

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761105Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)**

**Epidemiology: ARIA Sufficiency Memo
Version: 2018-01-24**

Date: April 19, 2019

Reviewer: Michelle R. Iannacone, PhD, MPH
Division of Epidemiology I

Team Leader: Patricia Bright, PhD, MSPH
Division of Epidemiology I

Division Deputy Director: Sukhminder K. Sandhu, PhD, MPH, MS
Division of Epidemiology I

Subject: Active Risk Identification and Assessment (ARIA) Sufficiency Memo:
Theoretical malignancy risk associated with risankizumab treatment
in psoriasis patients

Drug Name: Risankizumab

Application Type/Number: BLA 761105 / IND (b) (4)

Applicant/sponsor: AbbVie

OSE RCM #: 2019-679



EXECUTIVE SUMMARY (place "X" in appropriate boxes)

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	<u>Short-term</u> <u>Long-term</u> Lymphoma All Malignancies
-Yes	X
-No	X
If "No", please identify the area(s) of concern.	For long-term malignancy:
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Psoriasis is a chronic debilitating immunologic disease characterized by marked inflammation and thickening of the epidermis that result in thick, scaly plaques involving the skin. Psoriasis may undergo intermittent improvements and relapses in susceptible individuals over the course of their lifetime. Although traditional systemic therapies for psoriasis are effective, there may be a loss of efficacy during long-term use or patients may experience adverse events related to specific treatments.^a

The prevalence of psoriasis in the United States is approximately 2-4%, of which an estimated 20% have moderate-to-severe disease. Psoriasis can first appear at any age, but more commonly appears in adulthood. Two peaks in age of onset have been reported: one at 20-30 years of age and a second peak at 50-60 years of age.^b

Skyrizi (risankizumab) injection, for subcutaneous use, is indicated for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Risankizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that is specifically directed against IL-23 p19. The framework of the risankizumab antibody has been engineered with two mutations in the Fc region to reduce Fcγ receptor and complement binding. Binding of risankizumab to IL-23 p19 inhibits the action of IL-23 to induce and sustain T helper (Th) 17 type cells, innate lymphoid cells, γδT cells, and natural killer (NK) cells responsible for tissue inflammation, destruction, and aberrant tissue repair.^c

The recommended dose of risankizumab is 150mg (two 75mg injections) administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter. (b) (4)

d

1.2. Describe the Safety Concern

Similar to other psoriasis biologics (Table 1), risankisumab poses a theoretical increased risk for malignancies based on its immunosuppressive mechanism of action.

^a Vide J, Magina S. Moderate to severe psoriasis treatment challenges through the era of biological drugs. An Bras Dermatol. 2017; 92(5):668-674.

^b BLA 761105 Multi-disciplinary Review and Evaluation, Skyrizi (risankizumab). Version date: February 1, 2019.

^c Sponsor Original Submission, GlobalSubmit Review: Upload dated April 23, 2018, Risankizumab, Clinical Overview.

^d Risankizumab Provider Information Label. DARRTS ID: Pending.

Table 1. Psoriasis biologics currently marketed in the United States

Drug	Class	Approved for plaque psoriasis?	Postmarketing requirement for malignancy?	Approval date for plaque psoriasis
Stelara (ustekinumab)	Interleukin-12 and -23 antagonists	Yes	Yes	September 25, 2009
Cosentyx (secukinumab)	Interleukin-17A antagonist	Yes	Yes	January 21, 2015
Taltz (ixekizumab)	Interleukin-17A antagonist	Yes	Yes	March 22, 2016
Siliq (brodalumab)	Interleukin-17 receptor A (IL-17RA) antagonist	Yes	Yes	February 15, 2017
Tremfya (guselkumab)	Interleukin-23 blocker	Yes	Yes	July 13, 2017
Ilumya (tildrakizumab)	Interleukin-23 blocker	Yes	Yes	March 20, 2018

For the overall risankizumab drug development program, a total of 21 malignancies (excluding non-melanoma skin cancer) were reported in the risankizumab exposed group, which corresponds to a rate of 0.62 events/100 person-years. Of these, malignancies reported for more than one subject included breast cancer reported in seven subjects, prostate cancer in three subjects, and malignant melanoma in two subjects. This observation is consistent with the most common cancers seen in the United States (breast cancer is the most common, followed by lung and prostate cancers, and the incidence of melanoma of the skin has been rising).^b

For the active comparator groups, one case of malignancy for gallbladder cancer was reported for adalimumab and one case of malignancy was reported for prostate cancer for ustekinumab. Further, the rates of malignant tumors (excluding non-melanoma skin cancer) ranged from 0.31 – 0.49 events/100 person-years in the clinical development programs for ustekinumab, ixekizumab, secukinumab, and guselkumab. Although the event rate for malignancy is slightly higher in risankizumab users compared to the malignancy rates observed in the development programs for other biologics, there was only one death from malignancy in the risankizumab development program.^b

In the risankizumab development program, 25 non-melanoma skin cancer malignancies were reported; 10 events of Bowen's disease/squamous cell carcinoma (SCC) combined and 15 events of basal cell carcinoma (BCC). The observed ratio of SCC to BCC was 1:1.5. While this ratio is narrower than that seen in the immunocompetent general population, it is not inverted due to an increase in SCC as is observed in immunosuppressive populations (e.g., organ transplant recipients). This suggests that risankizumab has less of an immunosuppressive affect than observed in organ transplant patients.^b

The BLA Unireview concluded that the limited duration of observation during the clinical development program did not allow for detection of rare events with a long latency period such as that required by malignancy events.^b Therefore, postmarketing data are needed to evaluate the long-term risk of malignancy in patients with psoriasis receiving risankizumab.

The clinical evaluation of risankizumab had some notable parallels to the clinical evaluation of

both guselkumab^e and tildrakizumab^f, including the following:

“DDDP Clinical does not consider these clinical data to be a safety signal. The type of risk is considered to be a theoretical risk, where biological plausibility exists, yet clinical data are limited and not sufficient to support this suspicion of risk. DDDP described the safety concern as a variable-onset, where certain cancers may occur short-term, but there may also be a long-latency effect after initial exposure. The level of concern is moderate, taking into account that malignancy is a very serious adverse event, but the concern is largely theoretical. DDDP was also specifically interested in assessing the risk of lymphomas, which may have a shorter latency compared to other malignancies. DDDP hypothesized that the risk of lymphoma could be related to exposure with risankizumab.”

No carcinogenicity and mutagenicity studies have been conducted with risankizumab.

The patient information label does not include any warnings or precautions related to the potential malignancy risk. Further, the review team decided that a Risk Evaluation and Mitigation Strategy (REMS) is not needed.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

1.4. Statement of Purpose

This memo reflects the discussions, recommendations, and determinations between the Division of Epidemiology I (DEPI-I), the Division of Dermatology and Dental Products (DDDP), and CDER’s Sentinel Team. To better assess malignancy risk, the team considered whether ARIA was sufficient or whether to issue a PMR for an observational study to collect additional data on long-term safety and evaluate the occurrence of long-latency safety outcomes.

The purpose of this memo is to describe the determination of whether ARIA could be used to assess malignancy risk and lymphoma risk when clinical data could not confirm a safety signal, but theoretical concerns indicate the potential for a serious risk. The regulatory goal of ARIA is signal detection (i.e. postmarketing surveillance). The anticipated regulatory impact is to further characterize malignancy risk to inform labeling decisions. Because the events of interest are rare, typically have long-term latency periods (except for lymphoma), and because multiple products are available for treatment of the underlying disease (plaque psoriasis), the sufficiency determination primarily rests upon the need for a large sample size, the availability of long-term follow-up (except for lymphoma), the availability of relevant covariates, and on the ensuing market uptake of risankizumab.

1.5. Effect Size of Interest or Estimated Sample Size Desired

The postmarket uptake of risankizumab will in part influence the ARIA approach for the malignancy (including lymphoma) assessment. With the availability of comparators, the ARIA

^e Leishear White, Kira, Division of Epidemiology I, ARIA Sufficiency Memo for Guselkumab, BLA 761061, dated April 13, 2017, DARRTS Reference ID: 4084180.

^f Bright, Patricia, Division of Epidemiology I, ARIA Sufficiency Memo for Tildrakizumab, BLA 761067, dated March 16, 2018, DARRTS Reference ID: 4236035.

assessment could support an inferential analysis by determining the incidence rate between risankizumab exposure and malignancy as compared to the incidence rates following exposure to other individual psoriasis biologic medications (Table 1). ARIA could also evaluate a class-based effect by comparing the incidence rate of malignancy following exposure to any psoriasis biologic medications as compared to the incidence rate of malignancy following exposure to non-biologic systemic medications for the indication of psoriasis. Assessing a class-based effect would likely yield a higher number of users with events and might increase the capacity to detect a difference in effect size.

Sample size requirements and the corresponding effect estimates will be described in an ARIA Planning Concept Brief for any outcomes deemed sufficient to address through ARIA.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

Risankizumab is indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. All patients identified as having received a dispensing of risankizumab in Sentinel could be considered in the population for postmarket surveillance. A comparator population may include patients that have received a dispensing of other psoriasis biologics as listed in Table 1. To evaluate a class-effect, a comparator population of patients receiving non-biologic systemic medications for psoriasis treatment may be used.

2.2 Is ARIA sufficient to assess the intended population?

ARIA can be used to identify patients with a risankizumab dispensing in the claims data. If the underlying indication of psoriasis is needed to further target this population, the population can be screened for the ICD-10 code of L40.XX (psoriasis).

Few studies have been published that aimed to validate ICD-10 diagnostic codes for estimating the prevalence of psoriasis. A Swedish, population-based, validation study demonstrated the positive predictive values (PPV) of ICD-10 codes to range from 81% - 100% with a post-validation prevalence of 1.23% (95% CI: 1.21 – 1.25) for psoriasis. To date, no studies have validated the ICD-10 codes for estimating the prevalence of psoriasis in a U.S. population. However, several studies in the United States have aimed to validate ICD-9 diagnostic codes for psoriasis. These studies reported PPVs that aligned with the findings from the Swedish study.^{g,h} Taken together, findings from these studies suggest that performance of the ICD-10 codes (L40.XX) to identify psoriasis patients for surveillance purposes in the United States would be adequate.

ARIA is sufficient to identify the indicated population for this analysis and is not a limiting factor of concern. However, with several treatment options available to patients (Table 1), market uptake of risankizumab will affect whether enough users are available to further characterize lymphoma risk given the rarity of these outcomes. The extent of market uptake can only be evaluated post-approval.

^g Asgari MM, Wu JJ, Gelfand JM, et al. Validity of diagnostic codes and prevalence of psoriasis and psoriatic arthritis in a managed care population, 1996 – 2009. *Pharmacoepidemiol Drg Saf.* 2013; 22(8): 842 – 849.

^h Icen M, Crowson CS, McEvoy MT, Gabriel SE, Maradit Kremers H. Potential misclassification of patients with psoriasis in electronic databases. *J Am Acad Dermatol.* 2008; 59: 981 – 985.

3 EXPOSURES

3.1 Treatment Exposure

Patients with pharmacy benefits who receive at least one dispensing of risankizumab can be identified in health care claims data.

3.2 Comparator Exposure

As mentioned previously, the regulatory goal of this ARIA assessment is signal detection. However, to help interpret the observed incidence rates of lymphoma among psoriasis patients treated with risankizumab, two comparator populations may be used: 1) patients using other psoriasis biologic medications (Table 1) and 2) patients using non-biologic systemic medications (to establish a class-effect). Both of these comparator populations could be identified through the Sentinel health care claims data.

3.3 Is ARIA sufficient to identify the exposure of interest?

ARIA is sufficient to identify dispensings of both risankizumab and comparator biologics and non-biologic medications, and therefore is not a limiting factor.

4 OUTCOMES

4.1 Outcomes of Interest

The outcomes of interest are: 1) lymphoma and 2) all malignancies.

A Workgroupⁱ supporting Mini-Sentinel development reviewed the literature to identify algorithms that could be used in electronic claims-based data to identify cohorts of vulnerable groups, including persons with selected cancers of interest.

The Workgroup cautioned that:

“Cancers are not typically studied as a homogenous group, given differences in the histological type and primary site of lesion – each that often has its distinct risk factors, screening requirements, pathology, clinical manifestations, diagnostic testing, differential diagnoses, staging, treatment and prognosis, as examples. Therefore, studies examining algorithms for identifying person with any-type of cancer are scant.”ⁱ

Therefore, in the absence of cancer registry data, the Workgroup recommended against studying cohorts with an outcome of any cancer, but rather focusing on subcohorts with specific cancers. The Workgroup recommended that primary consideration should be given to the identification of person with hematopoietic cancers such as leukemias, lymphomas, and myelomas.

As part of the Workgroup’s deliverable, the Workgroup specified an algorithm for lymphoma that involved: two or more diagnoses of cancer (ICD-9 codes) within two months (algorithm 2); this algorithm performed with a PPV of 63% and a sensitivity of 80%.

4.2 Is ARIA sufficient to assess the outcome of interest?

Given the findings and recommendations from the Workgroup (as described above), ARIA was

ⁱ Leonard C, Freeman C, Razzaghi H, et al. Mini-Sentinel methods: 15 cohorts of interest for surveillance preparedness. https://www.sentinelinitiative.org/sites/default/files/Methods/Mini-Sentinel_Methods_15-Cohorts-of-Interest-for-Surveillance-Preparedness_0.pdf. Accessed March 29, 2019.

deemed sufficient to identify lymphoma as an outcome for studying safety in the postmarket setting among risankizumab users. However, grouping all malignancies together offers less scientific rigor, thus deeming ARIA insufficient.

The Tremfya (guselkumab) ARIA Sufficiency Memo provided the following additional information on validation:

“Validation of malignancy outcomes has not been assessed in Sentinel. However, there have been published validation studies using health care claims data for malignancy. In Medicare, a 63% positive predictive value was achieved using a complex algorithm.^j Different claims-based definitions used for specific types of incident cancers all had very high specificity (~99%); however, the sensitivity varied between 40 and 90% by type of cancer. Positive predictive value (PPV) also varied by type of cancer. Hence, depending on the type of cancer of interest, health care claims data may be acceptable. The various definitions used by Setoguchi et al. included 1) a combination of diagnosis and procedure codes on the same day or within the same hospitalization; 2) two diagnoses of specific cancer within two months; 3) either definition 1 or definition 2. For lymphoma, specificity was $\geq 99.7\%$ for all 3 definitions, sensitivity ranged from 55.2% to 83.3%, and PPV ranged from 56.6% to 62.8%, for the 3 definitions. A study validating ICD-9 codes using Veteran Affairs data, found non-Hodgkin’s lymphoma to have the highest PPV (91%) with 100% sensitivity.^k The PPV and sensitivity for Hodgkin’s lymphoma were not stated in the article. A Mini- Sentinel methods paper states that there are multiple types of lymphoma and multiple classifications for categorizing the types of lymphoma.^l These can be based on etiology (T-cell and B-cell lymphomas) or separated based on expected outcomes (e.g., curability). Validation studies for the many specific types of lymphoma are not available for claims data, and therefore, it is unknown whether there are certain types of lymphoma which may have poor validation.”^m

“In summary, the Medicare validation study of lymphoma in general performed reasonably well (i.e., PPV: 57-63%). The VA study showed high PPV (i.e., 91%) for non-Hodgkin’s lymphoma. These PPV values are considered to be acceptable for the purpose of surveillance.”

In addition to the limitation of validating overall malignancy outcomes of any type (i.e. variable PPV), there is insufficient long-term follow-up data. As described in the Figure below, roughly 3.1%, 6.6%, and 9.5% of the Sentinel patient population in age groups 18-30, 31-64, and 65+ years, respectively, would have at least 8 years of follow-up, as is required for the PMR observational study issued for risankizumab (see Section 7).

^j Setoguchi S, Solomon D, Glynn R, Cook E, Levin R, Schneeweiss S. Agreement of diagnosis and its date for hematologic malignancies and solid tumors between Medicare claims and cancer registry data. *Cancer Causes Control*. 2007;18 95 0:561-569.

^k Park LS, Tate JP, Rodriguez-Barradas MC, et al. Cancer incidence in HIV-infected versus uninfected veterans: Comparison of cancer registry and ICD-9 code diagnoses. *JAIDS Clin Res*. 2014, 5:7.

^l Schumock GT, Lee TA, Pickard AS, et al. Mini-Sentinel Methods: Alternative methods for health outcomes of interest validation. August 31, 2014.

^m Leishear White, Kira, Division of Epidemiology I, ARIA Sufficiency Memo for Guselkumab, BLA 761061, dated April 13, 2017, DARRTS Reference ID: 4084180.

Age Group (Years)	Percentage of Patients by Years of Follow-Up Time						
	<3	3+	4+	5+	6+	7+	8+
18-30	75.0%	25.0%	16.7%	11.2%	7.4%	4.9%	3.1%
31-64	66.1%	33.9%	24.6%	18.1%	13.2%	9.7%	6.6%
65+	56.9%	43.1%	32.8%	24.8%	18.6%	13.7%	9.5%

Figure 1. Proportion of Patients with Follow-up Time for Patients Diagnosed with Psoriasis in the Sentinel Distributed Databaseⁿ

Figure 1 includes data from 16 individual data partners. The start and end dates for data collection from these partners range from as early as January 1, 2000 through March 31, 2017.

Taken together, these limitations deem ARIA insufficient to assess malignancy of any type as the outcome of interest.

5 COVARIATES

5.1 Covariates of Interest

The covariates of interest include demographic (e.g., age, sex, calendar year, and geographic region), lifestyle (e.g., smoking status, alcohol use), medical history (e.g., family history of malignancy), and clinical (e.g., comorbidities and concomitant medications) characteristics.

5.2 Is ARIA sufficient to assess the covariates of interest?

Demographic and certain clinical characteristics could be assessed in ARIA. Additional characteristics such as smoking or personal or family history of cancer may not be obtained reliably. Duration and severity of psoriasis also may not be available in claims data. However, covariate information would be important for subsequent study analyses that assess risk factors for malignancy outcomes and for assessing bias when comparing incidence rates between risankizumab users and other biologic users (Table 1). Therefore, covariate information is not critical for the regulatory purpose of signal detection.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

As mentioned previously, the regulatory goal of ARIA is signal detection (i.e. postmarketing surveillance). As such, the study design involves identifying the incidence of lymphoma in patients exposed to risankizumab (the study would not address the incidence of all malignancies due to challenges to ARIA sufficiency described above). However, with the availability of comparators, it was also determined that the study design could support an inferential analysis that would compare the incidence rates of lymphoma between risankizumab users versus cohorts exposed to other psoriasis biologics (Table 1).

With a PPV of approximately 63%, nondifferential misclassification could undermine the ability of the inferential analysis to detect meaningful differences in lymphoma incidence rates between risankizumab users and other biologic users. Table 2 provides information that can be used to better understand the impact.

ⁿ Source: Michael D. Nguyen, MD. FDA Sentinel Program Lead. Modular Program Report (cder_mpl1p_wp006_nsdp_v01)



Table 2. Observed Relative Risk (RR) in the case of Non-Differential Misclassification

		PPV in the Comparator Group													
		0.40	0.45	0.50	0.55	0.60	0.65	0.70	0.75	0.80	0.85	0.90	0.95	1.00	
True RR	1.0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
	1.5	1.20	1.22	1.25	1.27	1.30	1.32	1.35	1.37	1.40	1.42	1.45	1.47	1.50	
	2.0	1.40	1.45	1.50	1.55	1.60	1.65	1.70	1.75	1.80	1.85	1.90	1.95	2.00	
	2.5	1.60	1.67	1.75	1.82	1.90	1.97	2.05	2.12	2.20	2.27	2.35	2.42	2.50	
	3.0	1.80	1.90	2.00	2.10	2.20	2.30	2.40	2.50	2.60	2.70	2.80	2.90	3.00	
	3.5	2.00	2.12	2.25	2.37	2.50	2.62	2.75	2.87	3.00	3.12	3.25	3.37	3.50	
	4.0	2.20	2.35	2.50	2.65	2.80	2.95	3.10	3.25	3.40	3.55	3.70	3.85	4.00	
	4.5	2.40	2.57	2.75	2.92	3.10	3.27	3.45	3.62	3.80	3.97	4.15	4.32	4.50	
	5.0	2.60	2.80	3.00	3.20	3.40	3.60	3.80	4.00	4.20	4.40	4.60	4.80	5.00	
	5.5	2.80	3.02	3.25	3.47	3.70	3.92	4.15	4.37	4.60	4.82	5.05	5.27	5.50	
	6.0	3.00	3.25	3.50	3.75	4.00	4.25	4.50	4.75	5.00	5.25	5.50	5.75	6.00	
	6.5	3.20	3.47	3.75	4.02	4.30	4.57	4.85	5.12	5.40	5.67	5.95	6.22	6.50	
	7.0	3.40	3.70	4.00	4.30	4.60	4.90	5.20	5.50	5.80	6.10	6.40	6.70	7.00	
	7.5	3.60	3.92	4.25	4.57	4.90	5.22	5.55	5.87	6.20	6.52	6.85	7.17	7.50	
	8.0	3.80	4.15	4.50	4.85	5.20	5.55	5.90	6.25	6.60	6.95	7.30	7.65	8.00	
8.5	4.00	4.37	4.75	5.12	5.50	5.87	6.25	6.62	7.00	7.37	7.75	8.12	8.50		
9.0	4.20	4.60	5.00	5.40	5.80	6.20	6.60	7.00	7.40	7.80	8.20	8.60	9.00		
9.5	4.39	4.82	5.25	5.67	6.10	6.52	6.95	7.37	7.80	8.22	8.65	9.07	9.50		
10.0	4.59	5.05	5.50	5.95	6.40	6.85	7.30	7.75	8.20	8.65	9.10	9.55	10.00		
Underlying Outcome Rate: 1/1000 person-years (produces worst case scenario estimate of bias)															

Underlying Outcome Rate: 1/1000 person-years (produces worst case scenario estimate of bias)

As described in Table 2, even with a true, modest relative risk of 1.5, a PPV as low as 60% would underestimate the relative risk of lymphoma after risankizumab exposure by approximately 20%. This would result in an observed relative risk of 1.3, demonstrating that the impact of the low PPV would still allow a detectable increase in risk of lymphoma in risankizumab users compared to users of other biologics if a risk was in fact present.

The analytic tools to conduct a surveillance study, an even an inferential assessment in this context, are available through ARIA.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

The analytic tools in ARIA are not a major limiting factor to feasibility. ARIA offers the tools needed to both describe the incidence of lymphoma and to conduct an inferential assessment comparing incidence rates to other psoriasis biologic medications and non-biologic systemic medications.

7 NEXT STEPS

ARIA was deemed sufficient to identify the risk of lymphoma with risankizumab treatment in psoriasis patients. The next step for assessing the lymphoma risk following risankizumab exposure is to fill out the ARIA Planning Concept Brief that prompts Sentinel's routine monitoring of market uptake for risankizumab. If market uptake reaches a level sufficient to trigger the analysis, FDA investigators can fill in the Analytic Concept Brief and launch the assessment.

ARIA was deemed insufficient for studying the outcome of 'all malignancies' among risankizumab users on account of the short length of follow-up in Sentinel and variable validation characteristics and sensitivity by malignancy. As such, the FDA is issuing a postmarket requirement to the Sponsor to evaluate malignancy risk following risankizumab exposure. This would be consistent with postmarketing requirements for the other approved products in this drug class.



FDA is proposing the use of the guselkumab and tildrakizumab PMR language as a model for the risankizumab PMR. The proposed language is as follows:

“Conduct an observational study to assess the long-term safety of risankizumab compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in the course of actual clinical care. The study’s primary outcome is long-term malignancy. Secondary outcomes include, but are not limited to, serious infections, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal and hematologic adverse events.

Describe and justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to risankizumab-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate(s), with a prespecified statistical analysis method. Specify concise case definitions and validation algorithms for both primary and secondary outcomes. For the risankizumab-exposed and comparator(s) cohorts, clearly define the study drug initiation period and any exclusion and inclusion criteria. Enroll patients over an initial 4-year period and follow for a minimum of 8 years from the time of enrollment.”^b

The finalized PMR language will be issued upon approval.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MICHELLE R IANNAcone
04/19/2019 09:48:16 AM

PATRICIA L BRIGHT
04/19/2019 09:50:00 AM

SIMONE P PINHEIRO on behalf of SUKHMINDER K SANDHU
04/19/2019 10:01:45 AM
signed as proxy for Dr. Sukhminder Sandhu, who has cleared this review but is currently out of office

MICHAEL D BLUM on behalf of JUDITH W ZANDER
04/19/2019 10:57:34 AM

MICHAEL D NGUYEN
04/19/2019 11:38:28 AM

ROBERT BALL
04/19/2019 04:41:01 PM



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)**

**Epidemiology: ARIA Sufficiency Memo
Version: 2018-01-24**

Date: April 19, 2019

Reviewer: Michelle R. Iannacone, PhD, MPH
Division of Epidemiology I

Team Leader: Patricia Bright, PhD, MSPH
Division of Epidemiology I

Deputy Division Director: Sukhminder K. Sandhu, PhD, MPH, MS
Division of Epidemiology I

Subject: Active Risk Identification and Assessment (ARIA) Sufficiency Memo
for Pregnancy Safety Concerns

Drug Name: Skyrizi (risankizumab)

Application Type/#: BLA 761105

Applicant/Sponsor: Abbvie Inc.

OSE RCM #: 2019-679



Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Psoriasis is a chronic debilitating immunologic disease characterized by marked inflammation and thickening of the epidermis that result in thick, scaly plaques involving the skin. Psoriasis may undergo intermittent improvements and relapses in susceptible individuals over the course of their lifetime. Although traditional systemic therapies for psoriasis are effective, there may be a loss of efficacy during long-term use or patients may experience adverse events related to specific treatments.^a

Skyrizi (risankizumab) injection, for subcutaneous use, is indicated for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Risankizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that is specifically directed against IL-23 p19. The framework of the risankizumab antibody has been engineered with two mutations in the Fc region to reduce Fcγ receptor and complement binding. Binding of risankizumab to IL-23 p19 inhibits the action of IL-23 to induce and sustain T helper (Th) 17 type cells, innate lymphoid cells, γδT cells, and natural killer (NK) cells responsible for tissue inflammation, destruction, and aberrant tissue repair.^b

The recommended dose of risankizumab is 150mg (two 75mg injections) administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter. (b) (4)

c

1.2. Describe the Safety Concern – Pregnancy Risk

The risankizumab BLA Unireview^d includes the following information on Human Reproduction and Pregnancy:

“In cynomolgus monkeys, a dose-dependent increase in fetal/infant loss was noted in the risankizumab-treated groups compared to the vehicle control group. The percent fetal/infant loss was 19%, 32%, and 43% in the vehicle control, 5 mg/kg, and 50 mg/kg groups, respectively.

In the risankizumab psoriasis clinical development program, male subjects and their female partners [who were not study subjects] were not required as per the protocols to use contraception. It is not expected that large molecule proteins would interact directly with DNA or other chromosomal material and the amount of risankizumab exposure to female partners transferred via seminal fluid is likely to be negligible.

Nine paternal exposure pregnancies were reported in the partner of a male study subject in the risankizumab clinical development program, no congenital anomalies were reported as outcome.

^a Vide J, Magina S. Moderate to severe psoriasis treatment challenges through the era of biological drugs. *An Bras Dermatol.* 2017;92(5):668-674.

^b Sponsor Original Submission, Global Submit Review: Upload dated April 23, 2018, Risankizumab, Clinical Overview.

^c Risankizumab Provider Information Label. DARRTS ID: Pending.

^d BLA 761105 Multi-disciplinary Review and Evaluation, Skyrizi (risankizumab). Version date: February 1, 2019. Referenced, April 4, 2019.

Female subjects of childbearing potential were required to use a highly effective method of birth control (that result in a low failure rate of less than 1% per year). Negative pregnancy tests were required at screening/baseline and urine pregnancy testing was performed at appropriate intervals. Subjects who became pregnant were to withdraw from treatment and were followed until delivery and outcome was reported. Pregnancy in a study subject was not considered an AE.

Seventeen maternal exposure pregnancies occurred in the risankizumab clinical development program, of which 14 occurred in studies for the indication of psoriasis and 3 occurred in studies for other indications...”

Pregnancy outcomes by treatment arm are shown in Table 1 below. All three risankizumab exposed pregnancies resulting in live birth without congenital anomaly were exposed to treatment prior to conception and during the first trimester of pregnancy. Two of the five pregnancies that ended by elective termination had information on timing of exposure; one pregnancy in the first trimester at the time of initial risankizumab exposure and one pregnancy in the post-treatment phase for approximately two to three months at the time of the report of pregnancy. One of the four ongoing pregnancies was also risankizumab exposed before conception and during the first trimester. No information was provided for the additional three ongoing pregnancies. Similar information was not provided for either of the two pregnancies that resulted in a spontaneous abortion.^e

Table 1. Summary of Pregnancy Outcomes in Risankizumab Clinical Program^f

Maternal Exposure Outcomes (N=17)	Risakizumab	Comparator	Placebo	Total
Live birth without congenital anomaly	3	0	0	3
Spontaneous abortion	2	2	0	4
Elective termination (no fetal defects or unknown)	5	1	0	6
Ongoing pregnancy	4	0	0	4
Total	14	3	0	17

The BLA Unireview^d also included the following details:

“Two pregnancies in which the mother was taking risankizumab occurred since the initial submission. Both cases occurred in subjects with Crohn's disease (CD); 1 pregnancy is ongoing and 1 was an elective termination due to fetal defects cystic hygroma and fetal hydrops. The case is as follows:

A 24-year-old white female with CD who was exposed to risankizumab for approximately 18 months including prior to conception and during the first trimester elected for termination of the pregnancy at 12 weeks due to a fetus with cystic hygroma and fetal hydrops. Concomitant medications included nortriptyline, paracetamol, and desogestrel. Chromosomal analysis from chorionic villus sampling was normal and human parvovirus

^e Sponsor Original Submission. Global Submit: Sequence 0001 (1); 04/23/2018; Section 2.7.4 Summary of Clinical Safety.

^f Original Source: BLA 761105 Unireview (as referenced in footnote A). Formatted to enhance readability.



testing was not suggestive of an acute infection. The Investigator considered the cystic hygroma and fetal hydrops to have a reasonable possibility of being related to study drug; however, AbbVie considered the causality to be not related due to the following:

Transfer of immunoglobulins across the placental syncytiotrophoblast requires the neonatal Fc receptor, which is barely detectable before gestational Week 14. Therefore, immunoglobulin G (IgG) placental transfer is minimal in the first trimester, hence limiting large molecule drug transfer to the fetus during the period of organogenesis (between gestational Weeks 3 and 8).

The Fc neonatal receptor (FcRn) has been demonstrated to play a critical role in mediating IgG transplacental transfer, but recent studies demonstrating distinct transfer efficiencies of different epitope specific-IgG suggest that other mechanisms could also contribute to the regulation of IgG transfer. IgG can be detected in cord blood as early as 8–10 weeks of gestation. IgG1 is the most efficiently transported subclass and efficiency of IgG transfer can vary from one antigen-specificity to another. Most of the information on maternal-fetal transfer comes from measurements of the concentrations of endogenous antibodies. It is unknown how efficiently risankizumab, an exogenous IgG1 antibody would transfer to the fetal circulation at therapeutic concentrations.

Cystic hygromas can occur as an isolated finding or in association with other birth defect as part of a syndrome. They result from environmental factors, genetic factors, or unknown factors. Chromosome abnormality does not appear to be a factor in this case. It is not stated whether viral studies other than parvovirus were done. While there are a number of possible factors (other viral infections, chemical exposures) that could be causal but are difficult to attribute, exposure to risankizumab cannot be ruled out.

One single case in the clinical development is not sufficient to assess a causal relationship between risankizumab and cystic hygromas with fetal hydrops...”

If risankizumab does cross the placental barrier, the long half-life (28 days) of risankizumab could increase the potential development risk of the fetus, even with a maintenance treatment regimen of one injection every 12 weeks. Thus, risankizumab exposure in women with psoriasis who are pregnant or of childbearing potential remains a potential safety concern.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- ☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
- ☐ No approved indication, but practitioners may use product off-label in pregnant women
- ☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

- ☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

- ☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- ☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.
- ☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- ☒ Pregnancy registry with internal comparison group
- ☐ Pregnancy registry with external comparison group
- ☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- ☐ Electronic database study with chart review
- ☒ Electronic database study without chart review
- ☐ Other, please specify:

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

- ☐ Study Population
- ☐ Exposures
- ☐ Outcomes
- ☐ Covariates
- ☒ Analytical Tools

For any checked boxes above, please describe briefly:

Analytical Tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

Because broad-based signal detection is not currently available, other parameters were not assessed.

2.5. Please include the proposed PMR language in the approval letter.

The following language (still in draft form) has been proposed for PMRs related to pregnancy outcomes:

A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to risankizumab during



pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including neonatal deaths, infections in the first 6 months of life, and effects on postnatal growth and development, will be assessed through at least the first year of life.

And

Conduct a retrospective cohort study using claims or electronic medical record data or a case control study to assess adverse pregnancy outcomes such as major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths, and infant infections in women exposed to risankizumab during pregnancy compared to an unexposed control population.

The finalized PMR language will be issued upon approval.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MICHELLE R IANNAcone
04/19/2019 09:02:40 AM

PATRICIA L BRIGHT
04/19/2019 09:19:07 AM

SIMONE P PINHEIRO on behalf of SUKHMINDER K SANDHU
04/19/2019 09:56:14 AM

Signed as proxy for Dr. Sukhminder Sandhu, who has cleared this memo but is currently out of the office

MICHAEL D BLUM on behalf of JUDITH W ZANDER
04/19/2019 10:51:40 AM

MICHAEL D NGUYEN
04/19/2019 11:38:00 AM

ROBERT BALL
04/19/2019 04:40:07 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 20, 2019
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	BLA 761105
Product Name and Strength:	Skyrizi (risankizumab-rzaa) Injection 75 mg/0.83 mL
Applicant/Sponsor Name:	AbbVie, Inc.
FDA Received Date:	January 15, 2019
OSE RCM #:	2018-886-2
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

Division of Dermatology and Dental Products (DDDP) requested that we review the revised container labels, carton and printmat labeling, Prescribing Information (PI), Medication Guide (MG), and Instructions for Use (IFU) for Skyrizi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container labels, carton and printmat labeling, Prescribing Information (PI), Medication Guide (MG), and Instructions for Use (IFU) for Skyrizi are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Patel, M. Label and Labeling Review for Skyrizi (BLA 761105). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 08. RCM No.: 2018-886-1.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MARCH 19, 2019

Container labels

(b) (4)



3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MADHURI R PATEL
03/20/2019 04:08:20 PM

SEVAN H KOLEJIAN
03/20/2019 04:09:31 PM

Clinical Inspection Summary

Date	February 28, 2019
From	Cheryl Grandinetti, Pharm.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Cristina Attinello, M.P.H, R.P.M. Amy Weitach, D.O., Clinical Reviewer David Kettl, M.D., Clinical Team Leader Kendal Marcus, M.D., Division Director Division of Dermatology and Dental Products
BLA #	761105
Applicant	AbbVie, Inc.
Drug	Skyrizi (risankizumab)
NME	Yes
Review Priority	Standard
Proposed Indication	treatment of adults with moderate to severe plaque psoriasis
Consultation Request Date	May 24, 2018 (amended June 11, 2018)
Summary Goal Date	March 1, 2019
Action Goal Date	April 9, 2019
PDUFA Date	April 23, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Toth, Hong, and Tying and the study sponsors, AbbVie, Inc. and Boehringer Ingelheim Pharmaceuticals, Inc. (BI) were inspected in support of this BLA to verify data from study Protocols M15-992 (1311.4), M15-995 (1311.28), and M16-008 (1311.3). The European Medicines Agency (EMA) has received the same marketing authorization application (MAA), and FDA and EMA conducted joint inspections of the study sponsors, AbbVie, Inc. and BI, as part of the FDA-EMA GCP Initiative.

During the sponsor inspection, the following data integrity concerns involving the Psoriasis Area and Severity Index (PASI) and Static Physician Global Assessment (sPGA) scores were identified:

- Inappropriate use of a medical scribe that resulted in no clearly attributable signature of a qualified assessor that was necessary for verifying the accuracy of the assessment data entered by the medical scribe
- Incorrect data attribution
- Alteration of the audit trail information

These observations identified above affected a small percentage of study subjects as follows:

- 54/1504 (3.6%) subjects across all three trials for Visits 2 and 6 PASI scores
- 26/1504 (1.7%) subjects across all three trials for Visits 2 and 6 sPGA scores

Based on preliminary information, OSI recommended in an email, dated December 19, 2018, that the review division conduct a sensitivity analysis excluding the PASI and sPGA data recorded during the corresponding study visits for these subjects.

Also noted were 718 cases of incorrect date and time stamps of PASI, sPGA, and Psoriasis Symptoms Scale (PSS) data that occurred when the batteries of the mobile devices used to capture this data were critically low. When date and time stamps could not be corrected, the Sponsor and the Contract Research Organization (CRO) who supplied the devices and data management services deleted the data. The date and time corrections did not impact the reliability of the data because we have confidence in the algorithm used to determine the actual dates and times the data were entered by the qualified assessors and study subjects.

Notwithstanding these observations that affected the reliability of the primary efficacy endpoint data for a small percentage of the study population across all three protocols, the studies appear to have been conducted adequately. The study data, including the primary efficacy endpoint data for the rest of the study population, appear acceptable in support of the respective indication.

The final compliance classification of the inspections of Drs. Toth and Hong was No Action Indicated (NAI). The final classification of the inspection of Dr. Tying was Voluntary Action Indicated (VAI). The final classification of the inspection of the current sponsor, AbbVie, was NAI, and the final classification of the initial sponsor, BI, was VAI.

Information under Confidentiality Agreement

II. BACKGROUND

AbbVie, Inc. submitted this BLA to support the use of Skyrizi (risankizumab) for the treatment of adults with moderate to severe plaque psoriasis. BI was the initial sponsor for all trials in the U.S. and outside of the U.S. However, after 17 October 2016, all protocols were sponsored by AbbVie in the United States (U.S.) and BI remained the sponsor for ex-U.S. sites. AbbVie also became the applicant for risankizumab in the U.S., Europe, and rest of the world on 17 October 2016. (b) (4)

(b) (4)

The key protocols supporting this application are as follows:

- M15-995 (1311.28): “BI 655066/ABBV-066 (Risankizumab) versus Ustekinumab and Placebo Comparators in a Randomized Double-Blind Trial for Maintenance Use in Moderate to Severe Plaque Type Psoriasis-2 (UltIMMa-2)”
- M16-008 (1311.3): “BI 655066/ABBV-066 (Risankizumab) Versus Ustekinumab and Placebo Comparators in a Randomized Double-Blind Trial for Maintenance Use in Moderate to Severe Plaque Type Psoriasis (UltIMMa-1)”
- M15-992 (1311.4): “BI 655066 (risankizumab) Versus Placebo in a Multicenter Randomized Double-Blind Study in Patients with Moderate to Severe Chronic Plaque Psoriasis Evaluating the Efficacy and Safety with Randomized Withdrawal and Re-Treatment”

Highlights of the three protocols are given below. Following this, the primary and secondary efficacy endpoints, which are the same for all three trials, will be presented.

M15-995 (1311.28)

- *Subjects:* 491 subjects were randomized, 482 completed Part A of the study and 459 subjects completed part B of the study
- *Sites:* 64 sites across 10 countries: Austria, Belgium, Canada, France, Germany, Mexico, Poland, Portugal, Spain, and the United States
- *Study Initiation and Completion Dates:* March 1, 2016 to September 4, 2017

M16-008 (1311.3)

- *Subjects:* 506 subjects were randomized, 496 completed Part A of the study and 478 completed Part B of the study.
- *Sites:* 79 sites across 8 countries: Australia, Canada, Czech Republic, France, Germany, Japan, Republic of Korea, and the United States
- *Study Initiation and Completion Dates:* February 24, 2016 to September 18, 2017

M15-995 (1311.28) and M16-008 (1311.3)

These were randomized, double-blind, double-dummy, placebo- and active-controlled, parallel design studies with the objective of assessing the safety and efficacy of risankizumab compared to ustekinumab and placebo in subjects with moderate to severe chronic plaque psoriasis. The studies were identical in design and conduct and consisted of

a screening period (ranging from 1 to 6 weeks) followed by a 16-week treatment period (Part A of the study). Subjects continued to receive treatment through Week 40 and were followed through at least 52 weeks (Part B of the study).

Eligible subjects were randomized (in a 3:1:1) ratio, and stratified by weight (less than or equal to 100 kg versus greater than 100 kg) and prior exposure to TNF antagonists (0 versus ≥ 1), via an Interactive Response (IRT) system to one of three treatment arms:

- Arm 1: Risankizumab 150 mg administered subcutaneously at weeks 0, 4, and then every 12 weeks until Week 40
- Arm 2: Ustekinumab 45 mg or 90 mg based on screening weight, administered subcutaneously at weeks 0, 4 and then every 12 weeks until Week 40
- Arm 3: Matching placebo administered subcutaneously at weeks 0 and 4

At Week 16, all subjects in Arm 3 (who were initially randomized to placebo) began receiving 150 mg risankizumab every 12 weeks thereafter until Week 40. To maintain the blind, the crossover was performed in a blinded fashion.

At Week 40, all subjects could then either end their study participation or enter the open-label extension (OLE) study provided they met eligibility criteria and desired to continue treatment. Subjects not wishing to continue in the open-label study had a final visit at Week 56.

M15-992 (1311.4)

- *Subjects:* 507 subjects were randomized, and 500 subjects completed Part A1 of the study; 403 subjects entered Part A2 of the study and 403 subjects completed Part A2 of the study; 336 subjects were re-randomized in Part B of the study
- *Sites:* 60 sites in 9 countries (Australia, Belgium, Canada, Czech Republic, France, Germany, Japan, Korea, and the United States)
- *Study Initiation and Completion Dates:* March 7, 2016 to September 22, 2017

This was a phase 3, randomized, double-blind, placebo-controlled study that evaluated the safety and efficacy of risankizumab compared to placebo for the treatment of moderate to severe chronic plaque psoriasis. The study included a 42-day screening period, an 88-week treatment period, and a 16-week follow-up period.

The primary objectives of the study were:

- To assess the safety and efficacy of risankizumab 150 mg compared to placebo in subjects with moderate to severe chronic plaque psoriasis with the primary efficacy evaluation at 16 weeks
- To assess the maintenance of response following drug withdrawal after Week 28 through Week 104, and the response after re-treatment in subjects who experienced relapse after drug withdrawal and were re-treated with risankizumab

Eligible subjects were randomized (4:1 ratio), and stratified by weight (less than or equal to 100 kg versus greater than 100 kg) and prior exposure to TNF antagonists (0 versus ≥ 1) via an IRT system to one of two treatment arms:

- Arm 1: Risankizumab 150 mg administered subcutaneously
- Arm 2: Matching placebo administered subcutaneously

All subjects received the first dose of study drug on Day 1 (randomization), the second dose at Week 4, and then every 12 weeks until the end of the treatment period (Week 88).

At Week 16, all subjects randomized to Arm 2 (placebo) received risankizumab 150 mg every 12 weeks until the end of the treatment period (Week 88). To maintain the blind, the crossover was performed in a blinded fashion.

Primary and Secondary Endpoints for Protocols M15-995 (1311.28), M16-008 (1311.3), and M15-992 (1311.4)

The co-primary endpoints for all three protocols were as follows:

- Achievement of greater than or equal to 90% reduction from baseline PASI score (PASI 90) at Week 16
- Achievement of a sPGA score of clear or almost clear (0 or 1) at Week 16

Secondary endpoints were as follows:

- Change from baseline in psoriasis symptoms evaluated using the total score on the Psoriasis Symptoms Scale (PSS) at Week 16
- Achievement of a Dermatology Life Quality Index (DLQI) score of 0 or 1 at Week 16
- Achievement of total score on the PSS of 0 at Week 16

The protocol required that the primary efficacy assessments be performed by a qualified efficacy assessor at the site and recorded by direct electronic capture methods using an electronic tablet (b) (4). The efficacy assessor had to be qualified and undergo the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) training requirements (b) (4). (b) (4) provided the (b) (4) used to record the clinician reported outcome assessments (ClinRO) and patient reported outcome (PRO) assessments. For each of the three protocols, during clinic visits, the subject would enter PRO assessments into a (b) (4). The subject would then log out of the (b) (4) and the clinical investigator (i.e., the qualified assessor) would log into the (b) (4) and complete the PASI and sPGA assessments while assessing the subject. The subject also used the (b) (4) to enter daily PRO assessments (e.g., PSS and DLQI). Assessment data (both the ClinRO and PRO data) that were entered on the (b) (4) and (b) (4) were immediately transferred from the mobile devices to the (b) (4) online portal (b) (4). The sponsor initially did not permit use of paper source to capture the endpoint data; however, on 22 May 2017, the sponsor implemented a paper backup method for recording

PRO and ClinRO assessments at key study visits in the event of technology failures only.

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, treatment effect, and prior inspectional history.

III. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects Enrolled	Inspection Dates	Classification
Site #10021 Stephen Keith Tying, M.D., Ph.D., M.B.A. Center for Clinical Trials Suite 200 1401 Binz Street Houston, TX 77004	M15-992 (1311.4) Subjects: 20 M16-008 (1311.3) Subjects: 21	17 to 20 Sept 2018	VAI
Site #20009 Chih-ho Hong, M.D. Dr. Chih-ho Hong Medical Inc. Suite 20, 15300-105 Avenue Surrey, British Columbia V3R 6A7 Canada	M16-008 (1311.3) Subjects: 20	3 to 6 December 2018	NAI
Site #20021 Darryl Toth, M.D. XLR8 Medical Research Inc. 2425 Tecumseh Road East, Suite 210 Windsor, Ontario N8W 1E6 Canada	M15-995 (1311.28) Subjects: 32 M15-992 (1311.4) Subjects: 12	5 to 14 Nov 2018	NAI
Sponsor: Boehringer-Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road Ridgefield, CT 06877-0368	M15-995 (1311.28) M16-008 (1311.3) M15-992 (1311.4)	12 Nov to 6 Dec 2018	VAI

Sponsor AbbVie, Inc. 1 N. Waukegan Road Dept. PA72/Bldg. AP30 North Chicago, IL 60064	M15-995 (1311.28) M16-008 (1311.3) M15-992 (1311.4)	5 to 16 Nov 2018	NAI
--	--	------------------	-----

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable

1. Stephen Keith Tyring, M.D.

At this site for Protocol M15-992 (1311.4), 22 subjects were screened, 20 were enrolled, 6 terminated the study early, and 14 subjects completed the treatment phase of the study. For Protocol M16-008 (1311.3), 25 subjects were screened, 21 were enrolled, 3 terminated the study early, and 18 subjects completed the treatment phase of the study. During the inspection, study and subject source records were reviewed for 21 subjects who were enrolled in M15-992 (1311.4) and for all 22 subjects who were screened for Protocol M16-008 (1311.3). Records reviewed included, but were not limited to, the study protocol and amendments, Institutional Review Board (IRB) submissions and approvals, subject selection criteria, informed consent, source data, case report forms, source records for the primary efficacy endpoint, financial disclosure, drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. There was one incident of late reporting of a serious adverse event that occurred in Protocol M16-008 (1311.3). According to the source documents, study personnel at the site became aware of Subject # (b) (6) who was hospitalized on (b) (6) (during the Week 4 visit). Site personnel did not notify the sponsor until (b) (6) 10 days after the protocol-required 24-hour time window for reporting serious adverse events to the sponsor.

Reviewer's comment: Although the clinical investigator did not report this event to the sponsor within the protocol-required timeframe, it likely does not have an impact on overall safety results of the study because the sponsor reported the serious adverse event in the data listing provided to the FDA. At end of the inspection, the late reporting issue was discussed with the clinical investigator and a Form FDA-483, Inspection Observations, was issued. Dr. Tyring acknowledged the late reporting, promised to make improvements, and adequately responded to the inspection finding in a written response dated October 4, 2018.

For Protocols M15-992 (1311.4) and M16-008 (1311.3), PASI and sPGA data for all enrolled subjects for Visits 2 (Baseline) and 6 (Week 16) (i.e., the critical timepoints for evaluating the primary efficacy endpoints) were reviewed and verified against the data listings provided by the sponsor. No discrepancies were noted. However, during review of the electronic source data and audit trail information in the (b) (4) online portal, it was noted that Dr. Tyring's

study coordinator entered PASI and sPGA data into the (b) (4) for Protocol M15-992 (1311.4). The study coordinator was not listed as a qualified assessor on the site delegation of authority log. In addition, there was no documentation at the site that demonstrated that the study coordinator took the protocol-required GRAPPA training.

Dr. Tying stated that the study coordinator acted as a medical scribe and entered data directly into the (b) (4) as a verbal order from Dr. Tying while he was assessing the study subjects. However, for much of the data entered by the study coordinator, there was no documentation (paper or electronic) at the site that Dr. Tying (or another qualified assessor) verified the accuracy of the data entered by the study coordinator. Specifically, a qualified assessor did not verify the accuracy of the PASI and sPGA assessment data entered for Visit 2 for subjects

(b) (6)

In addition, because the protocol and the technology were not originally designed to allow for the qualified assessors to use a medical scribe to enter efficacy assessment data on their behalf in the technology, a Form FDA-483, Inspection Observations, was issued at the end of the inspection for failure to adhere to the protocol. Dr. Tying responded to the inspection finding in a written response, dated October 4, 2018.

Reviewer's Comment: The field inspector was not able to verify that the Visit 2 PASI and sPGA data accurately represented the verbal assessments of the qualified assessors for 10 of the 20 (50%) subjects enrolled at this site for Protocol M15-992 (1311.4). Although the above finding was regulatory violation, given the relatively small contribution of subjects from this site, the described observation does not appear to have a significant effect on overall outcome of the study. Notwithstanding the above observation, the study data from this site for Protocol M16-008 (1311.3) appear acceptable in support of the respective indication.

2. Chih-ho Hong, M.D.

At this site for Protocol M16-008 (1311.3), 20 subjects were screened, 20 were enrolled, and 20 subjects completed the treatment phase of the study. Study and subject source records were reviewed during the inspection for the 20 enrolled subjects. Records reviewed included, but were not limited to, the study protocol and amendments, IRB submissions and approvals, subject selection criteria, informed consent, source data, case report forms, source records for the primary efficacy endpoint, financial disclosure, drug accountability, adverse event reporting, protocol deviations, monitor logs, and follow-up letters.

There was no evidence of under-reporting of adverse events. PASI and sPGA source data were reviewed and verified against the data listings provided by the sponsor for all 20 enrolled subjects. No discrepancies were noted. All PASI and sPGA assessments were performed and entered into the (b) (4) by a qualified assessor.

3. Darryl Toth, M.D.

At this site for Protocol M15-992 (1311.4), 13 subjects were screened, 12 were enrolled, 2 terminated the study early, and 10 subjects completed the treatment phase of the study. For Protocol M15-995 (1311.28), 34 subjects were screened, 32 were enrolled, 1 subject terminated the study early, and 31 subjects completed the treatment phase of the study. During the inspection, study and subject source records were reviewed for all 12 enrolled subjects for Protocol M15-992 (1311.4) and for 17 of the 32 subjects enrolled in Protocol M15-995 (1311.28). Records reviewed included, but were not limited to, the study protocol and amendments, IRB submissions and approvals, subject selection criteria, informed consent, source data, case report forms, source records for the primary efficacy endpoint, financial disclosure, drug accountability, adverse event reporting, protocol deviations, monitor logs, and follow-up letters.

There was no evidence of under-reporting of adverse events. PASI and sPGA source data were reviewed and verified against the data listings provided by the sponsor for all 12 enrolled subjects for Protocol M15-992 (1311.4), and for 17 of the 32 subjects enrolled in Protocol M15-995 (1311.28). No discrepancies were noted. All PASI and sPGA assessments were performed and entered into the (b) (4) by a qualified assessor. Of note, during review of the electronic source data and audit trail information in the (b) (4) database for M15-995 (1311.28), dates and times for patient diary entries for PSS scores for Subject # (b) (6) were noted to be incorrect (i.e., dates and times of diary entry occurred before the subject was enrolled and/or randomized). These patient entries should have been completed sometime after Visit 5 (b) (6)

Reviewer's comments: The field inspectors and OSI conducted a meeting with the sponsors (AbbVie and BI) and (b) (4) to discuss the issue. (b) (4) explained that this was a larger issue that occurred across multiple sites and studies. The (b) (4) and (b) (4) would record an incorrect date and time for data entered by the study subjects and assessors when the batteries for the (b) (4) and (b) (4) were critically low. (b) (4) explained that they either corrected the date and time when possible or deleted the data. The ePRO data for Subject (b) (6) for PSS #19 that should have been completed after (b) (4) were not deleted by (b) (4) although the date and time is incorrect. The PSS data appear in the data listings submitted to FDA by the sponsor with no date and time associated with it. Because the incorrect date and time identified above was a result of a technology malfunction and not from inappropriate activity by the site personnel, no FDA Form 483 was issued. See OSI's summary under the sponsor BI inspection results below for more detailed information on the battery issue and missing data or corrected dates and times by (b) (4)

4. Boehringer-Ingelheim Pharmaceuticals, Inc.

This inspection was conducted as a joint inspection with the EMA as part of the FDA-EMA GCP Initiative. The inspection of BI focused on the control, oversight, and management of the three protocols, M15-992 (1311.4), M15-995 (1311.28), and M16-008 (1311.3). As the initial sponsor, BI was responsible for the following:

- Selecting and granting final approval for vendors used to provide services during the conduct of the risankizumab trials
- Selecting and granting final approval for the clinical investigation sites
- Performing all administration functions related to developing the protocol, sample electronic case report forms, and sample ICFs
- Conducting the site initiation visits, site monitoring visits, and post-study visits
- Providing the clinical supplies for the protocols
- Creating the database for the protocols using a validated data management system

In addition, BI was responsible for maintaining the worldwide safety database until 17 October 2016, when the global safety database was transferred to AbbVie, the current sponsor of the trials. (b) (4)

The inspection covered roles and responsibilities, selection of clinical investigators, selection of monitors, monitoring procedures and activities, quality management, adverse event reporting, process for managing protocol deviations, data collection and handling, record retention, financial disclosure, electronic records compliance, electronic systems, and test article accountability. Records reviewed during the inspection included investigator agreements, vendor agreements, and contracts, written standard operating procedures, documentation of protocol deviations, validation documentation and audit trail information of electronic data capture systems, adverse event reporting, drug accountability, relevant communication and correspondence, and monitoring activities.

BI had a TORO agreement with (b) (4) to provide cardiac safety-related, respiratory-related, and electronic clinical outcome assessment-related services in support of the three pivotal trials for Skyrizi. Among other responsibilities, (b) (4) was responsible for designing and implementing electronic ClinRO and PRO assessments screens, diary/questionnaire logic, and workflow; designing and implementing the (b) (4) online database; database hosting; and providing server maintenance and project management. During the inspection, three data integrity issues were observed that involved the use of the (b) (4) and (b) (4) provided by (b) (4)

1. Inappropriate use of a medical scribe, data attributability, and alteration of the audit trail information by (b) (4)
2. Incorrect date and time stamps
3. Synchronization issues and loss of data

Inappropriate use of a medical scribe, lack of data attributability, and alteration of the audit trail information by (b) (4)

Although the protocols and (b) (4) were not originally designed to allow for a medical scribe to enter PASI and sPGA data into the technology on behalf of the qualified assessor, during inspection, it was observed that many sites (as indicated below) used a medical scribe to enter PASI and sPGA assessments in the technology:

- For Protocol M15-992 (1311.4): 18 sites inappropriately used a medical scribe to enter PASI and PGA data for 44 subjects

- For Protocol M15-995 (1311.28): 22 sites inappropriately used a medical scribe to enter PASI and PGA data for 35 subjects
- For Protocol M16-008 (1311.3): 13 sites inappropriately used a medical scribe to enter PASI and PGA data, for 18 subjects

It was found that in many cases the qualified assessor did not verify (by handwritten signature using an electronic stylus in the (b) (4) the accuracy of the PASI and sPGA data that the medical scribes entered into the (b) (4). Furthermore, because the sponsor did not permit qualified assessors to use paper back up methods to record their assessments, there were no paper source documents that could be used to verify the data.

Per our request during inspection, AbbVie, the current sponsor, did a thorough review of the PASI and sPGA data before September 2016 for these subjects for Visits 2 (Baseline) and 6 (Week 16) (i.e., the critical timepoints for evaluating the primary efficacy endpoints) only. This review showed the following:

- 54/1504 (3.6%) subjects across all three studies did not have a clearly attributable signature of a certified assessor to verify the accuracy of the data on the (b) (4) for the baseline and/or Visit 6 (Week 16) for the PASI endpoint
- 26/1504 (1.7%) subjects across all three studies did not have an attributable signature of a certified assessor on the (b) (4) for the Visit 6 for the sPGA data

In addition, through review of the audit trails information and data clarification forms submitted to (b) (4) by the clinical investigation sites, the field investigator noted that (b) (4) changed the data originators in the (b) (4) database from the medical scribes to the certified assessors for the PASI and sPGA data for these subjects, resulting in data that no longer met all the ALCOA (Attributable, Legible, Contemporaneous, Original, and Accurate) principles.

Reviewer's comment: Because the qualified assessors did not verify the accuracy of the data entered by the medical scribes, the inspector was unable to verify that the data listings submitted by the sponsor accurately represented the assessments made by qualified assessors. OSI recommended in an email, dated December 19, 2018 that our statisticians conduct a sensitivity analysis excluding this data (for the subjects and corresponding visit numbers) from the efficacy analysis for the primary efficacy endpoint.

BI and (b) (4) updated the (b) (4) in September 2016 (approximately 7 months after the first subject was enrolled) to allow the qualified assessors to use a medical scribe. However, BI provided poor guidance to clinical investigation sites on the “appropriate use” of the medical scribe. BI instructed qualified assessors to sign into (b) (4) and have the medical scribe enter assessment data into the (b) (4) under the login credentials of the qualified assessor. When the scribe completed their entries, the qualified assessor was required to check the entries and sign the assessment form in the (b) (4).

Reviewer's comment: Although the assessment data entered after the technology update (September 2016) do not meet some of the ALCOA principles, the data entered by the medical scribes represent the verified assessments made by the qualified assessors.

Finally, BI monitors failed to recognize and report that qualified assessors were not verifying the accuracy of the PASI and sPGA data that were entered by the medical scribes. For the above inspection findings, a Form FDA-483, Inspection Observations, was issued at the end of the inspection for failure to provide investigators with the information needed to conduct the study properly, ensure proper monitoring of the study, and ensure the study is conducted in accordance with the protocol and/ or investigational plan.

Incorrect Date and Time Stamps:

Also noted during inspection were incorrect date and time stamps for PRO and ClinRO data that occurred when the battery for the (b) (4) and (b) (4) was critically low. There were approximately 693 cases where (b) (4) corrected the date and time for PASI, sPGA, and PSS data that had an incorrect date and time noted. In addition, there were 25 PSS (b) (4) forms where diaries were affected by the critically low battery issue. (b) (4) did not correct the date and times in these cases, but rather deleted the data for the following:

- 19 PSS (b) (4) forms for Study M15-995 (1311.28) affecting 11 subjects
- 6 PSS (b) (4) Forms for Study M16-008 (1311.3) affecting 6 subjects

Reviewer's comment: Although there was an issue with the dates and times for these data points, (b) (4) and BI were able to resolve this issue sufficiently by correcting these date and time stamps. If (b) (4) and BI were unable to determine the correct date and time that the subjects entered PSS data in the (b) (4) the PSS data were deleted as noted above. The deleted PSS data was documented in their Corrective and Preventative Action (CAPA) report and appropriately captured in the audit trails in the (b) (4) online portal. During inspection, (b) (4) provided a copy of their CAPA report describing how they corrected the dates and times for these data points.

Synchronization Issues:

It was also noted during inspection that when (b) (4) implemented a software update to fix the battery issue, the new software caused synchronization errors that resulted in (b) (4) and (b) (4) being frozen. Any data that was locally stored in the (b) (4) and (b) (4) that had not yet been transferred to the online database was lost. BI stated that the synchronization errors affected 7 devices and 48 subjects at 6 sites from all 3 protocols. To minimize missing data due to technology failure, the sponsor implemented a paper backup method for recording PRO and ClinRO at key study visits on 22 May 2017.

5. AbbVie, Inc.

This inspection was conducted as a joint inspection with the EMA as part of the FDA-EMA GCP Initiative. The inspection of AbbVie, Inc. focused on the control and oversight of Protocols M15-992 (1311.4), M15-995 (1311.28), and M16-008 (1311.3). Of note, on 17 October 2016, AbbVie became of the sponsor for all trials conducted in the U.S. and BI remained the sponsor for ex-U.S. sites. In addition, after 17 October 2016, AbbVie was responsible for adverse event reporting to the IND and the global safety database, statistical analysis of the data, and the final clinical study report.

The inspection covered roles and responsibilities, organization and its personnel, registration of studies on clinicaltrials.gov, quality management, vendor oversight and management, adverse event reporting, data collection and handling, record retention, financial disclosure, and electronic records compliance. Records reviewed during the inspection included investigator agreements, vendor agreements, and contracts, written standard operating procedures, validation documentation of electronic data capture systems, adverse event reporting, drug accountability, and relevant communication and correspondence. The sponsor appears to have exercised adequate control and oversight of the studies.

Information under Confidentiality Agreement



Information under Confidentiality Agreement

{ See appended electronic signature page }

Cheryl Grandinetti, Pharm.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Susan D. Thompson, M.D. for
Phillip Kronstein, M.D. Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Kassa Ayalew, M.D., M.P.H Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm. BLA 761105
DDDP /Project Manager/Cristina Attinello
DDDP /Medical Officer/Amy Voitach
DDDP/ Clinical Team Leader/ David Kettl

DDDP/Division Director/Kendall Marcus
OSI/DCCE/Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Cheryl Grandinetti
OSI/ GCP Program Analysts/Yolanda Patague
OSI/Database Project Manager/Dana Walters

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHERYL A GRANDINETTI
02/28/2019 01:00:34 PM

SUSAN D THOMPSON
02/28/2019 01:28:53 PM

KASSA AYALEW
02/28/2019 01:45:57 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 8, 2019
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	BLA 761105
Product Name and Strength:	Skyrizi (risankizumab-xxxx) ^a Injection 75 mg/0.83 mL
Applicant/Sponsor Name:	AbbVie, Inc.
FDA Received Date:	January 15, 2019
OSE RCM #:	2018-886
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

Division of Dermatology and Dental Products (DDDP) requested that we review the revised container labels, carton and printmat labeling, Prescribing Information (PI), Medication Guide (MG), and Instructions for Use (IFU) for Skyrizi (Appendix A) to determine if label and labeling are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^b

2 CONCLUSION

The revised PI, MG, and IFU for Skyrizi are acceptable from a medication error perspective.

^a The proper name for proposed biologic product includes a distinguishing suffix (see Guidance on Nonproprietary Naming of Biological Products). We are using “-xxxx” as a placeholder until an acceptable suffix has been designated.

^b Patel, M. Human Factors Results and Label and Labeling Review for Skyrizi (risankizumab-xxxx) (BLA 761105). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 22. RCM No.: 2018-886 and 2018-910.

The revised container labels, carton and printmat labeling, are unacceptable from a medication error perspective. We previously recommended revising a statement on the printmat labeling for clarity of the net quantity, which read “ (b) (4) ” instead of “ (b) (4) ”. We note this recommendation was not implemented by AbbVie, Inc due to their concern that use of the "single-dose" package term associated with one pre-filled syringe will lead to confusion and will increase the opportunity for use error (e.g., result in using only one pre-filled syringe and under-dosing). We continue to defer to the Office of Pharmaceutical Quality (OPQ) regarding the acceptability of the “ (b) (4) ” package type term on labels and labeling. However, we still recommend adding the net quantity to the printmat labeling. We also previously recommended that the carton containing 2 syringes have a different NDC than the printmat labeling and container label that contain 1 prefilled syringe. AbbVie stated the intended saleable unit for Skyrizi is the carton that contains 2 pre-filled syringes (PFS) in separate blister trays; as such, consistent with their current labeling practices. AbbVie has assigned a (b) (4)

We continue to recommend a National Drug Code (NDC) with a different product code for the syringe label than the carton label. We note that two syringes are required for a full dose; hence, if in an inpatient setting the syringes are scanned, a different NDC would help ensure the patient receives the correct dose.

3 RECOMMENDATIONS FOR ABBVIE, INC.

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels & Carton Labeling)

1. We reference our advice letter^c dated May 4, 2018 informing you that the proper name suffix under review. Please continue to use “-xxxx” as a placeholder until an acceptable suffix has been designated for your proper name throughout the label and labeling. Once a suffix is designated for your proper name, you can add the suffix to the label and labeling and submit for our review.

B. Container Label

The carton NDC must be different than the NDC on any of the components in the carton. As currently presented, (b) (4)

Healthcare providers may rely on the NDC number and barcode for product verification during dispensing and administration. We note that two syringes are required for a full dose, a different NDC would help ensure the patient receives the correct dose, 2 pre-filled syringes. Therefore, revise the NDC numbers on the pre-filled syringe container label.

^c Bui Nguyen, T. Proprietary Name Acknowledgement Letter for BLA 761105. Silver Spring (MD): FDA, CDER, OSE (US) 2018 MAY 04.

C. Printmat (blister) Labeling

- a. Revise the statement appearing at the top of the blister underneath the NDC number from “(b) (4)” to read “1 x 0.83 mL single-dose prefilled syringe” to include the net quantity statement.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MADHURI R PATEL
02/08/2019 12:39:50 PM

SEVAN H KOLEJIAN
02/08/2019 12:43:12 PM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: February 6, 2019

To: Kendall Marcus, MD
Director
Division of Dermatology and Dental Products (DDDP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA, CPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Laurie Buonaccorsi, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): TRADENAME (risankizumab)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761105

Applicant: AbbVie Inc.

1 INTRODUCTION

On April 23, 2018, AbbVie Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761105 for TRADENAME (risankizumab) injection. The proposed indication for TRADENAME (risankizumab) injection is for the treatment of moderate-to-severe plaque psoriasis in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dental Products (DDDP) on January 24, 2019 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for TRADENAME (risankizumab) injection.

2 MATERIAL REVIEWED

- Draft TRADENAME (risankizumab) injection MG and IFU received on April 23, 2018, and received by DMPP and OPDP on January 24, 2019.
- Draft TRADENAME (risankizumab) injection Prescribing Information (PI) received on April 23, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 24, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU documents using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MORGAN A WALKER
02/06/2019 03:19:48 PM

LAURIE J BUONACCORSI
02/06/2019 03:27:28 PM

LASHAWN M GRIFFITHS
02/06/2019 05:08:37 PM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: January 30, 2019

To: Amy Woitch, DO, Clinical Reviewer,
Division of Dermatology and Dental Products (DDDP)

Cristina Attinello, Regulatory Project Manager, (DDDP)

Barbara Gould, Regulatory Project Manager, (DDDP)

Nancy Xu, Associate Director for Labeling, (DDDP)

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for SKYRIZI™ (risankizumab-xxxx) injection,
for subcutaneous use (Skyrizi)

BLA: 761105

In response to DDDP's consult request dated January 23, 2019, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and Instructions for Use (IFU) for the BLA submission for Skyrizi.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI, Medication Guide, and IFU received by electronic mail from DDDP on January 24, 2019, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on January 14, 2019, and our comments are provided below and on the attached label.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

Carton and Container Comments:

1. The established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features, according to 21 CFR 201.10 (g)(2). The use of [REDACTED] (b) (4)
[REDACTED] We recommend revising the established name to increase the prominence. Please apply this comment to all draft carton and container labels.
2. The nomenclature in the PI has been changed to single-dose and we recommend consistency with the PI on all carton/container labeling.
3. The order of the inactive ingredients has been changed in the PI to reflect the alphabetic listing and "di" has been added to sodium succinate hexahydrate. We recommend consistency with the PI on all carton/container labeling where the inactive ingredients are listed.

31 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LAURIE J BUONACCORSI
01/30/2019 11:08:38 AM



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: 04 December 2018

From: Fred Senatore, MD, PhD, FACC, Medical Officer, DCaRP

Through: Martin Rose, MD, JD, Clinical Team Leader, DCaRP
Norman Stockbridge, MD, PhD, Division Director, DCaRP

To: David Kettl, MD Clinical Team Leader, DDDP
Amy Weitach, DO, Medical Officer, DDDP
Cristina Attinello, MPH, Sr RPM, DDDP

Subject: BLA 761105: Risankizumab for the treatment of psoriasis: cardiovascular events

This memo responds to your consult to us requesting our review of cardiovascular (CV) events that were reported in the Risankizumab psoriasis program and provide recommendations regarding appropriate language for labeling. We received and reviewed the BLA submission package: [\\CDSESUB1\evsprod\BLA761105\761105.enx](#).

DCRP Summary and Assessment

The primary pooled safety dataset comprised of 1 Phase-2 and 4 Phase-3 trials evaluating risankizumab in patients with moderate-severe psoriasis. The arms of these studies included placebo (N=360), ustekinumab (N=239), adalimumab (N=304), risankizumab 90 mg (N=41), risankizumab 150 mg (N=1306) and risankizumab 150-180 mg (N=1348).

The patient characteristics, baseline cardiac risk factors, and baseline history of cardiovascular disease were evenly distributed amongst the arms of the trials comprising the primary pooled safety dataset.

The incidence of CV events was low in number and similar across all the arms of the trials for a mean treatment time of 111 days: placebo (1.7%), ustekinumab (1.7%), adalimumab (1.3%), risankizumab 90 mg (2.4%), risankizumab 150 mg (0.7%), and risankizumab 150-180 mg (0.7%). The estimated annualized rates of CV events were: placebo (5%), ustekinumab (5%),

adalimumab (4%), risankizumab 90 mg (7%), risankizumab 150 mg (2%), and risankizumab 150-180 mg (2%).

In a subset of 2 ustekinumab-controlled trials, there appeared to be an imbalance of adjudicated events: 4 events of supraventricular arrhythmia and 4 events of congestive heart failure (CHF) in the risankizumab arms (N=598) vs 0 events in the ustekinumab arms (N=199) that occurred in 7 patients. In the absence of imbalances in the larger sample size of the primary pooled safety population, this low-incidence observation was likely due to chance.

A literature search produced no evidence of a relationship between interleukin 12/23 agents and arrhythmic potential. In general, the association between MACE and the use of interleukin 12/23 agents is unclear (Lebwohl, 2012).

In summary, cardiovascular events were low in number, and similar among the arms of trials comprising the primary pooled safety dataset for risankizumab. There is no clinical concern from the cardiovascular perspective thus precluding the need for labeling language.

Background

Abbvie submitted BLA 761105 for risankizumab, a humanized IgG1 monoclonal antibody that targets the p19 subunit of human IL-23. The proposed indication is treatment of moderate to severe plaque psoriasis. Based on epidemiological associations between psoriasis and CV events, and the potential association between anti-cytokine therapies and CV events, the applicant conducted additional analyses on adjudicated MACE, extended MACE, and other CV events. See ([Appendix](#)) for adjudication committee membership and events pre-specified for adjudication.

Clinical Development Program

The risankizumab psoriasis clinical development program included 4 pivotal Phase 3 studies: M16-008 (1311.3), M15-992 (1311.4), M15-995 (1311.28) and M16-010 (1311.30). It also included a long-term, open-label extension (M15-997) of the 4 pivotal studies. There was a Phase 2 study (1311.2) and its open-label extension (1311.13), and a Phase 1 study (1311.1). The Phase 2 and Phase 3 studies (see description in [Table 1](#)) except the open label extension study (M15-997) constituted the primary safety pool used in the ISS.

The total exposures to risankizumab and to comparators from the trials comprising the primary safety pool based on randomization were as follows: risankizumab 18 mg (n=43), risankizumab 90 mg (n=41); risankizumab 150 mg (n=1306); risankizumab 180 mg (n=42); risankizumab 150-180 mg (n=1348); total risankizumab exposure-all doses except 18 mg (n=1389); placebo (n=300); ustekinumab (n=239); and adalimumab (n=304). The risankizumab 150-180 mg grouping is reported here because the ISS evaluated this group of combined dosing. The ISS dataset also excluded the 18 mg dosing from the primary safety analysis in evaluating cardiovascular risk and cardiovascular events.

Treatment duration for all risankizumab doses and comparators in the primary safety pool was 111 days (both mean and median, range 84-189 days). A total of 2236 subjects were exposed to risankizumab regardless of dose or timing (421 patient-years of exposure) (see

Table 2).

Table 1: Risankizumab Phase 2 and 3 studies for the Psoriasis Indication

Study/Design	Study Arms & Doses	Sample Size (by arm: e/c)
Study M16-008 (1311.3) (52 wks): P3, MC, DB RCT (pbo and active comparator controlled)	RZB: 150 mg SC at wks 0, 4, and 12 wks. UST: 45 mg SC (≤ 100 kg BW) or 90 mg SC (> 100 kg BW) at wks 0, 4, and 12 wks. Pbo: SC wk 0, 4 then switch to RZB at wk 16 and q 12 wks.	RZB: 304/289 UST: 100/94 Pbo: 102/96 (95 completed after switching to RZB)
Study M15-992 (1311.4) (104 wks): P3, MC, DB, RCT (Pbo controlled)	RZB: 150 mg SC at wks 0, 4 and 16. At wk 28, subjects with sPGA 0 or 1 re-randomized to RZB or Pbo. Subjects with sPGA ≥ 2 , at wk 28 received OL RZB q 12 wks. Pbo: SC at wks 0, 4; switch to blinded RZB at wk 16. At wk 28, subjects with sPGA 0 or 1 received blinded RZB q 12 wks; subjects with sPGA ≥ 2 received OL RZB q 12 wks. AT week 32, any subject with sPGA ≥ 3 received RZB loading dose and 4 wks later, and q12 wks.	RZB: 407/14 (363 ongoing at data cut-off) Pbo: 100/1 (84 ongoing at data cut-off after switching to RZB)
Study M15-995 (1311.28) (52 wks): P3, MC, DB RCT (Pbo and active comparator controlled)	RZB: 150 mg SC at wks 0, 4, and q12 wks UST: 45 mg SC (< 100 kg BW) or 90 mg SC (>100 kg BW) at wks 0, 4, and q 12 wks Pbo: SC wk 0, 4 then switch to RZB at wk 16 and q 12 wks	RZB: 294/278 UST: 99/91 Pbo: 98/94 (91 completed after switching to RZB)
Study M16-010 (1311.30) (44 wks; 48 wks for subjects not enrolling in OLE): P3, MC, DB, RCT (active comparator controlled)	RZB: 150 mg SC at wks 0, 4 and q 12 wks. ADB: 80 mg SC at wk 0; 40 mg q other wk from wk 1 to wk 15; at wk 16, subjects either continued on ADB, switched to RZB or were re-randomized to RZB or adalimumab, depending on the PASI score.	RZB: 301/274 ADB: 304/276
Study M15-997 (172 wks): P3, single arm, MC, OLE	RZB: 150 mg SC q 12 w	RZB: 1392/0
Study 1311.2 (24 wks; 48 wks for subjects not enrolling on OLE): P2, MC, DB, RCT (active comparator controlled)	RZB: Group 1: 18 mg at wk 0; Group 2: 90 mg at wks 0, 4, 16; Group 3: 180 mg at wks 0, 4 and 16. UST: 45 mg SC (BW ≤ 100 kg) or 90 mg SC (BW > 100 kg) at wks 0, 4, and 16.	RZB: 126/118 - 18 mg: 43/39 - 90 mg: 41/39 -180 mg: 42/40 UST: 40/39

P3=phase 3; P2=phase 2; MC=multi-center; DB= double-blind; RCT=randomized clinical trial; RZB= risankizumab, RZB= risankizumab; UST= ustekinumab; Pbo= placebo; e/c= entered/completed; sPGA= static physician global assessment; OL= open label; ADB= adalimumab; PASI= psoriasis area and severity index; OLE= open label extension. Source: 2.7.3 Summary of Clinical Efficacy correlated with ISS Table 2.1_1.1

Table 2: Study Drug Treatment Duration (Days)

Treatment	N	Mean (SD)	Median	Min	Max	Exposure (total pt years)
Placebo	300	109.5 (4.7)	111	84	115	90
Ustekinumab	239	110.5 (3.1)	111	84	119	72
Adalimumab	304	112.3 (7.7)	111	84	189	94
Risankizumab 90 mg	41	111.8 (4.8)	112	84	119	13
Risankizumab 150 mg	1306	110.6 (3.9)	111	84	161	395
Risankizumab 150-180 mg	1348	110.6 (3.9)	111	84	161	408
Risankizumab total	1389	110.6 (4.0)	111	84	161	421

Source: ISS Table 2.1_1.3

Pooled Subject Demographics and Characteristics

Baseline cardiovascular risk factors (Table 3) and baseline history of cardiovascular disease (Table 4) were evenly distributed among the risankizumab arms and control arms (ustekinumab, adalimumab, and placebo) of the studies comprising the primary safety pool. Prevalence of risk factors in the primary safety pool was approximately as follows: current smokers (30%), hypertension (30%), hyperlipidemia (25%), diabetes mellitus (15%), and obesity (50%). These numbers were generally higher than those observed in two population-based studies (Neimann 2006; and Kaye 2008) (see footnote).

In the primary safety pool of this BLA, the history of cardiovascular events reported at baseline was: myocardial infarction (2%), angina pectoris (1.5%), and stroke (1%). These were comparable to the history of events from the General Practice Research Database reported by Kaye (2008) and Mehta (2011) (see footnote).

Footnote

Neimann (2006): N= 127,706 patients with mild psoriasis and 3854 patients with severe psoriasis from the General Practice Research Database in the UK risk factors for patients with severe psoriasis, mild psoriasis, and matched controls respectively were: smoking (30%, 28%, 21%), hypertension (20%, 15%, 12%), hyperlipidemia (6%, 5%, 3%), diabetes mellitus (7%, 4%, 3%), and obesity (21%, 16%, 13%).

Kaye (2008): N=44,164 patients with a first time diagnosis of psoriasis from the General Practice Research Database (Kaye, 2008), the incidence of cardiovascular risk factors within 1 year of diagnosing psoriasis and at 10 years were as follows: hypertension (6% → 14%); hyperlipidemia (4% → 9%); diabetes mellitus (1% → 6%); and obesity (2% → 14%).

Mehta (2011): N=3603 patients with severe psoriasis: history of myocardial infarction (3%) and history of stroke (2%).

Table 3: Baseline Cardiovascular Risk Factors

				Risankizumab		
Risk	Placebo	UST	ADB	90 mg	150 mg	150-180 mg
N	300	239	304	41	1306	1348
Sex (Male)	219 (73%)	163 (68%)	212 (70%)	30 (73%)	908 (70%)	937 (70%)
Age < 65 years	261 (87%)	207 (87%)	276 (91%)	36 (88%)	1165 (89%)	1204 (89%)
Race (white)	240 (80%)	199 (83%)	263 (87%)	38 (93%)	1020 (78%)	1060 (79%)
Race (Black)	5 (2%)	4 (2%)	6 (2%)	0	17 (1%)	17 (1%)
Smoking n (%)						
-current	95 (32%)	75 (31%)	92 (30%)	20 (49%)	411 (32%)	426 (32%)
-ex smoker	85 (28%)	61 (26%)	71 (23%)	10 (24%)	354 (27%)	364 (27%)
-never smoked	120 (40%)	103 (43%)	141 (46%)	11 (27%)	541 (41%)	558 (41%)
-unknown	0	0	0	0	0	0
HTN n (%)						
-yes	89 (30%)	84 (35%)	102 (34%)	16 (39%)	422 (32%)	431 (32%)
-no	211 (70%)	153 (65%)	201 (66%)	25 (61%)	881 (68%)	914 (68%)
-missing	0	2	1	0	3	3
Hyperlipidemia n (%)						
-yes	75 (25%)	62 (26%)	60 (20%)	14 (34%)	303 (23%)	310 (23%)
-no	223 (75%)	176 (74%)	244 (80%)	27 (66%)	998 (77%)	1033 (77%)
-missing	2	1	0	0	5	5
Diabetes Mellitus n (%)						
-yes	46 (15%)	31 (13%)	50 (16%)	8 (20%)	203 (16%)	212 (16%)
-no	254 (85%)	208 (87%)	254 (84%)	33 (81%)	1101 (84%)	1134 (84%)
-missing	0	0	0	0	2	2
Obesity n (%)						
-yes	152 (51%)	93 (47%)	148 (49%)	0	641 (49%)	641 (49%)
-no	148 (49%)	106 (53%)	156 (51%)	0	665 (51%)	665 (51%)
-missing	0	40	0	41	0	42

UST= ustekinumab; ADB= adalimumab. Source: ISS Table 2.1_1.4.1; Table 2.1_1.5; ISS Table 2.1_1.6

Table 4: Baseline History of Cardiovascular Disease

				Risankizumab		
Risk	Placebo	UST	ADB	90 mg	150 mg	150-180 mg
N	300	239	304	41	1306	1348
Myocardial Infarction n (%)						
-yes	7 (2%)	10 (4%)	6 (2%)	2 (5%)	24 (2%)	26 (2%)
-no	293 (98%)	229 (96%)	298 (98%)	39 (95%)	1282 (98%)	1322 (98%)
-missing	0	0	0	0	0	0
Angina Pectoris n (%)						
-yes	10 (3%)	3 (1%)	2 (1%)	1 (2%)	14 (1%)	14 (1%)
-no	290 (97%)	236 (99%)	302 (99%)	40 (98%)	1289 (99%)	1331 (99%)
-missing	0	0	0	0	3	3
Transient Ischemic Attack n (%)						
-yes	2 (1%)	4 (2%)	3 (1%)	0	4 (0%)	4 (0%)
-no	298 (99%)	235 (98%)	301 (99%)	41 (100%)	1301 (100%)	1343 (100%)
-missing	0	0	0	0	1	1
Stroke n (%)						
-yes	2 (1%)	2 (1%)	0	0	12 (1%)	12 (1%)
-no	298 (99%)	237 (99%)	304 (100%)	41 (100%)	1294 (99%)	1336 (99%)
-missing	0	0	0	0	0	0

UST= ustekinumab; ADB= adalimumab. Source: ISS Table 2.1_1.6

Cardiovascular Events

MACE was defined as the composite of CV death, nonfatal myocardial infarction, and nonfatal stroke. Extended MACE was defined as the composite of MACE plus hospitalization for unstable angina and coronary revascularization procedures. Other CV events were defined as thrombotic events, cardiac arrhythmia, and congestive heart failure.

Cardiovascular events in the primary safety pool dataset are shown in [Table 5](#). The numbers of events were low and comparable across all arms: placebo (1.7%), ustekinumab (1.7%), adalimumab (1.3%), risankizumab 90 mg (2.4%), risankizumab 150 mg (0.7%), and risankizumab 150-180 mg (0.7%). The estimated annualized rates of CV events were: placebo (5%), ustekinumab (5%), adalimumab (4%), risankizumab 90 mg (7%), risankizumab 150 mg (2%), and risankizumab 150-180 mg (2%).

In all the subjects exposed to risankizumab regardless of dose or timing (N=2234), 60 subjects experienced one or more cardiovascular events (2.7% -reference: *ISS Table 2.2_4.3*). The most frequent events were 1st degree atrio-ventricular block (n=9), palpitations (n=8), “coronary artery disease” (n=8), tachycardia (n=6), atrial fibrillation (n=6), myocardial infarction (n=3), congestive heart failure (n=3), coronary artery occlusion (n=2), myocardial ischemia (n=2) intraventricular conduction defect (n=2), diastolic dysfunction (n=2), mitral valve incompetence (n=2), atrial flutter (n=2), tricuspid insufficiency (n=2), and a variety of single (n=1) events (e.g., sinus bradycardia, sinus tachycardia, Prinzmetal angina, ventricular extrasystoles, ventricular hypokinesia, ventricular tachycardia, aortic valve disease, mitral valve disease).

A pooling of ustekinumab-controlled trials (study 1311.3 and 1311.28) compared MACE, extended-MACE, and other CV events in the risankizumab 150 mg arms (N=598) to that in the ustekinumab arms (N= 199) (see [Table 6](#)). There were no reported events in the ustekinumab arms. The events in the risankizumab 150 mg arms (efficacious dose) were low: MACE (0.3%), extended MACE (0.7%) and “other events” that included cardiac arrhythmia (0.7%) and CHF (0.7%).

In the “other CV events” category of the ustekinumab-controlled trials, there appeared to be an imbalance (i.e. 4 events of arrhythmia and 4 events of CHF in the risankizumab arms vs 0 events in the ustekinumab arms) that occurred in 7 patients.

The results of a search of the case report forms detailing the adjudicated heart failure and arrhythmia events leading to the apparent imbalance between ustekinumab and risankizumab are shown in [Table 7](#). In the 4 cases of CHF, the verbatim reports were CHF, left cardiac decompensation (each required hospitalization), mitral valve incompetence and acute kidney failure superimposed on chronic kidney disease (each of these 2 required an urgent visit). There were 5 cases of supraventricular arrhythmia (SVA) none of which had ischemia. One of the cases was deemed a pre-existing condition and was not counted likely for that reason. Of the 4 remaining SVA events that were counted, the verbatim reports were atrial flutter with 4:1 AVB, “tachycardia”, atrial fibrillation, and AV nodal reentrant tachycardia. All were described as new onset. Subject (b) (6) had coronary bypass grafting reported as an adverse event one month earlier that may have been a confounder in the SVA event. The other cases of SVA did not have reported cardiac histories suggestive of an arrhythmic risk. In the absence of imbalances in the larger sample size of the primary pooled safety population, this low-incidence observation was likely due to chance.

A literature search produced no evidence of a relationship between interleukin 12/23 agents and arrhythmic potential. In general, the association between MACE and the use of interleukin 12/23 agents is unclear (Lebwohl, 2012).

Table 5: Cardiovascular adverse events from Primary Safety Pool

				Risankizumab		
Risk	Placebo	UST	ADB	90 mg	150 mg	150-180 mg
N	300	239	304	41	1306	1348
CV events n (%)	5 (1.7%)	4 (1.7%)	4 (1.3%)	1 (2.4%)	9 (0.7%)	9 (0.7%)
<i>Acute Myocardial Infarction</i>	0	0	0	0	1 (<0.1%)	1 (<0.1%)
<i>Angina Pectoris</i>	0	1 (0.4%)	0	0	0	0
<i>Aortic Valve Disease</i>	1 (0.3%)	0	0	0	1 (<0.1%)	1 (<0.1%)
<i>Atrial Fibrillation</i>	1 (0.3)	0	1 (0.3%)	0	1 (<0.1%)	1 (<0.1%)
<i>1st AV Block</i>	1 (0.3%)	0	0	0	1 (<0.1%)	1 (<0.1%)
<i>Bradycardia</i>	0	0	1 (0.3%)	0	0	0
<i>CHF</i>	0	0	1 (0.3%)	0	1 (<0.1%)	1 (<0.1%)
<i>Cardiomegaly</i>	0	0	0	0	1 (<0.1%)	1 (<0.1%)
<i>CAD</i>	0	1 (0.4%)	0	0	1 (<0.1%)	1 (<0.1%)
<i>IVCD</i>	0	0	0	0	1 (<0.1%)	1 (<0.1%)
<i>Hypertensive Heart Disease</i>	0	1 (0.4%)	0	0	0	0
<i>Palpitations</i>	2 (0.7%)	0	0	1 (2.4%)	2 (0.2%)	2 (0.1%)
<i>Sinus Tachycardia</i>	0	1 (0.4%)	0	0	1 (<0.1%)	1 (<0.1%)
<i>VPCs</i>	0	0	1 (0.3%)	0	0	0

CHF= Congestive Heart Failure; CAD= Coronary Artery Disease; IVCD= Intraventricular Conduction Defect; VPC= Ventricular Premature Contraction. Source: ISS Table 2.2_1.3

Table 6: Adjudicated CV Endpoints in Ustekinumab controlled Phase 3 Studies

Study 1311.3; 1311.28	UST	RST 150 mg	95% CI
N	199	598	
MACE n (%)	0	2 (0.3%)	-0.13—0.80
-CV Death	0	1 (0.2%)	
-Nonfatal MI	0	1 (0.2%)	
Extended MACE n (%)	0	4 (0.7%)	0.02—1.33
-CV Death	0	1 (0.2%)	
-Nonfatal MI	0	1 (0.2%)	
-Hospitalization for UAP	0	2 (0.3%)	
Other CV Events n (%)	0	7 (1.2%)	0.57—2.40
-Cardiac Arrhythmia	0	4 (0.7%)	
-CHF	0	4 (0.7%)	

UAP= unstable angina pectoris. Source: ISS Table 2.2_3.14.1

Table 7: Patient Data on Arrhythmia and Heart Failure Events from UST-controlled trials

Trial Number	Site #	Subject #	Verbatim	Adjudication Committee
1311.28		(b) (6)	Acute superimposed on CKD	HF-urgent visit
1311.28			Aflutter 4:1 AVB	SVA with no ischemia
1311.28			Symptomatic AF	SVA with no ischemia (<i>pre-existing</i>)
1311.28			Congestive HF	HF requiring hospitalization
1311.28			Tachycardia	SVA with no ischemia
1311.3			AF	SVA with no ischemia
1311.3			AVNRT	SVA with no ischemia
1311.3			Left Cardiac Decompensation	HF requiring hospitalization
1311.3			MV Incompetence	HF-urgent visit

CKD= Chronic Kidney Disease; HF= Heart Failure; SVA= Supraventricular Arrhythmia; AF= Atrial Fibrillation; AVNRT= AV Nodal Re-Entrant Tachycardia; MV= Mitral Valve. Source: CRF Event Adjudication

References

- Kaye, J, et al., 2008, Incidence of risk factors for myocardial infarction and other vascular disease in patients with psoriasis, British Journal of Dermatology, 159 (4): 895-902, <https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1365-2133.2008.08707.x>
- Lebwohl, M, 2012, Interleukin 12/23 agents and major adverse cardiac events, Archives of Dermatology, 148 (11): 1329, <https://jamanetwork.com/journals/jamadermatology/fullarticle/1392590>
- Mehta, N, et al., 2011, Attributable risk estimate of severe psoriasis on major cardiovascular events, The American Journal of Medicine, 124, 775.e1-775.e6, https://ac.els-cdn.com/S0002934311003275/1-s2.0-S0002934311003275-main.pdf?_tid=40368713-6cdd-46ed-b578-7e6b0124d395&acdnat=1541511554_ef82c97c735bc1c5487bacf5c0bca3dd
- Neimann, A, et al., 2006, Prevalence of cardiovascular risk factors in patients with psoriasis, Journal of the American Academy of Dermatology, 55: 829-835, https://ac.els-cdn.com/S0190962206023383/1-s2.0-S0190962206023383-main.pdf?_tid=c40aac25-707b-4578-9112-7c89fdb719ce&acdnat=1541457397_d6fe55ce1ac9da2e008c05fec7dea3f8

Appendix

The following are the AC Members and their specific function on the AC.



Source: 5.3.5.3/Legacy Clinical Study Report/Adjudication Committee Charter, version 2, 02 August 2017

The following cardiovascular events will be adjudicated:

- Cardiovascular Death
- Non-Cardiovascular Death
- Undetermined Cause of Death
- Myocardial Infarction (non-fatal)
- Heart Failure Event (non-fatal)
- Hospitalization for Unstable Angina (non-fatal)
- Coronary Revascularization Procedures (non-fatal)
- Stent Thrombosis (non-fatal)
- Clinically Significant Arrhythmia (no evidence of ischemia) (non-fatal)
- Hypertensive Emergency (non-fatal)

The following cerebrovascular events will be adjudicated:

- Stroke (fatal/non-fatal)
- Transient Ischemic Attack (non-fatal)

The following thrombotic events will be adjudicated:

- Deep Vein Thrombosis (DVT) (non-fatal)
- Other Venous Thrombosis, specified (non-fatal)
- Pulmonary Embolism (PE) (fatal/non-fatal)
- Non-Cardiac/Non-Neurologic Arterial Thrombosis/Thromboembolism (fatal/non-fatal)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

FORTUNATO F SENATORE
12/04/2018

MARTIN ROSE
12/05/2018

NORMAN L STOCKBRIDGE
12/05/2018

ICC1800541

BLA 761055, Risankizumab injection, Prefilled Syringe

Abbvie

Date	10/19/2018
To	Melinda Bauerlien CDER/OPQ/OPRO/DRBPMI/RBPMB
Requesting Center/Office	CDER/OPQ
OND Review Division	CDER/ODEIII/DDDP
From	Matthew Ondeck CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CAPT Alan Stevens CDRH/ODE/DAGRID/GHDB
Subject	Consult for BLA 761105 ICCR2018-03158 ICC1800541
Final Recommendation	CDRH is recommending that the device constituent of the combination product is approvable for the proposed indication.

Digital Signature Concurrence Table		
Reviewer	Matthew Ondeck -S	Digitally signed by Matthew Ondeck -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Matthew Ondeck -S, 0.9.2342.19200300.100.1.1=2002209640 Date: 2018.10.25 15:52:16 -04'00'
Branch Chief	 Alan M. Stevens -S	

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2018-03158
ICCR SharePoint Link	SP link
ICC tracking # (Lead)	ICC1800541
Submission Number	BLA 761105
Sponsor	Abbvie
Drug/Biologic	Risankizumab injection
Indications for Use	For the treatment of adult patients with moderate to severe plaque psoriasis
Device Constituent	Prefilled Syringe
Related Files	N/A

Table 2. Review Team				
Were other disciplines consulted?			<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
Below is a list of the Discipline Specific ICCR#, ICC# and CON#.				
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	ICCR #	ICC #	CON #
Office of Compliance	Isabel Tejero (CDRH/OC)	ICCR2018-03159	ICC1800541	CON1817195

Table 3. Important Dates	
Interim Due Dates	Due Date
Filing	Unknown
74-Day Letter	Unknown
Mid-Cycle	9/12/2018
Primary Review	10/23/2018
PDUFA/GDUFA Due Date	Unknown

2. PURPOSE/BACKGROUND

2.1. Scope

Abbvie is requesting approval of the risankizumab injection. The device constituent of the combination product is a prefilled syringe.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product on July 11, 2018:

Please assess all relevant documentation in BLA 761105 regarding the pre-filled syringe (PFS) device and needle shield to determine if the information provided is complete and in compliance. Determine if an inspection is needed for the relevant facilities regarding the PFS, including the sponsor of the BLA and/or the manufacturer of the PFS. If an inspection(s) is required, to perform the required inspection(s).

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

- Device performance
- Release Specifications for the device constituent
- Biocompatibility of the syringe components as the barrel is primary container closure

This review will not cover the following review areas:

- Compatibility of the drug with the device materials
- Human Factors
- Sterility of the syringe components as the barrel is primary container closure

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

2.2. Prior Interactions

There does not appear to be any related submissions/prior interactions.

2.3. Indications for Use

Table 1: Indications for Use

Combination Product	Indications for Use
Risankizumab injection	For the treatment of adult patients with moderate to severe plaque psoriasis
Prefilled Syringe	Delivery of the drug product

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Location
Container Closure System	Seq 0001(1)_3.2.P.7 Container Closure System
Container Closure System NSP-PFS	Seq 0001(1)_3.2.P.7 Container Closure System
Proposed- Labeling Text –SPL - psoriasis	Sequ0004(4)_1.14.1.3 Draft Labeling Text
Draft Container – risankizumab – syringe – 75mg0.83ml- label	Seq 0001(1)_1.14.1.1 Draft Carton and Container Labels
Draft Container – risankizumab – syringe – 75mg0.83ml- 2ct	Seq 0001(1)_1.14.1.1 Draft Carton and Container Labels
Draft Container – risankizumab – syringe – 75mg0.83ml- sample-printmat	Seq 0001(1)_1.14.1.1 Draft Carton and Container Labels

Specification	Seq0001(1)_3.2.P.5.1 Specification(s)
Specifications NSP-PFS	Seq0001(1)_3.2.P.5.1 Specification(s)
Extractable Volume	Seq0001(1)_3.2.P.5.3 Analytical Procedures
Break-out and Gliding Force	Seq0001(1)_3.2.P.5.3 Analytical Procedures
Container Closure Integrity	Seq0001(1)_3.2.P.5.3 Analytical Procedures
Validation of Analytical Procedures NSP-PFS	Seq0001(1)_3.2.P.5.3 Analytical Procedures
Batch Analyses	Seq0001(1)_3.2.P.5.4 Batch Analyses
Batch Analyses NSP-PFS	Seq0001(1)_3.2.P.5.4 Batch Analyses
NSP-PFS HFE/UE Report	Seq0001(1)_5.3.5.4 Study Report Body
Trace Matrix	Seq0001(1)_3.2.R Regional Information
Risk Management Information	Seq0001(1)_3.2.R Regional Information
Stability Summary and Conclusions	Seq0001(1)_3.2.P.8.1 Stability Summary and Conclusions
Accelerated and Long Term Stability data	Seq0001(1)_3.2.P.8.3 Stability Data
Stability Summary and Conclusions NSP-PFS	Seq0001(1)_3.2.P.8.1 Stability Summary and Conclusions
Container Closure System (shipping study)	Seq0001(1)_3.2.P.2 Pharmaceutical Development
Response to CMC Questions Dated August 3, 2018	Seq0006(6)_1.11.4 Multiple Module Information Amendment
Psoriasis FDA correspondence	Seq 0001(1)_1.6.3 Correspondence Regarding Meetings
Biocompatibility Statement (b) (4) Plunger Rod White	Seq0006(6)_3.2.R. Regional Information
Biocompatibility Statement (b) (4) Finger Flange White	Seq0006(6)_3.2.R. Regional Information
Letter of Authorization for (b) (4) -2018-Aug 21	Seq0008(8)_1.4.1 Letter of Authorization

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

4.1. PFS Description:

The container closure system of Risankizumab 75 mg/0.83 mL Pre-filled Syringe (PFS) consists of a 1 mL glass syringe, utilizing USP/Ph. Eur./JP (b) (4) glass. Each syringe includes a staked-in-place (integrated) 0.5 inch long, 29 gauge, thin wall stainless steel needle for subcutaneous injection, a (b) (4) rubber stopper and a rigid needle shield (RNS) (b) (4) Figure 1 depicts the container closure components. The PFS is assembled with a needle stick protection (NSP) device as a safety feature. The NSP components have no product contact. Details for the NSP are provided in Section 3.2.P.7 Container Closure System for the NSP-PFS. Details regarding the composition of the components of the syringe (glass barrel, needle and rigid needle shield), are included in Table 1. Glass barrels with staked needle and needle shield are received from the supplier (b) (4) sterile and non-pyrogenic (ready-to-fill). (b) (4) ; the rigid (b) (4) shell (b) (4) has no product contact. The sponsor also states that the plunger stopper are received from the supplier (b) (4) (b) (4) sterilized

(ready-to-use).

Figure 1. Expanded View Drawing of the Container Closure System



Table 2. Dimensions of the Glass Syringe

Parameter	Description	Nominal Dimensions
A	Inside diameter of barrel	(b) (4)
B	Outside diameter of barrel	
C	Total length of the barrel including needle shield	
D	Length of barrel under flange without needle shield	
E	Flange thickness	

Table 4. Dimensions of the Plunger Stopper

Parameter	Description	Nominal Dimensions
A	Outside diameter of plunger stopper lips	(b) (4)
B	Total length of the plunger stopper	

Reviewer Note:

The product has (b) (4) rigid needle shield (b) (4). The sponsor states that the supplier provides the barrel, needle, rigid needle shield, and plunger stopper are provided sterile.

They provide an LOA to DMF (b) (4) to confirm sterility of these syringe parts. Additionally, the fact that CDER will be reviewing the sterility of the drug product in the primary container closure and the extractables/leachables of the primary fluid path (including needle), I believe that the response is adequate.

4.2. Needle Safety Device Features:

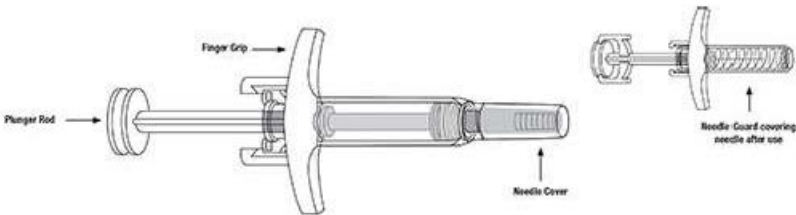
The (b) (4) provided by (b) (4) is a safety feature added to the PFS drug product as a secondary packaging component. The needle stick protection (NSP) device components include the (b) (4) a plunger rod (PR) and (b) (4) finger flange (b) (4) as described in Table 1.

Table 1. Description of the NSP-PFS Components

Component	Sub-Component	Component Material	Comment
(b) (4)			
Plunger Rod (PR)	N/A	(b) (4)	
(b) (4) Finger Flange (b) (4)	N/A	(b) (4)	
Pre-filled Syringe (PFS)	The PFS system is described in Section 3.2.P.7 Container Closure System of the PFS drug product.		



A schematic of the final finished device prefilled syringe is shown below:



Syringe Device Description

Device Characteristic	Description / Specification
Syringe Name	Risankizumab 75 mg/0.83 mL Pre-filled Syringe (PFS)

Syringe Platform Name (if applicable)	(b) (4) 1 mL syringe (not clear which model)
Priming Dose / Volume	N/A
Dose accuracy	(b) (4) mL
Injection Time	N/A
Injection Site	Abdomen or thigh
Injection tissue and depth of injection	subcutaneous
Audible / visual feedback	N/A
Cap Removal Force	(b) (4) N
Break/Glide Force	(b) (4) N
Visibility of medication container	Yes
Needle Specifications <ul style="list-style-type: none"> Length(s) Gauge(s) Connection type <ul style="list-style-type: none"> ISO 11608-2:2012 Prestaked 	0.5 inch 29 G Thin Walled – Stainles Steel Needle Prestaked
Type of Use (e.g. single use, disposable, reusable, other)	Single use
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Self administration
Method of actuation	Manual
Automated Functions	Needle Safety Device
Residual Medication	N/A
Drug Container Type	(b) (4) Glass
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	mg/mL
Environments of use	Home/clinical
Storage conditions and expiry	2-8 deg C, 24 months
Graduation marks / fill lines	N/A; single dose
Preparation and administration (describe all that are applicable) <ul style="list-style-type: none"> Warm to room temp prior to injection Assembling components Prime steps Setting dose Skin preparation steps (e.g., pinch skin, inject through clothing, etc.) Changing / disposing needles Etc. 	<ul style="list-style-type: none"> leave the carton at room temperature and out of direct sunlight for 15 to 30 minutes before injecting. Place the following on a clean, flat surface: <ul style="list-style-type: none"> 2 prefilled syringes and 2 alcohol swabs 2 cotton balls or gauze pads (not included) Sharps disposal container (not included) Wash and dry your hands Start with one syringe for first injection. Wipe the injection site in a circular motion with the alcohol swab (before both injections)
Safety Features	<ul style="list-style-type: none"> (b) (4)

<ul style="list-style-type: none"> Needle safety 	<ul style="list-style-type: none"> Rigid needle shield <div>(b) (4)</div>
Material composition of PFS	Glass

Device Description Recommendation	
The Sponsor Provided Complete Device Description for the Device Constituent	<input checked="" type="checkbox"/>

5. DESIGN CONTROL REVIEW

CDRH performed Filing Review	<input type="checkbox"/>
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	<input checked="" type="checkbox"/>

Table 4: Design Control Documentation Check

Design Control Requirement	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	X		0001(1)_3.2.R
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		0001(1)_3.2.P.5.4
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	X		0001(1)_3.2.R

Master File Review Instructions

Master File Stock IR

Design Controls Recommendation	
The Sponsor Provided Complete Design Controls for the Device Constituent	<input checked="" type="checkbox"/>

6. DESIGN VERIFICATION AND VALIDATION REVIEW

6.1. Summary of Design V&V Attributes

Table 5: Summary of Design V&V Attributes

Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial?		X (see	

			Section 6.2)	
Selectable dose range on device matches the labeled dose range for the medication?		X		
Verification methods relevant to specific use conditions as described in design documents and labeling		X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)		X		
Traceability demonstrated for specifications to performance data		X		
Stability and simulated shipping / transport data adequately verifies device will meet essential performance requirements at expiry		X		
Discipline -Specific Design Verification / Validation adequately addressed	Biocompatibility	X		
	Sterility	X		

Referenced Standards and Guidance Documents

Reference Standard / Guidance	Description / Extent of FDA Recognition	Documentation Adequate	
		Yes	No
ISO 11040-4 : Glass barrels for injectables	FDA recognized	X	
ISO 9626: Stainless Steel Tubing for the Manufacture of Medical Devices	FDA recognized	X	

6.2. Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase I/II/III Study utilized the to-be-marketed device		X (see below)	
A human factors validation study was conducted	X		

Clinical Validation:

The sponsor stated the following regarding clinical validation of the device:

“The to-be-marketed version of the combination product is the (b) (4) pre-filled syringe (PFS), (b) (4) (NSP), plunger rod (PR) and (b) (4) finger flange (b) (4), and was not used in the pivotal clinical studies. The syringe system used in the pivotal clinical studies was the same (b) (4) pre-filled syringe (b) (4). Although the (b) (4) commodities are similar but not identical between the clinical trials and the to-be-marketed version of the device, the principle of use is the same with respect to the administration parameters for a pre-filled syringe system.”

Review Note:

The sponsor states that the only differences between the clinical use device and the to-be-marketed version of the device is that (b) (4)

(b) (4). Given that these changes would not have any effect on the clinical outcome/performance of the device and that the use of the device was validated using HF studies, I do not believe additional bridging verification is necessary. Additionally, the Agency agreed in an end of phase 2 meeting, that additional bridging verification would be needed.

Human Factors Validation

The sponsor provided a human factors validation study. The review of the adequacy of the study is deferred to CDER/DMEPA. However a cursory review of the HF study is below.

The critical tasks that the sponsor identified are below. They seem appropriate.

Table 7: Critical Tasks

Task
1. Select injection site
2. Remove the needle cover
3. Slowly push plunger all the way in until all the liquid is injected and syringe is empty
4. Administer the second injection

The sponsor conducted the study then provided a critical task failure analysis. The failures that resulted were the following:

- Selecting Injection Site
 - Many patients chose incorrect sites such as incorrect part of abdomen or arms.
- Slowly push plunger all the way in until all the liquid is injected and the syringe is empty
 - Didn't remove needle cover, resulting in a wet injection.
 - User placing thumb on syringe plunger resulting in a loss of medication
 - Not holding syringe appropriately resulted in a loss of medication
- Administer the second injection
 - Some users only injected one dose, not the second based on preconceived notions
- Inspecting device for cloudiness/particles
 - One user stated that they should call their doctor rather than not use the product
- Should the product be returned?
 - One user stated that it should only be returned if syringe tray seal is damaged or broken

The sponsor made one change to the instructions for use by clarifying the instruction to return the syringe to the pharmacy if necessary. See below:

DO NOT use if syringe tray seal is broken or missing. Return product to the pharmacy.

I believe that the failures that were seen in the HF study were relatively minor and are not unique to this device. CDRH does not have outstanding review issues based on this information; however, as noted, we defer to DMEPA assessment on the risk associated with these errors.

Clinical Validation Stock IR

Design Validation Recommendation	
The Sponsor Provided Complete Design Validation for the Device Constituent	☑

**6.3. Design Verification Review***6.3.1. Design Verification Testing Summary*

Device Performance Requirement	Specification	Test Methods	Primary Spec Verified	Spec Verified to Expiry	Spec Verified after Shipping	Lot Release Specification (Y/N)
Dose Accuracy	(b) (4)	Adequate	All passed	All passed	All passed*	Y
Break Loose Force	(b) (4) N	Adequate	All passed	All passed	All passed	Y
Glide Force	N	Adequate	All passed	All passed	All passed	Y
Sharps Protection Activation	See Section 6.3.1.3	Adequate	All passed	All passed	All passed	Y
Container Closure Integrity	See Section 6.3.1.4	Adequate	All passed	All passed	All passed	Y***
Tip Cap Removal Force	See Section 6.3.1.5	Adequate	All passed	All passed**	All passed**	Y

*In lieu of conducted dose accuracy testing after the simulated shipping study, the sponsor conducted container closure testing with a methylene blue test to demonstrate the closure was not compromised. They also conducted plunger stopper movement to demonstrate that minimal movement occurred. Additionally, dose accuracy is a lot release specification. Given the testing that was to verify container closure, the fact that the device is a single dose injection, and that dose accuracy is a lot release specification, I believe that the sponsor has provided adequate mitigation to the risk of mis-dosing/loss of drug product after shipping.

**Although tip cap removal force was not tested up to expiry and after shipping, it is included as a lot release specification and was characterized. I believe that this is adequate.

***While container closure was not a lot release specification, bacterial endotoxin and sterility test via USP <71> are used as a lot release specifications to ensure sterility of the combination product. As this is the primary container closure, this lot release specification is under the review of CDER.

6.3.1.1. Dose Accuracy:

The sponsor provided testing that evaluated the dose accuracy of the syringe by weighing the amount of solution that was administered. Testing was completed with 05. in, 29 G needle. The specifications for device dose accuracy and break/glide force were taken from 0001(1)_3.2.P.7:

Table 1. Specification for Risankizumab 75 mg/0.83 mL Pre-filled Syringe

Test	Analytical Procedure	Acceptance Criteria	Where Applied	
			Release	Shelf-Life
Extractable volume	Ph. Eur. 2.9.17, USP <697> JP 6.05	(b) (4)	X	N/A
Functional Tests				
Container Closure Integrity	In-house method		N/A	X
Break-out force, gliding force	In-house method		X	X
Microbiological Tests				
Bacterial endotoxins	Ph. Eur. 2.6.14, USP <85>, JP 4.01		X	N/A
Sterility	Ph. Eur. 2.6.1, USP <71>, JP 4.06		X	X

This test method is adequate. The results are taken from 3.2.P.5.41

Test		Batch Numbers						
		606470	606471	606872	704790	704791	704999	704998
Nominal Fill Volume		0.83 mL/ syringe	0.83 mL/ syringe	0.83 mL/ syringe	0.83 mL/ syringe	0.83 mL/ syringe	0.83 mL/ syringe	0.83 mL/ syringe
General Tests								
pH		(b) (4)						
Osmolality	[mOsmol/kg]	290	292	293	283	282	268	269
Extractable Volume	[mL]	0.85	0.84	0.86	0.86	0.84	0.86	0.86

The sponsor states that 5 syringes per lot were tested in accordance with USP <697> Container Content For Injections. The extractable volume reported is the smallest volume reported. Therefore all syringes tested met the requirements for extractable volume.

Reviewer Note:

Some of the stability lots appear to exhibit an extractable of

(b) (4)

that the sponsor has shown that over multiple lots that the extractable volume of 0.83 mL is met up to the expiry, I believe that this is adequate.

Table 2. Summary of Extractable Volume Data for Risankizumab 75 mg/0.83 mL PFS from Section 3.2.P.8.3 Stability Data

Batch Number / Storage Condition	Nominal Fill Volume	Extractable Volume [mL]			
		0 months	12 months	24 months	36 months
603924 at 5°C	0.83 mL	0.86	0.86	n/a	n/a
603924 at 25°C		0.86	0.86	n/a	n/a
603923 at 5°C	0.83 mL	0.86	0.86	n/a	n/a
603923 at 25°C		0.86	0.86	n/a	n/a
505412 / 5°C	0.83 mL	0.86	0.86	0.86	n/a
505412 / 25°C		0.86	0.86	n/a	n/a
505410 / 5°C	0.83 mL	0.86	0.86	0.86	n/a
505410 / 25°C		0.86	0.86	n/a	n/a
T210515 / 5°C	0.8 mL	0.9	0.87	0.87	n/a
T210515 / 25°C		0.9	0.9	n/a	n/a
E5799S03 / 5°C	(b) (4)				
E5799S03 / 25°C					
E4744S01 / 5°C					
E4744S01 / 25°C					
E3744S02 / 5°C					
E3744S02 / 25°C					
E2744S02 / 5°C					
E2744S02 / 25°C					

6.3.1.2. Break & Glide Force:

The sponsor provided testing that evaluated the break and glide force of the syringe. Testing was completed with 05. in, 29 G needle. The specifications for device dose accuracy 0001(1)_3.2.P.7:

The test method appears to be a typical Instron equipment that measures the force needed to move the plunger. See 0001(1)_3.2.P.5.2 Analytical Procedures for more details. The sponsor states that 10 PFS's were tested. This is unclear if it was 10 from each lot or 10 in total. The results are below:

Test		Batch Numbers					
		606470	606471	606872	704790	704791	704999
Nominal Fill Volume		0.83 mL/ syringe	0.83 mL/ syringe	0.83 mL/ syringe	0.83 mL/ syringe	0.83 mL/ syringe	0.83 mL/ syringe
Functional Tests							
Break-out Force and Gliding Force	Break-out force [N]	4	4	4	4	4	4
	Break-out force, max [N]	5	4	4	4	4	4
	Gliding force [N]	8	8	9	7	7	8
	Gliding force, max [N]	9	10	9	9	8	9
Container Closure Integrity Test		n/a ^a	n/a ^a	n/a ^a	Pass	Pass	Pass

^a n/a not applicable, test not scheduled

^b Results generated without density correction

Given that the max glide and break force are (b) (4) The syringe meets the requirements for the syringe glide/break force.

The sponsor states: "For release testing of Break-out Force and Gliding Force 10 samples were used. This sample number was derived using a statistical experiment with data from the PFS platform in which it was demonstrated that testing more than 10 samples and up to 1000 samples will not significantly change the result. Assuming the break loose and glide forces for a PFS to be normally distributed with unknown variance and unknown mean, table D4 of ISO 16269-6 Annex

D for one-sided statistical tolerance limit factors was used to calculate with a confidence of 95% that 99% of the testing results of the complete batch of the representative platform product would lie within the statistical tolerance interval.”

6.3.1.3. *Needle Safety Device:*

The sponsor provided verification testing of needle safety device. The specifications for the needle safety device were taken from 0001(1)_3.2.P.7:

The NSD was verified through a manual and visual verification. See the methods below:

Appearance Testing

Appearance testing of the NSP-PFS is done visually.



Functionality Testing

Activation testing of the NSP-PFS is done manually and visually.



Table 4. Batch Analysis Results for the NSP-PFS Sample Sizes added from DVT Record.

Test	Acceptance Criteria (b) (4)	Batch Number Sample Size			
		16-006899	16-006843	16-006844	16-006835
Appearance		complies (n=195)	complies (n=196 ^a)	complies (n=195)	complies (200 ^b)
		complies (n=45)	complies (n=45)	complies (n=45)	complies (n=45)
		complies (n=195)	complies (n=196 ^a)	complies (n=195)	not planned
		complies (n=45)	complies (n=45)	complies (n=45)	not planned
Functionality		complies (n=60)	complies (n=60)	complies (n=60)	complies (n=60)
		complies (n=60)	complies (n=60)	complies (n=60)	complies (n=60)
		complies (n=91)	complies (n=91)	complies (n=91)	complies (n=91)
		complies (n=91)	complies (n=91)	complies (n=91)	complies (n=91)

a. When testing extractable volume T0, sample #06 was excluded from testing due to operator failure. An additional sample was tested successfully (details see raw data D-RDLU-000097_A01).

b. Five more samples were tested, as five reserve samples were needed

The sponsor's verification testing is adequate and demonstrates that the requirements of the needle safety device, met the performance requirements over multiple lots of device.

6.3.1.4. Container Closure Testing:

The sponsor provided testing of the syringe container closure to demonstrate that integrity of the container closure to not allow microbial ingress or leakage. The sponsor provided methylene blue testing and validated the test method in 3.2.P.5.3. The test method is below:

“The positive controls, the negative controls and the test samples are immersed in a methylene blue dye solution of different concentrations and a vacuum is applied in five subsequent cycles. After releasing the vacuum, the containers are rinsed with purified water to remove dye from the outer surfaces. After the rinsing procedures, the samples are taken from the sample rack and dried. Each PFS is classified as conforming if no trace of dye solution (dye visible) is in the content of the container.”

“The vacuum chamber is filled with methylene blue solution (0.1%) and the sample PFS as well as the positive and negative control are fixed in the sample holder and placed into the vacuum chamber such that all samples are completely covered by the dye. Five testing cycles of 10 minutes vacuum (≤ 50 mbar) and 1 minute ambient pressure are conducted. At the end of the testing cycles, the samples are incubated at ambient pressure for 30 min. Afterwards, the samples are removed from the vacuum chamber. The test samples are rinsed with deionized water. Finally the outer surface of the samples is dried.”

The acceptance criteria is below

Table 1. Validation Summary Table (continued)

Validation Parameter	Acceptance Criteria	Results
Robustness – Vacuum pressure cycle time	(b) (4)	Passed (b) (4)
Comparison blue dye ingress against microbial ingress		The LOD of the blue dye ingress method is (b) (4) mm OD of the copper wire. Compared with the LOD of the microbial ingress method ((b) (4) mm OD), the blue dye ingress is equally sensitive.

The results are below:

Test		Batch Numbers						
		606470	606471	606872	704790	704791	704999	704998
Nominal Fill Volume		0.83 mL/ syringe	0.83 mL/ syringe	0.83 mL/ syringe	0.83 mL/ syringe	0.83 mL/ syringe	0.83 mL/ syringe	0.83 mL/ syringe
Functional Tests								
Break-out Force and Gliding Force	Break-out force [N]	4	4	4	4	4	4	4
	Break-out force, max [N]	5	4	4	4	4	4	4
	Gliding force [N]	8	8	9	7	7	8	7
	Gliding force, max [N]	9	10	9	9	8	8	9
Container Closure Integrity Test		n/a ^a	n/a ^a	n/a ^a	Pass	Pass	Pass	Pass

^a n/a not applicable, test not scheduled

^b Results generated without density correction

The testing appears adequate. The sponsor states that 20 samples per lot were tested in the stability lots. While container closure was not a lot release specification, bacterial endotoxin and sterility test via USP <71> are used as a lot release specifications to ensure sterility of the combination product. As this is the primary container closure, this lot release specification is under the review of CDER.

6.3.1.5. **Tip Cap Removal Force**

Testing was evaluated against a specification of (b) (4) N. The summary data was included in 0001(1)_3.2.P.2. The sponsor states that all testing passed the acceptance criteria.

Filled Syringe		
n=10	Min. RNS Pull-off Force [N]	Max. RNS Pull-off Force [N]
Acceptance Criterion	Every single value must be between (b) (4) N	
Start	5.2	10.8
3 M/25°C	5.3	11.4
6 M/25°C	6.7	11.6
3 M/5°C	7.6	9.9
6 M/5°C	5.9	10.2
9 M/5°C	7.1	11.0
12 M/5°C	7.5	10.1
18 M/5°C	7.8	11.3
24 M/5°C	6.5	8.9

Additionally, the sponsor states that the RNS specification was validated in the human factors study “RNS removal was defined as a Critical Task and evaluated in the Human Factors Summative Validation study with the intended patient population. No difficulties were observed by participants in removing the RNS.”

“The specification for the final assembled NSP-PFS (see Section 3.2.P 5.1 Specification for the NSP-PFS) requires that “The PFS needle shield can be removed.” This functional requirement has been verified during design verification (refer to Section 3.2.P.2.4 Container Closure of the NSP-PFS, Chapter 6.2) and is tested for release of the combination product.”

This testing is adequate. Additionally, the sponsor states that the RNS removal force is a lot release specification.

6.3.1.6. **Verification up to Expiry:**

The sponsor states:

Real-time and accelerated stability are presented in Section 3.2.P.8.3 Stability Data for the NSP-PFS for the functionality of the device. A calculated simulated aging of secondary packaging components has been performed. The calculation indicates that storage at 38°C for 92 days (3 months) simulates 24 months storage at recommended storage conditions. All results for routine and additional developmental tests meet the acceptance criteria for the NSP-PFS samples stored at stressed conditions (40°C/75% RH) after three months and thereby support the claim for 24 months shelf-life at recommended conditions.

The performance requirements that continue to be tested for verification to the expiry are the following:

Table 6. Additional Developmental Tests and Acceptance Criteria for the Primary Stability Batches

Test Name	Acceptance Criteria	Test Reference
Extractable Volume	(b) (4)	Section 3.2.P.2.4, subsection 6.2.1.5
Liquid Leakage beyond Plunger Stopper		Section 3.2.P.2.4, subsection 6.2.1.7
Ejection and Activation Force Test		Section 3.2.P.2.4, subsection 6.2.1.8
Container Closure Integrity		Section 3.2.P.2.4, subsection 6.2.1.10

Reviewer Note:

The sponsor states that the performance requirements of the PFS device have been met up 24 month, which is what is being proposed as the product expiry.

(b) (4)

Table 1. Risankizumab 90 mg/mL PFS Primary Stability and PPQ Batches

DP Batch Number	DS Batch Number	Nominal Fill Volume	Date of Manufacture	Process/Material Format	Intended Use of Batch
704999	17210014	0.83 mL	25 Jul 2017	(b) (4)	PPQ
704791	17210015	0.83 mL	21 Jul 2017		PPQ
704790	17210013	0.83 mL	19 Jul 2017		PPQ
603924	17210003	0.83 mL	23 Jun 2016		Primary Stability
603923	17210001	0.83 mL	21 Jun 2016		Primary Stability
505412	17200002	0.83 mL	28 Jul 2015		Primary Stability
505410	17200000	0.83 mL	21 Jul 2015		Primary Stability
T210515	111100 111102	0.8 mL	21 May 2015		Primary Stability

Reviewer Note:

After examination of the stability testing (and lots) for the performance testing, (b) (4)

I do not have any additional concerns regarding this. In addition, all performance requirements have been listed lot release testing criteria.

6.3.1.7. Shipping Study

The sponsor provide testing of the device constituent after shipping conditions according to ASTM D999 Standard Methods for Vibration Testing of Shipping Containers, ASTM D4169 Standard Practice for Performance Testing of Shipping Containers and Systems, and ISTA Test Procedure 1A for Packaged Product.

After air shipment, ground transportation and drop/shake exposure, the PFS were visually inspected and then analyzed for:

- container closure integrity (sterility maintenance assessment)
- stopper movement
- break-out and gliding forces of the syringe plunger (syringe functionality)
- needle safety device activation and lock out test (needle safety device functionality)
- physico-chemical quality attributes of risankizumab DP (drug product integrity).

In total four batches were analyzed. Three batches were within 18 months or less, one batch was 26 months old to demonstrate the robustness of the formulation across its shelf life. During air transport the pre-filled syringes are exposed to air pressure changes. These reduced air pressure outside of the syringe might lead to stopper movement because of a relative overpressure inside the syringe. The stopper might come into contact with the non-sterile surface of the syringe. If the stopper subsequently moves back too far into the sterile area, the drug product solution may become contaminated. Results demonstrated that product integrity and PFS functionality was maintained after PFS exposure to air and ground transport conditions,

Tests	Test Atmosphere / Pre-conditioning	Acceptance Criteria	Lot No. 16-006843	Lot No. 16-006844	Lot No. 16-006835
Extractable Volume	Standard	≥ Label Volume	complies	complies	complies
	Warm		complies	complies	complies
	Cool		complies	complies	complies
	Vibration		complies	complies	complies
	Free-Fall		n.t.	n.t.	n.t.
	Simulated Shipping *		n.t.	n.t.	complies

NSP Mechanism Activation and Lock- Out Test	Standard	(b) (4)	complies	complies	complies
	Warm		complies	complies	complies
	Cool		complies	complies	complies
	Vibration		complies	complies	complies
	Free-Fall		n.t.	n.t.	n.t.
	Simulated Shipping *		n.t.	n.t.	complies
Tests	Test Atmosphere / Pre-conditioning	Acceptance Criteria	Lot No. 16-006843	Lot No. 16-006844	Lot No. 16-006835
Liquid Leakage Beyond Plunger Stopper	Standard	(b) (4)	complies	complies	complies
	Warm		complies	complies	complies
	Cool		complies	complies	complies
	Vibration		complies	complies	complies
	Free-Fall		n.t.	n.t.	n.t.
	Simulated Shipping *		n.t.	n.t.	complies
Ejection and Activation Force Test	Standard	(b) (4)	complies	complies	complies
	Warm		complies	complies	complies
	Cool		complies	complies	complies
	Vibration		complies	complies	complies
	Free-Fall		n.t.	n.t.	n.t.
	Simulated Shipping *		n.t.	n.t.	complies
Container Closure Integrity	Standard	(b) (4)	complies	complies	complies
	Warm		n.t.	n.t.	n.t.
	Cool		n.t.	n.t.	n.t.
	Vibration		n.t.	n.t.	n.t.
	Free-Fall		n.t.	n.t.	n.t.
	Simulated Shipping *		n.t.	n.t.	complies

Table 31. Study Results after Air Shipment and Drop/Shake Vibration

Batch Number	CCIT Pass/Fail	Stopper Movement max [mm]	Break-out Force max [N]	Gliding Force max [N]
602987	Pass	0.23	4.93	8.51
602988	Pass	0.31	4.48	7.70
603924	Pass	0.40	4.72	8.17
505413	Pass	0.36	5.03	8.37

The sponsor conducted container closure testing, break out glide force, and stopper movement testing, which all passed the acceptance criteria. They did not conduct dose accuracy because container closure testing as a proxy. This is adequate.

Reviewer Note:

It appears that the sponsor has identified the max movement that would result in the drug product becoming non-sterile:

Stopper position measurement in graphite dusted syringes was measured prior and after real-time air shipment. The stopper showed minimal movement (≤ 0.4 mm, see Table 31) satisfying the acceptance criteria ((b) (4) mm), which ensures no movement beyond the sterile area. This is adequate.

6.3.2. Biocompatibility Review

Biocompatibility Review Instructions

Biocompatibility Evaluation		
Materials List	Plunger	Yes
	Syringe Body	No (Evaluated by CDER; fluid path)
	Needle	No (Evaluated by CDER; fluid path)
	Accessories	Yes (Finger Flanges)
Additives/Colorants	In device biocomp	
Device Characteristics		
Category	<input checked="" type="checkbox"/> External communicating device	
Contact Type	<input type="checkbox"/> Blood path, indirect <input type="checkbox"/> CSF contacting ¹ ¹ consult biocompatibility consultant	
Contact Duration	<input checked="" type="checkbox"/> ≤24h (limited) <ul style="list-style-type: none"> Appropriate Endpoints: Cytotoxicity, Sensitization, Irritation, Acute systemic toxicity, Hemocompatibility (indirect hemolysis only), and Material-mediated Pyrogenicity <input type="checkbox"/> >24h to 30 days (prolonged) <ul style="list-style-type: none"> Appropriate Endpoints: Cytotoxicity, Sensitization, Irritation, Acute systemic toxicity, Hemocompatibility (indirect hemolysis only), Material-mediated Pyrogenicity, and Subchronic systemic toxicity <input type="checkbox"/> >30 days (permanent) <ul style="list-style-type: none"> Appropriate Endpoints: Cytotoxicity, Sensitization, Irritation, Acute systemic toxicity, Hemocompatibility (indirect hemolysis only), Material-mediated Pyrogenicity, Subchronic systemic toxicity, and Genotoxicity 	
Testing Performed	<div style="display: flex; justify-content: space-between;"> <div> <input checked="" type="checkbox"/> Cytotoxicity <input checked="" type="checkbox"/> Sensitization <input checked="" type="checkbox"/> Irritation or Intracutaneous Reactivity <input type="checkbox"/> Acute System Toxicity <input type="checkbox"/> Material-Mediated Pyrogenicity </div> <div> <input type="checkbox"/> Subacute/Subchronic Toxicity <input type="checkbox"/> Genotoxicity <input type="checkbox"/> Hemocompatibility <input type="checkbox"/> Carcinogenicity </div> </div>	

The components that are under the scope of the CDRH review are the finger flanges and plunger (limited duration skin contact), as they are not considered the primary container closure and are not part of the fluid administration path. The DMF holder provided summary and test reports with compliance statements for both components.

The summary results for both components are included below. The full test reports were examined for each component and they appear to be tested in accordance with and meet the requirements of the respective ISO 10993-1 section.

Finger Flanges:

ICC1800541

BLA 761055, Risankizumab injection, Prefilled Syringe

Abbvie

Studies results summary for TA 13T_58642
Flange):

(b) (4) Finger

IN VITRO STUDIES, Test Article 13T_58642

Test	Results
ISO 10993-5 Cell Cytotoxicity	Cytotoxicity : none Score = 0

IN VIVO STUDIES, Test Article 13T_58642

Test	Result
ISO 10993-10 Intracutaneous Reactivity	Negligible Irritant Score = 0.0 (SAL, SO)
ISO 10993-10 Guinea Pig Maximization Test	Nonsensitizer Score = 0 (SAL, SO)

Plunger Rod:

Studies results summary for TA 15-6201-022-D
plunger rod): Qualification of the

(b) (4)

(b) (4)

IN VITRO STUDIES, Test Article TA 15-6201-022-D

Test	Results
ISO 10993-5 Cell Cytotoxicity	Cytotoxicity : none Score = 0

IN VIVO STUDIES, Test Article TA 15-6201-022-D

Test	Result
ISO 10993-10 Primary Dermal Irritation	Negligible Irritant PII = 0 (SAL, PEG)
ISO 10993-10 Murine Local Lymph Node Assay	Nonsensitizer: SI = 1.03 (SAL) SI = 0.87 (DMSO)

No outstanding biocompatibility deficiencies exist.

Design Verification Recommendation

The Sponsor Provided Complete Design Verification for the Device Constituent



7. RISK ANALYSIS

7.1. Risk Analysis Attributes

Risk Analysis Summary

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		

7.2. Summary of Risk Analysis

The sponsor provided a risk analysis to demonstrate that they have mitigated the risk of the device to an as low as possible level. The appear to present a risk analysis in accordance with ISO 14971

Figure 1. Risk Acceptability Table

Risk Acceptability	Occurrence				
Severity	1	2	3	4	5
5	5	10	15	20	25
4	4	8	12	16	20
3	3	6	9	12	15
2	2	4	6	8	10
1	1	2	3	4	5

The sponsor presents risks such as:

- Sterility
- damage via shipping
- wrong injection site
- needle safety device does not function
- wrong dose is administered
- incorrect administration
- accidental exposure
- broken device
- user does not receive full dose
- skin irritation

The risk analysis presents verification/validation data as a mitigation to many of these risks, which I believe are adequate. I believe that they have identified many of the risks associated with PFSs and have presented testing to mitigate these risks to an as low as possible level.

Risk Analysis Recommendation

The Sponsor provided complete Risk Analysis for the Device Constituent



8. LABELING

Pre-Filled Syringe Labeling Checklist

Attribute		Present		
		Yes	No	N/A
Device Type	Type: Prefilled	X		
	Syringe Size(s): 0.83 mL	X		
	Needle Gauge	X		
	Needle Length	X		
	Quantity	X		
Prescription Statement under 801.109(b)(1), except for insulin syringes		X		

Special requirements for insulin syringes as described in 801.403 about mixing insulin, including "For use with U100 insulin only" on the barrel and gradations on the barrel in units;			X
Any instructions for using specialized syringes such as the anti-needlestick devices and cartridge syringes;	X		
Any specific drug or biologic use;	X		
Instructions on how to clean and sterilize any reusable components.			X

8.1. Device Labels

Syringe Label:

Outer Packaging:



Syringe Packaging:



Reviewer Comment:
The labeling/packaging is adequate.

8.2. Instructional Labeling

The instructions for use taken from Seq0004_1.14.1.3 is below:





Place the following on a clean, flat surface:

- 2 prefilled syringes and 2 alcohol swabs
- 2 cotton balls or gauze pads (not included)
- Sharps disposal container (not included)

Wash and dry your hands.

Start with one syringe for first injection.

1 Full Dose =  

For a full dose, 2 injections are required, one after the other.



Pick from the 3 injectable areas:

- Front of **left thigh** or **right thigh**
- Your **abdomen** (belly) at least 2 inches from your navel (belly button)



When using 2nd syringe: Pick an injection site **at least 1 inch away** from 1st site. **DO NOT** inject into the same site.

Wipe the injection site in a circular motion with the alcohol swab (before **both** injections)

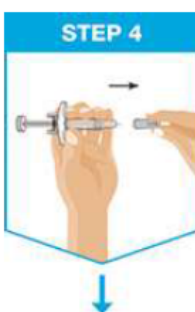
- **DO NOT** inject through clothes
- **DO NOT** inject into skin that is sore, bruised, red, hard, scarred, or has stretch marks, or into areas affected by psoriasis



Hold the syringe with covered needle facing down, as shown.

Check the liquid in the syringe.

- It is normal to see one or more bubbles in the window
- The liquid should look clear to slightly yellow and may contain tiny white or clear particles
- **DO NOT** use if liquid is **cloudy** or contains **flakes** or **large particles**



Remove the needle cover.

- Hold the syringe in one hand
- With the other hand, gently pull the needle cover straight off
- You may see a drop of liquid at the end of the needle. This is normal.
- Throw away the needle cover
- **DO NOT** touch the needle with your fingers or let the needle touch anything



Hold the body of the prefilled syringe in one hand between the thumb and index fingers.
Gently pinch the area of cleaned skin with your other hand and hold it firmly.
Insert the needle into the skin at about a **45-degree angle** using a quick, short movement. Hold angle steady.



Slowly push the plunger all the way in until all of the liquid is injected and the syringe is empty.
Pull the needle out of the skin while keeping the syringe at the same angle.
Release the plunger and allow the syringe to move up until the entire needle is covered by the needle guard.
The syringe needle guard will not activate unless all the liquid has been injected.

- Press a cotton ball or gauze pad over the injection site and hold for 10 seconds
- **DO NOT** rub the injection site. You may have slight bleeding. This is normal.



Repeat Steps 2 through 6 with the 2nd prefilled syringe for a **full dose**.

- Use 2nd syringe immediately following 1st syringe



(b) (4) used syringes in a sharps disposal container.

- **DO NOT** dispose of used syringes in the household trash

(b) (4)

For more information, see “**USED PREFILLED SYRINGE DISPOSAL**” section.

Reviewer Comment:

The instructions for use are adequate.

8.3. Warnings/Precautions/Contraindications

- Infections: TRADENAME may increase the risk of infection. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If such an infection develops, do not administer TRADENAME until the infection resolves. (5.1)
- Tuberculosis (TB): Evaluate for TB prior to initiating treatment with TRADENAME. (5.1)

Reviewer Comment

The warnings/precautions/contraindications are adequate.

Labeling Recommendation	
The Sponsor provided complete Labeling for the Device Constituent	<input checked="" type="checkbox"/>

9. DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

The following release specifications are included for the device constituent within eCTD Module 3.2.P.5:

Release Specifications

Attribute	Specification	Test Method
Dose Accuracy	X	X
Break Loose/Glide Force	X	X
PFS Needle Shield Removal force	X	X
PFS Needle Safety Device Functionality	X	X

See below taken from Seq0001(1)_3.2.P.5.1. The sponsor confirms that the dose accuracy, breakloose/glide force, and the device needle safety device will be tested at lot release using their verification test methods:

Table 1. Specification for Risankizumab 75 mg/0.83 mL Pre-filled Syringe

Test	Analytical Procedure	Acceptance Criteria	Where Applied	
			Release	Self-Life
Extractable volume	Ph. Eur. 2.9.17, USP <697> JP 6.05	(b) (4)	X	N/A
Functional Tests				
Container Closure Integrity	In-house method		N/A	X
Break-out force, gliding force	In-house method		X	X
Microbiological Tests				
Bacterial endotoxins	Ph. Eur. 2.6.14, USP <85>, JP 4.01		X	N/A
Sterility	Ph. Eur. 2.6.1, USP <71>, JP 4.06		X	X

Table 1. Specification for the NSP-PFS

Test	Acceptance Criteria	Where Applied	
		Release	Shelf-life
Appearance	(b) (4)	X	X
		X	X
		X	X
		X	X
Functionality		X	X
		X	X
		X	X
		X	X

Release Specifications Recommendation	
The Sponsor provided complete Release Specifications for the Device Constituent	<input checked="" type="checkbox"/>

10. QUALITY SYSTEMS REVIEW:

Isabel Tejero (CDRH/OC) was consulted for a review of the quality systems for the device constituent as well as to determine if an inspection was needed. She stated the following regarding the need for a compliance review/inspection:

“The BLA product is for treatment of psoriasis, no life-saving or critical treatment. The device constituent is a prefilled syringe with an external safety element to prevent needle sticks. Based on the tier chart we are using for the OPEQ project, CDRH doesn’t need to conduct a compliance evaluation of the application.”

Therefore no quality systems/inspection is needed for the subject product.

11.INTERACTIVE REVIEW

11.1. Filing Information Requests

Are there filing review information requests? ☒ No ☐ Yes

11.2. Interactive Review Request #1

Are there 74-Day Letter information requests? ☐ No ☒ Yes

Agency Information Request #1: Sent on 7/20/2018; returned 8/24/2018

1. In document "Container Closure System", 3.2.P.7, you state that the supplier provides the barrel, needle, rigid needle shield, and plunger stopper are provided sterile. While you provide verification of the sterility of the drug product, you do not provide information regarding the following:
 - a. The device components of the to-be-marketed device that are provided sterile to the user.

Sponsor Response:

The to-be-marketed combination product consists of a pre-filled syringe (PFS) assembled with a needle stick protection device (NSP). The final assembled NSP-PFS is packaged in a (b) (4) film blister and placed in a carton box. The PFS contains the risankizumab drug product solution that is provided as sterile to the user. (b) (4)

(b) (4) The glass barrel with staked needle and rigid needle shield is sterilized (b) (4). The plunger stopper is sterilized (b) (4). Additional information on the sterilization of the PFS components (glass barrel with staked needle and rigid needle shield, and plunger stopper) is provided in DMF (b) (4). A letter authorizing FDA to review and reference information in DMF (b) (4) on behalf of AbbVie is provided in Module 1.4.1 Letter of Authorization – (b) (4). The final assembled NSP-PFS is not provided as sterile to the user. The only part of the NSP-PFS that is inserted into the patient is the stainless steel needle of the PFS, and the sterility of this component is maintained by the needle shield until the time of use. In addition, as described in Section 3.2.P.2.4 Container Closure System for the NSP-PFS, Chapter 4.3.2, the NSP-PFS assembly process is designed such that neither of the container-closure integrity barrier points (PFS/needle shield and PFS/stopper) is breached, therefore sterilization after NSP-PFS assembly is not required.

FDA Response:

The sponsor's response is adequate. They state that the barrel, plunger stopper, needle, and rigid needle shield are provided sterile (b) (4). They provide an LOA to DMF (b) (4). Additionally, the fact that CDER will be reviewing the sterility of the drug product in the primary container closure and the extractables/leachables of the primary fluid path (including needle), I believe that the response is adequate.

- b. How sterility of the device components/drug product is maintained while the device is filled with the drug product and assembled.

Sponsor Response:

Risankizumab is manufactured using

(b) (4)

A large rectangular area of the document is redacted with a solid gray fill. It covers the majority of the page content below the 'Sponsor Response' header.

(b) (4)

A large rectangular area of the document is redacted with a solid gray fill. It covers the majority of the page content below the first redacted block.

FDA Response:

CDER will be reviewing the sterility of the drug product in the primary container closure and the extractables/leachables of the primary fluid path (including needle), therefore they will be responsible if determining if this response is adequate.

- c. If the primary device packaging is sterile for maintenance of sterility.

Sponsor Response:

Maintenance of sterility of the risankizumab drug product in the PFS primary container closure system (CCS) has been confirmed. Sterility testing of the risankizumab DP in PFS was performed to show that it remains sterile over the proposed shelf-life (see accelerated and long term data in Section 3.2.P.8.3 Stability Data). Container closure integrity (CCI) testing of the DP in PFS was performed to demonstrate protection from microbial contamination as well as no loss or leakage of the product during the stability studies (see procedure in Section 3.2.P.5.2 Analytical Procedure – Container Closure Integrity, and accelerated and long term data in Section P.8.3 Stability Data) as well as during transport simulation (air and ground transportation) studies (see Section 3.2.P.2.4 Container Closure System, Chapter 5.0). To further characterize the tightness of the CCS, additional helium leakage tests have been performed (see Section 3.2.P.2.4 Container Closure System, Chapter 3.5.2). These included all interfaces in the CCS, where a breach of CCI could occur:

- the rigid needle shield / needle interface
- the needle / needle glue / syringe glass-cone interface
- the plunger / syringe barrel interface

Container closure integrity as defined as a maximum allowable leakage limit according to USP <1207.1> was confirmed for the interfaces listed. Sterility testing is performed on DP in PFS as part of the routine release testing and is also monitored over shelf-life at the intended commercial storage condition of 2 - 8°C. Container closure integrity testing is also implemented in stability testing of DP in PFS as an additional control element to ensure protection from microbial contamination.

Additionally, container closure integrity of the final assembled combination product was evaluated and found acceptable during design verification as described in Section 3.2.P.2.4 Container Closure System for the NSP-PFS, Chapter 6.0. The following product requirements have been verified:

- Container Closure Integrity (CCI) must be maintained after storage at recommended conditions
- Container Closure Integrity (CCI) must be maintained after shipment.

FDA Response:

CDER will be reviewing the sterility of the drug product in the primary container closure and the extractables/leachables of the primary fluid path (including needle), therefore they will be responsible if determining if this response is adequate.

Provide the information that is specified above. If certain device components are not provided sterile to the end user, provide a rationale for why this does not affect the sterility of the drug product.

2. In document “Container Closure”, in 3.2.P.7, you provide a schematic of the syringe that includes (b) (4) rigid needle shield (b) (4)

Sponsor Response:

As indicated in Section 3.2.P.7 Container Closure System, the rigid shield (b) (4)

Therefore, the user is only instructed to remove (b) (4) the rigid needle shield (b) (4)

FDA Response:

(b) (4) The response is adequate.

3. Provide conformance to the following FDA recognized standards for your syringe and needle or provide comparative information:

- a. ISO 11608-1:2014 – Needle based injection systems – Requirements and Test Methods

Sponsor Response:

(b) (4) as manufacturer of the pre-fillable syringe does not consider ISO 11608-1 to be a relevant standard for pre-filled syringes. However, Abbvie has considered applicable parts of the standard and demonstrated compliance to them in the design verification testing. Refer to Section 3.2.P.2.4 Container Closure for the NSP-PFS. The related product requirement is:

The NSP-PFS must be functional at/after expected conditions outside of the range recommended for storage and handling, following ISO standard 11608-1 Needle-based injection systems for medical use - Requirements and test methods - Part 1: Needle-based injection systems.

Abbvie defined the conditions outside of the range recommended for storage and handling that typically may appear to be: Cool, standard, and warm preconditioning, in section 10.2.1., free fall testing in section 10.5.d (the sharps protection aspect only, as user is not permitted by PIL/IFU to administer dropped product) and after vibration in section 10.9. Functionality of the combination product was defined in the related product requirements:

- No liquid leakage is visible beyond plunger stopper according to ISO 11040-8 Prefilled syringes Part 8: Requirements and test methods for finished prefilled syringes
- The NSP-PFS must be fully activated by end of ejection stroke The NSP-PFS must resist inadvertent activation under expected conditions of storage/transport/use
- The maximum force on the plunger rod for ejection and activation must not be more than (b) (4) N

AbbVie does not consider dry heat and cold storage as pre-conditionings to be expected conditions during storage and handling, (b) (4)

(b) (4)

FDA Response:

The response is adequate

b. ISO 11608-2:2012 – Needles

Sponsor Response:

The FDA recognized standard ISO 11608-2:2012 'Needles' is classed as not applicable to the Risankizumab 75 mg/0.83 mL PFS as its scope explicitly excludes pre-filled syringe needles. The 29 G ½"- thin wall staked needle used for the Risankizumab 75 mg/0.83 mL PFS is made of stainless steel and is compliant to ISO 9626. (b) (4)

FDA Response:

The response is adequate

c. ISO 11608-5:2012 – Automated Functions

Sponsor Response:

According to section 3.16 of the standard, sharps injury protection is given by meeting the requirements of ISO 23908. ISO 23908 is implemented by the following technical product requirements:

- The NSP-PFS must resist inadvertent activation under expected conditions of storage/transport/use
- Complete dose administration and activation of the NSP-PFS must be indicated by tactile and/or visual cues
- The maximum force on the plunger rod for ejection and activation must not be more than (b) (4)N
- Once in a safe mode, the needle guard cannot be deactivated with an override compression force below (b) (4)N
- The guard must enclose the needle and prevent finger access (as described in ISO 23908 Sharps injury protection –Requirements and test methods –Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling: 6 mm sphere must not contact the extremity of the needle point)
- The NSP-PFS (after use) must fit into a sharps container
- The extractable volume must not be less than the label volume.

FDA Response:

The response is adequate. The sponsor provides verification of their sharps protection under ISO 23908

d. ISO 11040-4 : Glass barrels for injectables

Sponsor Response:

The syringe barrel with staked needle used for Risankizumab 75 mg/0.83 mL PFS is delivered from the supplier, (b) (4). The level of compliance to the FDA recognized standard ISO 11040-4 'Pre-filled syringes – Part 4: Glass barrels for injectable and sterilized sub-assembled syringe ready for filling' was evaluated by (b) (4) and considered as acceptable (see (b) (4) Conformity Statement - STMT-QE20170985rev05). In particular, characteristics of needle and barrel, as for instance dimensions and performance, are aligned with the standards additionally mentioned in ISO 11040-4 (e.g., ISO 7864, ISO 9626).

FDA Response:

The response is adequate. The sponsor conforms to dimensions, marking accuracy (1mL), etc. They also provide a conformity statement from (b) (4) stating where they align with the standard.

e. ISO 11040-5 : Plungers for injectables

Sponsor Response:

The FDA recognized standard ISO11040-5 'Plungers for Injectables' (b) (4)

does not apply.

FDA Response:

The response is adequate.

f. ISO 7886-1 : Sterile hypodermic syringes for manual use

Sponsor Response:

The FDA recognized standard ISO 7886-1 'Sterile hypodermic syringes for manual use' is classed as not applicable to the Risankizumab 75 mg/0.83 mL pre-filled syringe as its scope explicitly excludes single-use syringes made from glass, as well as syringes with staked needles.

FDA Response:

The response is adequate. They also provide a conformity statement from (b) (4) stating where they align with the standard.

g. ISO 7864: Sterile Hypodermic Needles for Single Use

Sponsor Response:

Hypodermic needles specified in the FDA recognized standard ISO 7864 'Sterile Hypodermic Needles for Single Use' are intended for use with syringes having a 6% Luer conical fitting as specified in various ISO standards. This ISO standard is therefore not applicable to the Risankizumab 75 mg/0.83 mL pre-filled syringe with staked needle. The syringe barrel with staked needle and rigid needle shield is delivered from the supplier (b) (4). The needles are free from defects and particles as per ISO 7864 'Sterile Hypodermic Needles for Single Use' requirements. Needle length nominal value and

needle lumen patency value follow ISO 7864 as well as bevel, dimensions and bond on the staked needle syringe barrels comply with ISO 7864 (see (b) (4) Conformity Statement - STMT-QE20170985rev05).

FDA Response:

The response is adequate. They also provide a conformity statement from (b) (4) stating where they align with the standard.

h. ISO 9626: Stainless Steel Tubing for the Manufacture of Medical Devices

Sponsor Response:

The tubing used to manufacture the stainless steel 29 G ½" - thin wall needle of the Risankizumab 75 mg/0.8 3mL PFS complies with ISO 9626 'Stainless steel tubing for the manufacture of medical devices' (see (b) (4) Conformity Statement - STMTQE20170985rev05).

FDA Response:

The response is adequate. They also provide a conformity statement from (b) (4) stating where they align with the standard.

4. Please state if the to-be-marketed version of the device was used in the pivotal clinical study. Alternatively, if it was not used in these trials, please provide a comparison of the clinical use device and the to-be-marketed version of the device and how the clinical use device supports the safety and effectiveness of the to-be marketed version to bridge the two devices.

Sponsor Response:

The to-be-marketed version of the combination product is the (b) (4) pre-filled syringe (PFS), (b) (4) (NSP), plunger rod (PR) and (b) (4) finger flange (b) (4), and was not used in the pivotal clinical studies. The syringe system used in the pivotal clinical studies was the same (b) (4) pre-filled syringe (b) (4). Although the (b) (4) commodities are similar but not identical between the clinical trials and the to-be-marketed version of the device, the principle of use is the same with respect to the administration parameters for a pre-filled syringe system.

FDA Response:

The sponsor states that the only difference between the to-be-marketed version of the device and the clinically studied device (b) (4) I do not believe that there is any functional differences in the syringes that would necessitate the need for bridging testing.

5. It is unclear how many syringes were tested for the dose accuracy testing provided in Seq0001_3.2.P.5.4. Please state how many syringes were tested from each lot and why this is a statistically relevant number to represent the variability between lots and syringes. Additionally, it appears that you provide the mean extractable volume. Please state if all syringes passed the acceptance criteria. If there were any failures, please provide a statement of pass/fail for each device tested. Please also state if any deviations occurred during your testing.

In addition in 3.2.P.8.3, document “Accelerated and Long-term Stability Data”, it appears that all of the product that you tested that were aged 12 months or more, resulted in a extractable volume of (b) (4) mL, which is significantly greater than your specification of 0.83 mL. Please provide a rationale for why it is acceptable that the product that is aged ≥ 12 months has an extractable volume (b) (4)

Note that if this rationale is not acceptable. Additional dose accuracy testing may be requested.

Sponsor Response:

In accordance with USP <697> Container Content For Injections, extractable volume testing is required to demonstrate that each container of an injection contains sufficient excess to allow withdrawal of the labeled quantity of the drug (i.e., to ensure dose accuracy). This testing is not intended to evaluate variability between lots. For injections in prefilled syringes with a nominal volume of 3 mL or less, USP <697> requires that 5 syringes per lot are tested.

As described in Section 3.2.P.5.2 Analytical Procedures - Extractable Volume, the reportable result is the smallest volume determined of the measured syringes. Thus, all tested syringes passed the acceptance criterion and no failures occurred. (b) (4)

Regarding extractable volume results on stability, the batches referenced in Section 3.2.P.8.3 Stability Data (b) (4)

(b) (4). For ease of review, data for both the 0.83 mL commercial presentation (b) (4) are tabulated below, along with one batch, T210515, with a 0.8 mL fill that was used only for stability testing. All data in Table 2 are also in Section 3.2.P.8.3 Stability Data – Accelerated and Long-term Stability Data, however only batches for which at least 12 months data have been recorded are presented. All drug product batches met the extractable volume acceptance criterion without significant changes during storage up to 36 months.

Table 2. Summary of Extractable Volume Data for Risankizumab 75 mg/0.83 mL PFS from Section 3.2.P.8.3 Stability Data

Batch Number / Storage Condition	Nominal Fill Volume	Extractable Volume [mL]			
		0 months	12 months	24 months	36 months
603924 at 5°C	0.83 mL	0.86	0.86	n/a	n/a
603924 at 25°C		0.86	0.86	n/a	n/a
603923 at 5°C	0.83 mL	0.86	0.86	n/a	n/a
603923 at 25°C		0.86	0.86	n/a	n/a
505412 / 5°C	0.83 mL	0.86	0.86	0.86	n/a
505412 / 25°C		0.86	0.86	n/a	n/a
505410 / 5°C	0.83 mL	0.86	0.86	0.86	n/a
505410 / 25°C		0.86	0.86	n/a	n/a
T210515 / 5°C	0.8 mL	0.9	0.87	0.87	n/a
T210515 / 25°C		0.9	0.9	n/a	n/a
E5799S03 / 5°C	(b) (4)				
E5799S03 / 25°C					
E4744S01 / 5°C					
E4744S01 / 25°C					
E3744S02 / 5°C					
E3744S02 / 25°C					
E2744S02 / 5°C					
E2744S02 / 25°C					

FDA Response:

This is adequate. The sponsor states the specific lots, number of devices, and ages of devices that were tested.

6. It is unclear how many syringes were tested for the Break and Glide force testing provided in Seq0001_3.2.P.5.4. Please state how many syringes were tested from each lot and why this is a statistically relevant number to represent the variability between lots and syringes. Please also state if there were any deviations that occurred during the testing.

Sponsor Response:

For release testing of Break-out Force and Gliding Force 10 samples were used. This sample number was derived using a statistical experiment with data from the PFS platform in which it was demonstrated that testing more than 10 samples and up to 1000 samples will not significantly change the result. Assuming the break loose and glide forces for a PFS to be normally distributed with unknown variance and unknown mean, table D4 of ISO 16269-6 Annex D for one-sided statistical tolerance limit factors was used to calculate with a confidence of 95% that 99% of the testing results of the complete batch of the representative platform product would lie within the statistical tolerance interval. For one sided statistical tolerance interval for unknown σ , the upper limit was calculated with data from measurement of 10 syringes. Using the same standard deviation as was obtained for the 10 syringes, a theoretical upper limit was calculated for sample sizes of 20, 50, 100 and 1000. The theoretical upper limit for break loose force and glide force decreased with increasing sample size through n=1000 relative to the sample size of 10, therefore it was determined that 10 syringes are sufficient to detect a defective syringe. Consistency in break-out and gliding force results was demonstrated during validation of the commercial manufacturing process, and results were comparable between samples collected at the beginning, middle and end of manufacture of a lot, and between the lots (see Section 3.2.P.3.5 Process Validation and/or Evaluation, Chapter 2.6.2, Table 101 and Table 102).

FDA Response:

This is adequate. The sponsor states the specific lots, number of devices, and ages of devices that were tested.

7. In 3.2.P.5.4 Batch Analysis NSP-PFS, you provided summary results of verification testing that was provided to verify the performance requirements of the needle safety device. However, you have not stated how many devices were tested, nor did you provide the outcome (pass/fail) for each device that was tested or if any had failed. In addition, you state: (b) (4)

[REDACTED]

[REDACTED] (b) (4)

Sponsor Response:

[REDACTED] (b) (4)

This comparison between the development and commercial manufacturing processes provides evidence that the development manufacturing process of the combination product (b) (4) used for the design verification testing is equivalent to the commercial manufacturing process for all relevant aspects.

[REDACTED] (b) (4)

. It can thus be concluded, that the development process used for manufacturing design verification testing supplies is comparable with the commercial process for all relevant aspects.

FDA Response:

This is adequate. The sponsor provided a comparability between (b) (4) After examination of the stability testing (and lots) for the performance testing, (b) (4)

Given that both were tested in the stability testing, I do not have any additional concerns regarding this. In addition, all performance requirements have been listed lot release testing criteria.

- b. Please provide the number of PFS devices that were tested in the needle safety device verification/validation testing and a rationale for why this is a statistically relevant number to represent the variability between lots and needle safety devices.

Sponsor Response:

The number of PFS devices that were tested in the needle safety device verification/validation testing is provided in Table 4. The statistical rationale for the sample sizes selected follows.

Table 4. Batch Analysis Results for the NSP-PFS Sample Sizes added from DVT Record.

Test	Acceptance Criteria	Batch Number Sample Size			
		16-006899	16-006843	16-006844	16-006835
Appearance	(b) (4)	complies (n=195)	complies (n=196 ^a)	complies (n=195)	complies (200 ^b)
		complies (n=45)	complies (n=45)	complies (n=45)	complies (n=45)
		complies (n=195)	complies (n=196 ^a)	complies (n=195)	not planned
		complies (n=45)	complies (n=45)	complies (n=45)	not planned
Functionality		complies (n=60)	complies (n=60)	complies (n=60)	complies (n=60)
		complies (n=60)	complies (n=60)	complies (n=60)	complies (n=60)
		complies (n=91)	complies (n=91)	complies (n=91)	complies (n=91)
		complies (n=91)	complies (n=91)	complies (n=91)	complies (n=91)

a. When testing extractable volume T0, sample #06 was excluded from testing due to operator failure. An additional sample was tested successfully (details see raw data D-RDLU-000097_A01).

b. Five more samples were tested, as five reserve samples were needed

When a recognized standard method (i.e., ISO standard, ICH guideline etc.) was used in the Design Verification, the recommended sample size from the standard was utilized. When the recognized standard method does not include a sample size or a recognized standard method is not used, a risk based sample size approach as provided in Table 5 and Table 6 was utilized by applying a risk management approach, based on evaluating the user risk(s) resulting from the device's failure to meet its performance requirements. The acceptance criterion for all tests was 0 failures.

Table 5. Risk Based Sample Size Determination, Variable Testing

Risk Level (Severity x Occurrence)	Reliability (1-AQL)	Confidence	Sample Size (n) ^a	k-Value 1-Sided Limit (b) (4)
Low risk	97.5 %	95 %	60	

a. ISO11608-1

Table 6. Risk Based Sample Size Determination, Attribute Testing

	Risk Level (Severity x Occurrence)	Reliability (1-AQL)	(n) 90% conf. ^{a, b}
Attributes	Low risk	95.0%	45
Attributes	Medium risk	97.5%	91

a. $n = \ln(1 - \text{Confidence}) / \ln(\text{reliability})$

b. QPP11-02-005-W001 "Design Verification Criteria"

For the variable test dose accuracy a sample size of 60 units with 95% confidence and 97.5 % reliability independent of risk level was used according to ISO 11608-1:2014(E) in ISO/table 3 test matrix, with acceptance based on k-values for the corresponding risk level. The respective k value is listed in Table 5. The minimal sample sizes according to DVT Plan and Risk Management are provided in Table 7:

Table 7. Minimal Sample Sizes

Test	Acceptance Criteria	Test Data	Associated Risk	Minimum Sample Size
Appearance	(b) (4)	Attributive	Low	45
		Attributive	Low	45
		Attributive	Low	45
		Attributive	Low	45
Functionality		Attributive	Low	45
		Variable testing	Low	60 (according to ISO 11608)
		Attributive	Medium	91
		Attributive	Medium	91

FDA Response:

The sponsor's verification testing is adequate and demonstrates that the requirements of the needle safety device, met the performance requirements over multiple lots of device.

- c. Please state if when you say that each lot "complies" if all test passed the acceptance criteria. If there were any failure, please prove a statement of pass/fail for each device tested. Please also state if any deviations occurred during your testing.

Sponsor Response:

For all tests the allowed failure rate is zero (0). If it's stated that a lot complies this means that all tested samples passed and no failures occurred.

FDA Response:

This is adequate.

- d. It does not appear that verification of the needle safety device was conducted after the shipping validation study. Given that you have determined that this is a device constituent essential performance requirement, please provide testing to verify the needle safety device. Alternatively, provide a rationale for why it is not necessary.

Sponsor Response:

Final assembled combination product, NSP-PFS, was evaluated for functionality and container closure integrity as part of the simulated shipping study. As the product was packaged in representative commercial packaging ((b) (4) film blisters and cartons) and shipped by or subjected to conditions representative of commercial shipping routes (air and ground), the simulated shipping study is considered representative of commercial shipping conditions. Results are provided in described in Section 3.2.P.2.4 Container Closure of the NSP-PFS, Chapter 6.2.1.11, Table 8.

FDA Response:

This is adequate. The sponsor specified the location of the summary shipping results showing the activation of the needle safety device. The results are adequate.

8. It is unclear how many syringes were tested for in the Container Closure Integrity testing provided in Seq0001_3.2.P.5.4. Please state how many syringes were tested from each lot and why this is a statistically relevant number to represent the variability between lots and syringes. Please also state if there were any deviations that occurred during the testing.

Sponsor Response:

Container closure integrity testing is only performed during stability testing. Although it is not a release test, the t=0 stability results are included in Section 3.2.P.5.4 Batch Analyses for the PPQ batches only.

For Container Closure Integrity Test (CCIT) during stability testing, 20 samples were used. Based on the required volume for sterility testing given in USP <71>, the same value was applied to CCIT, which per FDA guidance is used in lieu of sterility. The sample number for this volume container is 20. Given the similar nature of the test, this sample number was considered acceptable. No deviations occurred during testing.

FDA Response:

This is adequate. The sponsor specified the number of samples per lot tested.

9. We note that you have not provided a specification or testing to characterize the tip cap removal force of your device. Please provide a specification and base level verification testing of the tip cap removal to support the use of your device with the intended patient population.

Sponsor Response:

The Rigid Needle Shield (RNS) removal force was evaluated as described in 3.2.P.2.4 Container Closure System for the NSP-PFS, Chapter 3.3. Testing was evaluated against a specification of (b) (4) N. All testing passed the acceptance criteria.

Additionally, the Rigid Needle Shield (RNS) removal force is tested for each lot by manufacturer, (b) (4) and the test result is reported in the Certificate of Analysis (see Section 3.2.R Regional Information - (b) (4) (b) (4)). The (b) (4) specification is (b) (4) N for the RNS Pull-off Force test method.

The specification for the final assembled NSP-PFS (see Section 3.2.P 5.1 Specification for the NSP-PFS) requires that (b) (4). This functional requirement has been verified during design verification (refer to Section 3.2.P.2.4 Container Closure of the NSP-PFS, Chapter 6.2) and is tested for release of the combination product. RNS removal was defined as a Critical Task and evaluated in the Human Factors Summative Validation study with the intended patient population. No difficulties were observed by participants in removing the RNS. Refer to the Human Factors Summative Validation study summary in Section 3.2.P.2.4 Container Closure of the NSP-PFS, Chapter 7.6.7, and the full validation report in Module 5.3.5.4 Other Study Reports Human Factors Engineering and Usability Engineering Report.

FDA Response:

The sponsor has provided adequate testing to verify the RNS removal force. This is adequate.

10. In document “Stability Summary and Conclusions NSP-PFS” in 3.2.8.1, you state that “The stability testing data of the primary stability study up to six months are presented in Section 3.2.P.8.3 Stability Data for the NSP-PFS.” However you have not provided verification of the device constituent performance requirements up to the proposed expiry of 24 months. When available, provide the testing and results of the device performance requirements up to the proposed expiry of 24 months through real-time or accelerated aged.

Sponsor Response:

Real-time and accelerated stability are presented in Section 3.2.P.8.3 Stability Data for the NSP-PFS for the functionality of the device. A calculated simulated aging of secondary packaging components has been performed. The calculation indicates that storage at 38°C for 92 days (3 months) simulates 24 months storage at recommended storage conditions. All results for routine and additional developmental tests meet the acceptance criteria for the NSP-PFS samples stored at stressed conditions (40°C/75% RH) after three months and thereby support the claim for 24 months shelf-life at recommended conditions.

AbbVie will provide additional stability testing and results when available in the annual reports to the BLA in accordance with the stability protocol described in Section 3.2.P.8.2 Post Approval Stability Protocol and Stability Commitment for the NSP-PFS.

FDA Response:

This is adequate. The sponsor has provided accelerated aging up to 24 months.

11. We note in document “Container Closure System NSP-PFS”, 3.2.P.2, that you state:

According to Annex A of ISO 10993-1, the following biological evaluation tests were identified as appropriate for testing the NSP-PFS contact materials: cytotoxicity, sensitization and irritation (intra-cutaneous reactivity). All NSP components, i.e., the (b) (4) PR have been evaluated by (b) (4) according to ISO 10993-1 and are certified to meet the established criteria for preclinical toxicological safety evaluation. Likewise, the labeled PFS has also been evaluated and shown to be biocompatible.

However, you have not provided the biocompatibility documentation that was used to make this determination for the patient contacting components of the device constituent, including the syringe plunger, finger flanges, and needle safety device. The device constituent should be evaluated per the recommendations in the [FDA Guidance: Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"](#), and should include an evaluation of the following endpoints: cytotoxicity, sensitization, irritation. Please provide this documentation.

Sponsor Response:

The manufacturer, (b) (4), has evaluated biocompatibility for the devices in accordance with ISO 10993-1 "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process." (b) (4) has provided certificates of conformance to ISO 10993-1 for the (b) (4) syringe, plunger stopper, rigid needle shield, needle stick protection device, plunger rod and (b) (4) finger flange. Refer to the attached certificates provided in Section 3.2.R Regional Information:

FDA Response:

The sponsor needs to provide the full reports or refer to them within DMF. See follow-up deficiency 1. This deficiency was resolved interactively.

12. The instructions for use that you have provided does not include the specifications of the needle that is provided with the syringe; i.e. 0.5 inch, 29 G. Please list this information prior to the instructions for use.

Sponsor Response:

AbbVie agrees to include information on the length and gauge of the needle in the US package insert (USPI). AbbVie added the requested information to Section 11, Description, of the Full Prescribing Information to be consistent with other USPI's for products in pre-filled syringes. The revised draft labeling is provided with this amendment, in Module 1.14.1.3 Labeling.

FDA Response:

The sponsor made the requested changes. This is adequate.

11.3. Interactive Review Request #2

1. In response to deficiency 11, in the Agency's IR dated August 3, 2018, you provided biocompatibility statements from (b) (4) that address the type of biocompatibility testing that was completed on the patient contacting device components. However, this information does not include the test methods or full test results that were obtained in this testing. Please provide the full test reports per ISO 10993-1, that were used to verify the biocompatibility of the patient contacting components of the device. If you are choose to refer to a DMF, please provide the exact location within the DMF for each biocompatibility test report.

Sponsor Response:

The DME holder provided all biocompatibility test reports for the subject device. (b) (4)



FDA Response:

The response is acceptable. The sponsor provided the test reports to cover the biocompatibility testing under CDRH review.

RECOMMENDATION

CDRH is recommending that the device constituent of the combination product is approvable for the proposed indication.



Melinda
Bauerlien

Digitally signed by Melinda Bauerlien

Date: 11/01/2018 11:32:54AM

GUID: 508da6dc0002676de5faf5b4bf3d0f72

HUMAN FACTORS RESULTS AND LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 22, 2018
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	BLA 761105
Product Name and Strength:	Skyrizi (risankizumab-xxxx) Injection 75 mg/0.83 mL
Product Type:	Single Ingredient Combination Product (Drug-Device)
Rx or OTC:	Prescription
Applicant/Sponsor Name:	AbbVie, Inc.
FDA Received Date:	April 23, 2018, July 12, 2018, and August 24, 2018
OSE RCM #:	2018-886 and 2018-910
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader (Acting):	Teresa McMillan, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS

1 REASON FOR REVIEW

The Division of Dermatology and Dental Products (DDDP) requested that we review the proposed container labels, carton and printmat labeling, Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), and Human Factors (HF) Validation Study Results submitted on April 23, 2018 for Skyrizi (risankizumab-xxxx) Injection, BLA 761105, to determine if it is acceptable from a medication error perspective. We also note a revised PI was submitted on July 12, 2018 containing the following updated statement in Section 17 PATIENT COUNSELING INFORMATION: Advise the patient to read the FDA approved patient labeling (Medication Guide and Instructions for Use). A revised PI was also submitted on August 24, 2018 containing the following needle specification to be consistent with other USPIs for products in pre-filled syringes: supplied in a 1 mL glass syringe with a fixed 29 gauge ½ inch needle.

Abbvie is also seeking licensure for the following Skyrizi presentation:

75 mg/0.83 mL in a single dose prefilled syringe with a passive needle guard delivering 75 mg of risankizumab.

1.1 REGULATORY HISTORY

AbbVie, Inc. submitted a human factors validation study protocol to the Division of Dermatology and Dental Products (DPPP) under IND 113306 on June 29, 2017 and to Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) under IND (b) (4) on July 5, 2017. We identified deficiencies in the protocols and communicated them to the sponsor on September 22, 2017^a. On October 18, 2017, the sponsor submitted their revised Human Factors validation study protocol under IND (b) (4) and 113306. We recommended additional revisions to the moderator's script and informed the AbbVie there is no need to submit the revised moderator's script for our review^b.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C

^a Abraham, S. Human Factor Protocol Review for risankizumab IND 113306 and IND (b) (4) Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 SEP 22. RCM No.: 2017-1294 and 2017-1719.

^b Abraham, S. Human Factor Protocol Review for risankizumab IND 113306 and IND (b) (4) Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 27. RCM No.: 2017-1719-1.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our assessment of the container labels, carton and printmat labeling, Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), and Human Factors (HF) Validation Study for Skeyrzi (risankizumab-xxxx) are as follows.

3.1 HUMAN FACTORS (HF) STUDY RESULTS

AbbVie, Inc. performed a HF validation study to evaluate the use of the risankizumab-xxxx prefilled syringe, IFU, and Quick Tips in adults. DMEPA reviewed the HF study protocol^{c,d} for the proposed prefilled syringe prior to the Applicant initiating the study, and all of DMEPA's recommendations were implemented.

^c Abraham, S. Human Factor Protocol Review for risankizumab IND 113306 and IND (b) (4) Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 SEP 22. RCM No.: 2017-1294 and 2017-1719.

^d Abraham, S. Human Factor Protocol Review for risankizumab IND 113306 and IND (b) (4) Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 27. RCM No.: 2017-1719-1.

3.1.1 RESULTS AND ANALYSIS

Table 2 describes the study results for the critical tasks with use errors, the Applicant's analyses of the results, and DMEPA's analyses and recommendations.

We also note the Applicant has made one change to the IFU based on the knowledge assessment results. A modification was made that separates out a statement telling the user what to do if the syringe tray seal is broken or missing into two sentences with appropriate bolding. We find this change acceptable as it provides clarity and emphasis on important information.

Table 2. Summary and Analysis of Critical Task Use Errors and Close Calls					
Tasks (include C for critical and E for essential)	Number of Failures/Use Errors and Description of Use Errors	Number of Close Calls and Use Difficulties and Description of Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Select Injection Site (C)	<p>9</p> <p>1st injection - 6 (5 experienced, 1 naïve) 1 patient, 3 caregivers, 2 HCPs</p> <p>2nd injection - 3 (2 experienced, 1 naïve) 1 patient, 2 caregivers</p>	0	<p>The Sponsor provided RCA for all 6 participants.</p> <p><i>Violation of Existing Mental Model –</i> (P10) based actions of previous experiences of receiving injections in her arm (H08) approached task based on his experience with other subcutaneous injections where he chose the upper left arm for the privacy of the patient.</p> <p><i>Negative Transfer –</i></p>	<p>The Sponsor did not provide mitigation for these errors –</p> <p>Medically acceptable to inject into the upper arm and area of the navel. Instructions designed to recommend areas easier for self injection and minimize pain. Not associated with reduced safety or efficacy.</p>	<p>Although the Sponsor proposes no mitigation, for the injection site at the belly button we find in the Quick Tips, the unshaded circle area with the belly button mark in the middle surrounded by a yellow shaded area, may be misinterpreted by some users as a target/focus point and arrows could be misinterpreted as pointing towards the navel. Although the unshaded area of the abdomen indicates that area</p>

			<p>(C09) previous insulin injecting experience of injecting into arm person she cared for (C19) relied on previous experience of self-injections which led her to choose middle of abdomen</p> <p><i>Potential Result of Materials Accompanying Device:</i> <i>Instructions/ Label Design:</i> <i>Misleading Iconography -</i> (C19) Misinterpreted image in Step 1 of Quick Tips to indicate that the injection site shown was the middle of the abdomen. (C36) Misinterpreted image in Step 1 of Quick Tips to indicate that the injection site shown directly into the navel.</p> <p><i>Test Artifact of Simulated Use</i> (H11) Test environment such as cameras and people watching caused participant to rush and make unintended error of choosing injection site as one inch from the navel.</p>	<p>Navel injection site pain would not require further medical care.</p>	<p>is to be avoided, 2 participants provided subjective feedback who only referred to the Quick Tips and either injected 1 inch from the navel and directly into belly button. Per discussion with the medical officer, injecting directly into the umbilicus and/or too close to the umbilicus may affect bioavailability, however, since sites are rotated, and treatment involves multiple administrations, overall differences that would impact safety and/or efficacy are minimized. We note the Quick Tips image states " (b) (4) whereas the IFU for the belly option states specifically "Your abdomen (belly) at least 2 inches from your navel (belly button). We find the Quick Tips text can be more specific. We note participants that used the IFU correctly selected the injection site. Therefore, we recommend the image in Step 1 of the Quick Tips be revised to</p>
--	--	--	--	--	---

					<p>match the image in Step 2 of the IFU. We also ask the Applicant to consider revising the text (b) (4) to be more specific, similar to the IFU. Since there were no use errors in the selection of the injection site in participants that used the IFU, we do not believe additional human factors data will be needed if the Quick Tips is modified to align with the image and text in Step 2 of the IFU.</p>
Slowly push plunger all the way in until all the liquid is injected and syringe is empty (C)	<p>8</p> <p>1st injection – 6 (4 experienced, 2 naïve) 4 patients, 1 caregiver, 1 HCP</p> <p>2nd injection - 2 (2 experienced) 2 patients</p>	0	<p>The Sponsor provided RCA for all 7 participants.</p> <p><i>Test Artifact: Participant Inattentiveness</i> (P10) For 2nd injection, she did not remove needle cover and attempted to inject. Once she removed the needle cover, 3 or 4 drops of liquid spilled. She rushed through 2nd injection because she was in a hurry to get done with the session and was not taking the time to complete the tasks she would if this were an actual injection.</p> <p><i>Test Artifact of Simulated Use</i> (P11) Did not remove the needle cover and pushed down on the plunger. Appeared disengaged and tried and mentioned having a</p>	<p>The Sponsor did not provide mitigation for these errors –</p> <p>The amount of product lost to wet injection is unlikely to affect the efficacy of treatment for Ps/PsO. This is a level below which it is currently understood there is no compromised medical therapy. Continued loss of this amount (drops) of drug product through a pattern of wet injections is also of minimal clinical significance, not</p>	<p>The potential harm associated with loss of drug product due to wet injections is the risk of wrong dose errors and suboptimal treatment. However, our review of the IFU determines that Step 4 of the IFU and Step 2 of the Quick Tips provide clear text and both are accompanied by images of removing the needle cover. We find the IFU statements and images mitigate this use error adequately, and that no further mitigation is required.</p> <p>We also determine Step 5 of the IFU provides clear text to</p>

		<p>newborn. She stated she was 'lazy' and did not want to ready the full instructions. Believed there was only air in the syringe, not actual liquid, which influenced her behavior to push down on the plunger before she was ready to inject</p> <p>(P26) Pinched injection pad in such a way that caused a thin piece of material to raise on the injection pad and upon injecting came through the other side and pricked her thumb. Error was a test artifact because it is not possible to raise human skin in the same manner.</p> <p><i>Violation of Existing Mental Model –</i></p> <p>(P14) Had her thumb placed on the plunger prior to administering the first injection due to having a preconceived idea about how the PFS is to be held</p> <p>(C34) Pressed on plunger prior to inserting the syringe. Believed that a small amount lost from a pre-filled syringe is not significant and acceptable based on her own process. Stated "It's a prefilled amount so it will be the right amount regardless".</p> <p>(H16) Did not use any instructions. Stopped pressing on the plunger before the needle guard activated. Expected the device to function in</p>	<p>classified as compromised medical therapy and does not indicate potential harm.</p> <p>Raising a thin piece of injection pad is an artifact of simulated use and not a circumstance that would be seen in clinical practice.</p> <p>Potential harm associated with the amount of product (stream of liquid) lost to wet injections is suboptimal treatment of the condition that may in some circumstances require medical attention. This harm would not impact the clinical benefit of the product which still will improve the underlying condition.</p>	<p>hold the body of the prefilled syringe in one hand between the thumb and index fingers. We find the image in Step 9 of the IFU adequately reflect the important information needed to successfully perform this step of the injection process.</p> <p>We acknowledge the error of the thumb prick seen is a result of a test artifact of using an injection pad to simulate pinching the injection. The potential harm associated with this type of error is needle stick injury. However, the sponsor's root cause analysis showed that the participant pinched the injection pad in a manner that is not reflective of intended user pinching the skin.</p>
--	--	---	--	--

			<p>the same way as other devices she has worked with in the past.</p> <p><i>Negative Transfer –</i> (P31) For 1st and 2nd injection expelled liquid from each syringe prior to injections in an attempt to remove air bubbles based on extensive experience injecting another product and recalled training received from a HCP which influenced his behavior to remove air bubbles from the syringe.</p>		
Administer the second injection (C)	<p>3</p> <p>(3 experienced)</p> <p>1 caregiver</p> <p>2 HCPs</p>	0	<p>The Sponsor provided RCA for all 3 participants.</p> <p><i>Negative Transfer –</i> (C09) Only retrieved 1 blister from the refrigerator and left remaining materials in the refrigerator. Past experience of injecting insulin to the person she cared for was the main cause of her decision to only perform one injection. Did not look at any instructions.</p> <p><i>Violation of Existing Mental Model –</i> (H08) After 1st injection was complete, he put the carton with the second blister back into the refrigerator. He explained he approached the administration based on his previous experience with other subcutaneous injections. Initially stated he had administered a full dose but after being exposed</p>	<p>The Sponsor did not provide mitigation for these errors –</p> <p>Potential harm associated with failing to inject the 2nd syringe is suboptimal treatment of the condition that may in require medical attention. This harm would not impact the clinical benefit of the product which still will improve the underlying condition.</p>	<p>The potential harm associated with not comprehending the full dose requires 2 injections is the risk of wrong dose errors. We noticed that the errors were based on negative transfer from previous experience of using drugs that only required 1 injection.</p> <p>We note that of those participants that did not administer the second injection, none looked at the IFU and one participant only briefly looked at the Quick Tips. Our review of the labeling materials found that the statements and graphics in the Quick Tips and IFU clearly show the need for two injections for a full dose and</p>

			<p>to the instructions she stated he thought he was only performing a demonstration of the administration and at another point claimed he only administered one injection because that is what the doctor ordered. Did not use the IFU and briefly consulted the Quick Tips prior to administering first injection.</p> <p>(H16) Did not use any instructions and after the first injection placed the carton with the second blister still inside into the refrigerator and stated she was done. This is due to previous experiences with other prefilled syringes that only require one injection.</p>		determined that no further mitigation is required.
--	--	--	--	--	--

3.2 LABELS AND LABELING

We reviewed proposed container labels, carton and printmat labeling, PI, MG, and IFU to determine whether there are any significant concerns in terms of safety related to preventable medication errors. We note the placeholder “TRADENAME” should be replaced with the name “Skyrizi”, which was found conditionally acceptable on July 6, 2018^e. We also note the container labels and carton and printmat labeling can be improved to enhance the readability and prominence of important information (e.g. established name, storage) and help promote safe use of the product. Additionally, the carton labeling can be improved to remove a trailing zero from the presentation of syringe contents. The Quick Tips on the carton labeling can be improved considering the HF results to clarify the injection sites, particularly where on the abdomen the product can be injected. Also, as currently presented, the printmat and carton labeling and the IFU includes a package type term “(b) (4)” instead of “single-dose”. Because the rizankizumab product is packaged with two pre-filled syringes and both syringes are required to be injected to administer a complete dose, we considered whether the package type term “single-dose” may create confusion and lead users to think each prefilled syringe is a single dose and therefore lead to risk of under-dose errors. We consulted the Office of Pharmaceutical Quality (OPQ) via internal email on September 21, 2018 for the determination of the correct package term type. OPQ confirmed the appropriate package term type is “single-dose”, consistent with the guidance for industry entitled ‘Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use’^f. We defer to the Office of Pharmaceutical Quality (OPQ) regarding the acceptability of the “(b) (4)” package type term on labels and labeling.

We provide recommendations below in Sections 4.1 and 4.2 to help minimize the potential for medication errors to occur with the use of this product.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the human factors validation study results are adequate from a medication error perspective. However, we note that the container labels, carton and printmat labeling, PI, and Quick Tips can be improved to increase the clarity of information to promote the safe use of the product. Please see recommendations for the DDDP and Abbvie in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

^e Mena-Grillasca, C. Proprietary Name Review for Skyrizi (BLA 761105). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUL 06. Panorama No. 2018-22597352

^f Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>

1. Replace the name, "TRADENAME", with the conditionally acceptable proprietary name, "Skyrizi".
2. How Supplied Section
 - a. As currently presented, the National Drug Code (NDC) number is denoted by a placeholder (0074-XXXX-XX). We recommend adding the intended numbers.

4.2 RECOMMENDATIONS FOR ABBVIE, INC.

We recommend the following be implemented prior to approval of this BLA:

- A. General Comments (Container labels, Carton Labeling, and Printmat Labeling)
 1. Replace "Tradename" with the conditionally accepted proprietary name, Skyrizi. We acknowledge that your proposed non-proprietary name with the 4-letter suffix is currently under review. Replace the placeholder 'xxxx' once you have an approved non-proprietary name and submit the updated labels and labeling for review.
 2. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use (see below for examples):
 - a. DDMMYYYY (e.g., 31JAN2013)
 - b. MMMYYYY (e.g., JAN2013)
 - c. YYYY-MMM-DD (e.g., 2013-JAN-31)
 - d. YYYY-MM-DD (e.g., 2013-01-31)
- Additionally, we did not identify a placeholder ("LOT" or "EXP") for the lot number and expiration date on the proposed carton labeling. Ensure that the lot number and expiration date are presented in accordance with 21 CFR 201.10(i) and 21 CFR 201.17, and that they are clearly differentiated from one another.⁹

⁹ Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

Ensure that the lot number and expiration date are not located in close proximity to other numbers where the numbers can be mistaken as the lot number or expiration date.^h

APPEARS THIS WAY ON ORIGINAL

^h Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

3. The carton containing 2 syringes uses the same NDC as that on the printmat labeling and container labels. The printmat labeling and container label of one unit and the carton labeling of 2 units should have different NDC package codes (last 2 digits of the NDC). Revise the NDC numbers so that the carton labeling uses a different NDC package code than the printmat labeling and container labels.
- B. Carton Labeling
1. The established name is not at least half the size of the proprietary name. Thus, we request you revise the established name to be in accordance with 21 CFR 201.10(g)(2).
 2. As currently displayed, the font color selection (light grey) of the established name does not afford adequate contrast against the white background and makes this information difficult to read. We recommend revising the font color of the established name to increase readability as per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.
 3. There is a trailing zero following a decimal point in the presentation of syringe contents (e.g. 75.0 mg) that may lead to errors. We recommend eliminating the trailing zero, an error prone dose designation, which may be misinterpreted if the decimal point is not seenⁱ.
 4. Based on the data from the Human Factors (HF) validation study, the image in Step 1 of the Quick Tips showing injection sites with the arrow could be misinterpreted as showing the navel as the injection site. Revise the image in Step 1 of the Quick Tips to match the image in Step 2 of the Instructions for Use (IFU). Also consider revising the text (b) (4) to be more specific, similar to the IFU.

ⁱ ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2017[cited 2018 APR 12]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

C. Carton and Printmat Labeling

1. Revise and bold the statement “Must be refrigerated, store at 2°C to 8°C (36°F to 46°F)”. We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

D. Printmat Labeling

1. Consider revising the statement on the Principal Display Panel (PDP) for clarity of the net quantity (e.g. “1 Single-Dose Prefilled Syringe” instead of “(b) (4)”).
2. Decrease the prominence of the statement “Rx Only” as this information appears more prominent than the established name on the principal display panel.
3. Add the statement “Dispense the enclosed Medication Guide to each patient” or a similar statement prominently on the principal display panel (PDP) per 21 CFR 208.24 (d).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Skyrizi received on April 23, 2018 from AbbVie, Inc.

Table 2. Relevant Product Information for Skyrizi	
Initial Approval Date	N/A
Active Ingredient	risankizumab-xxxx
Indication	treatment of moderate to severe plaque psoriasis in adults
Route of Administration	subcutaneous
Dosage Form	injection
Strength	75 mg/0.83 mL (90 mg/mL)
Dose and Frequency	150 mg (two 75 mg injections) administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter
How Supplied	75 mg/0.83 mL (90 mg/mL) in a single-dose prefilled syringe
Storage	Store in a refrigerator at 2° C to 8° C (36° F to 46° F)
Container Closure	Carton containing 2 prefilled syringes and 2 alcohol pads

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 13, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, risankizumab. Our search identified two previous Human Factors protocol reviews^j, and we confirmed that our previous recommendations were implemented.

^j Abraham, S. Human Factor Protocol Review for risankizumab IND 113306 and IND (b) (4) Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 SEP 22. RCM No.: 2017-1294 and 2017-1719.

Abraham, S. Human Factor Protocol Review for risankizumab IND 113306 and IND (b) (4) Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 27. RCM No.: 2017-1719-1.

APPENDIX C. HUMAN FACTORS STUDY RESULTS (SUBMITTED APRIL 23, 2018)

[\\cdsesub1\evsprod\bla761105\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5354-other-stud-rep\hfeuer\human-factors-report-nsp.pdf](#)

APPENDIX D. ISMP NEWSLETTERS – N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) – N/A

APPENDIX F. OTHER – N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^k along with postmarket medication error data, we reviewed the following Skyrizi labels and labeling submitted by AbbVie, Inc.

- Container label received on April 23, 2018
- Carton labeling received on April 23, 2018
- Professional Sample Printmat Labeling received on April 23, 2018
- Professional Sample Label received on April 23, 2018
- Professional Sample Carton Labeling received on April 23, 2018
- Professional Sample Printmat Labeling received on April 23, 2018
- Instructions for Use received on April 23, 2018
- Medication Guide (Image not shown) received on April 23, 2018
- Prescribing Information (Image not shown) received on August 24, 2018

G.2 Label and Labeling Images

Container Labels



5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

^k Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MADHURI R PATEL
10/22/2018

TERESA S MCMILLAN
10/22/2018

QUYNHNHU T NGUYEN
10/22/2018