

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125521Orig1s000

CHEMISTRY REVIEW(S)



Office of Pharmaceutical Quality Integrated Review
BLA 125521 Taltz (Ixekizumab)
January 29, 2016

OPQ Recommendation: BLA 125521 is recommended for approval by CDER/OPQ.

Table with 2 columns: Attribute and Value. Rows include Drug Name/Dosage Form, Strength/Potency, Route of Administration, Rx/OTC Dispensed, Indication, Applicant/Sponsor, and US agent, if applicable.

Product Overview

Taltz is a humanized immunoglobulin IgG4 subclass monoclonal antibody that binds and neutralizes the pro-inflammatory cytokine interleukin-17A (IL-17A) by preventing cytokine receptor binding. IL-17A is produced by T helper 17 (Th 17) cells and is implicated in a variety of autoimmune diseases, including psoriasis. Ixekizumab does not bind to other IL-17 family members (e.g. IL-17B, IL-17C, IL-17D, IL-17E, or IL-17F).

[Redacted text block]

[Redacted text block]

(b) (4). The molecular weight of ixekizumab backbone is 146,158 daltons,

[Redacted text block]

The manufacturing process is well characterized using the principles of quality by design. The process is validated and demonstrated robust viral inactivation and clearance. Twenty six phase three clinical lots were used to justify the drug substance (DS) and drug product (DP) specifications. Real time stability results support the three year DS expiry and the two year Pre-Filled Syringe and Pre-Filled Auto Injector drug products expiry. All facilities involved in the production of Taltz were determined to be compliant with FDA cGMP requirements. There are two PMCs regarding the microbial drug product control strategy. In summary, the data submitted in this application are adequate to support the conclusion that the manufacture of Taltz is well controlled and leads to a product that is pure and potent. It is recommended that this



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product be approved for human use under the conditions specified in the package insert. Therefore from the product quality perspective this BLA is recommended for approval.

Quality Review Team and Signature Approval Section

DISCIPLINE	REVIEWER	OFFICE/DIVISION	E-Signature
Business Regulatory Process Manager	Anita Brown	OPRO/DRBPMI/RBPMBI	Signature not required
Drug Substance	Maria Cecilia Tami	OBP/DBRR III	Mariacec il Tami -S <small>Digitally signed by Mariacec Tami -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People Quality, email=Mariacec.Tami- S@FDA.HHS.gov, serial=10011, date=2016.02.29 10:41:15 -0500</small>
Drug Product	Xu (Michael) Di	OBP/DBRR III	Xu Di -S <small>Digitally signed by Xu Di -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People Quality, email=XuDi-S@FDA.HHS.gov, serial=10011, date=2016.02.29 10:41:15 -0500</small>
Facilities	Wayne Seifert	OPF/DIA/IAB1	Wayne E. Seifert -S <small>Digitally signed by Wayne E. Seifert DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People Quality, email=Wayne.E.Seifert-S@FDA.HHS.gov, serial=10011, date=2016.02.29 10:41:15 -0500</small>
Microbiology Drug Substance	Bo Chi	OPF/DMA/MABIV	Bo Chi -S <small>Digitally signed by Bo Chi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People Quality, email=BoChi-S@FDA.HHS.gov, serial=10011, date=2016.02.29 10:41:15 -0500</small>
Microbiology Drug Product	Colleen Thomas	OPF/DMA/MABIV	Colleen Thomas -S <small>Digitally signed by Colleen Thomas -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People Quality, email=Colleen.Thomas-S@FDA.HHS.gov, serial=10011, date=2016.02.29 10:41:15 -0500</small>
Immunogenicity	Maria Cecilia Tami	OBP/DBRR III	Mariacec il Tami -S <small>Digitally signed by Mariacec Tami -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People Quality, email=Mariacec.Tami- S@FDA.HHS.gov, serial=10011, date=2016.02.29 10:41:15 -0500</small>
Application Team Lead	Howard Anderson	OBP/DBRR III	Howard A. Anderson -S <small>Digitally signed by Howard A. Anderson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People Quality, email=Howard.A.Anderson-S@FDA.HHS.gov, serial=10011, date=2016.02.29 10:41:15 -0500</small>
Facilities Team Lead	Zhihao Peter Qiu	OPF/DIA/IAB1	Zhihao Qiu -S <small>Digitally signed by Zhihao Qiu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People Quality, email=Zhihao.Qiu-S@FDA.HHS.gov, serial=10011, date=2016.02.29 10:41:15 -0500</small>
Microbiology Team Lead	Patricia Hughes	OPF/DMA/MABIV	Patricia F. Hughestros t -S <small>Digitally signed by Patricia F. Hughestros t -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People Quality, email=Patricia.F.Hughestros- t-S@FDA.HHS.gov, serial=10011, date=2016.02.29 10:41:15 -0500</small>
Immunogenicity Team Lead	Susan Kirshner	OBP/DBRR III	Susan L. Kirshner -S <small>Digitally signed by Susan L. Kirshner -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People Quality, email=Susan.L.Kirshner-S@FDA.HHS.gov, serial=10011, date=2016.02.29 10:41:15 -0500</small>
Tertiary OBP Reviewer	Susan Kirshner	OBP/DBRR III	Susan L. Kirshner -S <small>Digitally signed by Susan L. Kirshner -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People Quality, email=Susan.L.Kirshner-S@FDA.HHS.gov, serial=10011, date=2016.02.29 10:41:15 -0500</small>



Multidisciplinary BLA 125521 Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	J. Paul Phillips	OND/ODEIII/DDDP
Cross-disciplinary Team Lead	Jill Lindstrom	OND/ODEIII/DDDP
Medical Officer	Jane Liedtka	OND/ODEIII/DDDP
Pharm/Tox	Jill Merrill (Barbara Hill TL)	OND/ODEIII/DDDP
Clinical Pharmacology	Jie Wang (Yow-Ming Wang TL)	OTS/OCP/DCPIII
Statistics	Matthew Guerra (Mohamed Alosh TL)	OTS/OB/DBIII

Quality Review Data Summary

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS

A. BLA 12251 Amendments Reviewed

Submissions Reviewed	Amendment Submission Date
	OBP
STN 125521/006	June 5, 2015
STN 125521/015	August 21, 2015
STN 125521/014	August 28, 2015
STN 125521/019	September 28, 2015
STN 125521/020	September 29, 2015
STN 125521/028	November 23, 2015
STN 125521/030	November 23, 2015
STN 125521/035	January 8, 2016
	DMA
STN 125521/002	May 8, 2015
STN 125521/010	July 8, 2015
STN 125521/015	August 21, 2015
STN 125521/022	October 26, 2015
STN 125521/024	October 30, 2015
STN 125521/026	November 12, 2015
STN 125521/027	November 12, 2015
STN 125521/036	January 21, 2016
STN 125521/041	February 12, 2015
	DIA
STN 125521/009	June 22, 2015



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B. DMFs:

DMF Number	Holder	Item referenced	Letter of cross-reference	Comments
[REDACTED]	[REDACTED]	[REDACTED]	(b) (4) Yes	(b) (4) information in DMF was reviewed for other applications and deemed adequate
			Yes	DMF not reviewed, adequate information in BLA
			Yes	DMF not reviewed, adequate information in BLA
			Yes	(b) (4) information in DMF was reviewed for other applications and deemed adequate
			Yes	DMF reviewed for this BLA and deemed adequate

3. NOMENCLATURE

- A. Names
- i. Proprietary Name: TALTZ
 - ii. Trade Name: TALTZ
 - iii. Non-Proprietary/USAN: Ixekizumab
 - iv. INN Name: Ixekizumab
 - v. Other: Anti-IL17A, LA426
 - vi. OBP systematic name: MAB HUMANIZED (IGG4) ANTI Q16552 (IL17_HUMAN) [LY2439821]
- B. Pharmacologic category: Therapeutic recombinant humanized interleukin-17A antagonist monoclonal antibody

4. CONSULTS: None



Integrated Review

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality recommends approval of STN 125521 for Taltz (ixekizumab) 80 mg injection, manufactured by Eli Lilly and Company. The data submitted in this application are adequate to support the conclusion that the manufacture of Taltz is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under the conditions specified in the package insert.

B. Benefit/Risk Considerations

Taltz is proposed for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. TALTZ antagonizes the proinflammatory cytokine IL-17A by preventing binding to IL-17 receptors on non-hematopoietic cells such as fibroblasts and epithelial cells and innate immune cells such as macrophages and neutrophils. Th17 cells are the major IL-17 producers. IL-17A receptor binding activates the production of multiple cytokines leading to the attraction and activation of neutrophils and macrophages. TALTZ neutralization of IL-17A has been demonstrated to reduce keratinocyte proliferation and activation. 160 mg (two doses) of TALTZ are administered to patients by subcutaneous injection at week 0, followed by an 80 mg injection at weeks 2, 4, 6, 8, 10, 12, and an 80 mg injection every 4 weeks, as needed. TALTZ is administered with either a prefilled syringe or auto-injector. TALTZ was found to be approximately five fold more effective in pivotal phase 3 studies than the FDA approved TNF antagonist Enbrel (Etanercept) product. TALTZ represents a superior new treatment for plaque psoriasis. Most severe adverse reactions included upper respiratory tract infections, injection site reactions, nausea, oropharyngeal pain, and tinea infections. In January 2015, the Novartis Cosentyx (secukinumab) anti-IL17A monoclonal antibody was approved by FDA for treatment of moderate to severe plaque psoriasis.

All facilities involved in TALTZ production were determined to be compliant with current FDA cGMP regulations. The DS manufacturing process is well controlled and consistently delivers DS of desired quality. No DS related PMCs are requested. The DP manufacturing process is well controlled and consistently delivers DP of desired quality. However, an additional confirmatory drug product (b) (4) challenge study is being requested to better validate the DP (b) (4) (b) (4), and an additional study is being requested to better support the approved maximum hold time for the pooled drug substance (b) (4). These two deficiencies pose very low risks to product safety and efficacy and can be adequately addressed as post marketing commitments (PMCs). The sponsor committed to performing the two studies as PMCs (see section C below).

The assays to detect anti-ixekizumab antibodies are suitable for use in clinical studies. Overall, the data from the pivotal trials show that development of anti-drug antibodies (ADA) does not raise safety concerns. The presence of high ADA titers and neutralizing activity is associated with reduced ixekizumab serum concentrations and a decrease or loss of efficacy.

C. Phase 4 Post-Marketing Commitment Recommendations

1. Perform a repeat microbial retention study for the (b) (4) using a suitable surrogate solution. Alternatively, perform the study using a modified process, a modified formulation, or a reduced exposure time for the challenge organism. Provide the summary data, the associated report, and justification for any modifications to the study. If any (b) (4) parameters are changed as a result of the study, update the BLA file accordingly.
2. Provide data from two additional commercial drug product batches to support the maximum hold time for pooled drug substance. The hold time study should include the maximum hold time (b) (4) followed by the maximum hold time under ambient conditions. Provide data from two additional commercial drug product batches to support the maximum hold time for drug product (b) (4). The supporting data should include bioburden and endotoxin testing results from samples (b) (4). Data from process simulations (b) (4) may be provided in lieu of data from drug product batches.

D. Approval action letter language

- Manufacturing location
 - Drug substance – Eli Lilly S.A. – Irish Branch, Dunderrow Kinsale, County Cork Ireland
 - Drug product – Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN
 - Device Assembly, Packaging, and Labeling - Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN
- Fill size and dosage form – 80 mg/ml in a single-dose prefilled auto-injector or single-dose prefilled syringe to deliver 1ml liquid solution SQ injection.
- Dating period
 - Drug product – 24 months; 5 °C
 - Drug substance – (b) (4)
 - Sponsor is not requesting extension of DS and DP expiries using an approved stability protocol.
- TALTZ is exempted from lot release and samples of future lots of TALTZ are not required to be submitted to the Director of the Center for Drug Evaluation and Research (CDER) for release under 21 CFR 610.2.

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and their control strategy that are relevant to both drug substance and drug product. For additional information see primary DS Product Quality, DS Microbiology, DP Quality and DP Microbiology reviews in Panorama.

Table 1: Taltz Drug Substance CQA Identification, Risk and Lifecycle Knowledge Management

CQA	Risk	Origin	Control Strategy	Comment
Potency	Efficacy	Antibody folding is impacted by bioreactor conditions	Cell Based Bioassay specification at release and on stability	Not stability indicating
Charge Variants	Immunogenicity, no impact on binding or potency	Incomplete antibody assembly during production, heat exposure and high pH can increase attribute	(b) (4) testing at release and on stability	Stability indicating
High Molecular Weight Impurities	Immunogenicity, Loss of efficacy due to decrease in potency	Heat exposure and low pH can increase attribute	(b) (4) specification at release and on stability	Stability indicating
Low Molecular Weight Impurities	Loss of efficacy due to decrease in potency	Incomplete antibody assembly during production, heat exposure and high and low pH can increase attribute	(b) (4) specification at release and on stability	Stability indicating
Glycosylation	None Expected	Taltz does not (b) (4) and does not have biological activity associated with the Fc region	Extensive characterization performed to remove testing at release and stability	Not stability indicating

B. Ixekizumab Drug Substance Quality Summary

Table 2 below is a summary of critical quality attributes and their control strategy that are relevant to both drug substance and drug product. For additional information see primary DS Product Quality and DS Microbiology Controls reviews in Panorama.

Table 2. CQA Identification, Risk and Live Knowledge Management

CQA	Risk	Origin	Control Strategy	Comment
Bioburden	Patient safety, product quality via degradation or modification	Bioburden can be introduced during manufacturing	(b) (4) (b) (4) bioburden test is part of the (b) (4) release testing. Specification at (b) (4).	None
Endotoxin	Patient safety	Endotoxin can be introduced during the manufacturing process	As part of the bioburden control strategy (b) (4) (b) (4) endotoxin test is part of (b) (4) and release testing. Specification at (b) (4).	None
(b) (4)	Safety and immunogenicity	(b) (4)	(b) (4)	(b) (4) None
	Safety			None
	Safety			None
	Safety and Immunogenicity			None
	Efficacy			None
Appearance, Physical Form Clarity, Color	Safety and Efficacy	Manufacturing process and formulation	Controlled by manufacturing process and formulation. Visual inspection of DS at release	None
Identity	Safety and Efficacy	NA	Controlled by (b) (4) potency bioassay at release	None
Leachable Impurities	Safety	Process-related impurities, and drug substance container closure system	Controlled by extractable/leachable studies on container closure and favorable product contact surfaces risk assessment.	None

1. Description

Taltz is a humanized immunoglobulin IgG4 subclass monoclonal antibody that binds and neutralizes the pro-inflammatory cytokine IL-17A. (b) (4)

(b) (4)

(b) (4) The molecular weight of ixekizumab backbone is 146,158 daltons, (b) (4)

(b) (4)

Taltz characterization studies are robust and utilized multi-variable design of experiments (DOE) strategies.

2. Mechanism of action

Taltz binds to and neutralizes the pro-inflammatory cytokine interleukin-17A (IL-17A) by preventing cytokine receptor binding. IL-17A is produced by Th17 cells and is implicated in a variety of autoimmune diseases, including psoriasis. Ixekizumab does not bind to the other IL-17 family members IL-17B, IL-17C, IL-17D, IL-17E, or IL-17F. (b) (4)

(b) (4)

3. Potency

Potency is defined relative to a qualified reference standard using a cell based bioassay. The acceptance criteria for the DS and DP release and stability specifications is not less than (b) (4)% and not more than (b) (4)% potency relative to the ixekizumab reference standard. (b) (4)

(b) (4)

(b) (4) Taltz binds to IL-17A and blocks IL-17A receptor binding resulting in a dose dependent inhibition of the luciferase signal. The inhibition is quantified using a four parameter logistic curve. Relative potency is calculated using the ratio of the EC₅₀ of the test sample to the EC₅₀ of the RS. The in-vitro cell based potency method is suitable to quantify Taltz activity because it reflects Taltz clinical mechanism of action, neutralization of IL-17 activity. The method is appropriately validated and specifications are supported by clinical experience and manufacturing capability. Additional information is located in the DS Product Quality review in Panorama.

4. Reference material(s)

The sponsor established a two tier reference standard (RS) qualification program as per ICH Q6B recommendations. (b) (4)

(b) (4). The primary RS is used to anchor future reference standard attributes such as potency, and purity to the Taltz product quality attributes



evaluated in the phase III clinical trials. The working RS is used for routine analytical testing. The current primary reference standard (b) (4) was evaluated in the Phase 3 clinical trial and was derived from drug substance lot (b) (4) 101835. The RS qualification program for this lot and future RS lots is rigorous and involves testing with release methods as well as with a variety of characterization methods. The working reference standard (b) (4) is a sub batch of the primary reference standard (b) (4). Additional information is located in the DS product quality review in Panorama.

5. Manufacturing process summary

The DS manufacturing process involves (b) (4)

(b) (4)

(b) (4)

(b) (4) and DS storage at (b) (4). The manufacturing process development included Quality by Design concepts consistent with ICH Q8, Q9, Q10, and Q11 recommendations.

Microbial quality of the DS is controlled by (b) (4) steps at critical places in the manufacturing process. Bioburden and endotoxin are tested at critical and appropriate places in the manufacturing process as well as at DS release and on stability. The (b) (4) is tested for integrity after use. (b) (4) stability studies include microbial monitoring.

The Taltz DS manufacturing process and control strategy in BLA 125521 are very similar to those described in three other Eli Lilly monoclonal antibody/Fc fusion protein product BLAs recently approved by the FDA. The other Eli Lilly products include Trulicity (2014, BLA 125469), Cyramza (2014 BLA, 125477), and Portrazza (2015 BLA, 125547). In summary, the BLA contains sufficient information and adequate validation results to indicate that the raw material program, the facilities and equipment, the manufacturing process, the release and the stability programs are adequately controlled resulting in the production of a consistent product with the potency required to meet the claims in the package insert. The manufacturing process was demonstrated to be robust for viral inactivation and removal and the control strategy ensures the process is free of adventitious agents and mycoplasma. Additional information can be found in the DS Product Quality and DS Microbial Control primary reviews in Panorama.

6. Container closure

The DS container closure system consists of an (b) (4) High Density Polyethylene (HDPE) container with an (b) (4) screw cap. The data provided in the BLA demonstrate that the container closure is appropriate for ixekizumab DS storage because the container materials are safe for use, prevent evaporation, and maintain integrity during shipping and storage. The BLA contains adequate studies that indicate no unsafe leachable materials contaminate the product during storage. There is no drug substance degradation during storage for the (b) (4) expiry.

7. Dating period and storage conditions

Real time stability results provided in the BLA support the storage of the drug substance at the specified temperature (b) (4). A commitment is made that one lot of drug substance will be placed into the annual stability program.

C. Taltz Drug Product Quality Summary

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and from general drug product attributes. For additional information see the primary DP Product Quality and DP Microbiology Control reviews in Panorama.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Knowledge Management

CQA	Risk	Origin	Control Strategy	Comment
Sterility	Patient safety (Infection), Efficacy (product quality via degradation or modification of products by contaminating microorganisms)	Adventitious agents could be introduced during the manufacturing process or by failure of container integrity	(b) (4) bioburden control.	Refer to section I.C for PMCs related to (b) (4)
			(b) (4) (b) (4) at release and on stability. Container closure integrity testing.	
Endotoxin	Patient safety (pyrogenic fever, increased immunogenicity risk)	Endotoxin can be introduced during the manufacturing process	(b) (4) bioburden control, sterility assurance, endotoxin (b) (4) test and specification at release and on stability (USP 85). The specification is (b) (4) EU/mg.	None
Particulate Matter	Blood vessel occlusion and Immunogenicity	Product or process related impurity	Controlled (b) (4) 100% visual inspection, release testing (USP 788).	None
Identity	Safety and efficacy	NA	Controlled by (b) (4) Bioassay testing at DP release.	None
Appearance Physical Form, Clarity, Color	Safety and efficacy	Manufacturing	Controlled by the manufacturing process including formulation, monitored by 100% (b) (4) visual inspection, tested at release.	

1. Potency and Strength

Potency is defined relative to a qualified reference standard using a cell based bioassay. The acceptance criteria for the DS and DP release and stability method is not less than (b) (4) % and not more than (b) (4) % potency relative to the ixekizumab reference standard. Taltz is marketed as a single 80 mg/ml strength.

2. Summary of Product Design

Taltz pre-filled syringes are available in cartons of 1, 2, or 3 components. Taltz is a 1 ml clear to (b) (4) solution for subcutaneous administration using a pre-filled syringe or a pre-filled auto-injector. The mechanical, functional, and design components of the pre-filled syringe and auto-injector are reviewed by CDRH ODE. The assembly facility cGMP compliance was reviewed by CDRH OC. CDRH is recommending approval of the BLA.

3. List of Excipients

Taltz 80 mg is formulated with 0.51 mg/ml citric acid anhydrous USP, 11.69 mg/ml sodium chloride USP, 5.11 mg/ml sodium citrate dihydrate USP, 0.30 mg/ml polysorbate 80 USP, and water for injection USP to a pH of 5.3 to 6.1. The excipients are free of animal derived material and considered low risk for viral and TSE contamination. All excipients are compendial grade and standard for biotechnology therapeutic monoclonal antibodies biopharmaceuticals. Additional information is located in the DP Product Quality primary review in Panorama.

4. Reference material(s)

The Taltz reference standard is the ixekizumab drug substance RS. There is no Taltz DP reference standard. Taltz RS information is located in the DS Product Quality primary review in Panorama.

5. Manufacturing Process

the information provided in the BLA demonstrates the process is robust and produces a consistent Taltz product with the desired attributes. As noted above, there are two PMCs to confirm that microbial control is maintained during hold of the bulk solution (b) (4) (b) (4) and to confirm that the product does not affect retentivity of the challenge organism that was used (b) (4) (microbial retention study).

6. Container Closure

The Taltz primary container closure is a (b) (4) syringe that consists of a 1 ml long Type I (b) (4) glass barrel with a small round flange, a 27G x 0.5 inch staked

needle with a (b) (4) plunger and a rigid needle shield. The (b) (4) syringe is assembled into the prefilled syringe or auto-injector device component. The Taltz (b) (4) syringe, prefilled syringe, and auto-injector closures are acceptable because the product remains stable throughout expiry when stored at the specified temperature of 2-8°C and protected from light.

D. Novel Approaches/Precedents: none

E. Product Quality Labeling Recommendations

Taltz must be protected from light until use, stored refrigerated at 2°C to 8°C, not frozen, not shaken, and discarded if frozen.

F. Establishment Information

Overall Facility Recommendation: Approve				
Drug Substance				
Site Name	Address	FEI Number	Responsibility	Final Recommendation
Eli Lilly S.A. – Irish Branch	Dunderrow Kinsale, County Cork Ireland	3002806888	DS manufacturer, storage, release and stability testing. DP potency release and stability testing.	Facility approved based on inspectional assessment.
Eli Lilly and Company	Lilly Corporate Center Indianapolis, Indiana United States	1819470 or 3000123645	DP manufacturer, device assembly, packaging and labeling and release and stability testing except potency. Storage facility for master and working cell banks.	Facility approved based on file review.

(b) (4)





(b) (4)



Drug Product				
Site Name	Address	FEI Number	Responsibility	Final Recommendation
Eli Lilly and Company	Lilly Corporate Center Indianapolis, Indiana United States	1819470	DP manufacturer, device assembly, packaging and labeling and release and stability testing except potency. Storage of master and working cell banks.	Facility approved based on file review.
Eli Lilly S.A. – Irish Branch	Dunderrow Kinsale, County Cork Ireland	3002806888	DS manufacture and storage. DS release and stability testing. DP potency release and stability testing.	Facility approved based on inspectional assessment.

(b) (4)



G. Facilities

BLA 125521 proposes the manufacture of TALTZ™ (ixekizumab) Drug Substance (DS) and Drug Product (DP), respectively, at Eli Lilly S.A. – Irish Branch, Kinsale, Ireland (FEI: 3002806888) and Eli Lilly and Company, Indianapolis, IN (FEI 1819470). Facilities supporting DS manufacture include the storage facility for the master and working cell bank (b) (4)

(b) (4) cell based potency assay for the bulk DS (b) (4) (b) (4) and mycoplasma and virus release testing of the unprocessed bulk (b) (4)

(b) (4)



Operations at the Eli Lilly S.A. – Irish Branch multi-product facility include manufacture of recombinant biotechnology products derived from mammalian cell culture that are intended for clinical and commercial use. The cell lines include Chinese Hamster Ovary (CHO) and murine myeloma (NSO). For this application, the facility will be responsible for DS manufacture, release/stability testing, and storage. It will also conduct DP potency release and stability testing. A pre-license inspection was conducted by OPQ on June 22 -26, 2015, and a one-item Form FDA 483 was issued to the firm. The inspection was classified VAI. Three preapproval inspections have occurred at the facility: December 2014, March 2014, and November 2011 for three BLA monoclonal antibody/Fc fusion protein products. The classification for the inspections was VAI or NAI.

For DP, TALTZ™ (ixekizumab) DP is manufactured at the Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN (FEI 1819470). DP potency release and stability testing are performed at Eli Lilly S.A. – Irish Branch, Kinsale, Ireland (FEI 3002806888), (b) (4)

(b) (4) The DP manufacturing site in Indianapolis consists of a (b) (4)

(b) (4). The facility is responsible for manufacture of ixekizumab DP, device assembly, packaging, labeling, master/working cell bank storage, and release/stability testing (except potency). CDRH ODE and CDRH OC have reviewed all facilities associated with the production of the pre-filled syringe and auto-injector, including assembly of the (b) (4) syringe into the devices. CDRH has recommended approval of the application and additional information is located in the CDRH device primary consult reviews.

In the last three years the Eli Lilly and Company, Lilly Corporate Center has been inspected five times. An inspection conducted in August 2015 was a routine surveillance inspection and follow up to previous inspection for manufacturing BLA DP. (b) (4)

No significant issues were found and all inspections were classified as NAI or VAI. The need for a preapproval inspection of this facility was waived for Taltz approval because the facility has an adequate cGMP compliance history.



H. Lifecycle Knowledge Management

1. Drug Substance

i. **Protocols approved:** annual stability protocol, qualification of new working reference standard, qualification of new working cell bank, protocol for the addition of a new product into (b) (4), and concurrent validation protocol for (b) (4) and (b) (4) bioburden (b) (4)

ii. **Outstanding review issues/residual:** None

iii. **Future inspection points to consider:** None

2. Drug Product

i. **Protocols approved:** annual stability protocol

ii. **Outstanding review issues/residual:** None

iii. **Future inspection points to consider:** None



Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
Product Type				
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/Source Material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non- Primate Mammalian Cell Substrate/Source Material	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal Sourced		X	
9.	Transgenic Plant Sourced		X	
10.	New Molecular Entity	X		
11.	PEPFAR Drug		X	
12.	PET Drug		X	
13.	Sterile Drug Product	X		
14.	Other _____			
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (# _____)		X	
16.	Comparability Protocol(s)	X		
17.	End of Phase II/Pre-BLA Agreements		X	
18.	SPOTS (Special Products On-line Tracking System)		X	
19.	USAN Name Assigned	X		
20.	Other _____			

**BLA 125521 Taltz (Ixekizumab) QUALITY REVIEW**

Quality Considerations					
21.	Drug Substance Coverage			X	
22.	Design Space	Formulation	X		
23.		Process		X	
24.		Analytical Methods		X	
25.		Other			
26.	Other QbD Elements			X	
27.	Real Time Release Testing (RTRT)			X	
28.	Parametric Release in lieu of Sterility Testing			X	
29.	Alternative Microbiological Test Methods			X	
30.	Process Analytical Technology in Commercial Production			X	
31.	Non-compendial Analytical Procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal Origin		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other _____				



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
DBRRIII
White Oak, MD 20003

Memorandum: Immunogenicity Review

STN: BLA 125559

Serial: 0

From: Maria Cecilia Tami, Ph.D., DBRRIII

Through: Susan Kirshner, Ph.D., Review Chief, DBRRIII

Product: TALTZ (ixekizumab, anti IL-17)

Sponsor: Eli Lilly and Company

Indication: Treatment of moderate to severe plaque psoriasis

Dose: 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80-mg injections at Weeks 2, 4, 6, 8, 10, and 12, and then 80 mg every 4 weeks.

Subject: Immunogenicity review

Mariacecil Tami -S

Susan L. Kirshner -A

Digitally signed by Mariacecil Tami -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300371991,
cn=Mariacecil Tami -S
Date: 2015.10.29 10:09:29 -0400

Digitally signed by Susan L. Kirshner -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300194629,
cn=Susan L. Kirshner -A
Date: 2015.10.29 12:37:49 -0400

Recommendation:

The assays to detect anti-ixekizumab antibodies are suitable for use in clinical studies. Overall, the data from the pivotal trials show that development of ADA does not raise safety concerns. The presence of high ADA titers and neutralizing activity is associated with reduced ixekizumab serum concentrations and decrease or loss of efficacy.

Some minor issues were identified during the review of the immunogenicity assays and immunogenicity data that were not addressed before the internal due date for this review. Specifically, regarding the assays, the sponsor did not justify their selection of system suitability criteria for the screening and neutralizing assays. In addition, the sponsor did not discuss whether NAb assay cut point data were normally distributed, although they used a cut point calculation that assumes data are normally distributed. Regarding the clinical data, the sponsor groups their analyses by titer $\leq 1:160$ and titer $\geq 1:160$. The rationale for grouping data based on those titers was not provided. The sponsor notes that ~4.5% of subjects screened positive at baseline, but did not attempt to explain the specificity or source of those antibodies. An information request will be sent requesting the Sponsor to clarify these issues. The responses to our information requests will be discussed in an addendum to this review memo.

Justification:

Approximately 20% of patients treated with ixekizumab across the phase 3 clinical studies developed anti-drug antibodies (ADA). This incidence includes all different dose schemes tested. Specifically, for patients dosed with the recommended commercial dose of 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by an 80 mg injection every 2 weeks for 12 weeks followed by 80 mg every 4 weeks, the incidence of ADA was approximately 20%. Overall, the data from the pivotal trials show that development of ADA was not associated with serious adverse events but was associated with reduced ixekizumab serum concentrations, especially in patients with higher ADA titers and neutralizing activity. Moreover, development of high ADA titers and antibody responses with neutralizing activity resulted in decreased or loss of efficacy as measured by sPGA and PASI75.

It is important to mention that the assay to test for the presence of neutralizing antibodies is sensitive to expected concentrations of ixekizumab in serum samples. Therefore, there is a possibility that the number of anti ixekizumab neutralizing samples is under reported and some patients are false negatives. The Sponsor acknowledges the limited tolerance of the assay and therefore, classifies those patients with levels of drug that can cause interference in the assay as inconclusive. There are other therapies available for this target population, patients have access to alternative treatments should the ADA responses result in substantial decrease or loss of clinical outcome.

There were no confirmed cases of anaphylaxis during ixekizumab clinical studies. Twenty nine patients had non anaphylaxis allergic reactions/hypersensitivity events associated with treatment emergent-ADA (TE-ADA)-positivity and three led to drug discontinuation. However, there was no apparent association between allergic reactions/hypersensitivity events and development of TE-ADA to ixekizumab. In most of the patients detection of ADA titers did not correlate with the occurrence of the adverse event, with the exception of individual cases of hypersensitivity where a temporal relationship between the event and ADA development existed. Injection site reactions were significantly more frequent in ixekizumab-treated patients than in placebo-treated patients, but there was no association between the presence of ADA and the incidence injection site reactions. Moreover, the incidence of injection site reactions was higher in patients negative for TE-ADA. The recommended commercial dose of ixekizumab is 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by 80 mg injections at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks. The data from the phase 3 clinical studies indicate that this is the most favorable dose scheme with regards to ADA incidence, titer status and neutralizing activity. The immunogenicity section of the label will specifically describe the development of ADA in this treatment group.

REVIEW:

To assess the immunogenicity of ixekizumab, patient samples were analyzed using a 4-tier approach (please refer to the immunogenicity testing approach section of this review). The Sponsor developed a screening, confirmatory, a titering and neutralizing assays. To assess the suitability of the assays to detect anti-ixekizumab antibodies in clinical samples, the documents listed below were reviewed:

- Validation report 08-011: An Affinity Capture Elution Enzyme-Linked Immunosorbent Assay to Detect Human Antibodies against LY2439821 in Human Serum.
- Validation report addendum number 12-196A. Addendum to validation report 08-011.
- Validation report addendum #2. Addendum to validation report addendum 12-196A.
- Validation report addendum #3. Addendum to validation report addendum 12-196A.
- Validation Report 10-192: Validation of an Anti-LY2439821 Neutralizing Antibody Assay
- Validation Report Addendum number 12-196B: Addendum to Validation report 10-192.

IMMUNOGENICITY ASSAYS

(Section 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies)

Screening assay (Tier 1)

The ACE enzyme-linked immunosorbent assay (ELISA) screening assay to detect ADA to ixekizumab was initially validated in 2008 (Report 08-011) and confirmatory validations were performed afterwards.

Assay description

(b) (4)

Confirmatory assay (Tier 2)

The screening assay is also used for confirmation of the specificity of the antibodies detected with the screening assay (tier 2)

(b) (4)

(b) (4)

Titering assay (Tier 3)

The screening assay format is used to determine anti-LY2439821 antibodies titers, testing serial two fold dilution of confirmed positive samples. Four or more dilutions are tested.

Titers are defined as the highest serum dilution that gives a signal above the cut point, where the following dilution renders a value below the assay cut point.

Reviewer’s comment: *The tiered approach to testing for the presence of ADA in the clinical samples is acceptable and in accordance with current FDA recommendations (Draft Guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins).*

The Sponsor included an [redacted] (b) (4)
 [redacted] (b) (4)

A summary of the screening assay validation results is provided in the Table below.

Table 2.7.2.9. Assay Parameters for the Ixekizumab Screening Immunogenicity Assay

Assay Parameter	Result	Conclusion
Minimum Required Dilution (MRD)		(b) (4)
Cut Point		
Sensitivity		
Drug Tolerance		
Precision	Intra-assay: 7.4% to 14.6% CV Inter-assay: 13.6% to 18.4% CV	The CV of ≤25% is acceptable.
Specificity	No signal above cut point obtained with a matched irrelevant antibody. Positive controls inhibited >80% with excess ixekizumab, but not by an irrelevant IgG ₄ .	Specificity of the assay for anti-ixekizumab ADA was confirmed by use of an irrelevant species-matched control antibody. Specificity of the assay for anti-ixekizumab ADA was confirmed by inhibition of positive controls (b) (4) with excess ixekizumab, but not by an irrelevant IgG ₄ .
Robustness	Deliberate changes in test method evaluated included incubation time, buffer pH, and hold time of plate prior to reading final results.	Assay is demonstrated to be robust, with all samples falling within a range of ±30% from baseline values.
Stability	6 freeze/thaw cycles: -17.9% to 6.2% difference 4 and 24 hours at ambient temperature (20°C to 25°C) and 2°C to 8°C: -5.5% to 12.6% difference	Assay is stable across 6 freeze/thaw cycles. Assay is stable at ambient temperature (20°C to 25°C) and 2°C to 8°C up to 24 hours, with all samples falling within a range of ±25% from reference values.
Serum Factor Interference	Hemolysis: -7.1% to 7.4% difference Lipemia: -5.6% to 17.4% difference Bilirubin: -2.4% to 15.7% difference	Multiple serum factors evaluated do not significantly affect the ability of the assay to detect ADA.
Titration	Signal titrates below cut point	Demonstrates the ability of the assay to titrate the high control below the cut point(s).

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IMMUNOGENICITY DATA

The ixekizumab development program included one Phase 1 study (RHAG), one Phase 2 study (RHAJ), three pivotal Phase 3 studies (RHAZ, RHBA, RHBC), a Phase 3, open-label study in Japanese patients (RHAT), and a Phase 3, randomized, open-label, pharmacokinetics (PK) study that compared the PK of ixekizumab administered via prefilled syringe and autoinjector devices (RHBL). Immunogenicity samples were collected in the phase 2 and phase 3 clinical studies. This review evaluates immunogenicity data obtained during the three pivotal Phase 3 studies performed to support this BLA application.

The design of studies RHAZ, RHBC and RHBA are shown in appendix 1 to this review. Briefly, each pivotal study evaluated short-term efficacy (12 weeks, Induction Period) of ixekizumab versus placebo. Studies RHAZ and RHBA evaluated maintenance of efficacy for an additional 48 weeks after induction treatment (up to Week 60, Maintenance Period) using a randomized withdrawal design for ixekizumab-treated patients who met the response criteria (static Physician Global Assessment, sPGA, (0,1) at Week 12). RHBA and RHAZ had a SC starting dose of 160 mg followed by SC 80 mg Q2W or Q4W or placebo for up to 12 weeks (Induction) followed by SC 80 mg Q4W or Q12W from Week 12 to Week 60. RHBC only included an induction period.

The ADA analyses were performed on N=2293 patients. These were ADA evaluable ixekizumab patients from the placebo controlled Phase 3 studies.

For the three studies, samples for immunogenicity were taken at week 0 (baseline), 4, 12 and 24, every 3 months at weeks 36, 48, 60, every 6 months at weeks 84, 108, 132, 156, 180, 204, 228 and 264 (end of treatment visit, ETV). Additional samples were taken 4, 12 and 24 weeks after the ETV.

Immunogenicity testing approach

Patient samples were analyzed using a 4-tier approach as shown in Figure 2.7.2.13 below. Samples from the phase 2 and phase 3 clinical studies were evaluated in the screening assay using a disease specific cut point.

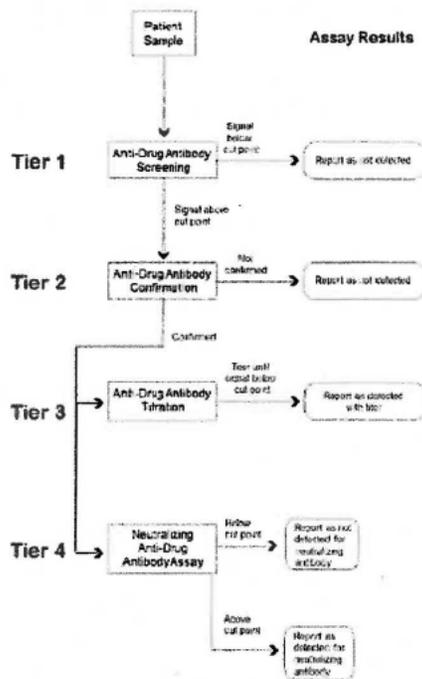


Figure 2.7.2.13. Flowchart for Anti-Drug Antibody assessments.

Immunogenicity samples were classified as follows:

- Unevaluatable sample: Sample could not be tested for ADA due to sample loss, mishandling, or errors in collection, processing, storage.
- ADA Positive sample: ADA are detected and confirmed. Samples are reported as positive and a titer value is reported.
- NAb Positive sample: NAb are reported as detected.
- ADA/Nab Negative sample: ADA are not detected and assay drug tolerance is not exceeded.
- Inconclusive sample: ADA/NAb not detected, but drug is present at a level that can cause interference in the assay. The negative ADA/NAb result cannot be confirmed and the sample is considered inconclusive.

ADA Positive (ADA+) samples were classified as follows:

- Treatment-emergent positive anti-drug antibody (TE-ADA positive): >4-fold (2 dilution) increase over a positive baseline antibody titer or an increase in titer to a level of $\geq 1:10$ for samples negative at baseline.
- Treatment-emergent persistent positive ADA patients: TE-ADA positive results detected at ≥ 2 sample times, and the first and last TE-ADA positive samples are separated by ≥ 12 weeks or if:
 - i. The last sample obtained while on study treatment or in the follow-up period is TE-ADA positive but with no further opportunity to assess persistence or;

- ii. The last sample obtained while on study treatment is TE-ADA positive and the first sample within the follow-up period is also positive.
- Treatment-emergent transient positive ADA patients: TE-ADA positive result(s) detected that do not satisfy the conditions required for TE-persistent positive ADA patients (time between the first and last positive sample is <12 weeks, the last obtained sample while on study treatment or in the follow-up period is ADA negative or if TE ADA positive, it does not persist into the follow-up period).

Samples were classified for their titer status as:

- Low Titer: <1:160
- Moderate-to-High Titer: ≥1:160

***Reviewer's comment:** the sponsor groups titer status for analyses by titer ≤1:160 and titer ≥1:160. The rationale for grouping data based on those titers was not provided. An IR will be sent requesting the Sponsor to provide a justification for their definition of titers status. The Sponsor's response will be discussed in an addendum to this review memo.*

Immunogenicity results

The overall immunogenicity incidence at baseline and during the induction period from pivotal studies RHAZ, RHBA and RHBC is summarized in Table 2.7.2.12 below.

**Table 2.7.2.12. Overall Immunogenicity Incidence at Baseline and during Induction Dosing Period
Ps Safety Population
Primary Psoriasis Placebo-Controlled Integrated Analysis Set (Studies RHAZ, RHBA, and RHBC)**

	Placebo N=791 n (%)	80-mg Q4W N=1161 n (%)	80-mg Q2W N=1167 n (%)	Total IXE N=2328 n (%)
Baseline (Week 0), Nx	781	1143	1150	2293
ADA Positive [1]	34 (4.4%)	51 (4.5%)	53 (4.6%)	104 (4.5%)
ADA Inconclusive [1]	0	0	0	0
ADA Negative [1]	727 (93.1%)	1064 (93.1%)	1078 (93.7%)	2142 (93.4%)
ADA Missing [1]	20 (2.6%)	28 (2.4%)	19 (1.7%)	47 (2.0%)
Overall, Nx	781 (98.7%)	1143 (98.4%)	1150 (98.5%)	2293 (98.5%)
Baseline ADA positive [1]	34 (4.4%)	51 (4.5%)	53 (4.6%)	104 (4.5%)
TE positive ADA result at any time Postbaseline [1]	4 (0.5%)	153 (13.4%)	103 (9.0%)	256 (11.2%)
Transient [2]	4 (100.0%)	39 (25.5%)	27 (26.2%)	66 (25.8%)
Persistent [2]	0	114 (74.5%)	76 (73.8%)	190 (74.2%)
TE-ADA Inconclusive [1]	0	0	0	0
TE-ADA Negative [1]	777 (99.5%)	990 (86.6%)	1047 (91.0%)	2037 (88.8%)
TE-ADA Positive NAb data				
NAb Positive [2]	1 (25.0%)	19 (12.4%)	5 (4.9%)	24 (9.4%)
NAb Negative [2]	2 (50.0%)	15 (9.8%)	4 (3.9%)	19 (7.4%)
NAb Inconclusive [2]	1 (25.0%)	119 (77.8%)	94 (91.3%)	213 (83.2%)
NAb Missing [2]	0	0	0	0

Overall Immunogenicity Incidence at Baseline and during Induction Dosing Period Ps Safety Population

Primary Psoriasis Placebo-Controlled Integrated Analysis Set (Studies RHAZ, RHBA, and RHBC) Abbreviations: ADA = anti-drug antibody; IXE = ixekizumab; n = number of patients at the specified category; N = number of patients in the analysis population; percentage is calculated by $n/N \times 100\%$; NAB = neutralizing anti-drug antibody; Nx = number of evaluable patients; Ps = plaque psoriasis; Q2W = every 2 weeks; Q4W = every 4 weeks; TE = treatment-emergent.

An evaluable patient is defined as: a) a patient with an evaluable baseline sample and at least 1 evaluable postbaseline sample (that is, sample after administration of study drug); b) a patient with no evaluable baseline sample whose evaluable postbaseline samples are all ADA negative. A TE-ADA positive patient is defined as: a) a patient with a ≥ 4 -fold increase over a positive baseline antibody titer; or b) for a negative baseline titer, a patient with an increase from the baseline to a level of $\geq 1:10$. TE-Persistent Positive ADA Patients: TE-ADA positive results detected at 2 or more sample times where the first and last TE-ADA positive samples are separated by ≥ 12 weeks or if a) the last sample obtained while on study treatment or in the follow-up period is TE-ADA positive but with no further opportunity to assess persistence; or b) the last sample obtained while on study treatment is TE-ADA positive and the first sample within the follow-up period is also positive. TE transient positive ADA patients: TE-ADA positive result(s) detected that do not satisfy the conditions required of TE persistent positive ADA patients. Scheduled visits only are included in the by visit summaries. Scheduled and unscheduled visits are included in the overall summaries.

[1] Percentages are based on the number of evaluable patients and are calculated by n/N_x .

[2] Percentages are based on the number of evaluable patients who are TE-ADA positive.

Reviewer's comment: TE-ADA in ixekizumab treated patients was 11.2% with slightly higher incidence observed in the 80-mg Q4W (13.4%) than in the 80-mg Q2W (9%). Because the tolerance of the screening assay is high, it is unlikely that the difference in ADA incidence is due to interference of higher serum levels of ixekizumab in samples from patients dosed more frequently in the screening assay. Of the ixekizumab-treated patients, 2.9% and 8.3% were transient- and persistent-TE-ADA positive, respectively. The incidence of neutralizing antibodies was 1%. In the TE-ADA positive patients group, 61.3% (157 of 256) had ADA titers $< 1:160$, that the Sponsor classifies as low, around 74% had persistent responses and approximately 9% tested positive for the presence of neutralizing antibodies. The proposed recommended dose for ixekizumab during the induction period in the label is 80-mg Q2W group. This is supported by a lower incidence of ADA and NAB, lower titers and less persistent responses in the 80-mg Q2W group than in the 80-mg Q4W group. Of note, similar ADA levels were present at baseline across all study groups. It is unclear whether these antibodies are product specific and whether the antibody titers increase over time. An IR will be sent requesting the Sponsor to provide this information. The Sponsor's responses will be discussed in an addendum to this review memo.

The overall ADA status at week 60 (at the end of the maintenance period) based on the treatment received in the induction and maintenance period is summarized in Table 2.7.2.14 below.

Table 2.7.2.14. Overall TE-ADA Status Maintenance Dosing Period (Maintenance Dosing Period Primary Population – Efficacy Evaluable) Psoriasis Maintenance Integrated Analysis Set (Studies RHAZ and RHBA)

	IXE/Placebo N=330 n (%)	IXE/80-mg Q12W N=329 n (%)	IXE/80-mg Q4W N=330 n (%)	IXE/IXE N=659 n (%)
TE-ADA Positive	80 (24.2%)	84 (25.5%)	57 (17.3%)	141 (21.4%)
TE-ADA Negative	250 (75.8%)	245 (74.5%)	273 (82.7%)	518 (78.6%)

Abbreviations: IXE = ixekizumab; n = number of patients in the specific category; N = number of patients; Q4W = every 4 weeks; Q12W = every 12 weeks; TE-ADA = treatment-emergent anti-drug antibody.

Reviewer's comment: The lowest incidence of ADA at the end of the maintenance period was observed in the ixekizumab/Q4W treated group and higher comparable levels were observed in the ixekizumab/Q12W and ixekizumab/placebo groups. Rates of shifting (TE-ADA negative to TE-ADA positive) were 11.3% in the ixekizumab/Q4W group, and 19.9% and 17.3% in the ixekizumab/Q12W and ixekizumab/placebo groups, respectively.

Some patients across the three groups shifted from positive to negative ADA status. In all groups, most of the TE-ADA positive patients had titers <1:160 (85.0%, 88.1% and 94.7% in the ixekizumab/placebo, ixekizumab/Q12W and ixekizumab/Q4W, respectively).

Incidence of Nab responses during the maintenance period is shown in table 2.7.2.17 below.

Table 2.7.2.17. **Nab Status at Week 60
Maintenance Dosing Period
(Maintenance Dosing Period Primary Population - Efficacy Evaluable Patients)
Psoriasis Maintenance Integrated Analysis Set (Studies RHAZ and RHBA)**

	IXE/Placebo N=330 n (%)	IXE/80-mg Q12W N=329 n (%)	IXE/80-mg Q4W N=330 n (%)	IXE/IXE N=659 n (%)
TE-ADA Status: TE-ADA Positive (Ns) [3]	80 (24.2%)	84 (25.5%)	57 (17.3%)	141 (21.4%)
Nab Status: Co-occurring Nab Positive (Ns) [3]	4 (1.2%)	4 (1.2%)	1 (0.3%)	5 (0.8%)
Nab Status: Co-occurring Nab Negative (Ns) [3]	68 (20.5%)	62 (18.8%)	1 (0.3%)	63 (9.6%)
Nab Status: Co-occurring Nab Inconclusive (Ns) [3]	8 (2.4%)	18 (5.5%)	55 (16.7%)	73 (11.1%)
TE-ADA Status: TE-ADA Negative (Ns) [3]	250 (75.8%)	245 (74.5%)	273 (82.7%)	518 (78.6%)

Abbreviations: IXE = ixekizumab; n = number of patients in the specific category; N = number of patients; Nab = neutralizing anti-drug antibody; Ns = number of patients; Q4W = every 4 weeks; Q12W = every 12 weeks; TE-ADA = treatment-emergent anti-drug antibody.
[3] Percentages are based on the number of evaluable patients and are calculated by Ns/Nx.

Reviewer's comment: A total of 9 patients were identified as Nab positive across all treatment groups and a high number of TE-ADA positive samples were classified as inconclusive for Nab status. This is due to the low tolerance of the neutralizing assay for on board drug. It is probable that the incidence of Nab is under reported due to assay limitations. This issue was communicated to the Sponsor during the mid-cycle meeting as well as included in an IR sent in September 16, 2015. The information provided by the Sponsor is discussed earlier in this memo.

In the group of patients randomized to placebo during induction that received 80-mg Q4W during the maintenance period, the incidence of TE-ADA positive was 13.6% (74 of 543), 70.3% had titers <1:160. From the ADA positive patients, 13 were Nab positive and 58 inconclusive. Most of the Nab positive patients show high ADA responses.

Reviewer's comment: Similar incidence of ADA-positive patients was observed in the group receiving 80-mg Q4W during induction (13.4%, Table 2.7.2.12) as in the group receiving placebo during the induction period and then switched to 80-mg Q4W during maintenance. Although this is not the proposed recommended dose, these data show consistent results for ADA rates.

The overall ADA status for patients exposed to ixekizumab is summarized in Table 2.7.2.18 below:

Table 2.7.2.18. Overall Immunogenicity Incidence
All Treatment Periods
All Ps Ixekizumab Exposures Safety Population
All Ps Ixekizumab Exposure Integrated Analysis Set

	Pooled IXE N=4204 n (%)
Baseline (Week 0), Nx	4107
ADA Positive [1]	186 (4.5%)
NAb Positive [2]	1 (0.5%)
NAb Negative [2]	132 (71.0%)
NAb Inconclusive [2]	0
NAb Unknown [2]	53 (28.5%)
NAb Missing [2]	0
ADA Inconclusive [1]	0
ADA Negative [1]	3873 (94.3%)
ADA Missing [1]	48 (1.2%)
Overall, Nx	4107 (97.7%)
Baseline ADA positive [1]	186 (4.5%)
TE positive ADA result at any time Postbaseline [1]	826 (20.1%)
Transient [2]	388 (47.0%)
Persistent [2]	438 (53.0%)
TE-ADA Inconclusive [1]	0
TE-ADA Negative [1]	3281 (79.9%)
NAb Positive [2]	89 (10.8%)
NAb Negative [2]	100 (12.1%)
NAb Inconclusive [2]	637 (77.1%)
NAb Missing [2]	0

Abbreviations: ADA = anti-drug antibody; IXE = Ixekizumab; n = number of patients at the specified category; N = number of patients in the analysis population; percentage is calculated by $n/N \times 100\%$; NAb = neutralizing anti-drug antibody; Nx = number of evaluable patients; TE = treatment-emergent.

An evaluable patient is defined as: a) a patient with an evaluable baseline sample and at least 1 evaluable postbaseline sample (that is, sample after administration of study drug); b) a patient with no evaluable baseline sample whose evaluable postbaseline samples are all ADA negative. A TE-ADA positive patient is defined as: a) a patient with a ≥ 4 -fold increase over a positive baseline antibody titer; or b) for a negative baseline titer, a patient with an increase from the baseline to a level of $\geq 1:10$. TE Persistent Positive ADA Patients: TE-ADA positive results detected at 2 or more sample times where the first and last TE-ADA positive samples are separated by ≥ 12 weeks or if a) the last sample obtained while on study treatment or in the follow-up period is TE-ADA positive but with no further opportunity to assess persistence; or b) the last sample obtained while on study treatment is TE-ADA positive and the first sample within the follow-up period is also positive. TE transient positive ADA patients: TE-ADA positive result(s) detected that do not satisfy the conditions required of TE persistent positive ADA patients.

[1] Percentages are based on the number of evaluable patients and are calculated by n/N_x .

[2] Percentages are based on the number of evaluable patients who are TE-ADA positive.

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Table 2.7.2.15 below shows TE-ADA positive patients analyzed by titer status. The Sponsor categorized low titers are those below 1:160.

Table 2.7.2.15. TE-ADA Positive by Titer Status
Maintenance Dosing Period
(Maintenance Dosing Period Primary Population – Efficacy Evaluable)
Psoriasis Maintenance Integrated Analysis Set (Studies RHAZ and RHBA)

	IXE/Placebo N=330 n (%)	IXE/80-mg Q12W N=329 n (%)	IXE/80-mg Q4W N=330 n (%)	IXE/IXE N=659 n (%)
TE-ADA Positive	N=80	N=84	N=57	N=141
Low Titer	68 (85.0%)	74 (88.1%)	54 (94.7%)	128 (90.8%)
Moderate-to-High Titer	12 (15.0%)	10 (11.9%)	3 (5.3%)	13 (9.2%)

Abbreviations: IXE = ixekizumab; n = number of patients in the specific category; N = number of patients; Q4W = every 4 weeks; Q12W = every 12 weeks; TE-ADA = treatment-emergent anti-drug antibody.

Reviewer's comment: 20% (826/4107) of patients treated with ixekizumab tested TE-ADA positive at some time point post baseline with 47% and 53% being transient and persistent-TE-ADA positive, respectively. The majority of the patients across dosing groups show titers below 1:160 (low titers). Among TE-ADA positive patients, 10.8%

tested positive for the presence of Nabs (2.2% of the ixekizumab treated patients). These results include all dosing groups evaluated in the Phase 3 studies. The recommended dose of ixekizumab is 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by an 80 mg injection at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks. The Sponsor did not provide an analysis of the incidence of ADA in the patients treated with the recommended dose schedule. Those data were analyzed by Mathew Guerra, from the Office of Biostatistics. His analysis is provided below:

Induction Period (Q2W)	Maintenance Period (Q4W)	Number of Subjects		
		Week 12 Responders	Week 12 Non-Responders	Overall
ADA Negative	ADA Negative	134 (78.4%)	78 (75.0%)	212 (77.1%)
ADA Positive	ADA Negative	8 (4.7%)	1 (1.0%)	9 (3.3%)
ADA Negative	ADA Positive	17 (9.9%)	8 (7.7%)	25 (9.1%)
ADA Positive	ADA Positive	12 (7.0%)	17 (16.3%)	29 (10.5%)

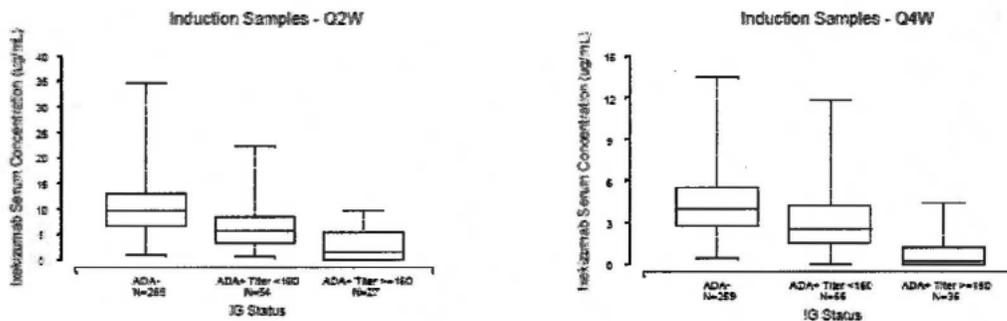
This analysis does not include those patients that may stop ixekizumab treatment after the induction dose (this would be similar to the placebo arm in the phase 3 maintenance period), therefore, the incidence of ADA could be higher.

The label will report the incidence of ADA and Nab in the proposed dose scheme.

Analysis of the impact of immunogenicity on ixekizumab exposure (PK)

The relationship between sera concentrations of ixekizumab and antibody responses (ADA and Nab) in the induction period are shown below based on data from the RHAZ study (as provided from the Sponsor).

Figure 2.7.2.14. Observed ixekizumab trough concentrations by titer category for Study RHAZ, 12 week Induction Period Dosing.

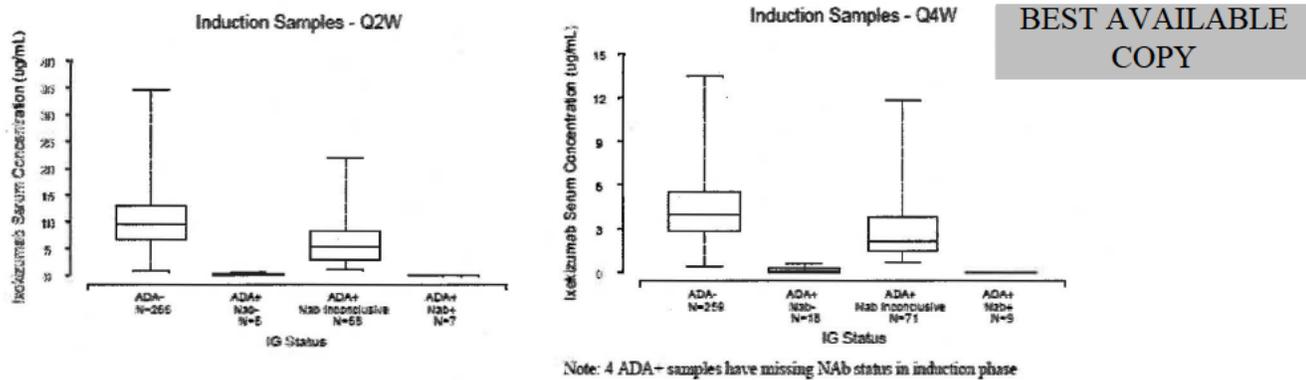


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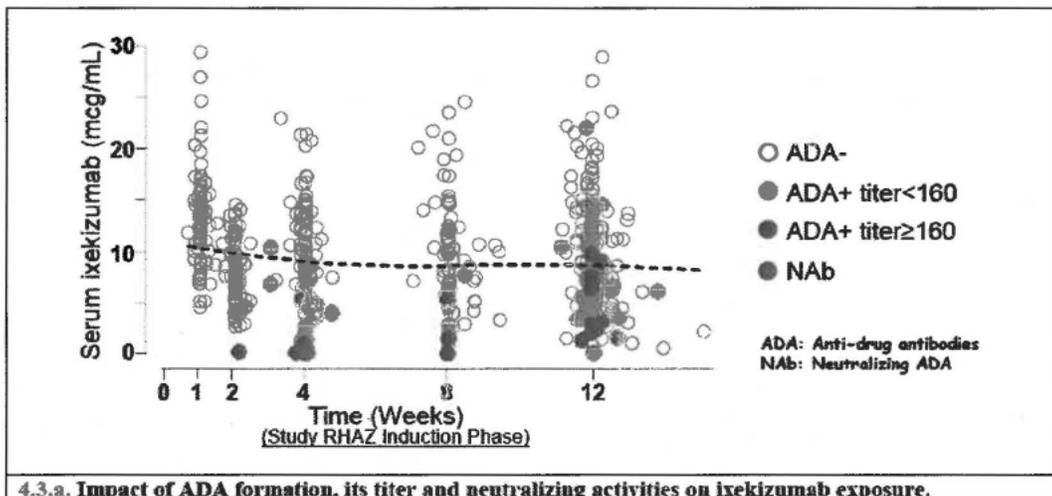
Reviewer’s comment: The data show that the presence of ADA is associated with reduced ixekizumab serum concentrations even in the patients with ADA levels <1:160 and this observation is more evident in patients with higher ADA titers in both induction dosing groups (Q2W and Q4W). Lower serum concentrations of ixekizumab were

observed in the Q4W group. This was expected due to longer dosing intervals and the fact that samples are collected before dosing.

Figure 2.7.2.15. Observed ixekizumab trough concentrations by Neutralizing antibody status: Study RHAZ, Induction Period Dosing (all ADA positive patients).



Reviewer's comment: For NAb positive patients, ixekizumab concentration in serum were substantially lower than for patients who were ADA negative or ADA positive/Nab inconclusive. It is expected that Nab inconclusive patients have higher ixekizumab concentrations than Nab positive patients since the samples were designated as inconclusive because ixekizumab concentrations were above the drug tolerance limit of the assay. The tolerance of the neutralizing assay to the presence of ixekizumab is low. Therefore, it is likely that the incidence of neutralizing antibodies in the clinical samples is under reported. However, available data indicate that patients with a clinically relevant NAb are those that have low ixekizumab concentration levels and these are within the detection limit of the NAb assay. The impact of antibodies on ixekizumab serum concentrations at different time points in the induction period are shown in the Figure 4.3.a as prepared by Jie Wang, the Clinical Pharmacology reviewer for this BLA.



Overall, the presence of anti-drug antibodies is associated with reduced ixekizumab serum concentrations, especially if the antibodies have neutralizing activity. According to a predictive exposure model, clearance of ixekizumab increased with increasing concentrations of ADA and the presence of Nabs was associated with lower exposure and low response rates.

Analysis of the impact of immunogenicity on efficacy

Efficacy was measured by static Physician Global Assessment, sPGA (0,1) and Psoriasis Area and Severity Index, PASI, scores (PASI 75). sPGA measures the physician’s impression of the disease at a single point. sPGA scores of 0 or 1 are considered responders. PASI includes the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease). PASI 75 represents the percentage of patients who have achieved a 75% or more reduction in their PASI score from baseline. PASI 100 indicates patients who have achieved a complete resolution of all disease.

Induction period

The efficacy responses among TE-ADA positive patients in the patients treated with ixekizumab during the induction period are shown in Table 2.7.3.23 below.

Table 2.7.3.23. sPGA (0,1) and PASI 75 Response Rates at Week 12, Effect of Immunogenicity Primary Psoriasis Placebo-Controlled Integrated Analysis Set ITT Population – RHZA, RHBA, and RHBC Induction Dosing Period

Endpoint	TE-ADA Status	NAb Status	FBO N=792 n (%)	80 mg Q4W N=1165 n (%)	80 mg Q2W N=1169 n (%)	All Ixekizumab N=2334 n (%)
<i>Evaluable patients</i>	NA	NA	781 (98.6)	1143 (98.1)	1150 (98.4)	2293 (98.2)
Patients in subgroup	Positive (low-titer, <1:160)		3 (0.4)	94 (8.0)	66 (5.7)	157 (6.8)
	Positive (mod-high titer, ≥1:160)		1 (0.1)	62 (5.4)	37 (3.2)	99 (4.3)
	Positive (all)	All	4 (0.5)	153 (13.4)	103 (9.0)	256 (11.2)
		Positive	1 (0.1)	19 (1.7)	5 (0.4)	24 (1.0)
		Negative	2 (0.3)	15 (1.3)	4 (0.3)	19 (0.8)
		Inconclusive	1 (0.1)	119 (10.4)	94 (8.2)	213 (9.3)
		Negative	NA	777 (99.5)	990 (86.6)	1047 (91.0)
sPGA (0,1)	Positive (low-titer, <1:160)		0	68 (74.7) ^b	52 (78.8) ^b	120 (76.4)
	Positive (mod-high titer, ≥1:160)		1 (100.0)	27 (43.5)	21 (56.8)	48 (48.5)
	Positive (all)	All	1 (25.0)	95 (62.1)	73 (70.9)	168 (65.6)
		Positive	1 (100.0)	1 (5.3) ^a	0	1 (4.2)
		Negative	0	6 (40.0)	2 (50.0)	8 (42.1)
		Inconclusive	0	88 (73.9)	71 (75.5)	159 (74.6)
		NA	30 (3.9)	777 (78.5) ^a	875 (83.6) ^b	1652 (81.1)
PASI 75	Positive	All	1 (25.0)	108 (70.6)	78 (75.7)	186 (72.7)
		Positive	1 (100.0)	2 (10.5) ^a	0	2 (8.3)
		Negative	0	6 (40.0)	2 (50.0)	8 (37.1)
		Inconclusive	0	100 (84.0)	76 (80.9)	176 (82.6)
		NA	34 (4.4)	841 (84.9) ^a	950 (90.7) ^a	1791 (87.9)

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sPGA (0,1) and PASI 75 Response Rates at Week 12, Effect of Immunogenicity
 Primary Psoriasis Placebo-Controlled Integrated Analysis Set
 ITT Population – RH4Z, RHBA, and RHBC
 Induction Dosing Period

Endpoint	TE-ADA Status	NAb Status	PBO N=792 n (%)	80 mg Q4W N=1165 n (%)	80 mg Q2W N=1169 n (%)	All Ixekizumab N=2334 n (%)
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Abbreviations: ITT = intent-to-treat; IXE = ixekizumab; N = number of patients in the analysis population; n = number of patients in the specified category; NA = not applicable; NAb = neutralizing antibody; NRI = nonresponder imputation; N_s = number of patients in each subgroup; N_x = number of evaluable patients; an evaluable patient is defined as: a) a patient with an evaluable baseline sample and at least 1 evaluable postbaseline sample (that is, sample after administration of study drug); b) a patient with no evaluable baseline sample whose evaluable postbaseline samples are all ADA negative; PASI = Psoriasis Area and Severity Index; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = static Physician Global Assessment; TE-ADA = treatment-emergent anti-drug antibody.

Notes: A TE-ADA positive patient is defined as: a) a patient with a ≥ 4 -fold increase over a positive baseline antibody titer; or b) for a negative baseline titer, a patient with an increase from the baseline to a level of $\geq 1:10$.

When ADA/NAb is not detected in a sample but drug is present in the same sample at a level that can cause interference in the ADA/NAb detection method, then the negative ADA/NAb result could not be incontrovertibly confirmed and the sample was considered inconclusive.

^a p < .001 versus PBO

^b p < .05 versus PBO (p-value versus placebo not calculated for Total IXE, NAb inconclusive. All TE-ADA Positive)

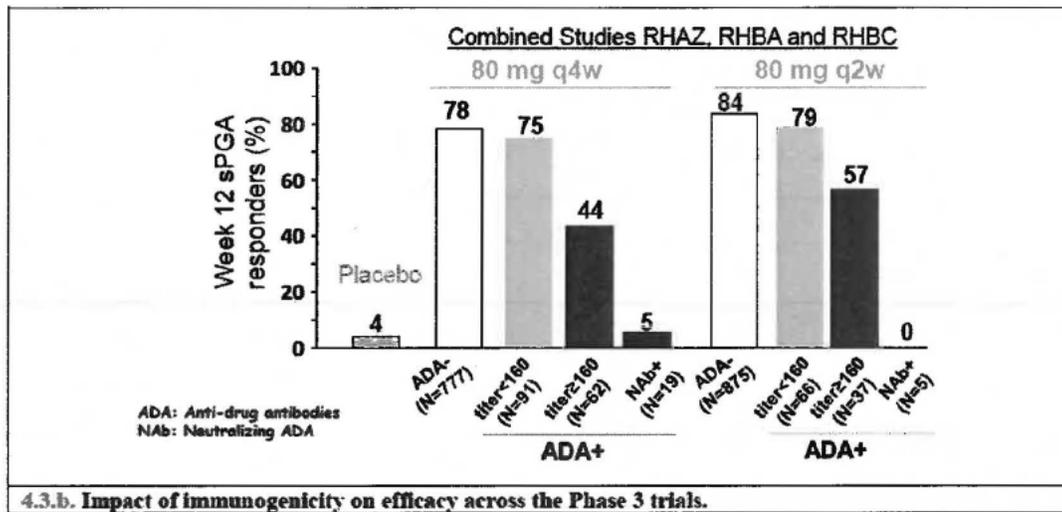
SOURCES: t_spgaresp_nab_nri_itt_i_ppc.rtf, t_pasiresp_nab_nri_itt_i_ppc.rtf, t_tesda_spgaresp_ada_nri_itt_i_ppc.rtf

Reviewer's comment: Overall, the presence of ADA negatively impacts response rates with higher titers generally resulting in lower responses. The presence of neutralizing antibodies consistently resulted in low efficacy outcome assessed with sPGA and PASI 75.

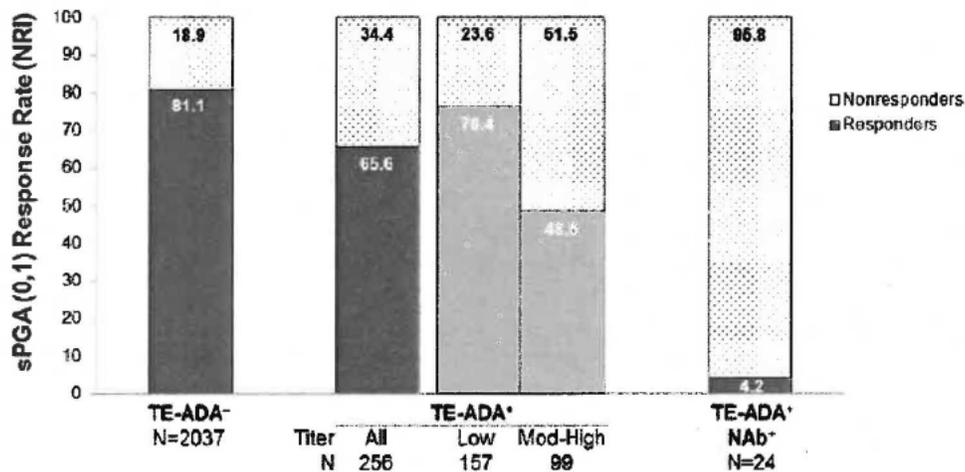
- sPGA (0,1) and PASI 75 scores were higher in ADA negative patients than in ADA positive patients (81.1% versus 65.5% and 87.9% versus 72.7% for sPGA and PASI 75, respectively).
- High titer ADA positive patients show lower response rates than low titer and negative ADA patients.
- Response rates by sPGA (0,1) and PASI 75 were very low in Nab positive patients (1 of 24 or 4.2%).

Response rates were higher in the 80 mg Q2W group than the 80 mg Q4W in both low and high ADA positive patients, supporting the selection of the 80 mg Q2W regimen.

The relationship between the presence of ADA and response measured by sPGA for each treatment group are shown in Figure 4.3.b below, prepared by Jie Wang, the Clinical Pharmacology reviewer for this BLA.



The overall relationship between the presence of ADA and response rate measured by sPGA is shown in Figure 2.7.3.22 below



Abbreviations: ITT = intent-to-treat; NAb = neutralizing antibody; NRI = nonresponder imputation; sPGA = static Physician Global Assessment; TE-ADA = treatment-emergent anti-drug antibody.
SOURCES: t_teada_spgaresp_ada_ari_itt_i_ppc.rtf, f_teada_nab_spga_itt.rtf

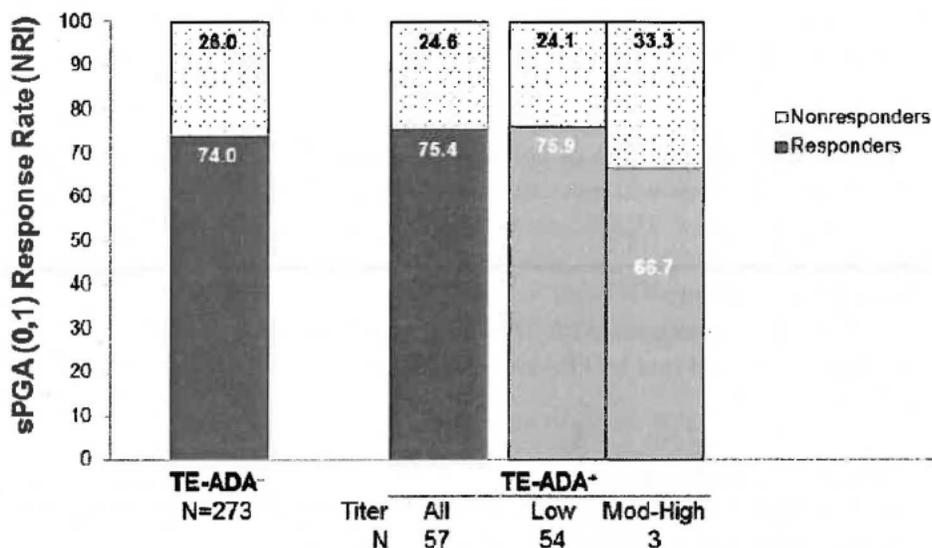
Figure 2.7.3.22. sPGA (0,1) response rates at Week 12 (NRI) by TE-ADA status and NAb positivity Psoriasis Placebo-Controlled Integrated Analysis Set ITT Population – RHAZ, RHBA, and RHBC Induction Dosing Period.

Maintenance period

Results obtained in the maintenance period were similar to those observed in the induction period (see Table 2.7.3.24 below).

Table 2.7.3.24. Effect of Immunogenicity on sPGA (0,1) and PASI 75 Response Rates (NRI) at Week 60 Maintenance Dosing Period Primary Population Efficacy Evaluable Patients – RHAZ and RHBA Psoriasis Maintenance Integrated Analysis Set Maintenance Dosing Period

Endpoint	TE-ADA Status	NAb Status	INE/PBO N=384 n (%)	INE/INE80Q12W N=355 n (%)	INE/INE80Q4W N=348 n (%)	INE/INE N=703 n (%)	
<i>Evaluable patients</i>	NA	NA	331 (86.2)	329 (92.7)	330 (94.8)	659 (93.7)	
<i>Patients in subgroup</i>	Positive (low-titer, <1:160)		68 (30.6)	74 (22.5)	54 (16.4)	128 (19.4)	
	Positive (mod-high titer, ≥1:160)		12 (3.6)	10 (3.0)	3 (0.9)	13 (2.0)	
	Positive (all)	All	80 (24.2)	84 (25.5)	57 (17.3)	141 (21.4)	
		Positive	4 (1.2)	4 (1.2)	1 (0.3)	5 (0.8)	
		Negative	68 (30.5)	67 (18.8)	1 (0.3)	63 (9.6)	
		Inconclusive	8 (2.4)	18 (5.5)	55 (16.7)	73 (11.1)	
	Negative	NA	250 (75.8)	245 (74.5)	273 (82.7)	518 (78.6)	
	sPGA (0,1)	Positive (low-titer, <160)		7 (10.3)	32 (43.2)	41 (75.9)	73 (57.0)
		Positive (mod-high titer, ≥160)		0	1 (10.0)	2 (66.7)	3 (23.1)
		Positive	All	7 (8.8)	33 (39.3)	43 (75.4)	76 (53.9)
		Positive	0	1 (25.0)	1 (100.0)	2 (40.0)	
		Negative	6 (8.8)	33 (37.1)	0	23 (36.5)	
		Inconclusive	1 (12.5)	9 (30.0)	42 (76.4)	51 (69.9)	
	Negative	NA	19 (7.6)	93 (38.0)	202 (74.0)	295 (56.9)	
PASI 75	Positive	All	9 (11.3)	39 (46.4)	48 (84.2)	87 (61.7)	
		Positive	0	2 (50.0)	1 (100.0)	3 (60.0)	
		Negative	8 (11.3)	26 (41.9)	0	26 (41.3)	
		Inconclusive	1 (12.5)	11 (61.1)	47 (85.5)	58 (79.5)	
	Negative	NA	19 (7.6)	112 (45.7)	217 (79.5)	329 (63.5)	



Abbreviations: NRI = nonresponder imputation; Q4W = every 4 weeks; sPGA = static Physician Global Assessment; TE-ADA = treatment-emergent anti-drug antibody.
SOURCE: t_teada_spgaresp_ada_nri_mpp_mrf

Figure 2.7.3.23.

sPGA (0,1) response rates at Week 60 by TE-ADA status (patients re-randomized to 80 mg Q4W) Maintenance Dosing Period Primary Population Efficacy Evaluable Patients – RHAZ and RHBA Psoriasis Maintenance Integrated Analysis Set Maintenance Dosing Period.

Reviewer's comment: during the maintenance period, the sPGA and PASI75 responses were similar between the ADA positive and negative patients in the IXE/80Q12W and the IXE/80Q4W groups as well as in the overall ixekizumab treated group. Response rates were higher in patients randomized to the 80Q4W group when compared to those randomized to the 80Q12W. The number of Nab positive patients was low. In general, efficacy responses were lower in this group. The number of TE-ADA positive patients with inconclusive Nab-positive results was high but these patients showed similar efficacy responses to the TE-ADA negative patients. Overall, a more favorable immunogenicity profile was observed in the group randomized to 80Q4W in the maintenance period.

Among patients randomized to placebo in the induction period who then received 80 mg Q4W during the maintenance period, response rates were in general lower than those observed in the other treatment groups. Response rates (sPGA) were similar between ADA positive patients and ADA negative patients (63.5% and 67.0%, respectively). Thirteen patients were Nab positive, 4 maintained or achieved sPGA (0,1) and 9 were non responders.

Analysis of the impact of immunogenicity on safety

Only TEAEs and discontinuations that occurred within 14 days before or after TE-ADA positive results are included in the analysis.

Induction overall observations:

The data provided (Table 2.7.4.85 of the submission) indicate the following regarding the ixekizumab-treated patients with persistent or transient TE-ADA+:

- 34.4% had at least 1 TEAE versus 58.3% of patients with TE-ADA negative status.
- No deaths occurred
- 3.1% vs 1.8% of patients with TE-ADA negative status had SAEs.
- 2.0% discontinued due to TEAEs vs 1.8% of patients with TE-ADA negative patients.

Maintenance overall observations:

The data provided (Table 2.7.4.87 of the submission) indicate the following regarding the patients with persistent or transient TE-ADA+:

- 47.2% had at least 1 TEAE versus 78.4% of patients who were negative for TE-ADA.
- No deaths in TE-ADA+ patients vs 4 deaths [0.1%] in patients negative for TE-ADA.
- 2.3% were discontinued due to TEAEs vs 4.4% of patients negative for TE-ADA.
- 8.0% had SAEs vs 6.9% in the patients negative for TE-ADA.
- Eight cases of hypersensitivity SAEs.

Allergic reactions/hypersensitivities

A list of general observations related to the incidence of allergic reactions/hypersensitivities in clinical studies is provided below:

- There were no confirmed cases of ixekizumab-related anaphylaxis events across the clinical development program.
- Allergic reactions/hypersensitivities were more frequent in ixekizumab-treated patients than in placebo-treated patients, but did not differ between patients treated with ixekizumab 80-mg Q2W and ixekizumab 80-mg Q4W.
- The rate of allergic reactions did not increase during the Maintenance Dosing Period.
- The Sponsor reports no association between allergic reactions/hypersensitivity events and treatment-emergent anti-drug antibodies. This observation was confirmed by the Dr. Jane Liedtka, the clinical reviewer for this BLA application.

Allergic reactions/Hypersensitivity AE by TE-ADA status***Treatment Emergent Adverse Events in the induction phase***

There were no confirmed cases of anaphylaxis during the induction period.

Regarding patients with non anaphylaxis allergic reactions/hypersensitivity events:

- Among the total ixekizumab-treatment group who had at least 1 non anaphylaxis allergic reaction/hypersensitivity event, the proportions of patients who were TE-ADA-positive or TE-ADA-negative were equal (3.1% in each group).
- There was inconsistency across ixekizumab dosing groups regarding the proportion of patients with a non anaphylaxis allergic reactions/hypersensitivity event: a higher proportion was found in the TE-ADA-positive than in the TE-ADA-negative in the ixekizumab 80-mg Q2W group (4.9% vs 2.7%, respectively) while the proportion was higher in the TE-ADA-negative than in the TE-ADA-positive patients in the ixekizumab 80-mg Q4W group (2.0% vs 3.6%, respectively).
- A relationship between the ADA titer and the incidence of non anaphylaxis allergic reactions/hypersensitivity event was not observed.
- Most of the non anaphylaxis TEAEs were mild in severity in those patients who were either TE-ADA-positive or TE-ADA-negative.
- Two patients had severe events in the ixekizumab 80-mg Q2W group and were TE-ADA-positive (both patients had events of urticaria, 1 of which was an SAE).
- There was no relationship between sPGA (0,1) status (response rates) and occurrence of non anaphylaxis allergic reaction/hypersensitivity events among ixekizumab-treated patients who were TE-ADA-positive.
- Eight patients (3.1%) in the total ixekizumab-treatment group versus 0 in the placebo group had non anaphylaxis events within the 14-day window around TE-ADA-positivity.
- Non anaphylaxis events were higher in TE-ADA-negative patients: 64 (3.1%) in the total ixekizumab group versus 15 (1.9%) in the placebo group.
- TE-ADA status had no apparent association with nonanaphylaxis/hypersensitivity events as TEAEs, SAEs, or discontinuation due to AEs.
- Severe events were observed in 0.9% (n=3) of ADA positive patients and 0.2% (n=4) of ADA negative patients.

Table 2.7.4.59 below shows a summary of allergic reaction/hypersensitivity non anaphylaxis events by TE-ADA status during the induction period.

Table 2.7.4.59. Summary of Allergic Reaction/Hypersensitivity Nonanaphylaxis Events by Treatment-Emergent ADA Status across Analysis Sets

TE-ADA Status	Primary Placebo-Controlled Analysis Set					Placebo- and Active-Controlled Integrated Analysis Set						All Psoriasis IXE-Exposure Analysis Set Pooled IXE
	Placebo	IXE80Q 4W	IXE80Q 2W	Total IXE	Treatment by TE-ADA Status Interaction	Placebo	ENT	IXE 80 mg Q2W	IXE80Q 2W	Total IXE	Treatment by TE-ADA Status Interaction	
Persistent or transient TE-ADA ^a	0%	2.0% (n=3)	4.9% (n=5)	3.1% (n=8)	0.290	0%	0%	3.0% (n=3)	4.8% (n=4)	4.4% (n=7)	0.707	3.5% (n=29)
No persistent or transient TE-ADA	1.9% (n=15)	3.6% (n=36)	2.7% (n=28)	3.1% (n=64)		2.0% (n=7)	2.1% (n=17)	3.2% (n=20)	2.7% (n=18)	3.0% (n=38)		8.6% (n=283)

Abbreviations: ENT = etanercept, IXE = ixekizumab, IXE80Q1W = ixekizumab 80 mg Q4W, IXE80Q2W = ixekizumab 80 mg Q2W; TE-ADA = treatment-emergent anti-drug antibody.

^a Number of patients with allergic reaction hypersensitivity nonanaphylaxis events within the 14-day window around TE-ADA-positive status.

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Reviewer's note: Data presented for the Active-Controlled Analysis Sets is not evaluated as part of this analysis. The etanercept group includes patients treated with US and EU products and the Sponsor did not provide adequate data to demonstrate that the EU and US etanercept products were comparable. Because the ixekizumab-treated patients in the Active-Controlled Analysis Sets were a subset of those in the Primary Placebo-Controlled Analysis Set, analysis of these data does not provide additional information.

Treatment Emergent Adverse Events in all ixekizumab exposed subjects

- Anaphylaxis Events

There were three cases of potential anaphylaxis associated with TE-ADA positivity (patients RHAJ 109-1901, RHAJ 200-5002, RHBA 110-01462). These patients were not considered by the Sponsor to meet the criteria for anaphylaxis including the proximity to drug administration (≤ 1 day). A patient in Study RHBL (Patient 122-5206) had a reported event of anaphylactic reaction. The patients had no baseline antibody sample and the sample was classified as unevaluable. After further review of the data, the patient was not considered to have an anaphylactic reaction due to lack of temporal proximity to study drug dosing.

A second patient in Study RHBA (Patient 161-3522) had a reported event of anaphylactic reaction with the event occurring outside of the 14-day window around TE-ADA-positive status and was not considered to have an anaphylactic reaction.

The information below was excerpted from Table 2.7.4.61, summarizing the patients with AE meeting Sampson's criteria for anaphylaxis.

Table 2.7.4.61. Studies of ixekizumab (LY2439821) in Patients with Plaque Psoriasis—Summary of Adverse Events Meeting Sampson's Criteria for Anaphylaxis that Occurred More Than 1 Day after Dose Administration

Patient ID	Treatment Period and Dose at Time of Event	Date of Last Dose Before Event	Event (Severity)	Reported Initiation Date of Event(s)	Reported Resolution Date of Event(s)	Sampson Criteria for Anaphylaxis	Met SMQ Anaphylaxis Criterion 2?	Event Associated with TE-ADA Positive? ^a	Treatment for Hypersensitivity Event(s) ^b
RHAJ-109-1901	DXE10Q4W	2010-06-30	Diarrhea (mild)	2010-07-03	2010-12-03	Criterion 2-CD	No	Yes	None
			Dizziness (mild)	2010-07-03	2010-10-01				
			Nausea (mild)	2010-07-03	2010-10-01				
RHAJ-200-5002	DXE75Q4W	2011-02-01	Dizziness (moderate)	2011-02-03	2011-02-28	Criterion 2-CD	No	Yes (Low Titer, no NAb)	None
			Nausea (mild)	2011-02-03	2011-02-28				
RHBA-110-1462	DXE80Q12W	2014-07-24	Puritus generalized (severe)	2014-08-05	2014-08-22	Criterion 2-AD	No	Yes (Low Titer, no NAb)	Cetirizine HCl
			Nausea (moderate)	2014-08-05	2014-08-16				
			Diarrhea (moderate)	2014-08-05	2014-08-16				
				2014-08-05	2014-08-16				

Reviewer's comment: Dr. Dr. Jane Liedtka, the clinical reviewer for this BLA application, agreed with the Sponsor in that these patients did not meet the criteria for anaphylaxis. However, the presence of ADA in all these patients may suggest some involvement of ADAs in the reported AE.

- Non anaphylaxis Events

There were 29 other patients with non anaphylaxis allergic reactions/hypersensitivity events associated with TE-ADA-positivity. Most of these events were non serious and mild-to-moderate in severity. Two of these patients had events that were serious (urticaria) and showed ADA titers around the time of the events. Three subjects had events that led to study drug discontinuation (1 event of urticaria, 1 of hypersensitivity, and 1 of rash).

In the total ixekizumab treatment group, 0.4% (n=4) of ADA-positive patients had an event, compared to 0.5% (n=15) of ADA-negative patients. Three of the 4 patients with ADA-positivity had persistent ADA.

There were two cases of hypersensitivity type SAEs occurring near the time of the drug injection (RHBC patient 229-3805 and RHBA patient 162-3554). Both of these patients were ADA negative.

Reviewer's comment: there was no apparent association between allergic reactions/hypersensitivity events and development of TE-ADA to ixekizumab. However, there were some individual cases of hypersensitivity where a temporal relationship between the event and ADA development is possible.

Injection Site Reactions

A summary of general observations regarding the incidence of injection site reaction is provided below:

- Injection site reactions were significantly more frequent in ixekizumab-treated patients than in placebo-treated patients.
- The majority was mild or moderate in severity and did not lead to treatment discontinuation.
- Higher frequency was observed for Q2W than for Q4W but the incidence rates per 100 active injections did not differ between these groups.
- No association between injection site reactions and TE-ADA was established.

Injection site reaction related AE by TE-ADA status

Treatment Emergent Adverse Events in the induction phase

No SAEs of injection site reactions were recorded in the Primary Placebo-Controlled Integrated Analysis Set.

- Among the total ixekizumab-treatment group who had at least 1 injection site reaction, the proportions of patients who were TE-ADA-positive was lower than the proportion that was TE-ADA-negative (7.4% versus 13.6%).

- Most of the injection site reactions were mild in severity in both TE-ADA positive and negative patients.
- A relationship between the ADA titer and the incidence of injection site reactions was not observed.
- There was no relationship between sPGA (0,1) status (response rates) and occurrence of injection site reaction among ixekizumab-treated patients who were TE-ADA-positive.
- Nineteen patients (7.4%) in the total ixekizumab-treatment group versus 0 in the placebo group had injection site reaction within the 14-day window around TE-ADA-positivity.
- Injection site reactions were higher in TE-ADA-negative patients: 277 (13.6%) in the total ixekizumab group versus 26 (3.3%) in the placebo group.
- No TE-ADA positive patients discontinued because of an injection site reaction AE.
- Patient RHAZ 259-5012 had an SAE of cellulitis that was reported on an injection site reaction eCRF and the patient was TE-ADA positive at the time of the event

A summary of injection site reactions in the induction phase is shown below.

Table 2.7.4.67. Summary of Injection Site Reactions by Treatment-Emergent ADA Status across Analysis Sets

TE-ADA Status	Primary Placebo-Controlled Analysis Set ^{a,b}					Placebo- and Active-Controlled Integrated Analysis Set^{a,b}						All Psoriasis IXE Exposure Analysis Sets ^{a,b}
	Placebo	IXE 90 mg Q4W	IXE 80 mg Q2W	Total IXE	Treatment by TE-ADA Status Interaction	Placebo	ETN	IXE 80 mg Q4W	IXE 80 mg Q2W	Total IXE	Treatment by TE-ADA Status Interaction	
Persistent or transient TE-ADA ^c	0%	4.6% (n=7)	11.7% (n=12)	7.4% (n=19)	0.429	0%	0%	3.0% (n=3)	11.9% (n=7)	6.3% (n=10)	0.525	7.4% (n=61)
No persistent or transient TE-ADA	3.3% (n=26)	11.5% (n=114)	15.6% (n=163)	13.6% (n=277)		3.7% (n=13)	17.7% (n=121)	12.1% (n=75)	16.5% (n=110)	14.4% (n=185)		13.3% (n=435)

Abbreviations: AE = adverse event; ETN = etanercept; IXE = ixekizumab; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; TE-ADA = treatment-emergent anti-drug antibody.

- ^a No reported SAE of injection site reaction in the total ixekizumab treatment group.
 - ^b No reported discontinuation due to an injection site reaction AE in ixekizumab-treated patients with persistent or transient TE-ADA.
 - ^c Number of patients with injection site reaction events within the 14-day window around TE-ADA positive status.
- Source: Home / lillyce / prd / by2439821 / integrations / ps_submission / programs_nonsdd / tfl_output_safety: t_injectteada_safety_i_ppc.rtf, t_injectteada_safety_i_pac.rtf, t_injectteada_aps.rtf.

APPEARS THIS WAY ON ORIGINAL

Reviewer’s comment: Please, refer to note for Table 2.7.4.59 regarding data derived from the active controlled analysis set. No correlation is observed between the ADA status and the incidence of injection site reactions during the induction phase.

Treatment Emergent Adverse Events in all ixekizumab exposed subjects

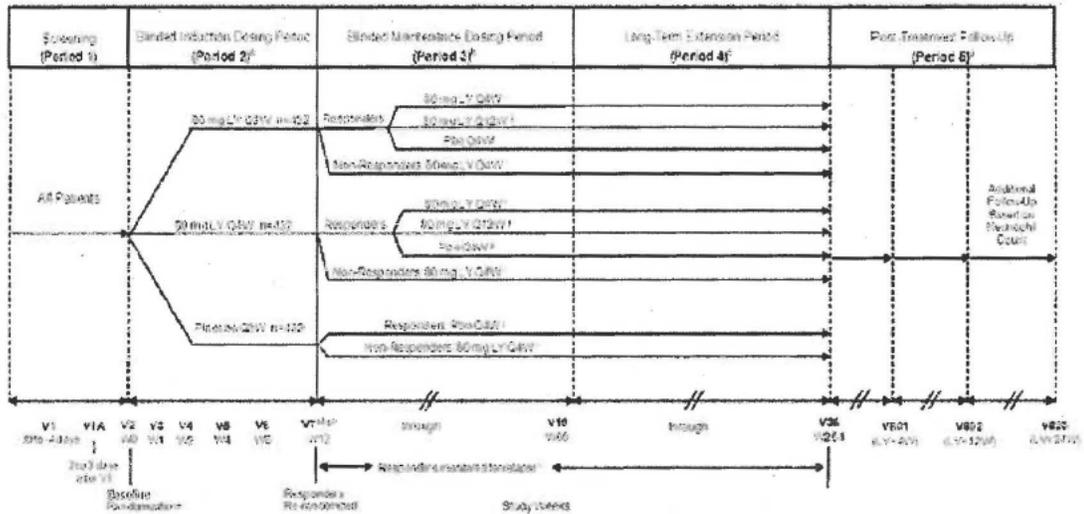
As shown in Table 2.7.4.67, a total of 7.4% of patients (n=61) had an injection site reaction temporally associated with the presence of TE-ADA. Most of these events were mild to moderate in severity. The rate of injection site reactions in patients negative for TE-ADA was higher (13.3% versus 7.4%). No injection site reaction SEAs were reported

in any of the ixekizumab treated patients. No TE-ADA positive patients discontinued due to injection site reactions AE.

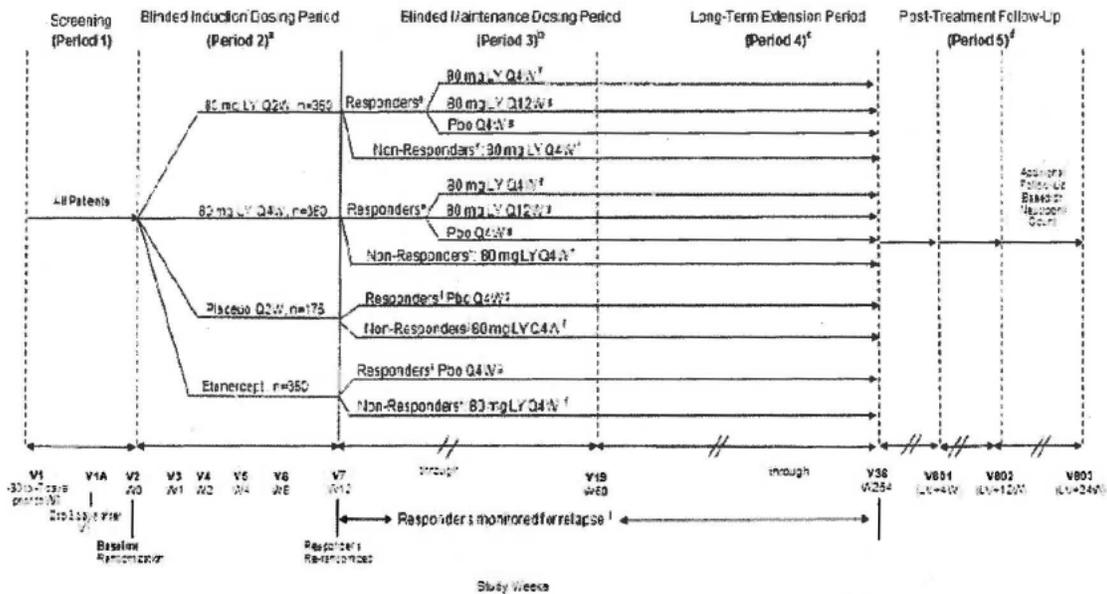
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APPENDIX 1: Phase 3 clinical studies design

RHAZ: 12 weeks blinded induction period, 48 weeks blinded maintenance and 3.9 years extension. 1296 patients enrolled and 865 randomized to ixekizumab in induction period.



RHBA: 12 weeks blinded induction period, 48 weeks blinded maintenance and 3.9 years extension. 1224 patients enrolled and 698 randomized to ixekizumab in induction period.



RHBC: 12 weeks blinded induction period, 4.8 years extension. 1346 patients enrolled and 771 randomized to ixekizumab in induction period.



DEPARTMENT OF HEALTH & HUMAN SERVICES

US Food & Drug Administration
Center for Drug Evaluation & Research
Office of Biotechnology Products
Division of Biotechnology Review and Research III

Date: October 19, 2015
To: BLA 125521
From: Maria Cecilia Tami, Ph.D.
Through: Howard Anderson, Ph.D.
Subject: Primary Review of the Drug Substance Section for Original BLA 125521 (TALTZ [Anti-Human IL-17])

PDUFA Date: March 23, 2016
Primary Review Goal Date: October 30, 2015

Signature Block

NAME	TITLE	SIGNATURE & DATE
Maria Cecilia Tami, PhD CDER/OPQ/OBP/DBRRIII	Primary Reviewer	Mariacecil Tami -S <small>Digitally signed by MariacecilTami -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=130037199 1, cn=Mariacecil Tami -S Date: 2015.10.27 13:27:40 -04'00'</small>
Howard Anderson, PhD CDER/OPQ/OBP/DBRRIII	Team Leader	Howard A. Anderson -A <small>Digitally signed by Howard A. Anderson -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000605 528, cn=Howard A. Anderson -A Date: 2015.10.27 13:31:10 -04'00'</small>

Recommendation

We recommend approval of this BLA from a drug substance perspective, pending an acceptable response from the Sponsor for an FDA's information request (IR) that will be sent to the Sponsor in the near future. The sponsor's response to the FDA IR will be assessed in an addendum to this review. This review covers the information provided in sections 3.2.S Drug Substance, 3.2.A.2 Adventitious Agents Safety Evaluation and 3.2.A.2, Regional Information. There are no issues identified so far in the reviewed sections that would preclude approval of this application, and it is anticipated that sponsor will be able to adequately address all items of the drug substance IR.

Drug substance- Justification and Outstanding Items

The data reviewed support the conclusion that the manufacture of ixekizumab drug substance is well controlled and leads to a product that is pure and potent. The drug substance is free of adventitious infectious agents, the conditions used in manufacturing have been sufficiently validated, and a consistent drug substance has been manufactured from multiple production runs.

The Sponsor provided (b) (4) real time stability data for ixekizumab drug substance to support their proposed (b) (4) expiry for the drug substance. No significant deficiencies have been identified at this time in the drug substance or adventitious agents sections of BLA 125521.

The adequacy of the immunogenicity assays and a risk assessment of the immunogenicity profile of ixekizumab are covered in a separate review memo.

The outstanding information requests to be communicated to the Sponsor are provided below. A discussion of these items is highlighted in yellow in the review. An assessment of the Sponsor's responses will be provided in an addendum to this review memo.

Drug substance Information Requests Items

- 1- There are no upper limits for the (b) (4) (b) (4). For the (b) (4), the proposed upper limit (b) (4) is not supported by the available data. Provide upper limits for these control parameters based on available small scale and full scale data or provide a justification to support that the proposed acceptance ranges will not adversely impact product quality.
- 2- Section 3.2.S.2.2, Description of the Manufacturing Process and Process Controls of the BLA submission does not adequately reflect the current process. During inspection of the drug substance manufacturing facility, the FDA observed (b) (4) (b) (4) (b) (4) Update the BLA to describe the (b) (4) (b) (4) circumstances (b) (4).
- 3- There are insufficient data to support the adequacy of your proposed hold time (b) (4) (b) (4) (b) (4) Provide a justification for the proposed (b) (4) hold time.
- 4- (b) (4) (b) (4) Provide a risk assessment of the potential impact that the worst case exposure levels of (b) (4) could have on patient safety.
- 5- The (b) (4) HDPE container closure system contains (b) (4) (b) (4). The BLA indicates the supplier (b) (4) provided a letter indicating the country of origin (b) (4) (b) (4). Submit the letter provided by the supplier (b) (4) (b) (4) to insure the material is safe and at low risk for adventitious agents.

- 6- Revise the specifications acceptance criteria (b) (4) (b) (4) to include an acceptance criterion for no new peaks above the limit of detection.
- 7- Some of the peaks observed in the (b) (4) electropherograms of drug substance under stress conditions have not been characterized (b) (4) (b) (4) (b) (4) Provide the characterization of all peaks that appear (b) (4) (b) (4) Alternatively update the BLA to contain a commitment to identify the peaks and provide the information in a future BLA annual report (if the application is approved).
- 8- The qualification data of the primary reference standard (Table 3.2.S.5.3-1) and the release data from the parental DS lot (b) (4) 101835 (Table 3.2.S.4.4.2-4 in section 3.2.S.4.4 of the eCTD submission, Batch analysis) show difference in the results obtained (b) (4) (b) (4) Provide an explanation for the observed discrepancy.
- 9- The testing frequency for the working reference standard is at year 1, 2, 4 and every 5 years thereafter. Provide a justification for the adequacy of the testing frequency and describe the procedures to address a potential reference standard out of specification result.
- 10- Potency of ixekizumab is reported as a value relative to the reference standard (RS). It is not clear from the BLA how reference standard were qualified for potency during early product development. The sponsor should provide the potency data for each RS used in development and information regarding the relative potency and IC50 results for the previous reference standard and new reference standard. The sponsor should indicate and provide the relative potency and IC50 value for all reference standards lots used for testing the phase III lots.
- 11- The characterization section of the BLA does not include an evaluation of the binding of ixekizumab to the IL-17. Provide data showing that ixekizumab binds to IL-17 and blocks binding of IL-17 to the IL-17 receptor. The sponsor should also provide the results of stress studies to determine whether the binding methods (e.g. (b) (4) and ELISA) are stability indicating.
- 12- The information provided in the method transfer package of the submission is insufficient to determine whether the analytical methods generate equivalent results at the original and new receiving labs. Additional information will be requested including a clarification on whether the data at the original and new receiving labs were generated with the same drug substance, drug product lot, or reference material.

ADMINISTRATIVE

1. Primary Review Team

Medical Officer: Jane Liedtka/ Jill Lindstrom (Team Leader)
Pharm/Tox: Jill Merrill/Barbara Hill (Team Leader)
Product Quality Team: Maria Cecilia Tami (Drug Substance)/Xu Di (Drug Product)/ Howard Anderson (Team Leader)
DMA: Bo Chi (Drug substance)/Colleen Thomas (Drug Product)/Patricia Hughes (Team Leader)
BMT or Facilities: Wayne Seifert/ Peter Qiu (Team Leader)
Clinical Pharmacology: Jie Wang/Yow-Ming Wang (Team Leader)
Statistics: Matthew Guerra/ Alish, Mohamed A (Team Leader)
OBP Labeling: Jibril Abdus-Samad
OBP RPM: Anita Brown
OND RPM: J. Paul Phillips

2. GRMP Review Deadlines

Filing Meeting: April 28, 2015
Mid-Cycle Meeting: August 14, 2015
Wrap-Up Meeting: January 8, 2016
Primary Review Due: October 30, 2015
Secondary Review Due: November 6, 2015
CDTL Memo Due: January 20, 2016
PDUFA Action Date: March 23, 2016

3. Request for a Waiver to Perform an Environment Evaluation

Refer to the review of the Drug Product section of this BLA

4. Communication with Sponsor (Drug Substance)

Communication/Document	Date
Mid-Cycle Communication	August 14, 2015
DS Information Request #1	August 10, 2015
DS Information Request #2	September 15, 2015

5. Submissions Reviewed

Submission	Date Received	Review Completed (Yes/No)
------------	---------------	---------------------------

STN 125521/0 Drug substance, Adventitious Agents and Regional information	March 23, 2015	Yes
STN 125521 /2 (Sponsor's Corrections to established conditions sections)	June 5, 2015	Yes
STN 125521 /15 (response to mid-cycle comment)	August 21, 2015	Yes
STN 125521 /14 (response to DS information request #1)	August 28, 2015	Yes
STN 125521 /19 (response to DS information request #2)	September 28, 2015	Yes
STN 125521 /20 (response to DS information request #2)	September 29, 2015	Yes

6. Drug Substance Master Files Referenced
None

6. Drug Substance Inspectional Activities

A pre-license inspection (PLI) for ixekizumab drug substance manufacturing site at Eli Lilly S.A. Irish Branch (FEI 3002806888), Dunderrow, Ireland was conducted on June 22-26, 2015 by DIA Branch 1 reviewers Michael Shanks and Wayne Seifert and OBP DBRR III reviewers Maria Cecilia Tami and Xu Michael Di. The site is responsible for manufacturing of drug substance and release testing. The inspection was system based and covered Quality, Facilities and Equipment, Production, Laboratory Control and Materials. One 483 observation was issued at the end of the inspection. It was recommended that the inspection be classified as no action indicated. The pre-license inspection of the drug product manufacturing site was waived. However, a surveillance inspection of the drug product manufacturing facility conducted during the review cycle of this BLA, from July 27, 2015 to August 4, 2015 and the status was NAI.

7. Drug Substance Consults Requested by OBP
None

8. Quality by Design Elements

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
X	Design of Experiments
X	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

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3.2.S. DRUG SUBSTANCE

3.2.S.1 GENERAL INFORMATION

3.2.S.1.2 Structure

Ixekizumab is a humanized immunoglobulin G4 (IgG4) isotype monoclonal antibody that binds and neutralizes the pro-inflammatory cytokine interleukin-17A (IL-17A) (b) (4)

(b) (4) Ixekizumab is expressed in a recombinant CHOK1SV cell line.

Ixekizumab consists of two identical k light chain polypeptides of a (b) (4)

(b) (4) (219 amino acid (b) (4)) and two identical heavy chain polypeptides (b) (4) (445 amino acid (b) (4)). The molecular weight of ixekizumab backbone is 146,158 Dalton, (b) (4)

(b) (4)

The amino acid sequence of the light and heavy chains are shown below.

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contains the release and stability results for the drug substance and drug product. However the results are not trended. This trend analysis will help better determine if significant changes have occurred in any product attribute. The batch analysis should be presented graphically in control charts for the critical quality attributes (CQAs). The CQAs should include UV/VIS assay for Quantity, Cell-based bioassay for Potency, (b) (4) for monomer Purity, (b) (4) for Purity, and (b) (4) for Charge Heterogeneity (main peak, total acidic and basic variants).

2. As a follow up to the sponsor's IR response for DP question 2, submitted to the FDA on September 28, 2015, in which the sponsor was asked to clarify the difference between syringe theoretical yield and actual yield. The sponsor did not provide the actual number of syringes that are discarded due to visual defects. The sponsor should provide the rejection rate results for all lots of the (b) (4) syringe in process visual inspection, prefilled syringe visual inspection, and auto injector visual inspection tests.

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ADMINISTRATIVE

1. GRMP Target Dates

Filing Meeting: April 28, 2015
 Mid-Cycle Meeting: August 14, 2015
 Primary Review Due: October 30, 2015
 Wrap-up Meeting: January 8, 2016
 PDUFA Action Date: March 13, 2016

2. Primary Review Team

Medical Officer: Jane Liedtka
 Pharm/Tox: Jill Merrill
 Product Quality Team: OBP: Cecilia Tami (Drug Substance) / Xu Di (Drug Product)
 DMA: Bo Chi (Drug Substance Microbial) / Colleen Thomas (Drug Product Microbial)
 OPF/DIA: Wayne Seifert (Facilities)
 Clinical Pharmacology: Jie Wang/ Dhananjay Marathe
 Statistics: Matthew Guerra
 OBP Labeling: Jibril Abdus-Samad
 OBP RPM: Anita Brown
 Clinical RPM: Paul Philips

3. Drug Product Sponsor Information Requests (IR) and Responses Reviewed

Communication/Document	Date requested	Date Received	Review Completed (Yes/No)
IR #1 Midcycle Communication – Removal of (b)(4) from Taltz package insert.	August 14, 2015	September 15, 2015	Yes (see * below)
IR #2	September 15, 2015	September 28, 2015	Yes
IR #3	To be sent Nov 2015		

* Proposed Taltz package insert contained language (b)(4) to support clinical claims. (b)(4)
 (b)(4). IR was sent to the sponsor requesting that the (b)(4) be removed from the label. The sponsor agreed updated the label to remove (b)(4). See DARRTS August 2015 for BLA 125521 the IR.

4. Drug Product Name/Code/Type:

- a. Proprietary Name: TALTZ
- b. Trade Name: TALTZ
- c. Non-Proprietary/USAN: Ixekizumab
- d. CAS name: 1143503-69-8

- e. Common name: TBD
- f. INN Name: Ixekizumab
- g. Compendial Name: TBD
- h. OBP systematic name: MAB HUMANIZED (IGG4) ANTI Q16552 (IL17_HUMAN) [LY2439821]
- i. Other Names: Anti IL-17A, LA426

5. Request for a Waiver to Perform an Environment Evaluation

The sponsor requests a categorical exclusion from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(b and c) and indicates that there are no extraordinary circumstances exist that may significantly affect the quality of the human environment. The claim of categorical exemption is acceptable because this is a protein product that occurs naturally and will be broken down in the environment.

6. Drug Product Quality by Design Elements

x	Design Space
x	Design of Experiments
x	Formal Risk Assessment / Risk Management
x	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

7. Drug Product Referenced Master Files (DMF)

DMF number	Holder	Item referenced	Letter of cross-reference	Comments
(b) (4)			Yes	DMF not reviewed, adequate information in BLA
			Yes	DMF not reviewed, adequate information in BLA
			Yes	DMF not reviewed, adequate information in BLA
			Yes	DMF not reviewed, adequate information in BLA
			Yes	DMF not reviewed, adequate information in BLA

8. DP Inspectional Activities

ORA conducted the inspection of the drug product facility. OBP did not participate in the cGMP inspection of the drug product facility. The drug product facility will be covered in a separate review.

9. OBP DP Requested Consults - None

REVIEW

3.2.P.1 Description and Composition of the Drug Product (DP)

Ixekizumab DP is a colorless to yellowish (b)(4) solution for subcutaneously single use injection. The ixekizumab DP has only one dosage strength at 80mg/ml. Quantity and function of each component for the ixekizumab DP is listed in Table 3.2.P.1.1-1.

Table 3.2.P.1.1-1 Composition of Ixekizumab Injection, 80 mg/1 mL

Ingredient	Quantity(mg) per Syringe	Function	Reference to Standards
Active Ingredient			
Ixekizumab	80	Active Ingredient	Internal Standard: See Section S.4.1. Specifications
Other Ingredients			
Sodium Citrate Dihydrate	5.11	(b)(4)	USP, Ph.Eur., JP
Citric Acid Anhydrous	0.51	(b)(4)	USP, Ph.Eur., JP
Sodium Chloride	11.69	(b)(4)	USP, Ph.Eur., JP
Polysorbate 80	0.30	(b)(4)	USP, Ph.Eur., JP
Water for Injection	(b)(4)	(b)(4)	USP, Ph.Eur., JP

The primary container closure for the ixekizumab DP is a 1ml-long Type I glass syringe barrel with small round flange, 27G thin wall x 1/2" staked needle with shield, closed with a (b)(4) (b)(4) plunger. This container closure filled with drug product is referred to as a (b)(4) (b)(4) syringe (b)(4) which can be further assembled to prefilled syringe or auto injector. Both devices are intended for single use.

FDA Reviewer Comments:

The (b)(4) syringe only includes the syringe barrel, needle with shield and plunger. It can be assembled to either the pre-filled syringe by combining plunger rod and backstop or auto injector by adding it into the auto injector cassette. CDRH is involved in reviewing the syringe and the auto injector.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2. P.2.1.1 Drug Substance (DS)

The ixekizumab DS includes the same (b)(4) composition (b)(4) as (b)(4) the ixekizumab DP as presented in Table 3.2.P.1.1-1. The only difference is (b)(4) The

sponsor indicates that the ixekizumab is (b) (4) to allow for development of the DS and DP.

FDA Reviewer Comments:

The quantity and composition of the DS and the DP are identical except for (b) (4)

3.2. P.2.1.2 Excipients

Table 3.2.P.1.1-1 above lists the composition, quantity, function and quality for individual ixekizumab DP excipients. (b) (4) (sodium citrate dihydrate and citric acid anhydrous,

(b) (4). The sodium chloride (b) (4)

(b) (4). The polysorbate 80 (b) (4)

(b) (4). Water for Injection (b) (4) for formulation of the ixekizumab.

FDA Reviewer Comments: The excipients are appropriate and of compendial grade. There is no concern with the excipients.

3.2.P.2.2 Drug Product Formulation Development and History

(b) (4)

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Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51, 10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 10/07/2015
To: Administrative File, STN 125521/0
From: Wayne Seifert, Reviewer, CDER/OPQ/OPF/DIA
Endorsement: Steven Fong, Ph.D., Acting Quality Assessment Lead, CDER/OPQ/OPF/DIA
Subject: New Biologic License Application (BLA)
US License: 1891
Applicant: Eli Lilly and Company
Mfg Facility: Drug Substance: Eli Lilly S.A. – Irish Branch, Kinsale (FEI 3002806888)
Drug Product: Eli Lilly and Company, Indianapolis, IN (FEI 1819470)
Product: TALTZ™ (ixekizumab)
Dosage: Pre-filled Syringe, solution for injection, 80mg/1 ml
Indication: Plaque Psoriasis
Due Date: March 23, 2016

RECOMMENDATION: This submission is recommended for approval from a facility review perspective.

SUMMARY

The subject BLA proposes manufacture of TALTZ™ (ixekizumab) Drug Substance (DS) and DP, respectively, at Eli Lilly S.A. – Irish Branch, Kinsale, Ireland (FEI: 3002806888) and Eli Lilly and Company, Indianapolis, IN (FEI 1819470). The storage facility for the master and working cell bank will occur (b) (4) Cell based potency assay for the bulk drug substance will occur (b) (4) (b) (4) Mycoplasma and virus release assays on unprocessed bulk will occur (b) (4)

DS MANUFACTURING ASSESSMENT

- **PROPOSED DS MANUFACTURING AND TESTING SITES.**

The facilities for manufacture of ixekizumab are listed below in Table 1.

Table 1: Manufacturers for ixekizumab DS

Site Name	Address	FEI Number	Responsibility
Eli Lilly S.A. – Irish Branch	Dunderrow Kinsale, County Cork Ireland	3002806888	DS manufacturer, storage, release and stability testing. DP potency release and stability testing.
Eli Lilly and Company	Lilly Corporate Center Indianapolis, Indiana United States	1819470 or 3000123645	DP manufacturer, device assembly, packaging and labeling and release and stability testing except potency. Storage facility for master and working cell banks.

(b) (4)

Review Comment 1: Storage of master and working cell banks at the Eli Lilly Kinsale, Ireland facility is an inspectional item. The facilities for manufacture, storage, release and stability testing for ixekizumab DS are adequately described.

- **FACILITY INSPECTIONS**

- **PLI Conducted in Support of Subject BLA.**

- **Eli Lilly S.A. – Irish Branch (FEI: 30022806888):** A pre-license inspection was conducted June 22 -26, 2015. At the close-out on June 26, 2015, the inspection team issued a one-item Form FDA 483 to the firm. The inspection was classified VAI.



CONCLUSION

The BLA was reviewed from a facilities perspective and is recommended for approval.

**Wayne E.
Seifert -S**

Digitally signed by Wayne E. Seifert -S
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ou=FDA, ou=People,
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cn=Wayne E. Seifert -S
Date: 2015.10.07 15:38:06 -04'00'

Wayne Seifert
Consumer Safety Officer
OPF Division of Inspectional Assessment, Branch 1
Branch 1

Steven Fong -S

Digitally signed by Steven Fong -S
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ou=FDA, ou=People, cn=Steven Fong -S,
0.9.2342.19200300.100.1.1=2000287433
Date: 2015.10.07 15:57:48 -04'00'

Steven E. Fong, M.S., Ph.D.
Microbiologist and Acting Quality Assessment Lead
OPF Division of Inspectional Assessment, Branch 1.

Questions Presented in IR Submitted 07/16/2015

1. In regard to (b) (4) (b) (4) (b) (4) describe (b) (4) and their associated hold times.
2. Provide (b) (4) specifications, (b) (4) (b) (4).
3. Provide (b) (4) acceptance criteria (b) (4) (b) (4).
4. Provide (b) (4) acceptance criteria (b) (4) (b) (4).
5. Provide (b) (4) criteria (b) (4) (b) (4).
6. Provide (b) (4) acceptance criteria (b) (4) (b) (4).
7. Provide (b) (4) (b) (4).
8. Provide (b) (4) (b) (4).