

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761044Orig1s000

PRODUCT QUALITY REVIEW(S)

First approval for indication**Recommendation: Approval****BLA 107644
Review 1
August 31, 2016**

Drug Name/Dosage Form	ustekinumab/injection
Strength/Potency	130 mg/26 ml (5 mg/ml)
Route of Administration	Intravenous infusion
Rx/OTC Dispensed	Rx
Proposed Indication	Crohn's disease
Applicant/Sponsor	Janssen Biotech Inc.

a. Names

- i. Proprietary Name: Stelara
 - ii. Trade Name: Stelara
 - iii. Non-Proprietary/USAN: ustekinumab
 - iv. CAS name: Immunoglobulin G1, anti-(human interleukin 12 p40 subunit) (human monoclonal CNTO 1275 γ 1-chain), disulfide with human monoclonal CNTO 1275 κ -chain, dimer, CAS number: 815610-63-0
 - v. Common name: n/a
 - vi. INN Name: ustekinumab
 - vii. OBP systematic name: MAB HUMANIZED (IGG1) ANTI P29460 (IL12_HUMAN) CNTO 1275]
 - viii. Other Names: CNTO 1275, CNTO 1275 IgG, anti-IL-12/23 p40 human IgG1kappa
- b. Pharmacology category: anti-interleukin 12 monoclonal antibody

Product Overview

Stelara (ustekinumab) is a humanized IgG1, kappa anti-interleukin-12 and anti-interleukin-IL23 monoclonal antibody produced in a (b) (4) cell line. Ustekinumab recognizes the p40 subunit common to both human IL-12 and IL-23. The heavy and light chains of ustekinumab are linked by 16 disulfide bond (b) (4)

(b) (4) The estimated molecular mass of ustekinumab is 148,079 to 149,690 Da.

Ustekinumab inhibits the binding of IL-12 and IL-23 to the IL-12 β 1 receptor chain and subsequent intracellular signaling by both cytokines. IL-12 induces immune cells toward a T helper 1 (Th1) phenotype (stimulates interferon-gamma production), while IL-23 induces a T helper 17 (Th17) pathway (promotes secretion of IL-17A, IL-21, and IL-22). Both cytokines stimulate TNF production, resulting in the intestinal inflammation and epithelial cell injury typical of Crohn’s disease. In this BLA, the sponsor requests approval of Stelara for treatment of Crohn’s disease.

Stelara has been approved previously for psoriasis and psoriatic arthritis under BLA 125261 from the same sponsor. The currently approved presentations include PFS and vial, both available in two strengths (90 mg/ml and 45 mg/0.5 ml). This BLA cross-references the drug substance section from BLA 125261. Therefore, this memo provides information only on the new drug product presentation available in 5mg/ml strength.

OPQ Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/ DIVISION
Drug Product	Zhenzhen Liu	Division of Biotechnology Review and Research III (DBRR III)
Drug Product Microbiology	Candace Gomez-Broughton	Division of Microbiology Assessment
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Facilities, Team Lead	Peter Qiu	Division of Inspectional Assessment
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Application Technical Lead	Maria-Teresa Gutierrez-Lugo	DBRR III
Tertiary Reviewer	Susan Kirshner	DBRR III

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
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Statistics	Min Min / Yeh-Fong Chen	



Quality Review Team - Signature Page

See electronic signatures at the end of the document.

DISCIPLINE	REVIEWER	BRANCH/ DIVISION	E-SIGNATURE
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Microbiology Drug Product Drug Product Microbiology Team Lead	Candace Gomez-Broughton Colleen Thomas Patricia Hughes	Division of Microbiology Assessment	
Facilities Facilities Team Lead	Marion Michaelis Peter Qiu	Division of Inspectional Assessment	
Application Technical Lead	Maria-Teresa Gutierrez-Lugo	Division of Biotechnology Review and Research III	
Tertiary Reviewer	Susan Kirshner	Division of Biotechnology Review and Research III	

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS

A. Submissions reviewed

Submission	Date Received	Review Completed (Yes/No)
STN 761044/0	11-25-2015	Yes
STN 761044/17	05-25-2016	Yes
STN 761044/23	07-08-2016	Yes
STN 761044/29	08-09-2016	Yes
STN 761044/30	08-10-2016	Yes
STN 761044/31	08-11-2016	Yes
STN 761044/32	08-15-2016	Yes
STN 761044/33	08-23-2016	Yes

B. DMFs:

DMF #	Type	HOLDER	ITEM REFERENCED	CODE¹	STATUS²	COMMENTS
(b) (4)	I	(b) (4)	(b) (4)	3	Adequate	
	I			3	Adequate	Cross-reference to BLA 125261

¹ Action codes for DMF Table: 1 – DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2 – Reviewed previously and no revision since last review; 3 – Sufficient information in application; 4 – Authority to reference not granted; 5 – DMF not available; 6 – Other (explain under "Comments")

² Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed).

3. CONSULTS:

None

Integrated Review

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761044 for Stelara (ustekinumab), manufactured by Janssen Biotech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Stelara is well controlled and leads to a product that is pure and potent. We recommend that Stelara be approved for human use under the conditions specified in the package insert.

a. Benefit/Risk Considerations

Stelara is an anti-IL-12 and anti-IL-23 monoclonal antibody intended for the treatment of Crohn's disease. The DS manufacturing process was previously reviewed and found to be well controlled and should consistently deliver DS of desired quality. The DP manufacturing process is well controlled and should consistently deliver DP of desired quality. No CMC PMCs are issued with this BLA. Overall the facilities have favorable compliance status.

b. Draft Action letter language

Manufacturing location:

- Drug substance – refer to BLA 125261
- Drug product – Cilag AG, Hochstrasse 201, 8200 Schaffhausen, Switzerland
- Fill size and dosage form – 130 mg/26 ml (5 mg/ml), injection
- Dating period:
 - Drug product – 24 months; 2-8 °C
 - Drug substance – refer to BLA 125261
- Exempt from lot release

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No CMC PMCs are issued with this BLA.

II. Summary of Quality Assessments

This BLA cross-references the drug substance section from BLA 125261 from the same sponsor. Therefore, this memo provides information on the drug product only.

A. Drug Product: Stelara Quality Summary

Table 1 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes. For additional information on the drug product see [Appendix A](#) Drug Product Quality Technical Report: OBP Assessment and [Appendix B](#) Drug Product Microbiology Review: Division of Microbiology Assessment.

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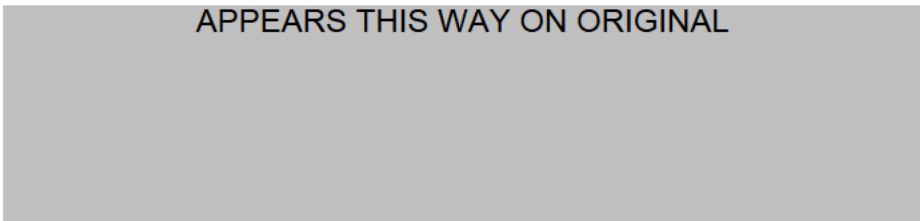


Table 3: Stelara CQA Identification, Risk, and Lifecycle Knowledge Management

CQA	Origin	Risk	Control Strategy
Color of solution	Color of solution may be impacted by the formulation. It may also be an indicator of product degradation or other changes to the product.	Safety and efficacy	(b) (4)
Appearance of Primary Container	Appearance of primary container may be impacted by (b) (4) process steps.	Safety	
Identity	Intrinsic property of the molecule. Identity may be impacted by the manufacturing process (e.g. using a different DS used for the manufacture of other products in the same facility).	Safety and efficacy	
Purity	Purity may be impacted by the manufacturing process, the quality of raw materials, and storage conditions.	Safety and efficacy	
Charge heterogeneity	Charge Heterogeneity may be impacted by the manufacturing process, the quality of raw materials, and storage conditions.	Safety, potential immunogenicity	
Extractable Volume	Extractable volume may be impacted by the (b) (4) process.	Safety and efficacy (low extractable volume)	
Potency	Potency might be impacted by the manufacturing process, the quality of raw materials, and storage conditions.	Efficacy	
Protein Content	Protein concentration is influenced by the (b) (4) steps.	Safety and Efficacy	
Sterility and Container	Sterility could be compromised by contaminants introduced throughout DP manufacturing process	Safety	

Closure Integrity (CCI)	or through a container closure integrity failure. CCI is a sterility assurance CQA.	
Endotoxins	Contaminant that could be introduced throughout DP manufacturing, raw materials, or container closure system. (b) (4)	Safety
pH	(b) (4)	Safety and efficacy
Particulate Matter (Visible Foreign)	Particulate matter may come from environmental contaminants, processing equipment, and primary package. (b) (4)	Safety
Particulate Matter (Visible Translucent)	(b) (4)	Safety
Particulate Matter (sub-visible translucent)	SVP could form throughout manufacturing and during DP storage.	Safety (capillary occlusion) and potential Immunogenicity
Turbidity	Turbidity may be impacted by the manufacturing process, protein concentration, and storage conditions	Safety
Osmolality	General CQA influenced by (b) (4) , and formulation of DP.	Safety
Excipient	It may be impacted by manufacturing process and	Safety and efficacy

Concentrations (EDTA, methionine, PS80, Histidine, Sucrose)	the quality of inactive ingredients (EDTA, methionine, PS80, Histidine, Sucrose (b) (4))		(b) (4)
Leachables	Leachables could potentially be introduced by any product contact equipment, container closure system and consumables.	Safety	
(b) (4)		Safety	

Stelara Drug Product Quality Summary (Cont.)

1. Potency and Strength:

Potency is defined as the percent activity relative to a qualified ustekinumab reference standard. The potency assay is the same as described in BLA 125261. Stelara's new presentation is in a 130 mg/26 ml (5 mg/ml) strength.

2. Summary of Product Design

Stelara is presented in a single-dose glass vial containing 130 mg/26 ml of ustekinumab. This presentation will be used as an initial induction dose based on body weight as defined in the labeling (e.g. $\leq 55\text{Kg}$, 260 mg using 2 vials of Stelara). This induction dose is administered by intravenous (IV) infusion after dilution with saline. After the induction dose, the patient will switch to a maintenance dose using the currently approved PFS presentation (approved under BLA 125261). The recommended maintenance dose is 90 mg administered subcutaneously, 8 weeks after the initial IV dose, then every (b) (4) weeks thereafter, depending on patient needs. For additional information on drug product manufacture see [Appendix A](#).

3. List of Excipients

The new ustekinumab presentation contains the following excipients per vial: EDTA disodium salt dihydrate (b) (4) mg), L-histidine (b) (4) mg), L-histidine hydrochloride monohydrat (b) (4) mg), methionine (b) (4) mg), Polysorbate 80 (b) (4) mg) and sucrose (b) (4) mg). For additional information see [Appendix A](#)

4. Reference material(s),

The same reference materials are used for DS and DP. Refer to BLA 125261.

5. Manufacturing process summary

The drug product manufacturing process consists

(b) (4)

(b) (4)

6. Container closure

Stelara is supplied as 30 ml vial containing 26 ml of ustekinumab at the concentration of 5 mg/ml (130 mg). The container closure system consist of a 30 ml Type I (b) (4) (b) (4) glass tubing vial, capped with a 20 mm stopper wit (b) (4) (b) (4) 20 mm aluminum seal a light green flip-off button. For additional information see [Appendix A](#) and [Appendix B](#).

7. Dating period and storage conditions:

The dating period for drug product is 24 months at $5 \pm 3^{\circ}\text{C}$.

8. List of co-packaged components: not applicable.

B. Novel Approaches/Precedents: N/A

C. Any Special Product Quality Labeling Recommendations

- Protect from light
- Do not freeze
- Do not shake
- Product does not contain preservative
- Discard any unused portion

D. Facilities

The function of the four facilities involved in the manufacture and testing of drug product is summarized in Table D below. As noted under inspectional observations (Table D), FDA issued no 483 observations for these facilities in the last 2-3 years and overall the facilities have a favorable compliance status. For additional establishment information see [Appendix C](#).

E. Lifecycle Knowledge Management

a. Drug Substance. Refer to BLA 125261.

b. Drug Product

- c. Protocols approved:
 - i. Annual stability protocol
 - i. Outstanding review issues/residual risk: none

d. Future inspection points to consider: none

F. Establishment Information

OVERALL RECOMMENDATION: Approve				
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
• Manufacture of drug product, labeling, and packaging. • Release testing for DP, except for the following eight methods (b) (4)	Cilag AG Hochstrasse 201, 8200 Schaffhausen, Switzerland	FEI 3002806695	None A PAI was conducted by ORA and CDER on April 4-8, 2016 and was classified as NAI. This facility has a favorable compliance status.	Approve. Based on file review
• Stability testing for CCI.				
• Stability testing for DP only for color of solution, cSDS (reduced and non-reduced), DW-SE-HPLC, cIEF, bioactivity, protein concentration, pH and turbidity.	Janssen Biologics, Barnahely, Ringaskiddy, P43 FA46, Co. Cork Ireland	(b) (4)	None A PAI for a different product was conducted by CDER/DIA on (b) (4). Prior to (b) (4) there were two inspections which were classified as NAI and VAI. This facility has a favorable compliance status.	Approve. Based on Profile
• Release and stability testing of			None	



QUALITY REVIEW BLA 761044 Stelara (ustekinumab)



following three methods: (b) (4) (b) (4) and CCI (stability)	2333 CB Leiden The Netherlands		A surveillance inspection was conducted on May 23-27, 2016 and was classified as NAI. This facility has a favorable compliance status.	Based on Profile
(b) (4)				Approve Based on Profile

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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_____		X	
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-NDA Agreements team)		X	
18.	SPOTS (Special Products On-line Tracking System		X	
19.	USAN Name Assigned	X		

20.	Other _____			X	
Quality Considerations					
21.	Drug Substance Overage				Refer to BLA 125261
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
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			Refer to BLA 125261
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 _____			X	

**APPENDIX A
DRUG PRODUCT TECHNICAL REPORT: OFFICE OF BIOTECHNOLOGY
PRODUCTS ASSESSMENT**

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The data submitted in this application support the conclusion that the manufacture of ustekinumab final vial product for intravenous injection [FVP (IV)] is well controlled, and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents, sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product is produced from the multiple production runs presented. It is recommended that this product be approved for human use under conditions specified in the package insert.

II. List Of Deficiencies To Be Communicated

None (review issues were communicated and addressed during review).

III. List Of Post-Marketing Commitments/Requirement

None.

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion

Previously in BLA 125261, a claim for categorical exclusion under 21 CFR 25.31 (c) and 21 CFR 25.34 (b) was made. To the sponsor's knowledge, no extraordinary circumstances exist relative to this action.

V. Primary Container Labeling Review

The CMC labeling review was performed by Jibril Abdus-Samad, OBP.

VI. Review Of Common Technical Document-Quality Module 3.2

This document contains the review of the information provided for ustekinumab FVP (IV) drug product (Section 3.2.P), facilities and equipment (3.2.A), and the method validation package and batch records (3.2.R).

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

The review of the immunogenicity assays is cross-referenced to BLA 125261 supplement 103 (Validation and cross-validation reports for the screening and confirmatory assay) and supplement 8 (b) (4) (Validation and cross-validation reports for the NAb assay). A review of addenda to these immunogenicity assays is provided at the end of the primary review document.

REVIEW

3.2.S DRUG SUBSTANCE

The drug substance section of this BLA is cross referenced to BLA 125261. Briefly, ustekinumab is a first-in-class fully human IgG1 κ monoclonal antibody that recognizes the p40 subunit common to both human IL-12 and IL-23. It is (b) (4) using (b) (4) cell li (b) (4)

(b) (4) The antibody is made up of 2 identical heavy chains and 2 identical light chains. The heavy and light chains are linked by both covalent and non-covalent disulfide bonds. There are also non-covalent heavy-heavy chain bonds. All cysteine residues are involved in disulfide bonds, resulting in a total of 16 disulfide bond (b) (4)

(b) (4) The estimated molecular mass of ustekinumab ranges from 148,079 to 149,690 Dalton (b) (4)

Ustekinumab has been shown to inhibit the binding of IL-12 and IL-23 to the IL-12 β 1 receptor chain and subsequent intracellular signaling by both cytokines. IL-12 induces immune cells toward a T helper 1 (Th1) phenotype (stimulates interferon-gamma [IFN- γ] production), while IL-23 induces a T helper 17 (Th17) pathway (promotes secretion of IL-17A, IL-21, and IL-22). Both cytokines stimulate TNF production, resulting in the intestinal inflammation and epithelial cell injury typical of Crohn's disease.

In vitro ustekinumab has been shown to inhibit human IL-12 and IL-23 induced signaling in human primary cells, human cell lines, and mouse splenocytes. This includes an inhibition of IL-12 induced IFN- γ secretion from an NK cell line, NK92MI, which is used as the potency assay for ustekinumab. In addition, ustekinumab has been shown *in vivo* to inhibit epidermal thickening and keratinocyte proliferation in a humanized mouse model of psoriasis.

Ustekinumab is not thought to induce antibody dependent cellular cytotoxicity (ADCC) or complement dependent cellular cytotoxicity (CDC). Ustekinumab could not bind to IL-12 or IL-23 that was already bound to IL-12 β 1 or dual receptors. Since ustekinumab cannot bind to IL-12 or IL-23 once they are receptor bound, ADCC by ustekinumab is not considered likely. Ustekinumab did not mediate CDC of PHA activated human PBLs. However, ustekinumab is able to bind to Fc-receptors. Furthermore, ustekinumab, captured on IL-12 containing beads, has

been shown to activate the complement pathway, as detected by soluble C5b-9 production, when human serum was used as a complement source.

(b) (4)



The ustekinumab 130 mg/26 mL (5 mg/mL) final vial drug product for intravenous administration [FVP (IV)] is made with the same drug substance used to manufacture the ustekinumab FVP for subcutaneous administration covered under BLA 125261. Therefore, the drug substance section in BLA 761044 is cross-referenced to BLA 125261. The drug substance information provided in BLA 125261 was found to be acceptable.

3.2.P DRUG PRODUCT

STELARA (ustekinumab) was approved in the U.S. on 25 September 2009 under BLA 125261 for the treatment of adults with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. On 20 September 2013, STELARA was approved for the treatment of adults with active psoriatic arthritis (PsA). STELARA is currently approved as 45 mg/0.5 mL and 90 mg/mL solution for SC injection (liquid in vial and prefilled syringe presentations).

On 25 November 2015, Janssen Biotech, Inc. submitted BLA 761044 providing data to support the safety and efficacy of ustekinumab in the treatment of adult patients with moderately to severely active Crohn’s disease and drug product data to support approval of a new presentation, a vial containing 130 mg/26 mL (5 mg/mL) solution for intravenous infusion, intended for use in Crohn’s disease IV induction therapy.

Status	BLA	Dosage Form, strength	Route of administration	Indication	Date of approval
Approved	125261	Injection, 45 mg/ 0.5 mL or 90 mg/mL	SC	Plaque Psoriasis	09/25/2009
				Psoriatic Arthritis	09/20/2013
Proposed	761044	Injection, 130 mg/26 mL (5 mg/mL)	IV	Crohn’s Disease	Pending

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

The ustekinumab FVP (IV) drug product is supplied as a single-dose, sterile solution designed to deliver 130 mg of ustekinumab in a 30 mL, Type-1 glass vial. The vials are stoppered with 20-mm (b) (4) stoppers and sealed with 20-mm aluminum flip-off seals. The ustekinumab FVP (IV) DP has only one dosage strength of 5 mg/mL. Quantity and function of each component for the ustekinumab FVP (IV) DP is shown in Table 1.

Table 1: Composition of Ustekinumab FVP (IV)

Component	Grade	Function	Mg/Vial	Concentration (mg/mL)
ustekinumab	NA	Active	(b) (4)	(b) (4)
L-Histidine	USP/Ph. Eur./JP	(b) (4)	(b) (4)	(b) (4)
L-Histidine Hydrochloride Monohydrate	Ph. Eur./JP	(b) (4)	(b) (4)	(b) (4)
Sucrose	NF/Ph. Eur./JP	(b) (4)	(b) (4)	(b) (4)
Polysorbate 80	NF/Ph. Eur./JP	(b) (4)	(b) (4)	(b) (4)
L-Methionine	USP/Ph. Eur./JP	(b) (4)	(b) (4)	(b) (4)
EDTA disodium salt dihydrate ^b	USP/Ph. Eur./JP	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

^b Denoted as: Edetate disodium in USP, disodium edetate in Ph. Eur., and disodium edetate hydrate in JP.

^c Drug product contains a target (b) (4) mL overfill to assure that a 26.0 mL nominal volume is delivered.

***FDA Reviewer Comment:** It is noted that the 26 mL ustekinumab FVP (IV) DP contains a target (b) (4) mL overfill. Per 21 CFR 201.51 (g) and USP <1151> Pharmaceutical Dosage Forms, each container of an injection is filled with a volume in slight excess of the labeled “size” or the volume that is to be withdrawn. The excess volume recommended for 30 mL (labeled size) mobile liquids is 0.8 mL and for 30 mL viscous liquids is 1.2 mL.*

3.2.P.2 Pharmaceutical Development

(b) (4)



3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

Batches: The following batches were placed in the stability study:

Table 2: FVP (IV) Stability Batches

Batch ID/ Batch Number	Batch Designation	Site of Manufacture	Date of Manufacture	Drug Substance Batch(es)
CGS3B/CGS25	Phase 3 Development	Cilag, Schaffhausen, Switzerland	(b) (4)	(b) (4)
CJS52/CJS23	Phase 3 Development	Cilag, Schaffhausen, Switzerland		
DDS4W/DDS2V	Phase 3 Clinical	Cilag, Schaffhausen, Switzerland		
DES1C/DDS4D	Phase 3 Clinical	Cilag, Schaffhausen, Switzerland		
DLS1Z/DLS0B	Phase 3 Clinical	Cilag, Schaffhausen, Switzerland		
(b) (4)	Process Validation	Cilag, Schaffhausen, Switzerland		
	Process Validation	Cilag, Schaffhausen, Switzerland		
	Process Validation	Cilag, Schaffhausen, Switzerland		

* These batches were not included in the statistical analysis due to limited data, as outlined in Section 6.

Storage Temperatures and Schedule of Testing: All batches were stored protected from light at the recommended temperature (b) (4) °C for (b) (4) months, at the accelerated temperature condition (b) (4) for (b) (4) months, and at the stressed temperature condition (b) (4) for (b) (4) months. The details of the stability protocols for each temperature condition were provided in the submission.

Analytical Procedures: The quality of the above FVP (IV) batches was evaluated using the following analytical procedures:

Table 3: Analytical Procedures for the Stability Monitoring Program for FVP(IV) Phase 3 Development, Phase 3 Clinical, and Process Validation Batches

Quality Attribute Category	Analytical Procedure
Potency	(b) (4)
Quantity	
Purity	
Charge Distribution	(b) (4)
Structure	
Appearance	
Safety	

General Attributes (b) (4)

^a This test is for characterization purposes only and not part of the specification for routine release and stability testing. The analytical procedure is described in 3.2.S.3.1, Elucidation of Structure and Other Characteristics.
^b Tested on process validation batches only.
^c This test is for characterization purposes only and not part of the specification for stability testing. The stability data are presented in 3.2.P.5.6, Justification of Specification(s). However, the test is part of the routine batch release program.

Available stability Data: The sponsor provided stability data under the recommended conditions for up to (b) (4) months for two phase 3 development batches and two phase 3 clinical batches (Table 7). Accelerated stability data for up to (b) (4) months for two phase 3 development batches and three phase 3 clinical batches were also provided along with stress data stored at (b) (4) °C for up to (b) (4) months (Tables 8 and 9 in the submission).

Table 7: Available Stability Data for FVP (IV) Phase 3 Development, Phase 3 Clinical, and Process Validation Batches Stored at 2-8 °C

Batch	Months of Storage						
	(b) (4)						
Development Batch CGS3B/CGS25	√	√	√	√	√	√	√
Development Batch CJS52/CJS23	√	√	√	√	√	√	√
Clinical Batch DDS4W/DDS2V	√	√	√	√	√	√	√
Clinical Batch DES1C/DDS4D	√	√	√	√	√	√	√
Clinical Batch DLS1Z/DLS0B	√	√	√	√	√	√	√
(b) (4)	√	√	√	√	√	√	√
(b) (4)	√	√	√	√	√	√	√
(b) (4)	√	√	√	√	√	√	√

In response to an IR dated 27 June 2016, the sponsor provided updated stability data for three process validation batches to support the proposed shelf life of 24 months. The table below summarizes the last completed time interval for each storage condition.

(b) (4)

Shelf Life: Based on available stability data at (b) (4) °C from these batches and supportive statistical trending analyses, the sponsor proposed the 24 month shelf life for FVP (IV) at the recommended storage condition (b) (4) °C and protected from light.

FDA Reviewer Comment: Although the sponsor only provide (b) (4) months of stability data for 1 validation batch and (b) (4) months of stability data for the other 2 validation batches, they provided (b) (4) months of stability data for 2 development batches and 2 clinical batches. Since these development and clinical batches were manufactured using the final commercial process and have the same formulation and container closure system as the validation batches, the stability data from the development and clinical batches can be used to support the proposed shelf life of 24 months. Furthermore, the FVP (IV) and FVP formulations are comparable (Refer to section 3.2.P.2.2.1.2 comparability) and they share similar degradation pathways and rates, therefore

the stability data for the FVP presentation further support the stability of the FVP (IV) presentation.

3.2.P.8.2 Post-Approval Stability Protocol and Commitment

Stability Commitment: Janssen provided a commitment (b) (4)

They also committed to report the out of specification results obtained at the recommended storage temperature to the Agency.

Stability Protocol - Annual: The sponsor stated that at least one FVP (IV) batch will be entered annually into the stability-monitoring program. The storage condition for the stability study with FVP (IV) is (b) (4) °C, and stored in a horizontal orientation protected from light. The testing schedule for the stability monitoring program for FVP (IV) (recommended condition (b) (4) °C) is presented in Table 1 below. All test methods and specifications are listed in 3.2.P.5.2 Analytical procedures and 3.2.P.5.1 Specifications.



FDA Reviewer Comment: The sponsor commits to put at least one FVP (IV) lot into the annual stability monitoring program, which is acceptable.

3.2.P.8.3 Stability Data

Included in this section are figures made for each analytical procedure at different stability storage temperatures and tables made for each FVP (IV) batch at different stability storage temperatures, but the linear mixed-effect model and trend lines were only determined for the 2-8 °C data. The stability data will be summarized by analytical method basis as below.

Test	2-8 °	(b) (4)	
Potency by (b) (4)	No failures or significant trends are noted.	All batches meet the proposed stability AC for (b) (4) months.	All batches meet the proposed stability AC for (b) (4) months.

		(b) (4)	(b) (4)
Protein concentration (b) (4)	No failures or significant trends are noted.	All batches meet the proposed stability AC for (b) (4) months. There are no obvious trends noted for most tested batches.	All batches meet the proposed stability AC for (b) (4) months. There are no obvious trends noted for most tested batches.
Purity by (b) (4)	No failures or significant trends in purity are noted. No impurities (b) (4) .	All batches meet the proposed stability AC for (b) (4) months. (b) (4)	All batches meet the proposed stability AC for (b) (4) months. (b) (4)
Purity by (b) (4)	No failures or significant trends are noted for (b) (4) contents.	All batches meet the proposed stability AC for (b) (4), and 3 months for (b) (4) respectively. (b) (4)	All batches meet the proposed stability AC fo (b) (4) months for (b) (4), respectively. (b) (4)
Charge Distribution by (b) (4)	No failures or significant trends are noted for sum of major peak percent areas and area percent at peak (b) (4)	All batches meet the proposed stability AC for (b) (4) months for sum of major peak percent areas and area percent at peak (b) (4) respectively. (b) (4)	All batches meet the proposed stability AC fo (b) (4) months for sum of major peak percent areas and area percent at peak (b) (4) respectively. (b) (4)

		peak ^{(b) (4)} over time.	
Color of Solution	All tested batches (n=8) conform to the proposed stability AC ^{(b) (4)} ^{(b) (4)}	All tested batches conform to the proposed stability AC ^{(b) (4)}	All tested batches conform to the proposed stability AC ^{(b) (4)}
Endotoxin	All tested batches (n=7, the results for one development batch CGS3B/CGS25 were not provided) conform to the proposed stability AC (^{(b) (4)} EU/mg protein). This issue should be addressed by DMA.	N.A.	N.A.
Sterility	All tested batches (n=7, the results for one development batch CGS3B/CGS25 were not provided) conform to the proposed stability AC ^{(b) (4)} ^{(b) (4)} . This issue should be addressed by DMA.	N.A.	N.A.
Container Closure Integrity Test (CCTI)	All tested batches (3 validation batches) conform to the proposed stability AC ^{(b) (4)} ^{(b) (4)}	N.A.	N.A.
pH	All tested batches (n=8) conform to the proposed stability AC ^{(b) (4)}	All tested batches (n=8) conform to the proposed stability AC ^{(b) (4)}	All tested batches (n=8) conform to the proposed stability AC ^{(b) (4)}
Particulate Matter (visible translucent) by ^{(b) (4)}	All tested batches (n=8) conform to the proposed stability AC (^{(b) (4)} particles/mL) Majority of the results are ^{(b) (4)} particles/mL, with the greatest value being ^{(b) (4)} particles/mL ^{(b) (4)} process validation batch ^{(b) (4)})	All tested batches (n=8) conform to the proposed stability AC ^{(b) (4)} particles/mL)	All tested batches (n=8) conform to the proposed stability AC (^{(b) (4)} particles/mL)

Particulate Matter (sub-visible translucent)	No failures or significant trends are noted for particulate matters: $\geq$ (b) (4) μm and (b) (4) μm The highest levels seen are 245 for (b) (4) μm particles and 74 for (b) (4) μm particles.	All tested batches meet the proposed stability AC for (b) (4) months The highest levels seen are 321 for (b) (4) μm particles and 31 for (b) (4) μm particles. There are no prominent trends noticed for either (b) (4) μm or (b) (4) μm particles over time.	All tested batches meet the proposed stability AC fo (b) (4) months The highest levels seen are 287 for (b) (4) μm particles and 38 fo (b) (4) μm particles. There are no prominent trends noticed for either (b) (4) μm or (b) (4) μm particles over time.
Turbidity	No failures or significant trends are noted.	All batches meet the proposed stability AC for (b) (4) months. There are no prominent trends noticed for turbidity over time.	All batches meet the proposed stability fo (b) (4) months. There are no prominent trends noticed for turbidity over time.
EDTA Concentration	No failures or significant trends are noted.	All batches meet the proposed stability AC for (b) (4) months. There are no prominent trends noticed for turbidity over time.	All batches meet the proposed stability f (b) (4) months. There are no prominent trends noticed for turbidity over time.
Methionine Concentration	No failures or significant trends are noted.	All batches meet the proposed stability AC for (b) (4) months. There are no prominent trends noticed for turbidity over time.	All batches meet the proposed stability fo (b) (4) months. There are no prominent trends noticed for turbidity over time.

Below is the summary of stability results available to date for FVP (IV):

- 1) At the recommendation temperature of 2-8 °C, all results meet the proposed commercial stability specifications for FVP (IV).
- 2) At the accelerated storage condition (b) (4), results exceeding the commercial stability specifications are observed for some batches (b) (4)

(b) (4)

- 3) At the stressed storage conditio (b) (4) results exceeding the commercial stability acceptance criteria were observed for some batches (b) (4)

FDA Reviewer Comment: Accelerated and stresses stability studies are usually designed and conducted to investigate the product degradation pathways. Thus, the results exceeding the proposed commercial specification at accelerated and stressed storage conditions are expected. The stability data suggest that fragments is the major degradation pathway for ustekinumab FVP (IV) DP.

Photostability Study

The sponsor performed photostability studies to assess the ability of the secondary packaging of FVP (IV) to protect the product from degradation due to light exposure.

(b) (4)

(b) (4)

FDA Reviewer Comment: After exposed to ICH light conditions (b) (4)°C, FVP (IV) in the representative secondary package remained unchanged and met the proposed commercial acceptance criteria. In contrast, FVP (IV) without the representative secondary package showed degradation (b) (4)

(b) (4) These results support that the secondary package proposed for FVP (IV) commercial use is able to provide adequate protection from the light conditions specified in ICH Q1B.

Temperature Cycling Study

The sponsor also conducted a temperature cycling study to provide stability data which would support potential temperature excursions that may be encountered during transportation, storage, and handling (b) (4)

(b) (4)

Temperature cycling data were provided as below.

FDA Reviewer Comment: There are no trends or failures noted, suggesting that the FVP (IV) products are not affected by temporary temperature alterations. The stability data supports potential temperature excursions during transportation, storage and handling.

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- 3.2.A.2 Adventitious Agents Safety Evaluation
- 3.2.A.3 Novel Excipients

3.2.R Regional Information (U.S.A.)

- 3.2.R.1 Executed Batch Records
- 3.2.R.2 Method Validation Package
- 3.2.R.3 Comparability Protocols

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Included in this section are 3 validation reports for immunogenicity assays to detect ADAs and neutralizing antibodies to ustekinumab in human serum:

Validation Report	cp2002v-080	cp2011v-035	cp2010v-050
Assay	Bridging enzyme immunoassay (EIA)	Immunochemilluminescence based immunoassay (ECLIA)	Competitive ligand-binding assay (CLBA)
Purpose	Screen, titer, and confirm ADA to ustekinumab	Screen, titer, and confirm ADA to ustekinumab	Detect neutralizing antibodies to ustekinumab
Regulatory Status	Reviewed in BLA125261 (dated July 15, 2008)	Reviewed in BLA125261/103 (dated July 31, 2013)	Reviewed in BLA125261/86 (b) (4) (dated April 1, 2013)
Clinical Studies	Phase 2 (C0397T07 and C0743T26)	Phase 1 (NAP1002) Phase 3 (CRD3002, CRD3002, and CDR 3003)	Phase 2 (C0743T26) Phase 3 (CRD3002, CRD3002, and CDR 3003)

1. EIA

The EIA method was original developed and validated to screen, titer and confirm ADA to ustekinumab in human serum. This bridging assay was used in the pivotal trials for psoriasis (C0743T08 and C0743T09). However, at the time BLA 125261 was approved, 48% and 90% of subjects in C0743T08 and C0743T09 (Psoriasis trials), respectively, had inconclusive ADA status due to drug interference. There was, therefore, a post-marketing commitment (PMC) to develop an ADA assay with improved drug tolerance. The method description and validation parameters of the EIA method were described in the original validation report

Mod5.3.1.4/CP2002V-080. This original validation report was reviewed by Laurie Graham, dated July 15, 2008 (Refer to BLA 125261). Seven addenda to the original validation report were finalized. This method was used in the Phase 2 clinical studies for Crohn’s disease (C0397T07 and C0743T26), but has since been replaced and is no longer in use.

FDA Reviewer Comment: Since the data from the above two Phase 2 clinical studies were not included in the assessment of immunogenicity incidence, this validation report and its addenda were not reviewed.

2. ECLIA

In order to improve drug tolerance, the sponsor developed a new electrochemiluminescence based immunoassay (ECLIA (b) (4)), to screen, titer and confirm ADA to ustekinumab in human serum. With the new assay, the sponsor estimated that 96% in each trial had post-treatment samples that were evaluable for ADA status (i.e., only 4% inconclusives). The method description and validation parameters were described in the validation report Mod5.3.1.4/CP2011V-035. This original validation report was reviewed by Laurie Graham, dated July 31, 2013 (Refer to review memo for BLA 125261/103). There are 6 addenda to the original validation report listed as below. The ECLIA method was used in the pivotal studies (CRD3002, CRD3002, and CDR 3003) and PK comparability study (NAP1002) for Crohn’s disease.

Addendum	Content	Reviewer Comment
CP2011V-035-A1	A correction to the stability section of the report	Refer to review memo for BLA 125261/103.
CP2011V-035-A2	A detailed description of the calculations used to determine the acceptance criteria (AC) for consistency controls and critical reagent qualification	Refer to review memo for BLA 125261/103.
CP2011V-035-A3	Typographical errors were corrected and clarifications to report text	Refer to review memo for BLA 125261/103.
CP2011V-035-A4	Long term stability updated	Refer to review memo for BLA 125261/103.
CP2011V-035-A5	The partial validation for the transfer of the MSD ECLIA method from t (b) (4) to t (b) (4) laboratories	The sponsor evaluated the consistency controls and specificity controls at the (b) (4) location. In the original addendum, the sponsor only provided the normalized ECL values for all control samples, which are not sufficient for evaluation of the success of the method transfer. In response to an IR dated 12 August 2016, the sponsor provided the inter-replicate CVs for the control samples, which are all (b) (4) (b) (4)% and meet the study phase control acceptance criteria.

		This updated partial validation results show acceptable performance of the ECLIA method after the (b) (4) (b) (4) laboratory relocation from (b) (4) to (b) (4)
CP2011V-035-A6	Long-term stability update	It reported the results of stability assessment timepoints conducted on low positive ADA (b) (4) (b) (4) The provided data were reviewed and they support the stability assessment for the method to detect ADA in human serum samples.

3. CLBA

A Competitive Ligand Binding Assay (CLBA) was developed and validated to detect neutralizing antibodies (NAb) to ustekinumab in human serum. The method description and validation parameters were described in the original validation report Mod5.3.1.4/CP2010V-050. This original validation report was reviewed by Laurie Graham, dated April 1, 2013 (Refer to BLA 125261/86 (b) (4)). There are 2 addenda to the original validation report listed as below.

Addendum	Content	Review Comment
CP2010V-050-A1	A partial validation of the method for detection of neutralizing antibodies to ustekinumab in primary biliary cirrhosis (PBC) patient serum	The sponsor provided a table to summarise the NAb responses of drug naïve normal and PBC human serum samples tested in the ustekinumab NAb assay and compared their cut point. The results show no difference in cut point among serum samples from normal and PBC population during validation. Thus, it is acceptable to apply the previously validated cut point for the NAb detection in human PBC serum samples. This is not relevant to the proposed indication in the current BLA.
CP2010V-050-A2	The partial validation for the transfer of the CLBA NAb method from the (b) (4) facilities to th (b) (4) (b) (4) laboratories	The sponsor evaluated the performance of assay controls at th (b) (4) location. The results show that all control samples performed with sufficient precision and generated results within their respective acceptance criteria as established during the method validation (CP2010V-050). Thus, the CLBA-based ustekinumab NAb assay performed in a manner consistent with the original validation after the method was transferred from th (b) (4) (b) (4) laboratory (b) (4) to (b) (4)

**APPENDIX B
DRUG PRODUCT MICROBIOLOGY REVIEW: DIVISION OF MICROBIOLOGY
ASSESSMENT**

Date: August 15, 2016

To: Administrative File, STN 761044/0

From: Candace Gomez-Broughton, Ph.D., Reviewer CDER/OPQ/OPF/DMA/ Branch IV

Endorsed: Patricia Hughes, Ph.D. Acting Branch Chief CDER/OPQ/OPF/DMA/Branch IV

Subject: Original Biologics License Application (BLA)

US License: 1864

Applicant: Janssen Biotech, Inc.

Facilities: Cilag AG, Schaffhausen, Switzerland
FEI: 3002806695

Product: Stelara® (ustekinumab)

Dosage: Sterile solution for intravenous infusion (5 mg/vial)

Indication: Treatment of adult patients with moderately to severely active Crohn's disease

Due date: September 23, 2016

Recommendation: The BLA is recommended for approval from a microbiology product quality perspective.

INTRODUCTION

Janssen Biotech, Inc. has submitted Biologic License Application (BLA) 761044 in eCTD format for the approval Stelara® (ustekinumab). The drug product (DP) is manufactured at Cilag AG (Cilag), Schaffhausen, Switzerland (FEI: 3002806695).

Drug substance information is cross-referenced to the approved Stelara® 90/mg/mL Final Vial Product (FVP) (BLA 125261) module 3.2.S.

Amendments reviewed:

- Sequence 0033 (08Aug2016): Response to Information Request sent 18Aug2016
- Sequence 0017 (25May2016): Response to Mid-Cycle Review Request 13May2016

ASSESSMENT**P Drug Product****P.1 Description and Composition of the Drug Product**

The ustekinumab final vial drug product for intravenous use (FVP (IV)) is supplied as a single-use sterile solution at a concentration of 130mg/26 mL. The DP is filled into 30 mL, Type-1 glass vials stoppered with 20-mm (b) (4) coat (b) (4) stoppers and sealed with 20-mm aluminum flip-off seals.

The FVP (IV) formulation consists of 5 mg/mL ustekinumab (b) (4) mM L-histidin (b) (4) (w/v) sucro (b) (4)% (w/v) polysorbate 8 (b) (4) mg/mL methionine, a (b) (4) mg/mL EDTA disodium salt dehydrate at pH (b) (4)

P.2 Pharmaceutical DevelopmentMicrobial Retention Studies

(b) (4)

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P.8 Stability

P.8.1 Stability Summary and Conclusion

Ustekinumab FVP (IV) has a proposed shelf life of 24 months when stored at 2-8°C protected from light based on 36 months of stability data at 2-8°C.

8 batches of VP (IV) manufactured (b)(4) at the commercial manufacturing facility have placed on stability. Descriptions of the batches placed on stability are provided in Table 2 from the submission and shown below.

Table 2: FVP (IV) Stability Batches

Batch ID/ Batch Number	Batch Designation	Site of Manufacture	Date of Manufacture	Drug Substance Batch(es)
CGS3B/CGS25	Phase 3 Development	Cilag, Schaffhausen, Switzerland		(b) (4)
CJS52/CJS23	Phase 3 Development	Cilag, Schaffhausen, Switzerland		
DDS4W/DDS2V	Phase 3 Clinical	Cilag, Schaffhausen, Switzerland		
DES1C/DDS4D	Phase 3 Clinical	Cilag, Schaffhausen, Switzerland		
DLS1Z/DLS0B	Phase 3 Clinical	Cilag, Schaffhausen, Switzerland		
(b) (4)	Process Validation	Cilag, Schaffhausen, Switzerland		
	Process Validation	Cilag, Schaffhausen, Switzerland		
	Process Validation	Cilag, Schaffhausen, Switzerland		

The stability studies include the following:

(b) (4)

The stability protocol includes endotoxin and sterility at the recommended storage temperature (b) (4). The data, included in section 3.2.P.8 meet specifications for endotoxin and sterility for the duration of the study (b) (4);).

P.8.2 Post-Approval Stability Protocol and Stability Commitment

Sterility, endotoxin, and container closure integrity tests will be performed (b) (4) on drug product placed on ability for up to (b) (4) months (b) (4)C.

CONCLUSION

The BLA is recommended for approval from a microbiology product quality perspective:

- I. The BLA is recommended for approval from a microbiology product quality perspective.
- II. CMC product specific information and data should be reviewed by the OBP reviewer.
- III. **No additional inspectional follow-up items were identified.**

Information Requested During Review Cycle**Information request sent 13May2016**

Please submit the [REDACTED] (b) (4)

1. Please provide descriptions of the bioburden and endotoxin tests in Section 3.2.P.5.2 of the BLA.
2. With regard to media fill studies; please provide the following information
 - a. Growth promotion study data
 - b. Definition of a media fill failure
 - c. Detailed description of the actions taken in the event of a media fill failure
3. Results from studies completed to determine the effect of hold time on endotoxin [REDACTED] (b) (4)

Information request sent 18Aug2016

Endotoxin sample storage time should be limited to (b) (4) hours based on the hold times study data provided in the BLA. Please amend the BLA to reflect th (b) (4)-hour storage time limit. Longer storage times are currently not supported by the data submitted. Supporting data from studies may be submitted when available to change the storage time.

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BLA STN 761044

STELARA[®] (ustekinumab)

Janssen Biotech, Inc.

Reviewer: Zhenzhen Liu, Ph.D.
Application Technical Lead: Maria Gutierrez-Lugo, Ph.D.
Review Chief: Susan Kirshner, Ph.D.
Division of Biotechnology Research and Review III
Office of Biotechnology Products

OBP CMC Review Data Sheet

1. **BLA#:** STN 761044
2. **REVIEW DATE:** Jan 05, 2016
3. **PRIMARY REVIEW TEAM:**
 - Medical Officer:** Kerry Jo Lee / Juli Tomaino
 - Pharm/Tox:** Jackye Peretz / Sushanta Chakder
 - Product Quality:** Zhenzhen Liu / Maria Gutierrez Lugo
 - Clinical Pharmacology:** Christine Hon and Anand Barakrishnan / Yow-Ming Wang
 - Pharmacometrics:** Jee Eun Lee/Nitin Mehrotra
 - Statistics:** Min Min / Yeh-Fong Chen
 - Microbiology:** Candace Gomez-Broughton/Colleen Thomas
 - Facilities:** Marion Michaelis/Peter Qiu
 - Labeling:** Joette Meyer
 - OBP Labeling:** Jibril Abdus-Samad
 - OND RPM:** Allan Lawrence
 - OPQ RPM:** Anita Brown
4. **MAJOR GRMP DEADLINES**
 - Filing Meeting:** 5 Jan 2016
 - Mid-Cycle Meeting:** 25 Apr 2016
 - Wrap-Up Meeting:** 25 Jul 2016
 - Primary Review Due:** 18 Aug 2016
 - Secondary Review Due:** 25 Aug 2016
 - CDTL Memo Due:** 2 Sep 2016
 - PDUFA Action Date:** 23 Sep 2016
5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
Filing Review Memo	02-05-2016
Mid-cycle Communication	04-29-2016
Information Request 1	06-27-2016
Information Request 2	07-01-2016
Information Request 3	08-02-2016
Information Request 4	08-08-2016
Information Request 5	08-09-2016
Information Request 6	08-12-2016
Information Request 7	08-19-2016

Information Request 8	08-22-2016

6. SUBMISSION(S) REVIEWED:

Submission	Date Received	Review Completed (Yes/No)
STN 761044/0 (BLA Original Submission)	11-25-2015	Yes
STN 761044/23 (Sponsor's response to IR1)	07-08-2016	Yes
STN 761044/23 (Sponsor's response to IR2)	07-08-2016	Yes
STN 761044/30 (Sponsor's response to IR3)	08-10-2016	Yes
STN 761044/29 (Sponsor's response to IR4)	08-09-2016	Yes
STN 761044/31 (Sponsor's response to IR5)	08-11-2016	Yes
STN 761044/32 (Sponsor's response to IR6)	08-15-2016	Yes
STN 761044/33 (Sponsor's response to IR7)	08-23-2016	Yes
STN 761044/33 (Sponsor's response to IR8)	08-23-2016	Yes

7. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name	STELARA
Trade Name	STELARA
Non-Proprietary/USAN	Ustekinumab
CAS name	Immunoglobulin G1, anti-(human interleukin 12p40 subunit)(human monoclonal CNTO 1275 γ 1-chain), disulfide with human monoclonal CNTO 1275 κ -chain, dimer, CAS# 815610-63-0
Common name	CNTO 1275, CNTO 1275 IgG, anti-IL-12/23 p40 human IgG1kappa
INN Name	Ustekinumab
Compendial Name	Not Applicable
OBP Systematic Name	MAB HUMAN (IGG1) ANTI P29460 (IL12B_HUMAN) [CNTO 1275]
Other Names	CNTO 1275 monoclonal antibody, 12B75, 12B75 IgG, anti-IL-12, human anti-IL-12 monoclonal antibody, human anti-IL-12 IgG1 monoclonal antibody, anti-IL-12p40, IL-12/23 monoclonal antibody, and anti-IL-12/23p40.

8. PHARMACOLOGICAL CATEGORY: Interleukine-12 and -23 antagonist. Human IgG1κ monoclonal antibody that recognizes the p40 subunit of IL-12 and IL-23.

9. DOSAGE FORM: Injection

10. STRENGTH/POTENCY:

- The ustekinumab FVP (IV) Drug Product is supplied as a 130 mg/26 mL (5 mg/mL) solution in a single-use vial.
- Potency is defined as the percent activity relative to the reference standard, using a cell-based assay that measures the ability of ustekinumab to inhibit IL-12 signaling (i.e., IFN-γ secretion) in an IL-12 dependent cell line (NK92 MI).

11. ROUTE OF ADMINISTRATION: Intravenous injection.

12. REFERENCED MASTER FILES:

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)			Yes	No review required as relevant information was provided in the BLA.
			Yes	(b) (4)

13. INSPECTIONAL ACTIVITIES: OBP did not participate in the inspection.

14. CONSULTS REQUESTED BY OBP: NONE.

15. 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

16. PRECEDENTS**17. ADMINISTRATIVE****A. Signature Block**

Name and Title	Signature and Date
Maria Gutierrez-Lugo, Ph.D. Team Leader Office of Biotechnology Products Division of Biotechnology Research and Review III	
Zhenzhen Liu, Ph.D. Primary Reviewer Office of Biotechnology Products Division of Biotechnology Research and Review III	

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The data submitted in this application support the conclusion that the manufacture of ustekinumab final vial product for intravenous injection [FVP (IV)] is well controlled, and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents, sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product is produced from the multiple production runs presented. It is recommended that this product be approved for human use under conditions specified in the package insert.

II. List Of Deficiencies To Be Communicated

None (review issues were communicated and addressed during review).

III. List Of Post-Marketing Commitments/Requirement

None.

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion

Previously in BLA 125261, a claim for categorical exclusion under 21 CFR 25.31 (c) and 21 CFR 25.34 (b) was made. To the sponsor's knowledge, no extraordinary circumstances exist relative to this action.

V. Primary Container Labeling Review

The CMC labeling review was performed by Jibril Abdus-Samad, OBP.

VI. Review Of Common Technical Document-Quality Module 3.2

This document contains the review of the information provided for ustekinumab FVP (IV) drug product (Section 3.2.P), facilities and equipment (3.2.A), and the method validation package and batch records (3.2.R).

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

The review of the immunogenicity assays is cross-referenced to BLA 125261 supplement 103 (Validation and cross-validation reports for the screening and confirmatory assay) and supplement 86 (b) (4) (Validation and cross-validation reports for the NAb assay). A review of addenda to these immunogenicity assays is provided at the end of the primary review document.

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REVIEW

3.2.S DRUG SUBSTANCE

The drug substance section of this BLA is cross referenced to BLA 125261. Briefly, ustekinumab is a first-in-class fully human IgG1 κ monoclonal antibody that recognizes the p40 subunit common to both human IL-12 and IL-23. It is grown (b) (4)

(b) (4)
The antibody is made up of 2 identical heavy chains and 2 identical light chains. The heavy and light chains are linked by both covalent and non-covalent disulfide bonds. There are also non-covalent heavy-heavy chain bonds. All cysteine residues are involved in disulfide bonds, resulting in a total of 16 disulfide bonds. (b) (4)

(b) (4)
The estimated molecular mass of ustekinumab ranges from 148,079 to 149,690 Daltons (b) (4)

Ustekinumab has been shown to inhibit the binding of IL-12 and IL-23 to the IL-12 β 1 receptor chain and subsequent intracellular signaling by both cytokines. IL-12 induces immune cells toward a T helper 1 (Th1) phenotype (stimulates interferon-gamma [IFN- γ] production), while IL-23 induces a T helper 17 (Th17) pathway (promotes secretion of IL-17A, IL-21, and IL-22). Both cytokines stimulate TNF production, resulting in the intestinal inflammation and epithelial cell injury typical of Crohn's disease.

In vitro ustekinumab has been shown to inhibit human IL-12 and IL-23 induced signaling in human primary cells, human cell lines, and mouse splenocytes. This includes an inhibition of IL-12 induced IFN- γ secretion from an NK cell line, NK92MI, which is used as the potency assay for ustekinumab. In addition, ustekinumab has been shown *in vivo* to inhibit epidermal thickening and keratinocyte proliferation in a humanized mouse model of psoriasis.

Ustekinumab is not thought to induce antibody dependent cellular cytotoxicity (ADCC) or complement dependent cellular cytotoxicity (CDC). Ustekinumab could not bind to IL-12 or IL-23 that was already bound to IL-12 β 1 or dual receptors. Since ustekinumab cannot bind to IL-12 or IL-23 once they are receptor bound, ADCC by ustekinumab is not considered likely. Ustekinumab did not mediate CDC of PHA activated human PBLs. However, ustekinumab is able to bind to Fc-receptors. Furthermore, ustekinumab, captured on IL-12 containing beads, has been shown to activate the complement pathway, as detected by soluble C5b-9 production, when human serum was used as a complement source.

(b) (4)

The ustekinumab 130 mg/26 mL (5 mg/mL) final vial drug product for intravenous administration [FVP (IV)] is made with the same drug substance used to manufacture the ustekinumab FVP for subcutaneous administration covered under BLA 125261. Therefore, the drug substance section in BLA 761044 is cross-referenced to BLA 125261. The drug substance information provided in BLA 125261 was found to be acceptable.

3.2.P DRUG PRODUCT

STELARA (ustekinumab) was approved in the U.S. on 25 September 2009 under BLA 125261 for the treatment of adults with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. On 20 September 2013, STELARA was approved for the treatment of adults with active psoriatic arthritis (PsA). STELARA is currently approved as 45 mg/0.5 mL and 90 mg/mL solution for SC injection (liquid in vial and prefilled syringe presentations).

On 25 November 2015, Janssen Biotech, Inc. submitted BLA 761044 providing data to support the safety and efficacy of ustekinumab in the treatment of adult patients with moderately to severely active Crohn's disease and drug product data to support approval of a new presentation, a vial containing 130 mg/26 mL (5 mg/mL) solution for intravenous infusion, intended for use in Crohn's disease IV induction therapy.

Status	BLA	Dosage Form, strength	Route of administration	Indication	Date of approval
Approved	125261	Injection, 45 mg/ 0.5 mL or 90 mg/mL	SC	Plaque Psoriasis	09/25/2009
				Psoriatic Arthritis	09/20/2013
Proposed	761044	Injection, 130 mg/26 mL (5 mg/mL)	IV	Crohn's Disease	Pending

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

The ustekinumab FVP (IV) drug product is supplied as a single-dose, sterile solution designed to deliver 130 mg of ustekinumab in a 30 mL, Type-1 glass vial. The vials are stoppered with 20-mm (b) (4); coated (b) (4) stoppers and sealed with 20-mm aluminum flip-off seals. The ustekinumab FVP (IV) DP has only one dosage strength of 5

mg/mL. Quantity and function of each component for the ustekinumab FVP (IV) DP is shown in Table 1.

Table 1: Composition of Ustekinumab FVP (IV)

Component	Grade	Function	Mg/Vial	Concentration (mg/mL)
ustekinumab	NA	Active		(b) (4)
L-Histidine	USP/Ph. Eur./JP	(b) (4)		
L-Histidine Hydrochloride Monohydrate	Ph. Eur./JP			
Sucrose	NF/Ph. Eur./JP			
Polysorbate 80	NF/Ph. Eur./JP			
L-Methionine	USP/Ph. Eur./JP			
EDTA disodium salt dihydrate ^b	USP/Ph. Eur./JP			
	(b) (4)			(b) (4)

FDA Reviewer Comment: It is noted that the 26 mL ustekinumab FVP (IV) DP contains a target (b) (4) mL overfill. Per 21 CFR 201.51 (g) and USP <1151> Pharmaceutical Dosage Forms, each container of an injection is filled with a volume in slight excess of the labeled "size" or the volume that is to be withdrawn. The excess volume recommended for 30 mL (labeled size) mobile liquids is 0.8 mL and for 30 mL viscous liquids is 1.2 mL (b) (4)

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)

(b) (4)



3.2.P.8.1 Stability Summary and Conclusion

Batches: The following batches were placed in the stabil

Table 2: FVP (IV) Stability Batches

Batch ID/ Batch Number	Batch Designation	Site of Manufacture	Date of Manufacture	Drug Substance Batch(es)
CGS3B/CGS25	Phase 3 Development	Cilag, Schaffhausen, Switzerland		(b) (4)
CJS52/CJS23	Phase 3 Development	Cilag, Schaffhausen, Switzerland		
DDS4W/DDS2V	Phase 3 Clinical	Cilag, Schaffhausen, Switzerland		
DES1C/DDS4D	Phase 3 Clinical	Cilag, Schaffhausen, Switzerland		
DL S1Z/DL S0R (b) (4)	Phase 3 Clinical	Cilag, Schaffhausen, Switzerland		
	Process Validation	Cilag, Schaffhausen, Switzerland		
	Process Validation	Cilag, Schaffhausen, Switzerland		
	Process Validation	Cilag, Schaffhausen, Switzerland		

* These batches were not included in the statistical analysis due to limited data, as outlined in Section 6.

Storage Temperatures and Schedule of Testing: All batches were stored protected from light at the recommended temperature of (b) (4)°C for (b) (4) months, at the accelerated temperature condition (b) (4) for (b) (4) months, and at the stressed temperature condition (b) (4) RH) for (b) (4) months. The details of the stability protocols for each temperature condition were provided in the submission.

Analytical Procedures: The quality of the above FVP (IV) batches was evaluated using the following analytical procedures:

Table 3: Analytical Procedures for the Stability Monitoring Program for FVP(IV) Phase 3 Development, Phase 3 Clinical, and Process Validation Batches

Quality Attribute Category	Analytical Procedure
Potency	(b) (4)
Quantity	
Purity	
Charge Distribution	
Structure	
Appearance	
Safety	
General Attributes	

^a This test is for characterization purposes only and not part of the specification for routine release and stability testing. The analytical procedure is described in 3.2.S.3.1, Elucidation of Structure and Other Characteristics.
^b Tested on process validation batches only.
^c This test is for characterization purposes only and not part of the specification for stability testing. The stability data are presented in 3.2.P.5.6, Justification of Specification(s). However, the test is part of the routine batch release program.

Available stability Data: The sponsor provided stability data under the recommended conditions for up to (b) (4) months for two phase 3 development batches and two phase 3 clinical batches (Table 7). Accelerated stability data for up to (b) (4) months for two phase 3 development batches and three phase 3 clinical batches were also provided along with stress data stored at (b) (4) °C for up to (b) (4) months (Tables 8 and 9 in the submission).

Table 7: Available Stability Data for FVP (IV) Phase 3 Development, Phase 3 Clinical, and Process Validation Batches Stored at (b) (4)

Batch	Months of Storage						
Development Batch CGS3B/CGS25	√	√	√	√	√	√	√
Development Batch CJS52/CJS23	√	√	√	√	√	√	√
Clinical Batch DDS4W/DDS2V	√	√	√	√	√	√	√
Clinical Batch DES1C/DDS4D	√	√	√	√	√	√	√
Clinical Batch DLS1Z/DLS0B	√	√	√	√	√	√	√
(b) (4)	√	√	√	√	√	√	√

In response to an IR dated 27 June 2016, the sponsor provided updated stability data for three process validation batches to support the proposed shelf life of 24 months. The table below summarizes the last completed time interval for each storage condition.

Table 10: Storage Conditions and Last Completed Time Intervals (months)

(b) (4)

Shelf Life: Based on available stability data at 2-8 °C from these batches and supportive statistical trending analyses, the sponsor proposed the 24 month shelf life for FVP (IV) at the recommended storage condition of 2-8 °C and protected from light.

FDA Reviewer Comment: Although the sponsor only provided 18 months of stability data for 1 validation batch and (b) (4) months of stability data for the other 2 validation batches, they provided (b) (4) months of stability data for 2 development batches and 2 clinical batches. Since these development and clinical batches were manufactured using the final commercial process and have the same formulation and container closure system as the validation batches, the stability data from the development and clinical batches can be used to support the proposed shelf life of 24 months. Furthermore, the FVP (IV) and FVP formulations are comparable (Refer to section 3.2.P.2.2.1.2 comparability) and they share similar degradation pathways and rates, therefore the stability data for the FVP presentation further support the stability of the FVP (IV) presentation.

3.2.P.8.2 Post-Approval Stability Protocol and Commitment

Stability Commitment: Janssen provided a commitment to continue the stability studies on all above 8 FVP (IV) batches through (b) (4) months at 2-8 °C and on 3 validation batches through (b) (4) months (b) (4). They also committed to report the out of specification results obtained at the recommended storage temperature to the Agency.

Stability Protocol - Annual: The sponsor stated that at least one FVP (IV) batch will be entered annually into the stability-monitoring program. The storage condition for the stability study with FVP (IV) is (b) (4) °C, and stored in a horizontal orientation protected from light. The testing schedule for the stability monitoring program for FVP (IV) (recommended condition (b) (4) °C) is presented in Table 1 below. All test methods and specifications are listed in 3.2.P.5.2 Analytical procedures and 3.2.P.5.1 Specifications.

Table 1: Stability Monitoring Program for FVP (IV) (Recommended Condition (b) (4))

Test Method	Months of Storage							
	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sterility	√	NR	NR	NR	√	NR	√	√
Endotoxin	√	NR	NR	NR	√	NR	√	√
Container Closure Integrity	√	NR	NR	NR	√	NR	√	√
Particulate Matter (sub-visible)	√	√	√	√	√	√	√	√
Particulate Matter (visible translucent by MDI)	√	√	√	√	√	√	√	√
Color of Solution	√	√	√	√	√	√	√	√
Turbidity	√	√	√	√	√	√	√	√
Protein Concentration by A ₂₈₀	√	√	√	√	√	√	√	√
cSDS (Reduced)	√	√	√	√	√	√	√	√
cSDS (Non-reduced)	√	√	√	√	√	√	√	√
DW-SE-HPLC	√	√	√	√	√	√	√	√
pH	√	√	√	√	√	√	√	√
cIEF	√	√	√	√	√	√	√	√
Bioactivity Assay	√	√	√	√	√	√	√	√
Methionine Concentration	√	√	√	√	√	√	√	√
EDTA Concentration	√	√	√	√	√	√	√	√

^a Test results at time zero will be derived from release testing excluding CCIT which is not a release test.

FDA Reviewer Comment: The sponsor commits to put at least one FVP (IV) lot into the annual stability monitoring program, which is acceptable.

3.2.P.8.3 Stability Data

Included in this section are figures made for each analytical procedure at different stability storage temperatures and tables made for each FVP (IV) batch at different stability storage temperatures, but the linear mixed-effect model and trend lines were only determined for the 2-8 °C data. The stability data will be summarized by analytical method basis as below.

Test	2-8 °C	(b) (4)	
Potency by bioactivity assay	No failures or significant trends are noted.	All batches meet the proposed stability AC f (b) (4) months.	All batches meet the proposed stability AC f (b) (4) months.
Protein concentration By A₂₈₀	No failures or significant trends are noted.	All batches meet the proposed stability AC f (b) (4) months. There are no obvious trends noted for most tested batches.	All batches meet the proposed stability AC f (b) (4) months. There are no obvious trends noted for most tested batches.
Purity by cSDS (reduced and non-reduced)	No failures or significant trends in purity are noted. No impurities (b) (4)	All batches meet the proposed stability AC f (b) (4) months.	All batches meet the proposed stability AC f (b) (4) months.
Purity by DW-SE-HPLC	No failures or significant trends are noted for (b) (4)	All batches meet the proposed stability AC f (b) (4) months.	All batches meet the proposed stability AC f (b) (4) months.
Charge Distribution by cIEF	No failures or significant trends are noted for sum of major peak percent areas and area percent at peak (b) (4)	All batches meet the proposed stability AC f (b) (4) months for sum of major peak percent areas and area percent	All batches meet the proposed stability AC f (b) (4) months for sum of major peak percent areas and area percent at peak

		at peak (b) (4) respectively.	(b) (4) respectively.	(b) (4)
Color of Solution	All tested batches (n=8) conform to the proposed stability AC (b) (4)	All tested batches conform to the proposed stability AC (b) (4)	All tested batches conform to the proposed stability AC (b) (4)	
Endotoxin	All tested batches (n=7, the results for one development batch CGS3B/CGS25 were not provided) conform to the proposed stability AC ((b) (4)U/mg protein). This issue should be addressed by DMA.	N.A.	N.A.	
Sterility	All tested batches (n=7, the results for one development batch CGS3B/CGS25 were not provided) conform to the proposed stability AC (b) (4) his issue should be addressed by DMA.	N.A.	N.A.	
Container Closure Integrity Test (CCTI)	All tested batches (3 validation batches) conform to the proposed stability AC (b) (4)	N.A.	N.A.	
pH	All tested batches (n=8) conform to the proposed stability AC (b) (4)	All tested batches (n=8) conform to the proposed stability AC (b) (4)	All tested batches (n=8) conform to the proposed stability AC (b) (4)	
Particulate Matter (visible translucent) by MDI	All tested batches (n=8) conform to the proposed stability AC (b) (4) particles/mL) Majority of the results are (b) (4) particles/mL, with the greatest value being (b) (4) particles/mL (b) (4)s	All tested batches (n=8) conform to the proposed stability AC ((b) (4) particles/mL)	All tested batches (n=8) conform to the proposed stability AC (b) (4) particles/mL)	

Particulate Matter (sub-visible translucent)	No failures or significant trends are noted for particulate matters: (b) (4) μm and (b) (4) μm The highest levels seen are (b) (4) fo (b) (4) μm particles and 74 for (b) (4) μm particles.	All tested batches meet the proposed stability AC fo (b) (4) The highest levels seen are (b) (4) 1 fo (b) (4) μm particles and (b) (4) for (b) (4) μm particles. There are no prominent trends noticed for eith (b) (4) μm or (b) (4) μm particles over time.	All tested batches meet the proposed stability AC (b) (4) The highest levels seen are (b) (4) 7 fo (b) (4) μm particles and 38 for (b) (4) μm particles. There are no prominent trends noticed for eith (b) (4) μm or (b) (4) μm particles over time.
Turbidity	No failures or significant trends are noted.	All batches meet the proposed stability AC (b) (4) There are no prominent trends noticed for turbidity over time.	All batches meet the proposed stability f (b) (4) There are no prominent trends noticed for turbidity over time.
EDTA Concentration	No failures or significant trends are noted.	All batches meet the proposed stability AC (b) (4). There are no prominent trends noticed for turbidity over time.	All batches meet the proposed stability f (b) (4). There are no prominent trends noticed for turbidity over time.
Methionine Concentration	No failures or significant trends are noted.	All batches meet the proposed stability AC (b) (4). There are no prominent trends noticed for turbidity over time.	All batches meet the proposed stability f (b) (4) There are no prominent trends noticed for turbidity over time.

Below is the summary of stability results available to date for FVP (IV):

- 1) At the recommendation temperature of 2-8 °C, all results meet the proposed commercial stability specifications for FVP (IV).
- 2) At the accelerated storage conditi (b) (4), results exceeding the commercial stability specifications are observed for some batches (b) (4)
- 3) At the stressed storage conditi (b) (4), results exceeding the commercial stability acceptance criteria were observed for some batche (b) (4)

FDA Reviewer Comment: Accelerated and stresses stability studies are usually designed and conducted to investigate the product degradation pathways. Thus, the results exceeding the proposed commercial specification at accelerated and stressed storage conditions are expected. The stability data suggest tha (b) (4) is the major degradation pathway for ustekinumab FVP (IV) DP.

Photostability Study

The sponsor performed photostability studies to assess the ability of the secondary packaging of FVP (IV) to protect the product from degradation due to light exposure.

(b) (4)

(b) (4)

FDA Reviewer Comment: After exposed to ICH light conditions at (b) (4)°C, FVP (IV) in the representative secondary package remained unchanged and met the proposed commercial acceptance criteria. In contrast, FVP (IV) without the representative secondary package showed degradation by (b) (4)

(b) (4) these results support that the secondary package proposed for FVP (IV) commercial use is able to provide adequate protection from the light conditions specified in ICH Q1B.

Temperature Cycling Study

The sponsor also conducted a temperature cycling study to provide stability data which would support potential temperature excursions that may be encountered during transportation, storage, and handling

(b) (4)

(b) (4)

(b) (4)

Temperature cycling data were provided as below

(b) (4)

(b) (4)

FDA Reviewer Comment: There are no trends or failures noted, suggesting that the FVP (IV) products are not affected by temporary temperature alterations. The stability data supports potential temperature excursions during transportation, storage and handling.

3.2.A Appendices Table of Contents

3.2.A.1 Facilities and Equipment

3.2.A.2 Adventitious Agents Safety Evaluation

3.2.A.3 Novel Excipients

3.2.R Regional Information (U.S.A.)

3.2.R.1 Executed Batch Records

3.2.R.2 Method Validation Package

3.2.R.3 Comparability Protocols

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Included in this section are 3 validation reports for immunogenicity assays to detect ADAs and neutralizing antibodies to ustekinumab in human serum:

Validation Report	cp2002v-080	cp2011v-035	cp2010v-050
Assay	Bridging enzyme immunoassay (EIA)	Immunochemilluminescence based immunoassay (ECLIA)	Competitive ligand-binding assay (CLBA)
Purpose	Screen, titer, and confirm ADA to ustekinumab	Screen, titer, and confirm ADA to ustekinumab	Detect neutralizing antibodies to ustekinumab
Regulatory Status	Reviewed in BLA125261 (dated July 15, 2008)	Reviewed in BLA125261/103 (dated July 31, 2013)	Reviewed in BLA125261/86 and (b) (4) (dated April 1, 2013)
Clinical Studies	Phase 2 (C0397T07 and C0743T26)	Phase 1 (NAP1002) Phase 3 (CRD3002, CRD3002, and CDR 3003)	Phase 2 (C0743T26) Phase 3 (CRD3002, CRD3002, and CDR 3003)

1. EIA

The EIA method was original developed and validated to screen, titer and confirm ADA to ustekinumab in human serum. This bridging assay was used in the pivotal trials for psoriasis (C0743T08 and C0743T09). However, at the time BLA 125261 was approved, 48% and 90% of subjects in C0743T08 and C0743T09 (Psoriasis trials), respectively, had inconclusive ADA status due to drug interference. There was, therefore, a post-marketing commitment (PMC) to develop an ADA assay with improved drug tolerance. The method description and validation

parameters of the EIA method were described in the original validation report Mod5.3.1.4/CP2002V-080. This original validation report was reviewed by Laurie Graham, dated July 15, 2008 (Refer to BLA 125261). Seven addenda to the original validation report were finalized. This method was used in the Phase 2 clinical studies for Crohn’s disease (C0397T07 and C0743T26), but has since been replaced and is no longer in use.

FDA Reviewer Comment: Since the data from the above two Phase 2 clinical studies were not included in the assessment of immunogenicity incidence, this validation report and its addenda were not reviewed.

2. ECLIA

In order to improve drug tolerance, the sponsor developed a new electrochemiluminescence based immunoassay (ECLIA ^{(b) (4)}), to screen, titer and confirm ADA to ustekinumab in human serum. With the new assay, the sponsor estimated that 96% in each trial had post-treatment samples that were evaluable for ADA status (i.e., only 4% inconclusives). The method description and validation parameters were described in the validation report Mod5.3.1.4/CP2011V-035. This original validation report was reviewed by Laurie Graham, dated July 31, 2013 (Refer to review memo for BLA 125261/103). There are 6 addenda to the original validation report listed as below. The ECLIA method was used in the pivotal studies (CRD3002, CRD3002, and CDR 3003) and PK comparability study (NAP1002) for Crohn’s disease.

Addendum	Content	Reviewer Comment
CP2011V-035-A1	A correction to the stability section of the report	Refer to review memo for BLA 125261/103.
CP2011V-035-A2	A detailed description of the calculations used to determine the acceptance criteria (AC) for consistency controls and critical ^{(b) (4)} qualification	Refer to review memo for BLA 125261/103.
CP2011V-035-A3	Typographical errors were corrected and clarifications to report text	Refer to review memo for BLA 125261/103.
CP2011V-035-A4	Long term stability updated	Refer to review memo for BLA 125261/103.
CP2011V-035-A5	The partial validation for the transfer of the MSD ECLIA method from th ^{(b) (4)} to the ^{(b) (4)} laboratories	The sponsor evaluated the consistency controls and specificity controls at th ^{(b) (4)} location. In the original addendum, the sponsor only provided the normalized ECL values for all control samples, which are not sufficient for evaluation of the success of the method transfer. In response to an IR dated 12 August 2016, the sponsor provided the inter-replicate CVs for the control samples, which are all under ^{(b) (4)} and meet the study phase control acceptance criteria.

		This updated partial validation results show acceptable performance of the ECLIA method after th (b) (4) laboratory relocation from (b) (4) to (b) (4)
CP2011V-035-A6	Long-term stability update	It reported the results of stability assessment timepoints conducted on low positive ADA (b) (4). The provided data were reviewed and they support the stability assessment for the method to detect ADA in human serum samples.

3. CLBA

A Competitive Ligand Binding Assay (CLBA) was developed and validated to detect neutralizing antibodies (NAb) to ustekinumab in human serum. The method description and validation parameters were described in the original validation report Mod5.3.1.4/CP2010V-050. This original validation report was reviewed by Laurie Graham, dated April 1, 2013 (Refer to BLA 125261/86 (b) (4)). There are 2 addenda to the original validation report listed as below.

Addendum	Content	Review Comment
CP2010V-050-A1	A partial validation of the method for detection of neutralizing antibodies to ustekinumab in primary biliary cirrhosis (PBC) patient serum	The sponsor provided a table to summarise the NAb responses of drug naïve normal and PBC human serum samples tested in the ustekinumab NAb assay and compared their cut point. The results show no difference in cut point among serum samples from normal and PBC population during validation. Thus, it is acceptable to apply the previously validated cut point for the NAb detection in human PBC serum samples. This is not relevant to the proposed indication in the current BLA.
CP2010V-050-A2	The partial validation for the transfer of the CLBA NAb method from the (b) (4) facilities to the (b) (4) laboratories	The sponsor evaluated the performance of assay controls at the (b) (4) location. The results show that all control samples performed with sufficient precision and generated results within their respective acceptance criteria as established during the method validation (CP2010V-050). Thus, the CLBA-based ustekinumab NAb assay performed in a manner consistent with the original validation after the method was transferred from the (b) (4) (b) (4) (b) (4) t (b) (4)



Maria
Gutierrez Lugo

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