

I6T-MC-AMAJ(1.1) Clinical Protocol Addendum

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Efficacy and Safety of Mirikizumab to Secukinumab and Placebo in Patients with Moderate-to-Severe Plaque Psoriasis (OASIS-2)

NCT03535194

Date: 26-Apr-2018

**1. Protocol Addendum I6T-MC-AMAJ(1.1)  
A Multicenter, Randomized, Double-Blind, Placebo-  
Controlled Study Comparing the Efficacy and Safety of  
Mirikizumab to Secukinumab and Placebo in Patients with  
Moderate-to-Severe Plaque Psoriasis  
OASIS-2**

**Confidential Information**

The information contained in this protocol addendum is confidential and is intended for the use of clinical investigators. It is the property of Eli Lilly and Company or its subsidiaries and should not be copied by or distributed to persons not involved in the clinical investigation of mirikizumab (LY3074828), unless such persons are bound by a confidentiality agreement with Eli Lilly and Company or its subsidiaries. This document and its associated attachments are subject to United States Freedom of Information Act (FOIA) Exemption 4.

Mirikizumab (LY3074828)

This addendum is to be performed in addition to all procedures required by protocol I6T-MC-AMAJ or any subsequent amendments to that protocol.

Eli Lilly and Company  
Indianapolis, Indiana USA 46285

Protocol Addendum (1) Electronically Signed and Approved by Lilly: 8 March 2018.  
Revised Protocol Addendum(1.1) Electronically Signed and Approved by Lilly on date  
provided below.

Approval Date: 26-Apr-2018 GMT

## 2. Table of Contents

### Protocol Addendum I6T-MC-AMAJ(1.1) A Multicenter, Randomized, Double-Blind, Placebo- Controlled Study Comparing the Efficacy and Safety of Mirikizumab to Secukinumab and Placebo in Patients with Moderate-to-Severe Plaque Psoriasis OASIS-2

Section	Page
1. Protocol Addendum I6T-MC-AMAJ(1.1) A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Efficacy and Safety of Mirikizumab to Secukinumab and Placebo in Patients with Moderate-to-Severe Plaque Psoriasis OASIS-2 .....	1
2. Table of Contents .....	2
3. Rationale for Addendum .....	6
4. Protocol Additions .....	8
4.1. Section 2: Schedule of Activities .....	8
4.2. Section 4: Objectives and Endpoints .....	12
4.3. Section 5: Study Design .....	12
4.4. Section 6: Study Population .....	15
4.5. Section 7.7: Concomitant Therapy .....	17
4.6. Section 8.2: Discontinuation from the Study .....	19
4.7. Section 9: Study Assessments and Procedures .....	19
4.8. Section 10: Statistical Considerations .....	21
5. References .....	23

**List of Tables**

<b>Table</b>	<b>Page</b>
Table AMAJ(1).1. Objectives and Endpoints.....	12
Table AMAJ(1).2. Excluded Classes of Concomitant Medications or Classes with Restricted Use .....	18

**List of Figures**

**Figure**

**Page**

Figure AMAJ(1).1. Illustration of study design for Clinical Protocol I6T-MC-AMAJ  
addendum (1)..... 14

**List of Attachments**

<b>Attachment</b>		<b>Page</b>
Attachment 1.	Protocol Addendum AMAJ(1) Clinical Laboratory Tests.....	24
Attachment 2.	Protocol Addendum Revisions.....	25

### 3. Rationale for Addendum

The following additions are being made to Protocol I6T-MC-AMAJ (AMAJ) for patients in Japan in order to conform with local requirements. This addendum is to be performed in Japan in addition to all procedures required by this protocol or any subsequent amendments to this protocol.

This addendum enables the inclusion of patients with generalized pustular psoriasis (GPP) and erythrodermic psoriasis (EP). These variants of psoriasis are relatively rare but can be more severe than chronic plaque psoriasis. GPP is characterized by multiple sterile pustules all over the body and may be accompanied by systemic symptoms including fever, chills, severe itching, dehydration, rapid pulse rate, exhaustion, anemia, weight loss, and muscle weakness. For this addendum, the eligibility criteria for GPP are set by the Japan Ministry of Health, Labour and Welfare (MHLW). EP is a particular inflammatory type of psoriasis that can affect the whole body. The reddening and shedding of the skin are often accompanied by severe itching and pain, heart rate increase, fluid loss, and fluctuating body temperature. For this addendum, the eligibility criteria for EP are based on the accepted current medical practice (Takigawa et al. 2010). Both psoriasis subtypes can sometimes be life-threatening without adequate treatment. The treatment options available for severe plaque psoriasis have been used in both subtypes, but often these subtypes are refractory to existing therapies. There are significant unmet medical needs for effective treatments for patients with GPP or EP.

Based on (1) postmarketing findings in Japanese patients with rheumatoid arthritis who were receiving anti-tumor necrosis factor (TNF) agents (Takeuchi et al. 2008; Koike et al. 2009), (2) recommendations set by the Japanese Dermatological Association for use of biologics in psoriasis (Ohtsuki et al. 2013), and (3) possible safety issues of Japanese patients with general autoimmune disease who received immunomodulators or immunosuppressants, the following additions are being made to Protocol AMAJ for patients in Japan:

- Chest radiography will be performed:
  - at Week 52
  - for subjects who discontinue the study early, if more than 12 weeks have elapsed since the previous study radiography was obtained. If medically indicated, this radiography may be performed even when 12 weeks have not elapsed since the previous study radiography
  - chest radiography may be performed at any time during the study, including the follow-up period, if medically necessary in the opinion of the investigator
- Added explicit exclusion criteria and discontinuation criteria for patients with pneumocystis pneumonia (PCP)
- Added testing of serum beta-D-glucan levels (Tasaka et al. 2007)

- Added testing of serum KL-6 levels
- Discontinuation criterion added to discontinue patients who have any positive hepatitis B deoxyribonucleic acid (HBV DNA) test at any time during the study
- Modified HBV DNA monitoring for patients who are positive for anti-hepatitis B core antibody (HBcAb+) and/or positive for anti-hepatitis B surface antibody (HBsAb+) at screening
- Exclusion criteria modified to permit the use of concomitant therapy for GPP and EP

All Japanese patients must participate in this addendum and must provide informed consent to the addendum.



## 4. Protocol Additions

The added underlined text or ~~striketrough~~ text in the following sections shows the changes applicable to patients participating in Study AMAJ in Japan. Additionally, a list of additional clinical laboratory tests is provided in [Attachment 1](#).

### 4.1. Section 2: Schedule of Activities

Section 2: Schedule of Activities

Procedure <sup>a</sup>	Screening Period	Baseline	Induction Period							Maintenance Period								
			V3	V4	V5	V6	V7	V8	V9	V 10	V 11	V 12	V 13	V 14	V 15	V 16	V 17	V 18
Visit Number	V1 <sup>b</sup>	V2	V3	V4	V5	V6	V7	V8	V9	V 10	V 11	V 12	V 13	V 14	V 15	V 16	V 17	V 18
Week	-4	0	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52
Day with Visit Tolerance Interval	≤28 days from V2	1	8 ± 3	15 ± 3	22 ± 3	29 ± 3	57 ± 5	85 ± 5	113 ± 5	141 ± 5	169 ± 5	197 ± 5	225 ± 5	253 ± 5	281 ± 5	309 ± 5	337 ± 5	365 ± 5
Chest Radiography for TB Screening <sup>e</sup>	X <sup>e</sup>																	X
Investigator Completed Clinical Efficacy Scales																		
Assessment of dermal symptoms		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Global improvement score				X		X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Tests																		
HBV DNA testing <sup>n</sup>	X					X	X	X	X	X	X	X	X	X	X		X	
Beta-D-glucan*	X																	
KL-6**	X																	

## Section 2: Schedule of Activities

Procedure <sup>a</sup>	ETV <sup>s</sup>	Follow-up Period <sup>t</sup>	
		V801	V802
Visit Number		V801	V802
Week		LV+4W	LV+12W
Day with Visit Tolerance Interval		29 ± 5	85 ± 5
<u>Chest Radiography for TB Screening<sup>e</sup></u>	X		
<b>Investigator Completed Clinical Efficacy Scales</b>			
<u>Assessment of dermal symptoms</u>	X		
<u>Global improvement score</u>	X		
<b>Laboratory Tests</b>			
HBV DNA testing <sup>n</sup>	X	X	X

Abbreviations: DNA = deoxyribonucleic acid; ETV = early termination visit; HBcAb = anti-hepatitis B core antibody; HBsAb<sub>±</sub> = hepatitis B surface antibody positive; HBV = hepatitis B virus; IP = investigational product; LV = last study visit; PCP = pneumocystis pneumonia; TB = tuberculosis; V = visit; W = weeks.

- <sup>a</sup> All activities should be completed prior to any study dose administration unless otherwise stated.
- <sup>b</sup> Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the allowable visit tolerance (at least 3 days should be allowed for receipt of laboratory test results).
- <sup>e</sup> Chest radiography will be performed locally at screening unless it has been performed within 3 months before initial screening (provided the radiographs and/or formal report are available for the investigator's review). In addition, chest radiography will be performed at Week 52, or for subjects who discontinue the study early if more than 12 weeks have elapsed since the previous study radiography was obtained. This radiography may be performed within 12 weeks if medically indicated. In the opinion of the investigator, if evaluating chest radiography is medically necessary, the investigator may do so any time during the study, including the follow-up period. For additional details, see revised Section 9.4.5.3 in Section 4.7 of the addendum.
- <sup>n</sup> Any enrolled patient who is HBcAb<sup>+</sup> and/or HBsAb<sup>+</sup> will undergo periodic monitoring of HBV DNA with HBV DNA testing (JSH 2017) (see revised Section 9.4.5.4 in Section 4.7 of the addendum). Any patient with a positive HBV DNA test at any time must be discontinued from the study and receive appropriate follow-up medical care, including consideration for antiviral therapy. (Refer to revised Section 9.4.5.4 in Section 4.7 of the addendum for further information regarding the timing of discontinuation).
- <sup>s</sup> If a patient discontinues IP early, the patient will complete the ETV and then enter the Post-Treatment Follow-up Period (V801 + V802).
- <sup>t</sup> All patients who receive IP but do not participate in Study I6T-MC-AMAH must enter the Follow-up Period and complete V801 + V802.
- <sup>\*</sup> Beta-D-glucan is required at screening and, if an investigator believes it is warranted, at subsequent visits; a beta-D-glucan test may be included in the work up panel at any time during the study, including in the follow-up period. If the beta-D-glucan test is positive, PCP needs to be ruled out. If PCP is ruled out and the investigator deems the patient fit to continue, the patient may continue in the study. If a patient has a confirmed diagnosis of PCP during the study, the patient must discontinue the study.

\*\* KL-6 is required at screening and, if an investigator believes it is warranted, at subsequent visits; a KL-6 test may be included in the work-up panel at any time during the study, including in the follow-up period.

## 4.2. Section 4: Objectives and Endpoints

Objectives in the main protocol are not applied to GPP and EP patients. Selected endpoints in the main protocol are applied to GPP and EP patients. The following objectives and endpoints are added to the study as exploratory objectives:

**Table AMAJ(1).1. Objectives and Endpoints**

<p><b>Exploratory</b>  <u>To assess the efficacy of mirikizumab in patients with GPP.</u></p>	<p><b><u>GPP ONLY</u></b></p> <p><u>Time course of response to treatment as measured by the following measures:</u></p> <ul style="list-style-type: none"> <li>• <u>global improvement score</u></li> <li>• <u>assessment of dermal symptoms for GPP</u></li> <li>• <u>change from baseline in PASI</u></li> <li>• <u>change from baseline in DLQI total score</u></li> </ul> <p><u>At Week 16 and Week 52:</u></p> <ul style="list-style-type: none"> <li>• <u>change from baseline in global improvement score</u></li> <li>• <u>change from baseline in assessment of dermal symptoms for GPP</u></li> <li>• <u>change from baseline in PASI</u></li> <li>• <u>change from baseline in DLQI total score</u></li> </ul>
<p><u>To assess the efficacy of mirikizumab in patients with EP</u></p>	<p><b><u>EP ONLY</u></b></p> <p><u>Time course of response to treatment as measured by the following measures:</u></p> <ul style="list-style-type: none"> <li>• <u>global improvement score</u></li> <li>• <u>change from baseline in PASI</u></li> <li>• <u>change from baseline in DLQI total score</u></li> </ul> <p><u>At Week 16 and Week 52:</u></p> <ul style="list-style-type: none"> <li>• <u>global improvement score</u></li> <li>• <u>change from baseline in PASI</u></li> <li>• <u>change from baseline in DLQI total score</u></li> </ul>

Abbreviations: DLQI = Dermatology Life Quality Index; GPP = generalized pustular psoriasis; PASI = Psoriasis Area and Severity Index.

## 4.3. Section 5: Study Design

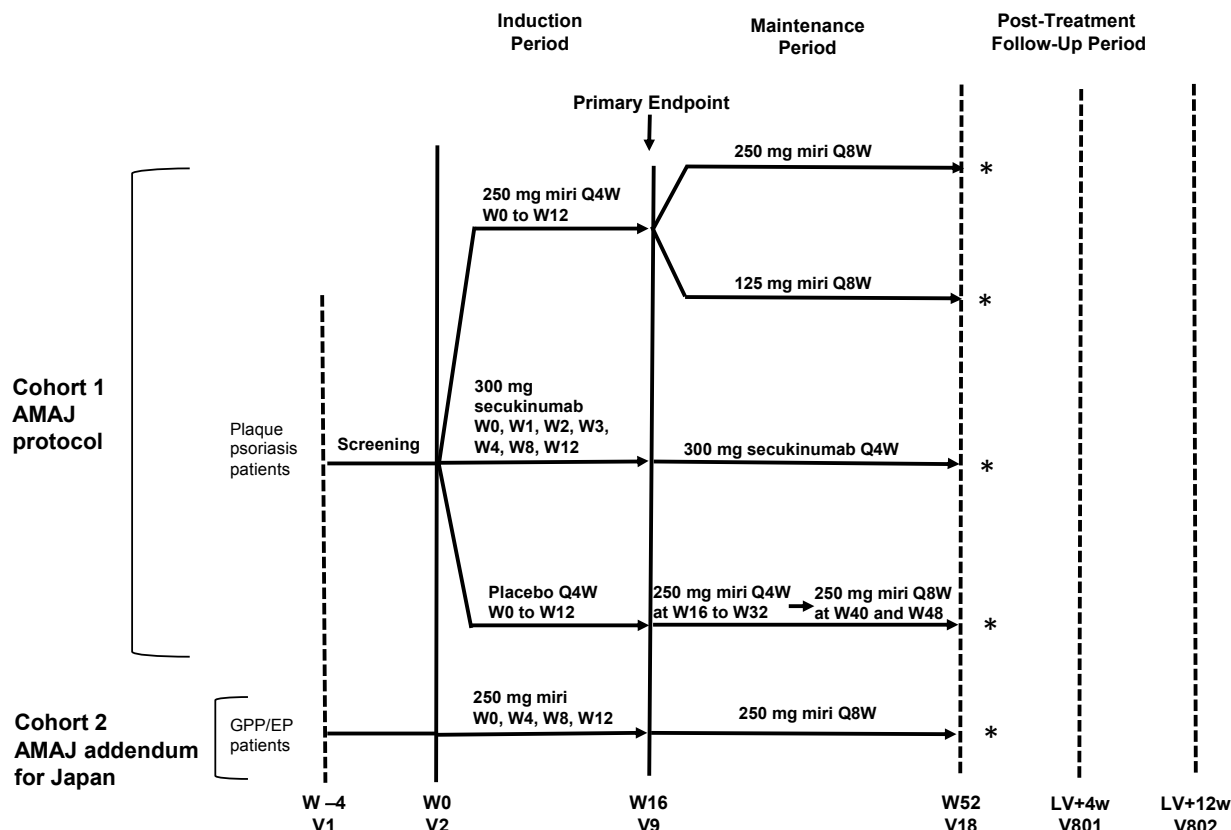
### 5.1. Overall Design

Study I6T-MC-AMAJ is a Phase 3 multicenter, randomized, double-blind, placebo- and active-controlled, parallel group, multi-period study in adult patients with moderate-to-severe plaque psoriasis. Approximately 1443 patients will be randomized to treatment groups involving

different mirikizumab doses, placebo, or secukinumab. The study is comprised of 2 treatment periods (Induction, and Maintenance) which together lasts for up to 52 weeks, followed by a 12-week Post-Treatment Follow-Up period. The main protocol for Study AMAJ will enroll patients with plaque psoriasis (Cohort 1).

In parallel, the AMAJ(1) addendum will enroll Japanese patients who are diagnosed as GPP by the Japanese Dermatological Association or EP who have  $\geq 80\%$  body surface area (BSA) involvement (with inflammatory erythema) (Cohort 2). Approximately 8 patients with GPP and 8 patients with EP will be enrolled in Cohort 2 in Japan. During the Induction Period, GPP and EP patients will receive 250 mg mirikizumab subcutaneously (SC) at Weeks 0, 4, 8, and 12. During the Maintenance Period, starting at Week 16, GPP and EP patients will receive 250 mg mirikizumab every 8 weeks (Q8W) SC for up to a total of 52 weeks. Placebo control is not required for the GPP and EP patient arms because placebo-controlled studies are not ethical for patients with these severe conditions. The enrollment period of Cohort 2 will begin in parallel with the enrollment period of Cohort 1, but Cohort 2 enrollment may continue for a longer period of time if necessary to achieve the numbers planned for Cohort 2.

Figure AMAJ(1).1 illustrates the study design.



Abbreviations: EP = erythrodermic psoriasis; GPP = generalized pustular psoriasis;  
 LV = last study visit; miri = mirikizumab; Q4W = every 4 weeks; Q8W = every 8 weeks; V = visit; w = weeks; W = week.

\* Option to enter Study AMAH or to enter the Post-Treatment Follow-Up Period.

Note: At Week 0 (V2), patients will be randomized in a 4:4:4:1 ratio to one of the following induction and maintenance period treatments: a) 250 mg miri at Weeks 0, 4, 8, 12 followed by 250 mg miri SC Q8W starting at Week 16; b) 250 mg miri at Weeks 0, 4, 8, 12 followed by 125 mg miri Q8W starting at Week 16; c) 300 mg secukinumab at Weeks 0, 1, 2, 3, 4, followed by 300 mg secukinumab Q4W starting at Week 4; d) placebo at Weeks 0, 4, 8, 12, followed by 250 mg miri Q4W starting at Week 16 through Week 32 followed by Q8W thereafter. Patients will receive placebo to maintain the study blind across treatment groups. Dosing is via subcutaneous injection (SC) for all treatments in all periods.

At Week 0 (V2), patients with GPP/EP will be assigned to 250 mg miri at Weeks 0, 4, 8, 12, followed by 250 mg miri SC Q8W starting at Week 16. Dosing is via SC injection for all treatments in all periods.

**Figure AMAJ(1).1. Illustration of study design for Clinical Protocol I6T-MC-AMAJ addendum (1).**

## 4.4. Section 6: Study Population

### 6.1. Inclusion Criteria

#### Type of Patient and Disease Characteristics

- [1] Present with chronic plaque psoriasis based on an investigator confirmed diagnosis of chronic psoriasis vulgaris for at least 6 months prior to baseline and meet the following criteria:
- A. Plaque psoriasis involving  $\geq 10\%$  body surface area (BSA) and absolute PASI score  $\geq 12$  in affected skin at screening (Visit 1) and baseline (Visit 2), and
  - B. sPGA score of  $\geq 3$  at screening (Visit 1) and baseline (Visit 2).
- [2] Candidate for systemic therapy and/or phototherapy
- [36] GPP ONLY:  
Meet the criteria for GPP set by the MHLW at screening (Visit 1) and baseline (Week 0; Visit 2).
- [37] EP ONLY:  
Diagnosed to have BSA  $\geq 80\%$  involvement (with inflammatory erythema) at screening (Visit 1) and baseline (Week 0; Visit 2).

### 6.2. Exclusion Criteria

- [13] Have hepatitis B or test positive for hepatitis B virus (HBV) at screening, defined as:
- A. Positive for hepatitis B surface antigen (HBsAg+),  
OR
  - B. Positive for hepatitis B core antibody (HBcAb+) in conjunction with positive confirmatory HBV for HBV deoxyribonucleic acid (DNA) test,  
OR
  - C. ~~Positive HBV DNA, regardless of anti-hepatitis B surface antibody (HBsAb) status.~~ Positive for hepatitis B surface antibody (HBsAb+) and positive confirmatory for HBV DNA

Note: Patients who are HBcAb+ and/or HBsAb+ and HBV DNA negative may be enrolled in the study. Patients who meet these criteria at screening will be monitored during the study as detailed in revised protocol Section 9.4.5.4 (Section 4.7 of this addendum).



- [16] Have had serious, opportunistic (see Section 9.2.3 and Appendix 4), or chronic/recurring infection (including pneumocystis pneumonia [PCP]) within 3 months prior to screening. Examples include, but are not limited to, infections requiring IV antibiotics, hospitalization, or prolonged treatment.
- [23] Have any other skin conditions (excluding plaque psoriasis, pustular psoriasis, and erythrodermic psoriasis) that would affect interpretation of the results (including, but not limited to, scleroderma, eczema, drug-induced psoriasis, guttate psoriasis, ~~pustular psoriasis~~, parapsoriasis, or cutaneous manifestations of other autoimmune diseases such as systemic lupus erythematosus).

### Prior/Concomitant Therapy

- [24] Have received systemic nonbiologic therapy (including, but not limited to, oral psoralen plus ultraviolet A [PUVA] light therapy; cyclosporine; corticosteroids; methotrexate; oral retinoids; apremilast; tofacitinib; mycophenolate mofetil; thioguanine; hydroxyurea; sirolimus; tacrolimus; azathioprine; leflunomide; fumaric acid derivatives; or 1, 25 dihydroxy vitamin D3 and analogues) or phototherapy (including either oral and topical PUVA light therapy, ultraviolet B, excimer laser, or self treatment with tanning beds or therapeutic sunbathing) within 28 days prior to baseline.

#### [24a] GPP/EP ONLY:

- Methotrexate or oral retinoids will be permitted before and during the study if doses are not greater than that of baseline.
- Oral corticosteroids will be permitted before and during the study, if average daily doses are not greater than 10 mg/day of prednisone or its equivalent.
- Cyclosporine will be permitted until Week 2 (Visit 4), if daily doses are not greater than that of baseline.

- [25] Have received topical treatment (including, but not limited to, corticosteroids [mild or least potent topical steroids will be permitted for use limited to the face, axilla, or genitalia], crisaborole, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, pimecrolimus, tacrolimus, emollients and other nonprescription topical products containing urea, >3% salicylic acid, alpha- or beta-hydroxyl acids, or medicated shampoos [for example those that contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues]) within 14 days prior to baseline.

#### [25a] GPP/EP ONLY:

- All topical treatment will be permitted before and during the study.

- [28] Have previous exposure to any biologic therapy targeting IL-12/23 (p40 subunit) or IL-23 (p19 subunit) or IL-17, either marketed or investigational.

#### [28a] GPP/EP ONLY:

- Previous exposure targeting IL-17 is permitted before the study, unless the patient received anti-IL-17 targeting biologics within 12 weeks prior to baseline.

### Other Exclusions

[38] Have a positive beta-D-glucan test at screening.

#### **4.5. Section 7.7: Concomitant Therapy**

All concomitant medications taken during the study must be recorded on the applicable Concomitant Medication electronic case report form (eCRF). All patients should maintain their usual medication regimens for concomitant conditions or diseases throughout the study unless those medications are specifically excluded in the protocol.

Patients taking concomitant medications should be on stable dosages at the time of baseline and should remain at stable dosages throughout the study unless changes need to be made because of AEs.

For patients with GPP or EP, methotrexate and oral retinoids will be permitted before and during the study if the patients have been using such medication before starting the study and if doses are not greater than that of baseline. Oral corticosteroids will be permitted before and during the study, if the patients have been using such medication before starting the study and if average daily doses are not greater than 10 mg/day of prednisone or its equivalent. Cyclosporine will be permitted until Week 2 (Visit 4), if the patients have been using such medication before starting the study and if daily doses are not greater than that of baseline. For methotrexate, oral retinoids, oral corticosteroids and cyclosporine, dose reductions are allowed but dose increases of these drugs are not allowed during the study. All topical treatment will be permitted before and during the study.

Additional systemic drugs are to be avoided during the study, unless required to treat AEs. If the need for concomitant medication arises for an AE or for appropriate medical management (including the limited use of therapeutic agents which, if used under treatment regimens other than for treating an AE or for appropriate medical management, might be considered psoriasis therapies), the investigator should base decisions on the patient and clinical factors. Other medications may be allowed if they are approved by the Sponsor or its designee.

Use of nonlive (killed, inactivated, or subunit) vaccinations are allowed for all patients; however, their efficacy with concomitant mirikizumab is unknown. Use of live, attenuated vaccines are prohibited.

Classes of therapies not permitted during the course of the study or permitted with use restrictions are specified in [Table AMAJ\(1\).2](#) (see also the Exclusion Criteria [[Section 6.2 of the protocol](#)]):

**Table AMAJ(1).2. Excluded Classes of Concomitant Medications or Classes with Restricted Use**

Drug Class	Allowed for Chronic Use	Allowed with Restrictions	Conditions for Allowed Use
Topical treatment for psoriasis or any other skin condition <i>(including but not limited to, corticosteroids, crisaborole, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, pimecrolimus, tacrolimus, emollients and other nonprescription topical products containing urea, &gt;3% salicylic acid, alpha- or beta-hydroxyl acids)</i>	N	N	<u>Exception: For patients with GPP or EP, all topical treatments will be permitted. These topical medications should not be used within approximately 12 hours prior to study visits.</u>
Topical treatment for psoriasis limited to face, axilla, or genitalia	N	Y	Mild or least potent topical steroids will be permitted for use limited to the face, axilla, and/or genitalia, as needed. These topical medications should not be used within approximately 24 hours prior to study visits.
Photochemotherapy <i>(for example, PUVA)</i>	N	N	
Phototherapy <i>(for example, UVA, UVB, excimer laser)</i>	N	N	
Biological immunomodulating agents <i>(for example, alefacept, briakinumab, efalizumab, ixekizumab, secukinumab, etanercept, adalimumab, infliximab, certolizumab)</i>	N	N	
Other systemic immunomodulating treatments <i>(for example, MTX, cyclosporine A, corticosteroids, cyclophosphamide)</i>	N	N	<u>Exception: For patients with GPP or EP, methotrexate will be permitted before and during the study if doses are not greater than that of baseline, oral corticosteroids will be permitted before and during the study, if average daily doses are not greater than 10 mg/day of prednisone or its equivalent, and cyclosporine will be permitted until Week 2 (Visit 4), if daily doses are not greater than that of baseline. For these treatments, dose reductions are allowed but dose increases are not allowed during the study.</u>

Drug Class	Allowed for Chronic Use	Allowed with Restrictions	Conditions for Allowed Use
*Systemic immunomodulating treatments ( <i>corticosteroids only</i> )	N	Y	Limited use of systemic corticosteroid ONLY as needed for limited, short-term medical management of TEAE may be considered. Such drug class might be considered psoriasis therapy if used under other regimens. Limited use during TEAE management is considered to not be consistent with psoriasis therapy.
Systemic psoriasis therapies ( <i>for example, retinoids, fumarates, apremilast</i> )	N	N	<u>Exception: For patients with GPP or EP, oral retinoids will be permitted before and during the study if doses are not greater than that of baseline. For this treatment, dose reductions are allowed but dose increases are not allowed during the study.</u>
Bacillus Calmette-Guerin (BCG) vaccinations or live virus vaccinations ( <i>prohibited throughout the study and for 12 months or 12 weeks, respectively, after discontinuation of study drug</i> ).	N	N	
Any investigational treatment	N	N	

Abbreviations: EP = erythrodermic psoriasis; GPP = generalized pustular psoriasis; MTX = methotrexate; N = No; PUVA = psoralen and ultraviolet A; TEAE = treatment-emergent adverse event; UVA = ultraviolet A; UVB = ultraviolet B; Y = Yes.

#### 4.6. Section 8.2: Discontinuation from the Study

In addition, patients who meet any one of the following criteria should be discontinued from the investigational product and enter the Post-Treatment Follow-Up Period, and discontinue from the study.

- If a patient has a confirmed diagnosis of PCP during the study, the patient must discontinue the study (protocol Section 9.4.3.2 in Section 4.7 of this addendum).

#### 4.7. Section 9: Study Assessments and Procedures

##### 9.1.4. Exploratory Efficacy Assessments for Patients at Sites in Japan

###### Assessment of Dermal Symptoms

Assessment of dermal symptoms, according to the Japanese Dermatological Association GPP revised criteria (Terui et al. [WWW]), will be performed only for patients with GPP. Skin symptoms are assessed by the score with the area of erythema (on a 0-3 scale), erythema with

pustules (on a 0-3 scale), and area of skin edema (on a 0-3). The total score will be assessed at visits indicated in the Schedule of Activities (Section 4.1 of this addendum).

### **Global Improvement Scores**

Global improvement scores will be collected for patients with GPP or EP from Week 2. Global improvement will be assessed in the 4 grades by comparing the psoriatic findings: (1) resolved, (2) improved, (3) unchanged, (4) worsened. The global improvement score is assessed based on the comparison of the psoriatic findings, sPGA, PASI score, and other evaluations with those at the baseline. The global improvement score will be assessed at visits indicated in the Schedule of Activities (Section 4.1 of this addendum).

#### **9.2.1. Serious Adverse Events**

When an in-hospital patient enters the study (GPP, EP), the investigator should consider their past experience of treatment of psoriasis to evaluate whether mirikizumab prolonged the hospital stay of a patient. Only if the investigator considers that mirikizumab truly prolonged the inpatient hospitalization, then worsening of the underlying condition of GPP or EP can be considered as an SAE.

#### **9.4.3. Laboratory Tests**

##### **9.4.3.2 Laboratory Tests for Patients at Sites in Japan**

Beta-D-glucan levels and KL-6 levels (biomarkers for PCP and interstitial lung disease, respectively) will be measured at screening and, if an investigator believes it is warranted, at subsequent visits. Either test may be included in the work up panel at any time during the study, including in the follow-up period.

If the beta-D-glucan test is positive, PCP needs to be ruled out. If PCP is ruled out and the investigator deems the patient fit to continue, the patient may continue in the study. If a patient has a confirmed diagnosis of PCP during the study, the patient must discontinue the study.

##### **9.4.5.3. Chest Radiography**

Posterior-anterior (PA) chest x-ray (CXR) will be obtained at screening (Visit 1) unless, in the opinion of the investigator or based on local standard of care, both PA and lateral views are indicated. In addition, chest radiography will be performed at Week 52, or for subjects who discontinue the study early if more than 12 weeks have elapsed since the previous study radiography was obtained. If medically indicated, this radiography may be performed even when 12 weeks have not elapsed since the previous study radiography. Chest radiography may be performed at any time during the study, including the follow-up period, if medically necessary in the opinion of the investigator.

A CXR does not have to be performed if the patient has had a CXR that is sufficient for TB evaluation according to local standard of care within 3 months of screening, and the CXR film(s) or a radiology report is available to the investigator for review.

##### **9.4.5.4. Hepatitis B Screening**

Patients who test HBsAg+, test HBcAb+ in conjunction with positive confirmatory HBV DNA test, or have positive HBV DNA test, regardless of HBsAb status, at screening will be excluded.

Any enrolled subject who is HBcAb+ and/or HBsAb+ will undergo periodic monitoring of HBV DNA per the Schedule of Activities (Section 2).

In addition to the above, any enrolled subject who is HBcAb+ and/or HBsAb+ and who experiences an elevated ALT or AST level  $>3 \times$  ULN must undergo HBV DNA testing. If the HBV DNA test is negative, the investigator should consult with the Lilly-designated medical monitor regarding further management of the patient.

If the result of the HBV DNA test is positive but below quantification study drug should be withheld and a repeat test done immediately. The Lilly-designated medical monitor should be contacted regarding study status of the patient. If the result of the HBV DNA test is DNA positive and quantifiable, the patient must be discontinued from the study and should receive appropriate follow-up medical care, including consideration for antiviral therapy. A specialist physician in the care of patients with hepatitis (for example, infectious disease or hepatologist subspecialists) should be consulted, and the patient should potentially be started on antiviral therapy prior to discontinuation of any immunosuppressant therapy (including study drug). Timing of discontinuation from the study treatment, the study, and of any immunosuppressant therapy (including study drug) needs to be based on the recommendations of the consulting specialist physician in conjunction with the investigator and medical guidelines/standard of care.

## 4.8. Section 10: Statistical Considerations

### 10.1. Sample Size Determination

In Cohort 1 (patients with plaque psoriasis), approximately 1443 patients will be randomized at a 4:4:4:1 ratio in the Blinded Induction Period to receive 250 mg mirikizumab SC at Weeks 0, 4, 8, and 12, then 250 mg mirikizumab SC Q8W, 250 mg mirikizumab SC at Weeks 0, 4, 8, and 12, then 125 mg mirikizumab SC Q8W, 300 mg secukinumab Q4W, or placebo. Stratified block randomization will be performed with the following stratification factors: previous exposure to biologic therapy (yes/no), body weight ( $<100$  kg or  $\geq 100$  kg), and geographic region (North America, Europe or Other).

Eight patients with GPP and 8 patients with EP will be enrolled in Cohort 2 in Japan. All patients in Cohort 2 will receive 250 mg mirikizumab SC at Weeks 0, 4, 8, and 12 during the Induction Period. During the Maintenance Period, starting at Week 16, GPP and EP patients will receive 250 mg mirikizumab Q8W SC for up to a total of 52 weeks. The number of patients with GPP and EP is based on the population size of these patients being very small in Japan (Umezawa et al. 2003, Rosenbach et al. 2010).

#### 10.3.1. General Statistical Considerations

The benefit/risk profile to support global registrations will be based on the analysis of Cohort 1.

Patients enrolled in Cohort 2 will not be included in the analysis supporting global registrations. To support registration in Japan, efficacy and safety analysis for plaque psoriasis, GPP, and EP

will be conducted separately. Safety data for all patients (plaque psoriasis, GPP, EP) will also be assessed.

**10.3.8. Interim Analyses**

In addition, the sponsor may consider interim analyses of Cohort 2 for Japan regulatory communication purposes. In this case, collected data may be summarized.

## 5. References

- [JSH] Drafting Committee for Hepatitis Management Guidelines and the Japan Society of Hepatology. JSH guidelines for the management of hepatitis B virus infection. *Hepatol Res*. 2017(suppl S3):127-128.
- Koike T, Harigai M, Inokuma S, Inoue N, Ishiguro N, Ryu J, Takeuchi T, Tanaka Y, Yamanaka H, Fujii K, Freundlich B, Suzukawa M. Postmarketing surveillance of safety and effectiveness of etanercept in Japan. *J Rheumatol*. 2009;36(5):898-906.
- Ohtsuki M, Terui T, Ozawa A, Morita A, Sano S, Takahashi H, Komine M, Etoh T, Igarashi A, Torii H, Asahina A, Nemoto O, Nakagawa H; Biologics Review Committee of the Japanese Dermatological Association. Japanese guidance for use of biologics for psoriasis (the 2013 version). *J Dermatol*. 2013;40(9):683-695.
- Rosenbach M, Hsu S, Korman NJ, Lebwohl MG, Young M, Bebo BF Jr, Van Voorhees AS; National Psoriasis Foundation Medical Board. Treatment of erythrodermic psoriasis: from the medical board of the National Psoriasis Foundation. *J Am Acad Dermatol*. 2010;62(4):655-662.
- Takeuchi T, Tatsuki Y, Nogami Y, Ishiguro N, Tanaka Y, Yamanaka H, Kamatani N, Harigai M, Ryu J, Inoue K, Kondo H, Inokuma S, Ochi T, Koike T. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. *Ann Rheum Dis*. 2008;67(2):189-194.
- Takigawa M, Tomita Y, Hashimoto T, Iwatsuki K (eds). Standard Textbook of Dermatology. 9th ed. Tokyo: Igaku-Shoin; 2010:p106-109.
- Tasaka S, Hasegawa N, Kobayashi S, Yamada W, Nishimura T, Takeuchi T, Ishizaka A. Serum indicators for the diagnosis of pneumocystis pneumonia. *Chest*. 2007;131(4):1173-1180.
- Terui T, Akiyama M, Ikeda S, Ozawa A, Kanekura T, Kurosawa M, Komiyane M, Sano S, Nemoto O, Muto M, Yamanishi K, Iwatsuki K. Practice Guidelines 2014 for generalized pustular psoriasis (GPP). Available at: <https://www.dermatol.or.jp/uploads/uploads/files/guideline/nouhouseikansenguideline.pdf>. Accessed January 16, 2017.
- Umezawa Y, Ozawa A, Kawasima T, Shimizu H, Terui T, Tagami H, Ikeda S, Ogawa H, Kawada A, Tezuka T, Igarashi A, Harada S. Therapeutic guidelines for the treatment of generalized pustular psoriasis (GPP) based on a proposed classification of disease severity. *Arch Dermatol Res*. 2003;295 Suppl 1:S43-S54.



---

## Attachment 1. Protocol Addendum AMAJ(1) Clinical Laboratory Tests

---

In addition to the clinical laboratory tests included on Appendix 2 of the protocol, the following laboratory tests are required under this addendum:

---

### Clinical Chemistry

#### Serum Concentrations of:

Beta-D-glucan

KL-6

#### Other

HBV DNA test<sup>c</sup>

---

- <sup>c</sup> Following screening, patients will not undergo monitoring for Hepatitis C unless liver enzymes are elevated. Hepatitis B monitoring will be performed at protocol-specified intervals in patients who test positive for anti-hepatitis B core antibody and/or positive for anti-hepatitis B surface antibody.

---

## Attachment 2. Protocol Addendum Revisions

---

### Overview

Protocol Addendum I6T-MC-AMAJ(1) [A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Efficacy and Safety of Mirikizumab to Secukinumab and Placebo in Patients with Moderate-to-Severe Plaque Psoriasis] has been amended due to trial site requests regarding concomitant medication. The revised protocol addendum is indicated by revision (1.1) and will be used in place of any preceding version of this protocol addendum.

The overall change made to this protocol addendum is as follows:

- Methotrexate or oral retinoids is permitted in addition to oral corticosteroids and cyclosporine

## Revised Protocol Addendum

**Note:** Deletions have been identified by ~~strikethroughs~~.  
 Addition to I6T-MC-AMAJ Clinical Protocol have been identified by the use of underscore.  
 Changes to I6T-MC-AMAJ (1.1) Clinical Protocol Addendum have been identified by the use of double underscore.

### Section number was arranged.

- |          |      |   |
|----------|------|---|
| [Before] | 4.5. | Section 8.2: Discontinuation from the Study |
|          | 4.6. | Section 7.7: Concomitant Therapy            |
| [After]  | 4.5. | Section 7.7: Concomitant Therapy            |
|          | 4.6. | Section 8.2: Discontinuation from the Study |

## 4.2. Section 4: Objectives and Endpoints

**Table AMAJ(1).1. Objectives and Endpoints**

<p><u>To assess the efficacy of mirikizumab in patients with EP</u></p>	<p><b><u>EP ONLY</u></b></p> <p><u>Time course of response to treatment as measured by the following measures:</u></p> <ul style="list-style-type: none"> <li>• <u>global improvement score</u></li> <li>• <u>change from baseline in PASI</u></li> <li>• <u>change from baseline in DLQI total score</u></li> </ul> <p><u>At Week 16 and Week 52:</u></p> <ul style="list-style-type: none"> <li>• <u>global improvement score</u></li> <li>• <u>change from baseline in PASI</u></li> <li>• <u>change from baseline in DLQI total score</u></li> </ul>
---	--

## 4.3. Section 5: Study Design

In parallel, the AMAJ(1) addendum will enroll Japanese patients who are diagnosed as GPP by the Japanese Dermatological Association or EP who have  $\geq 10$ 80% body surface area (BSA) involvement (with inflammatory erythema) (Cohort 2). Approximately 8 patients with GPP and 8 patients with EP will be enrolled in Cohort 2 in Japan.

## 4.4. Section 6: Study Population

## 6.2. Exclusion Criteria

Have hepatitis B or test positive for hepatitis B virus (HBV) at screening, defined as:

- A. Positive for hepatitis B surface antigen (HBsAg+),  
OR
- B. Positive for hepatitis B core antibody (HBcAb+) in conjunction with positive confirmatory HBV for HBV deoxyribonucleic acid (DNA) test,  
OR
- C. ~~Positive HBV DNA, regardless of anti-hepatitis B surface antibody (HBsAb) status.~~ Positive for hepatitis B surface antibody (HBsAb+) and positive confirmatory for HBV DNA

Note: Patients who are HBcAb+ and/or HBsAb+ and HBV DNA negative may be enrolled in the study. Patients who meet these criteria at screening will be monitored during the study as detailed in revised protocol Section 9.4.5.4 (Section 4.7 of this addendum).

## Prior/Concomitant Therapy

[24] Have received systemic nonbiologic therapy (including, but not limited to, oral psoralen plus ultraviolet A [PUVA] light therapy; cyclosporine; corticosteroids; methotrexate; oral retinoids; apremilast; tofacitinib; mycophenolate mofetil; thioguanine; hydroxyurea; sirolimus; tacrolimus; azathioprine; leflunomide; fumaric acid derivatives; or 1, 25 dihydroxy vitamin D3 and analogues) or phototherapy (including either oral and topical PUVA light therapy, ultraviolet B, excimer laser, or self treatment with tanning beds or therapeutic sunbathing) within 28 days prior to baseline.

[24a] GPP/EP ONLY:

- Methotrexate or oral retinoids will be permitted before and during the study if doses are not greater than that of baseline.
- Oral corticosteroids will be permitted before and during the study, if average daily doses are not greater than 10 mg/day of prednisone or its equivalent.
- Cyclosporine will be permitted until Week 2 (Visit 4), if daily doses are not greater than that of baseline ~~or its equivalent.~~

## 4.5. Section 7.7: Concomitant Therapy

For patients with GPP or EP, methotrexate and oral retinoids will be permitted before and during the study if the patients have been using such medication before starting the study and if doses are not greater than that of baseline. ~~O~~ral corticosteroids and ~~all topical treatment~~ will be

permitted before and during the study, if the patients have been using such medication before starting the study and if average daily doses are not greater than 10 mg/day of prednisone or its equivalent, and Cyclosporine will be permitted until Week 2 (Visit 4), if the patients have been using such medication before starting the study and if daily doses are not greater than that of baseline or its equivalent. For methotrexate, oral retinoids, oral corticosteroids and cyclosporine, dose reductions are allowed but dose increases of these drugs are not allowed during the study. All topical treatment will be permitted before and during the study.

**Table AMAJ(1).2. Excluded Classes of Concomitant Medications or Classes with Restricted Use**

Drug Class	Allowed for Chronic Use	Allowed with Restrictions	Conditions for Allowed Use
<p>Topical treatment for psoriasis or any other skin condition (including but not limited to, corticosteroids, crisaborole, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, pimecrolimus, tacrolimus, emollients and other nonprescription topical products containing urea, &gt;3% salicylic acid, alpha- or beta-hydroxyl acids)</p>	N	N	<p><u>Exception: For patients with GPP or EP, all topical treatments will be permitted. These topical medications should not be used within approximately 12 hours prior to study visits.</u></p>
<p>Other systemic immunomodulating treatments (for example, MTX, cyclosporine A, corticosteroids, cyclophosphamide)</p>	N	N	<p><u>Exception: For patients with GPP or EP, methotrexate will be permitted before and during the study if doses are not greater than that of baseline, oral corticosteroids will be permitted before and during the study, if average daily doses are not greater than 10 mg/day of prednisone or its equivalent, and cyclosporine will be permitted until Week 2 (Visit 4), if daily doses are not greater than that of baseline. For these treatments, dose reductions are allowed but dose increases are not allowed during the study.</u></p>
<p>*Systemic immunomodulating treatments (corticosteroids only)</p>	N	Y	<p>Limited use of systemic corticosteroid ONLY as needed for limited, short-term medical management of TEAE may be considered. Such drug class might be considered psoriasis therapy if used under other regimens. Limited use during TEAE management is considered to not be consistent with psoriasis therapy. <u>Exception: For patients with GPP or EP, oral corticosteroids permitted if average daily doses are not greater than 10 mg/day of prednisone or its equivalent.</u></p>

Drug Class	Allowed for Chronic Use	Allowed with Restrictions	Conditions for Allowed Use
Systemic psoriasis therapies <i>(for example, retinoids, fumarates, apremilast)</i>	N	N	<u>Exception: For patients with GPP or EP, oral retinoids will be permitted before and during the study if doses are not greater than that of baseline. For this treatment, dose reductions are allowed but dose increases are not allowed during the study.</u>

Leo Document ID = 6222d326-ace9-457b-b374-ac10dd058be3

Approver: PPD  
Approval Date & Time: 26-Apr-2018 20:56:10 GMT  
Signature meaning: Approved

Approver: PPD  
Approval Date & Time: 26-Apr-2018 20:56:10 GMT  
Signature meaning: Approved