CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761067Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: BLA Approval

BLA/NDA Number: 761067
Review Number: 01
Review Date: 11/10/2017

Drug Name/Dosage Form	Ilumya (tildrakizumab) / 100 mg at week 0, 4, and every 12 weeks thereafter; (b) (4)
Strength/Potency	100 mg/mL
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Applicant/Sponsor	Merck Sharp and Dohme
US agent, if applicable	n/a

Product Overview

Ilumya (tildrakizumab) is a humanized IgG1K antibody that specifically binds to the p19 subunit of interleukin-23 (IL-23) inhibiting its interaction with the IL-23 receptor. Tildrakizumab is produced in a recombinant CHO cell line and has an approximate molecular mass of 147 kilodaltons. Ilumya is a sterile, clear to slightly opalescent, colorless to slightly yellow solution. Ilumya is supplied in a single-dose prefilled syringe with a glass barrel and 29-gauge fixed, 1/2-inch needle fitted with a passive needle guard and a needle cover. Each Illumya prefilled syringe contains 100 mg of tildrakizumab formulated in: L-histidine (0.495 mg), L-histidine hydrochloride monohydrate (1.42 mg), polysorbate 80 (0.5 mg), sucrose (70.0 mg), and Water for Injection, USP. The Ilumya solution has a pH of 5.7-6.3.

Discipline	Reviewer	Branch/Division
Drug Substance	Arulvathani Arudchandran	OBP/DBRRII
Drug Product	Anjali Shukla	OBP/DBRRII
Immunogenicity	Anjali Shukla	OBP/DBRRII
Labeling	Vicky Hemphill-Borders	OBP
Facility	Thuy Thanh Nguyen	OPF/DIA
Microbiology – DS	Reyes Candau-Chacon	OPF/DMA
Microbiology – DP	Monica Commerford	OPF/DMA
QAL Microbiology - DP	Dupeh Palmer	OPF/DMA
Application Team Lead	William Hallett	OBP/DBRRII

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Dawn Williams	DDDP
Cross-disciplinary Team Lead	Giordana Diglisic	DDDP
Medical Officer	Melinda McCord, Kevin Clark	DDDP
Pharm/Tox	Jianyong Wang, Barbara A Hill	DDDP
Clinical Pharmacology	Jie Wang, Yow-Ming Wang	OCP/DCPIII
Statistics	Matthew Guerra, Mohamed Alosh	OB/DBIII

1. Names:
   a. Proprietary Name: Ilumya
   b. Trade Name: Ilumya
   c. Non-Proprietary/USAN: Tildrakizumab
   d. CAS name: 1326244-10-3
   e. Common name: MK-3222
   f. INN Name: Tildrakizumab
   g. Compendial Name: None
   h. OBP systematic name: MAb Humanized (IgG1) ANTI Q9NPF7 (IL23A_HUMAN)[MK3222]
   i. Other Names: SCH 900222

2. Pharmacologic category: Therapeutic recombinant human monoclonal antibody

Submissions Reviewed:

Submission(s) Reviewed	Document Date
Module 3 Quality #0000	March 23 2017
Information Request Response #0005	July 28 2017
Information Request response #0009	August 15, 2017
Information Request Response #0010	August 18 2017
Information Request response #0011	August 18 2017
Information Request response #0015	September 19 2017
Information Request response #0018	October 6, 2017
Information Request response #0019	October 6, 2017
Information Request response #0021	October 17, 2017
Information Request response #0023	October 25, 2017
Information Request response #0024	October 25, 2017
Information Request response #0027	November 3, 2017
Information Request response #0030	November 7, 2017
Information Request response #0031	November 7, 2017
Information Request response #0032	November 9, 2017
Information Request response #0035	November 20, 2017

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

   A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Letter of Cross-Reference	Comments
(b) (4)	Type III	(b) (4)		Yes	Not reviewed. Sufficient Leachables and Extractables data and primary stability program in BLA. DMF previously reviewed and no revision since last review.
	Type III			Yes	
	Type III			Yes	
	Type III			Yes	DMF was not reviewed. Sufficient information was provided in the BLA.
	Type II			Yes	

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application. None

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:
The Office of Biotechnology Products, OPQ, CDER, recommends approval of STN 761067 for Ilumya manufactured by Merck Sharp & Dohme. The data submitted in this application are adequate to support the conclusion that the manufacture of Ilumya 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 conditions specified in the package insert.

B. Approval Action Letter Language:

Manufacturing location:
- Drug Substance: (b) (4)
- Drug Product: MSD Ireland, Dublin Road, Carlow, Ireland

- Fill size and dosage form: 100 mg/ 1 mL single-dose prefilled syringe with staked needle and rigid needle shield
- Dating period:
  - Drug Product: 36 months: 2-8°C
  - Drug Substance: (b) (4)
  - Stability:
    - We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release
  - Ilumya is exempted from lot release because it is a specified product per 601.2(a)

D. Benefit/Risk Considerations:

Tildrakizumab is an inhibitor of IL-23 indicated for the treatment of psoriasis. The data submitted in this application support the conclusion that the manufacture of tildrakizumab is well controlled and yields a consistently high quality product. The conditions used in manufacturing have been sufficiently validated, and a consistent product is prepared from the multiple production runs presented. From a product quality perspective, this product is approvable for human use.

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

There are no PMCs from the CMC review team.

II. Summary of Quality Assessments:

Table 1 below is a summary of critical quality attributes and the associated control strategies for attributes that are relevant to both Drug Substance and Drug Product. For additional

information, see the technical document on primary reviews of the Drug Substance Quality and Drug Product Quality by OBP/DBRR-II and the Drug Substance Microbiology and the Drug Product Microbiology by OPF/DMA.

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other
Biological Potency by Cell Based Assay	Efficacy	Intrinsic to the molecule, impacted by oxidation, glycation, deamidation, aggregation, and fragmentation	(b) (4)	N/A
Protein Concentration	Efficacy and Safety	Manufacturing Process		N/A
Identity	Safety and Efficacy	Intrinsic to molecule		N/A
High Molecular Weight (HMW) species/Aggregates	Efficacy, Pharmacokinetics, and Safety/Immunogenicity	Manufacturing process and exposure to heat, light, and low and high pH stress		N/A
Fragmentation (%IgG monomer)	Efficacy, Pharmacokinetics, and Immunogenicity	Affected by manufacturing and storage conditions. Can form due to agitation, temperature, or light.		N/A
Fragmentation (%light chain and %heavy chain)	Efficacy, Pharmacokinetics, and Immunogenicity	Affected by manufacturing and storage conditions. Can form due to agitation, temperature, or light.		N/A
Charge Variant Profile (deamidation, C-terminal and N-terminal variants, and oxidation)	Efficacy, Pharmacokinetics, and Immunogenicity	Bioreactor conditions and degradation during manufacture and storage		N/A

B. Drug Substance Tildrakizumab Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA (type)	Risk	Origin	Control Strategy	Other

Appearance	Safety	Controlled by the manufacturing process	Controlled during manufacture and at DS release	N/A
Host Cell Proteins (process-related impurity)	Safety and Immunogenicity	(b) (4)	(b) (4)	Process Validation studies show minimal host cell protein level observed (b) (4)
Host Cell DNA (process-related impurity)	Safety	(b) (4)		N/A
(b) (4) process-related impurity	Safety and Immunogenicity	Process-related impurity (b) (4) (b) (4)		N/A
(b) (4)	Safety	(b) (4)		N/A
cDNA Sequence	Safety	Inherent to the product		N/A
Viruses (contaminant)	Safety	Contamination during manufacture, mostly likely during cell culture operations		N/A
Mycoplasma (contaminant)	Safety	Mycoplasma would most likely be introduced during cell culture operations		N/A
Leachables (Process-related impurity)	Safety	Process-related impurities potentially from manufacture and the DS container closure system (CCS)		N/A
Endotoxin	Safety and Purity	Raw materials or contamination during manufacturing		N/A
Bioburden	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials or contamination during manufacturing		N/A

- Description:
  Tildrakizumab is a recombinant humanized IgG1K monoclonal antibody that binds human IL-23p19. The amino acid sequence of the variable domain is of murine origin and that of the constant region is of human origin. Tildrakizumab consists of 4 polypeptide chains (b) (4) (b) (4) and has a molecular weight of 147 kDa. The tildrakizumab expression construct is expressed in a CHO cell line. Amino acid sequencing and tryptic peptide mapping with mass spectrometry analysis confirms the

correct amino acid sequence. Tildrakizumab drug substance has the same formulation as the drug product and is stored (b) (4)

- Mechanism of Action (MoA):
  Tildrakizumab binds specifically to IL-23p19 and blocks interaction with IL-23R. IL-23 is a naturally occurring cytokine known to be involved with multiple inflammatory pathways. Engagement of IL-23R by IL-23 leads to JAK2-mediated phosphorylation of tyrosine residues. This initiates downstream signaling cascade where STAT3 is recruited and homodimered. A signal from the phosphorylated homodimer STAT3 complex is sent to the nucleus to induce a transcription of the inflammatory cytokines, IL-17. IL-17 activates inflammatory pathways associated with psoriasis. Tildrakizumab binds to the p19 subunit of IL-23 and binds to IL-23 molecules and prevents its interaction with the IL-23R, blocking the downstream signaling cascade.

- Potency Assay:
  The potency assays is a cell-based assay that measures neutralization of soluble IL-23. In the assay, tildrakizumab binds to IL-23 via its p19 subunit preventing IL-23 binding to the IL-23R, resulting in inhibition of IL-23-induced STAT3 phosphorylation. Cells are lysed and p-STAT3 is measured by ELISA. The loss of signal from the ELISA from the neutralization activity of tildrakizumab is dose-dependent and is reported as a relative percentage of the activity of the reference standard.

- Reference Materials:
  A well characterized primary reference standard was derived from a clinical batch. Merck has a two-tiered reference standard system with appropriate protocols in place that will ensure sufficient inventory of working reference standard for routine release and stability testing while minimizing drift by linking working reference standard activity to a single primary reference standard.

- Critical starting materials or intermediates:
  The Master Cell Bank (MCB) was prepared from a CHO (b) (4) cell line and adapted to serum free media. The Working Cell Bank (WCB) was prepared by expansion and aliquoting of the MCB, and an adequate protocol is in place to manage the release of additional WCBs. Raw materials used in commercial manufacture are of non-animal origin.

- Manufacturing process summary:

(b) (4)

(b) (4)

- Container closure:
  Tildrakizumab is stored in (b) (4) bags (b) (4) (b) (4) (b) (4)

- Dating period and storage conditions:
  The sponsor conducted real-time, accelerated, and stressed stability studies on 3 intended-for-commercial lots, and 5 clinical lots to support a proposed dating period of (b) (4)

C. Drug Product Ilumya 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 general drug product attributes.

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

CQA (type)	Risk	Origin	Control Strategy
Sterility (contaminant)	Safety, Purity, and Efficacy (via degradation or modification of the product by contaminating microorganisms)	Contaminants could be introduced during the manufacturing process or through container closure integrity test failure	Control of bioburden (b) (4) (b) (4). Adequate validation data supporting sterility assurance of the finished drug product. Sterility testing of the DP is performed at release and container closure integrity test is included in stability program.
Endotoxin	Safety (pyrogenic fever, increased immunogenicity risk) and Purity	Contaminants could be introduced throughout drug product manufacturing or due to container closure integrity failure	The control strategies described for sterility assurance also limit the introduction of endotoxin. The DP release endotoxin specification is (b) (4) EU/mg.
Container Closure Integrity	Safety	May be impacted by storage conditions	Container closure integrity testing is included in the DP stability specification. Container closure integrity testing is performed using a validated test.
Color and Degree of Opalescence	Safety and Efficacy	Formulation, Contamination, or Degradation	Controlled through the manufacturing/formulation process, and tested for drug product lot release and stability testing
Polysorbate 80 Concentration	Safety	Manufacturing process	Controlled through the formulation process, and tested for drug product release and stability
Osmolality	Safety, Efficacy (control of	Formulation	Controlled at drug product lot release and stability

	degradation through formulation)		
pH	Safety and Efficacy	Formulation	Controlled at drug substance and drug product lot release and stability
Particulate Matter	Safety / Immunogenicity	Manufacturing process and container closure system	Controlled through the manufacturing process and preparation of the container closure system. Controlled by drug product release and stability testing.
Extractable Volume	Efficacy / Dosing	Manufacturing process	Controlled through (b) (4)
Syringe Functionality (Break-Loose Force and Glide Force)	Efficacy / Dosing	Manufacturing process	Controlled through manufacturing process, and tested for DP lot release and stability
Leachables (process-related impurities)	Safety	Manufacturing equipment and CCS	Extractables study conducted on drug product container closure system

- Potency and Strength:
  Tildrakizumab is supplied at 100 mg / 1 mL syringe. Potency of tildrakizumab is determined as a percent IL-23 neutralization activity to the current reference standard. The potency assay is the same as described in the drug substance section of this review.

- Summary of Product Design:
  Tildrakizumab is supplied as a sterile, single-dose, preservative-free solution for subcutaneous injection in a pre-filled syringe that is assembled with a safety device. The drug product formulation consists of (b) (4) histidine, 7% (w/v) sucrose, and 0.05% (w/v) polysorbate 80 at pH 6.0. The extractable volume is 1.0 mL.

- List of Excipients:
  Excipients include (b) (4) histidine, 7% (w/v) sucrose, and 0.05% (w/v) polysorbate 80.

- Reference Materials:
  The same reference material is used for drug substance and drug product.

- Manufacturing process summary:

(b) (4)

(b) (4)

- Container closure:
  The primary container closure system for tildrakizumab drug product consists of a 1 mL syringe barrel with a staked needle, rigid needle shield and plunger stopper. The safety device components include a needle guard, plunger rod, and finger flange (b) (4) (b) (4). Appropriate compatibility studies were performed for the container closure system.

- Dating period and storage conditions:
  The dating period for tildrakizumab drug product is 36 months at 2-8°C, protected from light.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:

Store in a refrigerator at 2°C to 8°C (36°F to 46°F).
Store in product carton until time of use.
Protect from light.
Do not freeze.

F. Establishment Information:

There are no outstanding inspection or facility issues. The Division of Inspectional Assessment recommends approval of the BLA. The manufacturing and testing facilities, their responsibilities in tildrakizumab production, and inspectional outcomes are summarized in the table below.

Overall Recommendation:			
DRUG SUBSTANCE			
Function	**Site Information**	**DUNS/FEI Number**	**Facility Status**
- Master Cell Bank (MCB) and Working Cell Bank (WCB) preparation -MCB and WCB testing	(b) (4)		No Further Evaluation
- MCB and WCB sterility testing			No Further Evaluation

- MCB and WCB cell-based mycoplasma testing	(b) (4)	No Further Evaluation
- MCB and WCB storage		No Further Evaluation
- MCB and WCB storage		No Further Evaluation
- WCB Storage - Drug substance manufacturing - Release and stability testing of drug substance (bacterial endotoxins)		PLI 10/31 – 11/7/2017 Acceptable.
- Release and stability testing of drug substance (residual host cell DNA, bioburden) - Unprocessed bulk testing (microbial contamination and mycoplasma).		No Further Evaluation
- Release and stability testing of drug substance (biological potency by cell-based functional assay)		Acceptable
- Release and stability testing of drug substance		Acceptable
- Drug substance storage		No Further Evaluation
- Unprocessed bulk testing: adventitious viruses (in vitro)		No Further Evaluation
- Unprocessed bulk testing: MVM		No Further Evaluation

DRUG PRODUCT			
Function	Site Information	DUNS/FEI Number	Facility Status
Manufacturing of Drug Product	MSD Ireland (Carlow) Dublin Road	3008694906 SVS	PLI conducted 8/16-22/2017

	Carlow, Ireland		Acceptable
- Assembly of combination product - Secondary packaging and labeling - Combination product release testing	(b) (4)		Acceptable
- Bulk DP syringe storage			No Further Evaluation

G. Facilities:

Tildrakizumab drug substance is manufactured at (b) (4) Cell banking operations occur at (b) (4) (b) (4), (b) (4)

A Pre-License Inspection was performed at (b) (4). A six item Form FDA 483 was issued. The firm is acceptable. In addition, a Pre-License Inspection was performed at MSD Ireland (Carlow) (b) (4). A one item FDA Form 483 was issued. The firm is acceptable. The DS manufacturing and testing sites were inspected multiple times within the recent past, demonstrating acceptable compliance.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:
- annual stability protocol
- qualification of new working reference standard
- concurrent validation of column resin lifetime

ii. Outstanding review issues/residual risk:
-n/a

iii. Future inspection points to consider:
- Follow up on 483 observations
- Evaluate trending of release and in-process tests results

b. Drug Product

i. Protocols approved:
- annual stability protocol

ii. Outstanding review issues/residual risk:
See Post-Marketing Commitments in Section IB

iii. Future inspection points to consider:
- Follow up on 483 observation

- Evaluate trending of release and in-process tests results

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 source			X	
9.	Transgenic Plant source			X	
10.	New Molecular Entity		X		
11.	PEPFAR drug			X	
12.	PET drug			X	
13.	Sterile Drug Product		X		
14.	Other: [fill in information]			X	
	Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]			X	
16.	Comparability Protocol(s)			X	
17.	End of Phase II/Pre-NDA Agreements tem			X	
18.	SPOTS (special products on-line tracking system)			X	
19.	USAN assigned name			X	
20.	Other [fill in]				
	Quality Considerations				
21.	Drug Substance Overage			X	
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
26.	Other QbD Elements		X		Design of experiments used in manufacturing process development
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 {fill-in}			X	