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?	Short-term Lymphoma	Long-term 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 GI (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) [redacted] [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

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.