Stat Analysis Plan Blinding and Unblinding Plan

A Phase 3, Multicenter Study with a 36-Week Open-Label Period Followed by a Randomized Double-Blind Withdrawal Period from Week 36 to Week 104 to Evaluate the Long-Term Efficacy and Safety of Ixekizumab (LY2439821) 80 mg Every 2 Weeks in Biologic Disease-Modifying Antirheumatic Drug–Naive Patients with Active Psoriatic Arthritis

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1. Blinding and Unblinding Plan for Protocol I1F-MC-RHBF: A Phase 3, Multicenter with a 36-Week Open-Label Period Followed by a Randomized Withdrawal Period from Week 36 to Week 104 to Evaluate the Long-Term Efficacy and Safety of Ixekizumab (LY2439821) 80 mg Every 2 Weeks in Biologic Disease-Modifying Antirheumatic Drug-Naïve Patients with Active Psoriatic Arthritis

Confidential Information

Ixekizumab (LY2439821)

I1F-MC-RHBF is a Phase 3, multicenter study with a 36-week initial open-label treatment period examining the effect of ixekizumab 80 mg every 2 weeks (Q2W) in patients with active psoriatic arthritis (PsA) who are conventional disease-modifying (cDMARD) inadequate responders (IRs) and biologic disease-modifying (bDMARD) naïve followed by a randomized, double-blind withdrawal period from Week 36 to Week 104 examining the effect of ixekizumab 80 mg Q2W compared to that of Placebo.

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Protocol I1F-MC-RHBF
Phase 3

Document History	
Version Number	**Brief Description of Change**
1.0	**Original Blinding and Unblinding Plan**
2.0	**Updated for the Open-Label Treatment Period to remain unblinded**
3.0	**Updated to add flexible wording around the occurrence of the two interim analyses**

Approval Date: 27-Oct-2017 GMT

2. Objective of This Document

The objective of the blinding and unblinding plan is to serve as a source for operational details, roles, and responsibilities around delivering data, either datasets or tables, figures, and listings (TFLs) in either a blinded or unblinded fashion per the objectives of the protocol.

As described in the Study I1F-MC-RHBF (RHBF) protocol and statistical analysis plan, the first interim database lock may occur after the last patient completes Visit 19 (Week 64) or the early termination visit (ETV). At this time, the analysis using only data from the open-label treatment period will be performed. This interim analysis may be planned when all enrolled patients have had the chance to complete the open-label treatment period (Period 2). The second interim database lock may occur when all patients complete Week 104 or discontinue study treatment prior to the end of the randomized double-blind withdrawal period . At this time, unblinding will occur and the primary analysis will be performed.

A final database lock will occur after the Post-Treatment Follow-Up Period (Period 4) is completed, when no further unblinding is needed.

The purpose of RHBF blinding and unblinding plan is to detail procedures in place to minimize bias while preparing for or conducting any summary or analysis of Study RHBF for data reviews, development safety update report (DSUR), periodic safety update report (PSUR), trial level safety reviews (TLSR), documents for the PsA submission and regulatory updates, and for the two potential interim analysis database locks, which may be used for the interim clinical study report (CSR).

3. Creating the Blind: General Blinding Requirements Specific to This Study

For Study RHBF, the following data must be blinded to patients, sites and study team members before the randomized double-blind withdrawal period database is locked:

- Treatment assignment from interactive web-response system (IWRS)
- LY2439821 serum concentrations and immunogenicity data from Lilly Generic Lab System (GLS) collected during the randomized double-blind withdrawal period.

Treatment assignment and dose adjustments are both blinded and unblinded in the interactive web-response system (IWRS). The data extract tool (DEX) is use to extract either the blinded or the unblinded IWRS data. Following the randomized withdrawal period interim lock, the data movement group (DMG) extracts the unblinded IWRS data and subsequently transfers the data to SAS drug development (SDD) system. Only the personnel from the functions listed below are unblinded to the treatment assignment and dose adjustments before the second interim database locks:

- IWRS Global support
- eCTS Randomization/Dispensing Associate
- All roles with Clinical Trial (CT) Supply Planning Organization
- DMG Associates

The ixekizumab serum concentrations and immunogenicity data could potentially unblind the dosing regimen during the randomized double-blind withdrawal period to sites and study team members; therefore, the investigator sites will not have access to the data prior to the the randomized withdrawal period interim lock. The study team will not have access to the data collected during the randomized double-blind withdrawal period prior to the interim database lock following the randomized double-blind withdrawal period. These laboratory analytes during the randomized double-blind withdrawal period must be blinded for all transfers of these laboratory data prior to the randomized withdrawal period interim lock. Clinical Laboratory Operations (CLO) sets up blinding flags to the ixekizumab serum concentrations and immunogenicity analytes in the GLS data for the data collected during the randomized double-blind withdrawal period. Subsequently the DMG applies these flags to the data collected during the randomized double-blind withdrawal period during the data transfer. After the randomized withdrawal period interim lock, these laboratory analytes results will be unblinded (meaning the DMG will not apply the blinding flag) when transferring the GLS data. Subsequently, the transferred data is stored in SAS drug development (SDD) either in a blinded or unblinded area, as appropriate. Only the personnel listed below are unblinded to these laboratory analytes results before the interim database lock:

- CLO unblinded Lab Associates
- DMG Associates

If unintentional unblinding occurs,

- When a subject's treatment group is unexpectedly unblinded during the randomized double-blind withdrawal period and the unblinding occurs at a site, notify the monitor or site manager.
- When a subject's treatment group is unexpectedly unblinded during the randomized double-blind withdrawal period and the unblinding occurs at a location other than the site, the person who identifies the unblinding notifies his or her immediate supervisor or Medical Quality representative in accordance with the requirements described in the Deviation Management (SEQSQ104-001) procedure.

The procedure for the emergency unblinding is described in the protocol.

The unintentional unblinding and the emergency unblinding, if they occur, will be documented in the CSR.

After the randomized withdrawal period interim lock, study team members will be unblinded. There is no blinding restriction for the final database lock at the time the Post-Treatment Follow-Up Period is completed. Sites and patients unblinding to treatment assignment will occur after the study is complete.

4. Details of Maintaining the Blind

The details of data blinding before the randomized withdrawal period interim lock is presented in Table 1. After interim database lock, these data will be unblinded to generate the final standard data tabulation model (SDTM), analysis data model (ADaM) datasets, and TFLs for interim analyses, interim CSR and subsequent disclosures.

Table 1. Details of Data Blinding Before the Randomized Withdrawal Period Database Lock

Data to be Blinded (Source)	Blinded Data Format	Deliverable Type	How Data be Blinded
Randomized treatment assignment and dose adjustments (IWRS)	Raw data and all subsequent deliverables based on the raw data (SDTM, ADaM, TFLs, or customized datasets/reports)	Test transfers before the interim locks, DSURs and PSURs before interim lock, TLSRs, documents for the PsA submission, other regulatory transfers before the second interim lock	Scrambled data
LY2439821 serum concentrations (GLS) collected during the randomized double-blind withdrawal period	Raw data and all subsequent deliverables based on the raw data (SDTM, ADaM, TFLs, or customized datasets/reports)	Test transfers before the interim locks, DSURs and PSURs before both interim locks, TLSRs, documents for the PsA submission, other regulatory transfers before the second interim lock	Blinded. Include the word 'BLINDED' instead of the actual result
Immunogenicity data (GLS) collected during the randomized double-blind withdrawal period	Raw data and all subsequent deliverables based on the raw data (SDTM, ADaM, TFLs, or customized datasets/reports)	Test transfers before the interim locks, DSURs and PSURs before both interim locks, TLSRs, documents for the PsA submission, other regulatory transfers before the second interim lock	Missing data

Table 2 provides the details of blinded and unblinded data transfers, including the functions to deliver the data and the locations of the data for the deliverables.

Table 2. Blinded and Unblinded Data Transfers and Locations

Blinding Status	Data Format	Function to Deliver Data[a]	Deliverable Type	CLUWE Location	Other Location
Blinded	Raw data	inVentiv DMG	Test transfers before second interim lock	\\statsclstr\lillyce\qa\ly2439821\i1f_mc_rhbf\intrm*n*\data\raw\shared\ Note: *n* indicates the sequence number of the test transfer	Source: GLS, IWRS, Inform, ePRO
			DSURs/PSURs/Documents for the PsA submission/ other regulatory transfers before the interim lock following the RDBWP	\\statsclst\lillyce\prd\ly2439821\i1f_mc_rhbf\ regulatory_mmm*yyyy*\data\raw\shared\ Note: mmm*yyyy* indicates the month and year of transfer, same below.	Source: GLS, IWRS, Inform, ePRO
			TLSRs	\\statsclstr\lillyce\prd\ly2439821\i1f_mc_rhbf\safety_review*n*\data\raw\shared\ Note: *n* indicates the sequence number of TLSR, same below.	Source: GLS, IWRS, Inform, ePRO
	SDTM	Lilly Statistics	Test Transfers before interim lock following the RDBWP	\\statsclstr\lillyce\qa\ly2439821\i1f_mc_rhbf\intrm*n*\data\observed\shared\	
			TLSRs	\\statsclstr\lillyce\prd\ly2439821\i1f_mc_rhbf\safety_review*n*\data\observed\shared\	
	ADaM	Lilly Statistics	Test Transfers before second interim lock	\\lillyce\qa\ly2439821\i1f_mc_rhbf\intrm*n*\data\analysis\shared\	
	TFLs	Lilly Statistics	Test Transfers before interim lock following the RDBWP	\\statsclstr\lillyce\qa\ly2439821\i1f_mc_rhbf\intrm*n*\output\shared\	
	Customized datasets or reports	Lilly Statistics	DSURs/PSURs/Documents for the PsA submission/ other	\\statsclstr\lillyce\prd\ly2439821\regulatory_mmm*yyyy*\data\analysis\custom	

Blinding Status	Data Format	Function to Deliver Data[a]	Deliverable Type	CLUWE Location	Other Location
			regulatory transfers before the interim lock following the RDBWP		
			TLSRs	\\statsclsr\lillyce\prd\ly2439821\i1f_mc_rhbf\safety_review*n*\data\observed\shared\custom	Reports are stored in Spotfire
Unblinded	Raw data	inVentiv DMG	Interim	\\statsclstr\lillyce\prd\ly2439821\i1f_mc_rhbf\intrm*n*\data\raw\shared\	Source: GLS, IWRS, Inform, ePRO
			DSURs/PSURs/Documents for the PsA submission other regulatory transfers after interim lock following the RDBWP and before final lock	\\statsclstr\lillyce\prd\ly2439821\i1f_mc_rhbf\regulatory_mmm*yyyy*\data\raw\shared\	Source: GLS, IWRS, Inform, ePRO
			Final	\\statsclstr\lillyce\prd\ly2439821\i1f_mc_rhbf\final\data\raw\shared\	Source: GLS, IWRS, Inform, ePRO
	SDTM	Lilly Statistics	Interim	\\statsclstr\lillyce\prd\ly2439821\i1f_mc_rhbf\intrm*n*\data\observed\shared\	
			Final	\\statsclstr\lillyce\prd\ly2439821\i1f_mc_rhbf\final\data\observed\shared\	
	ADaM	Lilly Statistics	Interim	\\statsclstr\lillyce\prd\ly2439821\i1f_mc_rhbf\intrm*n*\data\analysis\shared\	
			Final	\\statsclstr\lillyce\prd\ly2439821\i1f_mc_rhbf\final\data\analysis\shared\	
	TFLs	Lilly Statistics	Interim	\\statsclstr\lillyce\prd\ly2439821\i1f_mc_rhbf\intrm*n*\output\shared\	
			Final	\\statsclstr\lillyce\prd\ly2439821\i1f_mc_rhbf\final\output\shared	
	Customized datasets	Lilly Statistics	DSURs/PSURs/Documents for the PsA submission/ other regulatory	\\statsclstr\lillyce\prd\ly2439821\\regulatory_mmm*yyyy*\data\observed\custom	

Blinding Status	Data Format	Function to Deliver Data[a]	Deliverable Type	CLUWE Location	Other Location
			transfers after interim lock following the RDBWP and before final lock		

RDBWP = Randomized Double-Blind Withdrawal Period

[a] The personnel in the function to deliver the data will have access in CLUWE to check containers before transfer.