested on the SAE form. Information must include a description of the SAE in sufficient detail to allow for a complete medical assessment of the case and independent determination of causality. In the case of a subject death, a summary of autopsy findings, if available, must be submitted as soon as possible to the Sponsor. The Investigator will ensure that information reported immediately by telephone or other means and information entered on the SAE form is accurate and consistent.

9.3 Other Safety Considerations

Any clinically important changes noted during interim or final physical examinations, ECGs, x-rays, or any other potential safety assessments, whether or not these procedures are required by the protocol, must also be recorded on the appropriate eCRF page and SAE form, as appropriate, in order for the Sponsor to collect additional information about that abnormality, including information regarding relationship to study drug, any action taken, and resolution.

9.4 Adverse Event Contacts

All non-emergency inquiries and general information regarding this study should be directed to the Sponsor or designee.

Serious adverse event reports and follow-up SAE documentation for subjects in the US, UK, and Australia should be forwarded to the KKD Drug Safety Surveillance Department:

[redacted]

Serious adverse event reports and follow-up SAE documentation for subjects in Japan should be forwarded to the KHK Drug Safety Surveillance Department:

[redacted]

9.5 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB), whose composition, roles and responsibilities are described in a separate DSMB charter, will oversee subject safety in the trial. The DSMB consists of at least 2 medical doctors and a statistician.

10 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

The number of subjects enrolled and discontinued will be presented. A summary of reasons for discontinuation will be provided. The number of subjects in the Intent-to-Treat (ITT), Safety Analysis, and Efficacy Evaluable Sets (see Section 10.1) will be presented by treatment arm and combined.

Demographic and other baseline subject characteristics will be summarized by treatment arm for the ITT Set. These summaries will include demographics (including age, race, sex, height, weight, and body surface area) and baseline values for disease information.

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) for continuous variables and frequency distributions and percentages for discrete variables will be utilized.

10.1 Populations to be Analyzed

The following analysis sets will be used in the study:

- Intent-to-Treat Set: Includes all subjects randomized to a therapy and assigned a study number.
- Safety Analysis Set: Includes all subjects who received at least one dose of the assigned study agent (even a partial dose).
- Efficacy Evaluable Set: Includes all subjects who receive the first cycle of treatment and who have baseline and the Day 26-28 on-study assessment for response.
- Pharmacokinetic (PK) Analysis Set: All subjects who provide at least one post-dose KW-0761 concentration measurement will be included in the PK analysis dataset.

10.2 Analyses of Safety Data

The safety and tolerability of KW-0761 and vorinostat is determined by reported AEs, physical examinations, ECGS, vital signs, and laboratory tests. All summaries for the Safety Analysis Set will be prepared for each treatment arm. For those subjects in the vorinostat arm who cross over to KW-0761 treatment arm, AEs with an onset date/time after the first dose of KW-0761 will be summarized separately within that KW-0761 crossover group.

The World Health Organization (WHO) Drug Dictionary will be used to classify prior and concomitant medications by therapeutic class and Preferred Term. Prior medications include medications that were taken within 30 days prior to the Pre-treatment Visit. Concomitant medications include medications that started at any time and were taken at any time after the start of treatment until the end of the entire treatment period.

Adverse events are collected from the time the subject signs the ICF until 90 days after the last dose or initiation of alternative therapy, whichever comes first. In all subjects who cross over from vorinostat to KW-0761, the causality should be assessed for both drugs for 30 days after vorinostat was stopped (or later if the event is considered to be related to vorinostat). The NCI-CTCAE v4.0 system will be used to grade AEs. Treatment-emergent AEs will be grouped and tabulated by MedDRA preferred terms and system organ class. AEs will be

classified by body system, incidence, severity, and causality. All treatment-emergent AEs will be summarized showing the number and percent of subjects for each outcome.

The results from physical examination will be presented in the subject data listings. Vital sign measurements will be summarized at each time point. The incidence of clinically significant laboratory abnormalities will be presented, and laboratory data will be summarized at each time point by the NCI-CTCAE v4.0 toxicity grade. Laboratory data will be presented for subjects having Grade 3 or 4 changes from baseline by treatment arm.

Pre- and post-treatment serum samples will be assayed for development of human antibodies to KW-0761 (anti-KW-0761).

10.3 Analyses of Efficacy Data

Disease status will be assessed every 4 weeks in skin and blood. In the first year of treatment, response in lymph nodes and viscera and the overall global composite score will be documented every 8 weeks. After the first year, response in the lymph nodes and viscera and the overall global composite score will be documented every 16 weeks. Additionally, if clinical progression is noted, efficacy assessments are performed to fully document disease progression.

These assessments will be compared with the baseline assessment to determine response. Subjects will be evaluated for response in each compartment. Progressive-free survival, overall response, duration of response, and QoL will be analyzed. For any time-to-event endpoints, the date of disease progression will be determined by both the on-site investigator's assessment and the IR. All efficacy analyses will be conducted on both the ITT and Efficacy Evaluable sets.

The primary comparison of PFS between both arms will be performed on the ITT set based upon the results of the on-site investigator's assessment using a stratified Log-rank test at the one-sided 2.5% significance level. Stratification is done by disease type, either SS or MF, and disease stage, either IB/II or III/ IV. A similar secondary analysis will be performed on the results based on the IR. Each analysis will also be conducted for the Efficacy Evaluable Set. Progressive-free survival, which will be analyzed using Kaplan-Meier survival analysis methods, is defined as the time from the day of randomization to a treatment arm until documented progression or death. For subjects who exhibit conditions of disease progression, but continue on the study due to a questionable clinical impression as described in Sections 5.2.1.4 and 5.2.2.3, the subject is not considered to have progressed unless disease

progression is confirmed at least 4 weeks after the date of the initial questionable disease progression. In this case, the initial date will be used as the date of disease progression.

For PFS events, all deaths will be attributed to progression and, hence, the TTP will equal the time to death and will be uncensored. Subjects who die without a reported prior progression will still be considered to have progressed on the day of their death. In the event that a randomized subject withdraws from the study for any reason before documented progression, the time from the day of randomization to the last tumor assessment (from any compartment) will be used as a censored time point. For all subjects randomized to a treatment arm but withdrawing prior to first tumor assessment for any reason other than disease progression, the PFS time will be censored at the last documented visit. Sensitivity analyses for PFS will be performed, with the details specified in the Statistical Analysis Plan.

Frequency tables will be used to display best response. Best response will be presented for all subjects by treatment arm. The best overall response is the best response from the start of treatment until disease progression/recurrence. The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria. Response data will be analyzed for both the ITT and the Efficacy Evaluable Set for each treatment arm. Exact 95% confidence intervals for response rate will be calculated for each of these groups along with the difference in response rates between the 2 treatment arms. All 95% confidence intervals on individual rates will be computed using exact computational methods. Any confidence interval on the difference of proportions will be computed using exact unconditional confidence limits for the risk difference. These confidence intervals can be constructed using SAS version 9.2 with the **FREQ** procedure specifying the RISKDIFF option in the EXACT statement (Santner, 1980). ORR will be calculated as the proportion of subjects who are responders (CR and PR) and the 95% exact confidence interval for response will be calculated.

The duration of response (DOR), which will be estimated using survival analysis methods, is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that PD or death is objectively documented (taking as a reference for PD that smallest measurement recorded since the treatment started). Subjects who do not relapse will be censored at the day of their last tumor assessment. The DOR will be estimated separately for each treatment arm. Because the DOR is a conditional estimate (conditional on having a response), comparison between KW-0761 and vorinostat would not be based on randomized groups and therefore will not be made.

The Pruritus Evaluation (Likert scale & Itchy QoL) and Skindex-29, FACT-G and EQ-5D-3L assessments will be summarized at baseline and at the timepoints specified in the study procedures tables for each arm. The improvement (change from baseline) for each of these measures will also be summarized and analyzed using repeated measures ANCOVA utilizing time points through the 6-month assessment.

For those subjects who crossover from the vorinostat arm to the KW-0761 arm, these assessments within the second arm of the study will be measured at the end of the first cycle after the first day of dosing for KW-0761. Baseline measurements for crossover subjects are those documented closest to and before the first KW-0761 infusion. No statistical comparisons will be made for information gathered in the crossover from the vorinostat arm to the KW-0761 arm. All summaries for this arm will be purely descriptive.

Progression-free survival is the primary endpoint in this study. There are four key secondary endpoints in this study that require a comparison between treatment arms: ORR, Skindex-29, FACT-G, and EQ-5D-3L. Comparisons of these four secondary endpoints between the 2 treatment arms will be conducted using p-values that are adjusted to control the overall study-wise Type 1 error rate to be less than 0.05. Since these tests are not independent, the four secondary tests will be conducted using the Sidak adjusted p-value method defined as

Adjusted p-value = $\mathbf{1-(1-p)^4}$ where **p** is the original p-value of the individual test

These adjusted p-values will then be compared to .05 for each test.

Comparisons between treatment arms for all other secondary endpoints such as Likert scale, and Itchy QoL will be conducted with no adjustment for multiple comparisons used for those statistical tests. Exploratory subset analyses for PFS and any of the secondary endpoints by region, study site, compartment involvement, CCR4 expression status, disease subtypes, and medical history may be conducted. Details of such subset analyses will be provided in the Statistical Analysis Plan. Although overall survival (OS) is not a secondary endpoint, each subject will be followed in this study for a minimum of 2 years to generate information on OS. Using this follow-up information, a comparison between treatment arms for OS will also be conducted and considered exploratory. Statistical analyses on OS using follow-up data may take place after database lock for the study and will be reported as supplemental to the Clinical Study Report.

Randomization will be stratified within the 2 disease types, SS and MF and 2 disease stages IB or II and III or IV. The efficacy analyses described in this section will be conducted as stratified tests but may also be conducted as a subset analysis within each of these disease-type groups and disease stages. Comparison of endpoints between these 2 groups and

stages will be conducted for each treatment assuming adequate sample sizes in the respective groups.

Exploratory analyses based on other subject groupings and with other parameters may also be conducted.

Since the primary endpoint is PFS, the reference median PFS for vorinostat is assumed to be 169 days. The median PFS for KW-0761 therapy is targeted for 254 days, a 50% improvement over this reference median. For a 24-month accrual and 12 month follow-up on the last subject dosed, Table 10.3-1 gives the power and the number of PFS events required to show superior PFS for KW-0761 therapy over vorinostat at the one-sided 0.025 significance level. The ITT set is used for this primary analysis. The same analysis conducted using the Efficacy Evaluable set is considered secondary.

Under these assumptions, for the ITT population, a total of 255 PFS events will give 90% power (row is in bold in Table 10.3-1). For this study, the final primary analysis comparing PFS between treatment groups will not be conducted until 255 PFS events occur or until a maximum of 24 months after the last randomized subject's first dose, whichever comes first. In the event that the study is stopped prior to 255 PFS events are observed, the primary test will be performed at less than 90% power under the current assumptions according to Table 10.3-1.

Each of these calculations uses a log-rank test to compare the 2 survival curves. Sample size calculations were computed using SAS software version 9.3 using PROC POWER, Twosamplesurvival test = logrank.

Table 10.3-1 Required PFS Events and Power for Comparison of PFS Kaplan-Maier Curves Between the Vorinostat and KW-0761 Arms at the 0.025 Level

Vorinostat Median PFS = 169 Days, KW-0761 Median PFS = 254 Days		
Power	**Total Required PFS Events**	**Expected Total Sample Size to Achieve The Required Events**
90	**255**	**288**
89	247	280
88	239	270
87	231	262
86	225	254
85	218	248
84	212	240
83	206	234
82	201	228
81	196	222
80	191	216

The total sample size of 288 represents the approximate number of subjects that may be necessary for 255 PFS events to occur within the projected 36 months of the trial. If a 10% inflation factor is applied to this total (about 29 subjects) to take into account those subjects that may be lost to follow-up prior to documented progression, a total of 317 enrolled subjects may be necessary in order to observe 255 PFS events.

The observed rates of PFS events, recruitment, and drop-outs will be monitored throughout the study and may be used to alter the number of sites, the accrual period, and the follow-up period to achieve the required 255 PFS events in a timely manner. If the 255 PFS events are not observed within 36 months from the start of enrollment the study will be stopped at approximately 24 months after the last randomized subject's first dose.

10.4 Exposure-Response Analysis

Values for individual drug concentrations and descriptive statistics for each blood sample for PK assessment will be provided at each scheduled time point of collection.
Exposure-response analysis using population-based methods will be presented in a separate report.

11 ETHICAL ASPECTS

11.1 Ethics and Good Clinical Practice

This study will be conducted in compliance with the International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) guidance, and the most recent version

of the Declaration of Helsinki as amended in 2008. In addition, all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents in the countries involved will be adhered to.

11.2 Ethics Committee/Institutional Review Board

Prior to implementation of the study, the protocol and the proposed informed consent form must be reviewed and approved by a properly constituted EC/IRB. A dated statement that the protocol and informed consent have been approved by the EC/IRB must be provided to the Sponsor prior to study initiation. Any amendments to the protocol will also require EC/IRB approval, except in the case of changes made to protect subject safety, which may be implemented immediately. The name and occupation of the chairperson and the members of the EC/IRB will be provided.

The Investigator will provide progress reports to the EC/IRB as required by the EC/IRB. The Investigator will provide a final report to the EC/IRB within three months after completion of participation in the study.

The Investigator will not start this study, nor will study drug be shipped to the Investigator's site, before providing the Sponsor or designee with evidence of EC/IRB approval.

11.3 Informed Consent

The Investigator must explain to each subject the research nature of the study, its purpose, procedures, expected duration and the potential risks and benefits involved in study participation. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her right to the most appropriate medical treatment or affect the doctor/subject relationship.

The informed consent should be given by means of a standard written statement. The informed consent document should be written so as to be easily understood by the subject or the subject's legal representative. The subject or the subject's legal representative should be given time to read and understand the information before signing the informed consent document. The subject should receive a copy of the written informed consent document once he/she has signed.

If signed consent is not possible, then it is also possible to obtain consent orally, in which case, the act of informed consent should be established by an additional signed statement from an independent witness. The Investigator should explain in the chart why direct-signed

consent was not possible. Each investigator must provide a copy of the signed informed consent form to the subject. A subject may not be admitted to the study unless informed consent of the subject (or his/her legally authorized representative) has been obtained.

Subjects will be asked to consent to allow the sponsor, sponsor representative or regulatory auditor to review their medical records to confirm compliance with GCP and the protocol.

The standard written informed consent statement forms a part of the protocol that is submitted to the EC/IRB for approval. The Investigator must submit a specimen copy of the EC/IRB-approved informed consent document to be used in the study before the study is initiated.

12 INVESTIGATOR OBLIGATIONS AND STUDY MANAGEMENT

12.1 Administrative

All references to KKD in this section include all designees e.g., Contract Research Organizations or Consultants acting on behalf of KKD.

12.2 Changes in Protocol

Any change to the protocol will be made by written amendment to the Investigational New Drug Application (IND) and Clinical Trial Authorization (CTA) (if required) and approved by KKD and the Principal Investigator(s) before the change is implemented. All amendments to the protocol and informed consent form, which require regulatory and/or EC/IRB approval/favorable opinion, must be reviewed and approved by KKD, the EC/IRB and/or local authorities before being implemented. Amendments should not be implemented until all necessary approvals have been obtained, except when necessary to eliminate an immediate hazard(s) to study subjects.

12.3 Protocol Deviations

KKD, as the protocol sponsor, is responsible for implementing and maintaining quality assurance and quality control to ensure that studies are conducted according to the protocol, GCPs and all applicable regulatory requirements. A protocol deviation is any noncompliance with the protocol. Noncompliance can be on the part of the study participant, the Investigator or the study site staff. Deviations to the protocol are not permitted except when necessary to eliminate an immediate hazard(s) to study subjects.

12.4 Monitoring and Quality Assurance

The Sponsor of this study, KKD, has responsibilities to health authorities to take all reasonable steps to ensure the proper conduct of the study as regards to ethics, protocol adherence, integrity, validity of the data recorded on the eCRF and adherence to regulations regarding GCP and the protection of human subjects.

If the study site has not participated in a KKD sponsored trial within the past year, KKD or its designee will assess the study site prior to study initiation to verify the qualifications of the Investigator, inspect the study site's facilities and inform the Investigator of his/her responsibilities and the procedures for ensuring adequate and correct documentation.

During the course of the study, the study monitor will make routine site visits to review protocol compliance, compare eCRFs with individual subject's original source documents, assess drug accountability and ensure that the study is being conducted according to the pertinent regulatory requirements. The review of the subject's medical record will be performed in a manner to ensure that the subject's confidentiality is maintained. Monitoring visits will occur approximately every 6-8 weeks. Frequency of visits may be modified based on the rate of enrollment or as otherwise necessary to ensure GCP compliance. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing case report forms, are resolved.

Regulatory authorities and/or the KKD staff may carry out source document verification visits and/or site inspections/audits. Direct access to original source data will be required for inspections/audits, which will be carried out giving due consideration to data protection and subject confidentiality.

12.5 Electronic Case Report Forms (eCRFs) and Source Documentation

The investigator is required to prepare and maintain adequate and accurate case histories (i.e., medical records) designed to record all observations and other data pertinent to the study for each study participant.

It is the responsibility of the Principal Investigator to prepare and maintain adequate and accurate eCRFs that have been designed by the Sponsor to record all observations and other data pertinent to the clinical investigation.

Electronic Case Report Forms are used to record information collected in the performance of this study and to transfer the data into the study database. These eCRFs are organized as an ordered series of electronic data entry modules specific for each scheduled and unscheduled study visit.

The electronic data capture (EDC) users at the study site will exercise due diligence in ensuring that study subject data are entered accurately and in their entirety from the investigative site's source documents and flow sheets into the appropriate data entry fields. Only staff listed on the "Delegation of Authority" page in the study file notebook and who have been appropriately trained will be issued a user ID enabling them to make entries and edits to the electronic trial database and to respond to queries. Only the Principal Investigator will be issued a user ID allowing the application of an electronic signature to a completed

study subject record signifying the data has been reviewed and verified as complete and accurate.

Upon completion of the study, validated study subject records will be published electronically along with the Principal Investigator's electronic signature in a Portable Document Format (PDF) file and transferred to a CD-ROM. The compact disc(s) will then be distributed to the Study Site to be retained by the Principal Investigator as a component of the required records for this study.

At the time of implementation of Amendment 10, the electronic data capture system defined as the clinical database will be terminated for all subjects (see Section 7.8).

12.6 Record Retention

Study data and other essential documents should be retained by the study site for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements. KKD or its designee will inform the investigator, in writing, as to when these documents no longer need to be maintained.

12.7 Confidentiality

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure the confidentiality of those data, and in accordance with applicable national and/or local laws and regulations on personal data protection.

Monitors, auditors, and other authorized agents of KKD and/or its designee, the EC/IRBs approving this research, and the regulatory authorities, as well as that of any other applicable government agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

12.8 Disclosure

By conducting this study, the Investigator agrees that all information provided will be maintained by the Investigator and his/her staff in strict confidence. Such information may be communicated to the Scientific Committee and/or EC/IRB under a similar, appropriate understanding of the confidential nature of the information. Study documents provided (protocols, IBs, case report forms and other material) will be stored appropriately to ensure their confidentiality. It is understood that the confidential information provided to the Investigator will not be disclosed to others without written authorization from KKD, except to the extent necessary to obtain informed consent from those subjects who are eligible and choose to participate in the study.

Such information will not be provided to potential subjects by telephone or to any other individual.

12.9 Termination of Study

The Sponsor reserves the right to terminate the study or individual study sites at any time. Reasons for study termination include, but may not be limited to, manufacturing problems, a request to discontinue the study from a regulatory authority, a corporate decision to discontinue development of KW-0761, AE incidence or severity not consistent with the potential benefit of the drug, poor enrollment or inadequate adherence to GCP guidances. In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interest. If the trial is terminated prematurely, the EC/IRB and regulatory authorities (if required) will be notified.

12.10 Final Report/Publications

The study is part of a multicenter study; accordingly, the Institution and Principal Investigator of the study agree that the first publication of the results of the study shall be made in conjunction with the presentation of a joint, multicenter publication of the study results with the Investigators and the Institutions from all appropriate sites contributing data, analyses and comments. However, if such a multicenter publication is not submitted within 12 months after the database has been locked, abandonment or termination of the study at all sites, or after Sponsor confirms there will be no multicenter study publication, the Institution and/or such Principal Investigator may publish the results from the institution site individually in accordance with the following requirements. Prior to submission of any materials for publication or presentation, the Institution will provide such materials or manuscript to the

Sponsor for review. Details of the Sponsor's publication policy can be found in the Clinical Trial Agreement.

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14 APPENDICES

Appendix 1 Modified ISCL/EORTC Revisions to the TNMB Classification of MF/SS

Appendix 2 Eastern Cooperative Oncology Group (ECOG) Scale

Appendix 3 NYHA Classification

Appendix 4 Autoimmune Screening Questionnaire

Appendix 5 Itchy Quality of Life Questionnaire

Appendix 6 Skindex-29

Appendix 7 FACT-G

Appendix 8 EQ-5D-3L

Appendix 9 Likert Scale for Pruritus Evaluation