Protocol Addendum IDRM06-AD07/J2T-DM-KGAA (11)

A Long-Term Study to Assess the Safety and Efficacy of Lebrikizumab in Patients with Moderate-to-Severe Atopic Dermatitis

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Title Page

Protocol Title:
A Long-Term Study to Assess the Safety and Efficacy of Lebrikizumab in Patients with Moderate-to-Severe Atopic Dermatitis

Protocol Number: DRM06-AD07/J2T-DM-KGAA

Addendum Number: 11

Addendum Statement: This addendum is to be performed in addition to all procedures required by protocol DRM06-AD07/J2T-DM-KGAA or any subsequent amendments to that protocol.

Compound: Lebrikizumab (DRM06/LY3650150)

Sponsor Name: Dermira, Inc., a wholly owned subsidiary of Eli Lilly and Company
Legal Registered Address: Lilly Corporate Center, Indianapolis, IN 46285 USA

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Document ID: VV-CLIN-134334

Protocol Addendum Substantiality

Not applicable; this study addendum does not include any sites in the European Union.

Table of Contents

1. Rationale for Addendum

The rationale for this addendum is to add the Q8W dosing regimen for lebrikizumab to Study J2T-DM-KGAA (KGAA) via extending the study treatment period by an additional 32 weeks beyond the main protocol.

This addendum will apply only to KGAA study participants who

- meet the addendum entry criteria, and
- are included in the study sites in the following countries:
  - Australia
  - Canada
  - Korea
  - Mexico
  - Singapore
  - Taiwan, and
  - the United States.

See Section 2.1 of this addendum for rationale for including the Q8W dosing regimen for lebrikizumab.

2. Protocol Additions

The procedures described in this addendum are in addition to the requirements of the main KGAA protocol, unless otherwise specified. Some of the information is repeated from the main KGAA protocol for clarity. The original section numbers from the protocol are included in the addendum headings for ease of reference.

2.1. Protocol Section 1.4. Rationale for Dose and Treatment Regimen

To date, the Q8W dosing regimen of lebrikizumab has not been evaluated in clinical trials.

This proposed dosing regimen was selected for this addendum based on the AD Phase 3 data, including the PK-PD modeling for efficacy in AD.

Lebrikizumab demonstrated a durable treatment effect in the Phase 3 AD studies. In addition, the placebo (lebrikizumab withdrawal) arm in the maintenance period exhibited a durable and prolonged efficacy response after the last dose of lebrikizumab at Week 14, with a slow and gradual decline in response noted by Week 52.

These Phase 3 clinical data, together with the long half-life of lebrikizumab (mean = 24.5 days), prompted Lilly to evaluate a 250 mg Q8W dosing frequency CCI

2.2. Protocol Section 2. Study Objectives and Endpoints

The primary objective of this addendum is to assess efficacy of lebrikizumab 250 mg Q4W and Q8W during the additional 32 weeks of extension treatment. The endpoints for this addendum include

- proportion of patients who achieve IGA 0 or 1 at Week 32, and
- proportion of patients who achieve EASI-75 (≥75% reduction in EASI from baseline of parent study) at Week 32.

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E. Handling of ICEs:

a. Treatment discontinuation due to lack of efficacy: composite strategy. Patients who discontinue treatment due to lack of efficacy will be considered as treatment failures (non-responders).

b. Treatment discontinuation due to any other reasons: a hypothetical strategy will be used to estimate what the response would have been if subjects continued with treatment.

c. Dose modification to lebrikizumab 250 mg Q2W: composite strategy. Patients whose dose is modified to lebrikizumab 250 mg Q2W will be considered as treatment failures (non-responders).

2.3. Protocol Section 3. Study Design

Eligible patients will enter this 32-week open-label extension of the study and will be randomly assigned to the following lebrikizumab treatment groups, regardless of their previous treatment regimen (that is, Q2W or Q4W):

- lebrikizumab 250 mg Q4W, or
- lebrikizumab 250 mg Q8W

See Section 2.5 of this addendum for randomization ratio and stratification factors.

Patients who complete this study addendum or who terminate early will return to the clinic for a safety follow-up visit 12 weeks after the last study drug injection.

A patient is considered to have completed the study addendum if he/she has completed all required phases of the study, including the last visit as shown in the Schedule of Visits and Procedures of this addendum (Section 2.14).

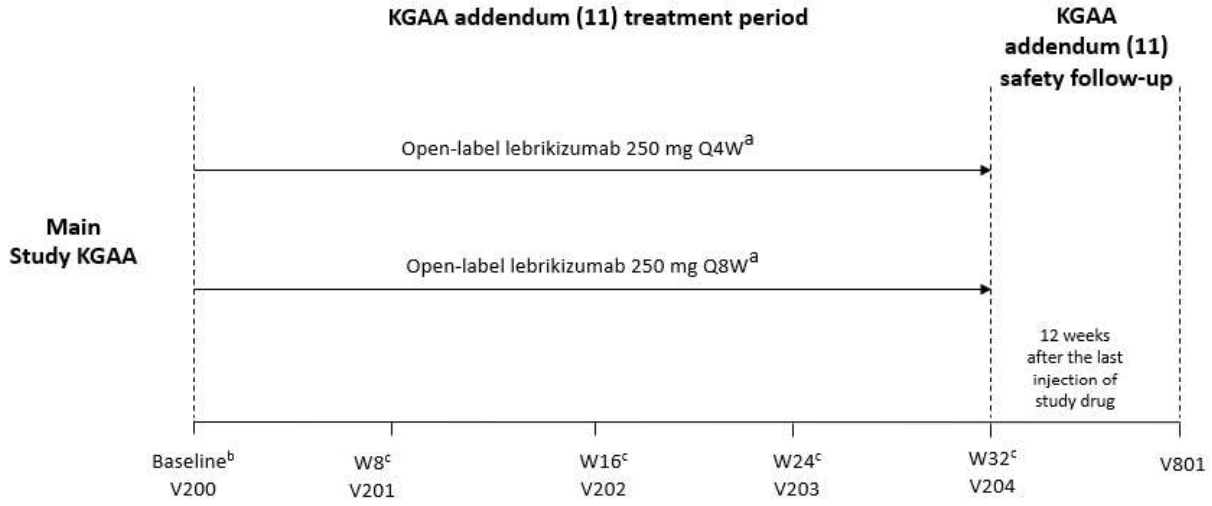
The end of the study for participants in the KGAA addendum (11) is defined as the date of the last visit of the last patient in the study shown in the Schedule of Visits and Procedures for this addendum.

Dose modification

Starting from Visit 201, patients enrolled in this study addendum who do not maintain an EASI-50 response (from the parent study baseline) will move to lebrikizumab 250 mg Q2W for the remainder of this addendum.

Addendum schema

This schema summarizes the design of this addendum.



[a] Starting at Visit 201 of this addendum, patients who do not maintain an EASI-50 response (from the parent study baseline) will move to lebrikizumab 250 mg Q2W dosing regimen for the remainder of this addendum.

[b] Patients may enter the addendum

- at Week 100 of Study KGAA, or
- after Week 100 of Study KGAA provided they have not yet completed the safety follow-up visit for Study KGAA.

[c] From KGAA addendum (11) baseline.

2.3.1. Protocol Section 3.1. Duration of the Study

The maximum duration of a patient's participation in this study addendum will be up to 42 weeks (32 weeks of the open-label extension period plus addendum safety follow-up visit 12 weeks following the last injection of study drug).

2.3.2. Protocol Section 3.2. Study Population and Number of Patients

Up to approximately 213 patients are expected to enroll in this study addendum:

- Q4W treatment group: N = 106
- Q8W treatment group: N = 107

2.4. Protocol Section 4. Selection of Patients

2.4.1. Protocol Section 4.1. Inclusion Criteria

Patients must meet all the following criteria to be eligible for this study addendum:

[1] Have completed Week 100 (Visit 11) of Study KGAA and have not yet completed the safety follow-up visit for the main study.

[2] Are willing and able to comply with all clinic visits and addendum-related procedures.

[3] For women of childbearing potential: agree to remain abstinent (refrain from heterosexual intercourse) or use a highly effective contraceptive method during the treatment period and for at least 18 weeks after the last dose of lebrikizumab.

NOTE: A woman of childbearing potential (WOCBP) is defined as a postmenarcheal female, who has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause) and has not undergone surgical sterilization (removal of ovaries and/or uterus).

NOTE: The following are highly effective contraceptive methods: combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation, progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, bilateral tubal ligation, vasectomized partner, or sexual abstinence. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
If the highly effective contraceptive methods are contraindicated or strictly declined by the patient, acceptable birth control methods may be considered. These may include a combination of the following methods:

- male or female condom with spermicide, and
- cap, diaphragm, or sponge with spermicide.

[4] Male patients are not required to use any contraception except in compliance with specific local government study requirements.

[5] Have given written informed consent for participating in this addendum that has been approved by the ethical review board governing the site prior to any addendum-specific procedures being initiated.

2.4.2. Protocol Section 4.2. Exclusion Criteria

Patients meeting any of the criteria below will not be included in this study addendum:

[1] Have, during their participation in Study KGAA, developed a serious adverse event (SAE) deemed related to lebrikizumab, which in the opinion of the investigator or of the medical monitor could indicate that continued treatment with lebrikizumab may present an unreasonable risk for the patient.

[2] During their participation in Study KGAA, developed an AE that was deemed related to lebrikizumab and led to study treatment discontinuation, which in the opinion of the investigator or of the medical monitor could indicate that continued treatment with lebrikizumab may present an unreasonable risk for the patient.

[3] Developed conditions in Study KGAA consistent with protocol-defined criteria for permanent study drug discontinuation, if deemed related to lebrikizumab or led to

investigator- or sponsor-initiated withdrawal of patient from the study (e.g., non-compliance, inability to complete study assessments, etc.).

[4] Have initiated treatment with a medication prohibited by Study KGAA (see Section 6 of the main KGAA protocol) before addendum baseline. This includes use of biologics for AD (for example, dupilumab and tralokinumab) during the safety follow-up period of Study KGAA.

[5] Are pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study.

2.5. Protocol Section 5.3. Study Drug Assignment

Patients eligible to participate in this open-label study addendum will be randomly re-assigned to the Q4W and Q8W treatment groups in a 1:1 ratio.

Participants will be stratified at the addendum baseline by

- IGA score (0,1 vs. >1), and
- region (US vs. non-US).

2.6. Protocol Section 5.4. Study Blinding

This addendum is open label.

2.7. Protocol Section 6. Concomitant Medications and Procedures

See Section 6 of the main KGAA protocol and Exclusion Criterion 4 for this addendum.

2.8. Protocol Section 7. Study Procedures

See the Schedule of Visits and Procedures for this addendum (Section 2.14).

2.9. Protocol Section 8.4. Study Termination

For discontinuation criteria, see the following sections of the main KGAA protocol:

- Section 8.4.1: early termination of study patients
  Exception: The following discontinuation criterion from the main protocol will *not* apply to this addendum: “Not achieving an EASI-50, from parent study baseline, by Week 16, maintaining an EASI-50 response, or not achieving clinical benefit based on PI discretion should be terminated from this study.” As indicated in Section 2.3 of this addendum, patients who do not maintain an EASI-50 response (from the parent study baseline) will move to lebrikizumab 250 mg Q2W.
- Section 8.4.3: temporary and permanent discontinuation of study drug

2.10. Protocol Section 9.1. General Statistical Methodology

All statistical processing will be performed using SAS® unless otherwise stated.

Descriptive statistics will be used to provide an overview of the efficacy results. For categorical parameters, the number and percentage of patients in each category will be presented. For

continuous parameters, descriptive statistics will include n (number of patients), mean, standard deviation, median, minimum, and maximum.

Demographic data will be summarized by treatment group using descriptive statistics.

The number of patients in each analysis set will be summarized. Reasons for study withdrawal and treatment withdrawal during the study will be summarized using frequencies and percentages by treatment group.

A statistical analysis plan (SAP), describing all statistical analyses will be provided as a separate document.

2.10.1. Protocol Section 9.1.1. Populations Analyzed

Efficacy analysis will be performed using the ITT population. The ITT population consists of all patients assigned to treatment in this study addendum, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow this addendum.

2.10.2. Addendum Baseline Definition

Patients may enter the addendum

- at Week 100 of Study KGAA, or
- after Week 100 of Study KGAA provided they have not yet completed the safety follow-up visit for Study KGAA.

For the efficacy measures, addendum baseline is defined as the last available value before the first injection in this addendum period, which in most cases will be the value recorded at the addendum baseline visit (Visit 200). Efficacy analysis will be reported by visit from the addendum baseline visit to Week 32 of the addendum period. The baseline used to derive efficacy endpoints is the parent study baseline.

2.11. Protocol Section 9.2. Efficacy Assessments

The following efficacy assessments will be summarized:

- proportion of patients with IGA score 0 or 1 at Week 32, and
- proportion of patients with EASI-75 (≥75% reduction in EASI scores compared to parent study baseline) at Week 32.

Supportive estimand for the primary endpoints will be provided in detail in SAP.

No statistical testing will be performed.

2.12. Protocol Section 9.3. Exposure and Compliance

Details will be provided in the SAP for this addendum.

2.13. Protocol Section 9.6. Sample-Size Determination

This addendum will aim to enroll up to approximately 213 patients into the additional 32-week extension treatment period. The sample size is based on the number of patients available in Study KGAA at the time of addendum approval and is not based on a statistical power calculation. After 32 weeks of treatment in this addendum, a sample size of 106 per arm will provide 95% confidence intervals (CIs) of

- 76% to 90% based on a hypothesized EASI-75 response rate of 83% for Q4W, and
- 60% to 78% based on a hypothesized 69% response rate for Q8W.

2.14. Appendix 1. Schedule of Visits and Procedures for KGAA Addendum (11)

Note: For information on assessments that do not need to be repeated at addendum baseline, see footnotes 1 and 3 below.

Study Procedure						
Week (W)	**KGAA Addendum (11) Study Periods**					
	Baseline[1]	**32-Week Open-Label Extension Period**				**Safety Follow-Up Visit**
		8W from KGAA Addendum (11) Baseline	**16W from KGAA Addendum (11) Baseline**	**24W from KGAA Addendum (11) Baseline**	**32W from KGAA Addendum (11) Baseline/ Addendum ET**	**12W After the Last Injection of Study Drug**
Visit Number	200	201	202	203	204	801
Visit Window	At or up to 10 weeks after W100 of Study KGAA[1]	±5d	±5d	±5d	±5d	±5d
Enrollment						
Informed Consent/Assent for KGAA Addendum (11)	X					
Inclusion/Exclusion Criteria for KGAA Addendum (11)	X					
Safety						
Physical Exam	X				X	
Height and Weight	X[2]				X[2]	
Vital Signs	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X
Concomitant Medications/Procedures	X	X	X	X	X	X
Hematology, Chemistry	X[3]				X	
HBV DNA[4]	X		X		X	
Estradiol or Testosterone[5]	X[3]				X	
Urinalysis	X[3]				X	
Pregnancy Testing[6]	X	X	X	X	X	
Efficacy						
IGA	X	X	X	X	X	
BSA	X	X	X	X	X	
EASI	X	X	X	X	X	
POEM (in office collection only)[7]	X	X	X	X	X	

Study Procedure						
Week (W)	**KGAA Addendum (11) Study Periods**					
	Baseline[1]	**32-Week Open-Label Extension Period**				**Safety Follow-Up Visit**
		8W from KGAA Addendum (11) Baseline	**16W from KGAA Addendum (11) Baseline**	**24W from KGAA Addendum (11) Baseline**	**32W from KGAA Addendum (11) Baseline/ Addendum ET**	**12W After the Last Injection of Study Drug**
PK and Immunogenicity						
Pre-dose PK[8]	X[3]	X	X	X	X	X
Pre-dose ADA[8,9]	X[3]			X	X	X
Study Treatment						
Study Drug Administration[10]	X	X	X	X		
Dispense Study Drug[11]	X	X	X	X		

[1] Patients may enter the addendum
- at Week 100 of Study KGAA, or
- after Week 100 of Study KGAA provided they have not yet completed the safety follow-up visit for Study KGAA.

Unless specified otherwise, if the baseline visit for this addendum occurs on the same day as Week 100 visit for Study KGAA, do not repeat assessments completed at Week 100.

[2] Collect height in adolescents only at these visits. Collect weight in all patients.

[3] Do not repeat this assessment at the addendum baseline if it was completed within 4 weeks from the Week 100 visit of the main study.

[4] Only for participants who are anti-HBc reactive and anti-HBs nonreactive at screening (Section 8.2.3 of the KGAA protocol) or participants who are anti-HBc reactive and anti-HBs reactive at parent study screening (KGAA Addendum (10), if applicable).

[5] Collect estradiol in adolescent females only and testosterone in adolescent males only. Stop hormone tests when the patient reaches 18 years of age.

[6] Urine pregnancy tests for women of childbearing potential (Section 8.2.3 of the main KGAA protocol).

[7] In-office POEM only collected for patients who participated in DRM06-AD04, DRM06-AD05, DRM06-AD06, and DRM06-AD18. In-office POEM should be completed prior to any other study assessments.

[8] PK and ADA are pre-dose collections if a dose is administered at the visit.

[9] Neutralizing antibodies testing conducted for positive treatment-emergent ADA responses. Additional immunogenicity sample collected for any patient experiencing a hypersensitivity reaction during study.

[10] For patients assigned to Q4W or Q2W dosing, study drug administration will also occur between visits (at home).

[11] Sufficient drug is dispensed to cover injections through next visit.

Acronyms

Acronym	Term
AD	atopic dermatitis
ADA	anti-drug antibody
AE	adverse event
BSA	body surface area
CI	confidence interval
d	day
EASI-50 or -75	Eczema Area and Severity Index: 50% or 75% improvement from baseline
ET	early termination
HBV	hepatitis B virus
ICE	intercurrent event
IGA	Investigator's Global Assessment
ITT	intent to treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
MCMC-MI	Markov Chain Monte Carlo – Multiple Imputation
PD	pharmacodynamic
PI	principal investigator
PK	pharmacokinetic
POEM	Patient Oriented Eczema Measure
Q2W	every 2 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
SAE	serious adverse event
SAP	statistical analysis plan
V	visit
W	week

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