Safety Signal Identification for Risankizumab-rzaa in the Sentinel Distributed Database Using Self-Controlled and Active Comparator Study Designs

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Conflict of Interest Statement

- The authors have no conflicts of interest to disclose.
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Background

- The Sentinel Distributed Database (SDD) is a national distributed data network of electronic healthcare databases used by FDA for active surveillance of medical product safety.
- Application of tree-based scan statistics (TreeScan™) to the SDD allows for untargeted safety signal identification using a hierarchical outcome tree with simultaneous adjustment for multiple scanning of correlated outcomes.[1]
- TreeScan™ analyses may be implemented using self-controlled risk interval (SCRI) or active comparator (AC) designs.
- Risankizumab-rzaa, FDA-approved in 2019, is an IL-23 inhibitor currently indicated for the treatment of plaque psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis.[2]

Objective

- To detect new potential safety signals following the initiation of risankizumab-rzaa using both SCRI and AC study designs.

Methods

Study Specifications

- We conducted two TreeScan™ signal identification studies in risankizumab-rzaa new users aged 18 years or older in the SDD using the following:
  - **Study period**: April 23, 2019, through a maximum of September 30, 2023
  - **Exclusion criteria**: ongoing pregnancy or recent pregnancy delivery
  - **Outcomes assessed**: non-pregnancy and non-malignancy ICD-10-CM diagnoses
  - **Outcome settings**: inpatient and emergency department
  - **Statistical alert threshold**: $p \leq 0.05$

SCRI Study Design

- We constructed the following two cohorts for primary analyses to identify imbalances in incident outcome occurrence and timing among new users of risankizumab-rzaa:
  - **Fixed risk window**: 1 to 28 days post-index with a pre-exposure control window -56 to -29 days pre-index (**Figure 1**); analyzed using a conditional Bernoulli model
  - **Variable risk window**: 1 to 183 days post-index (**Figure 2**); analyzed using a tree-temporal scan statistic conditioned on outcome node and time

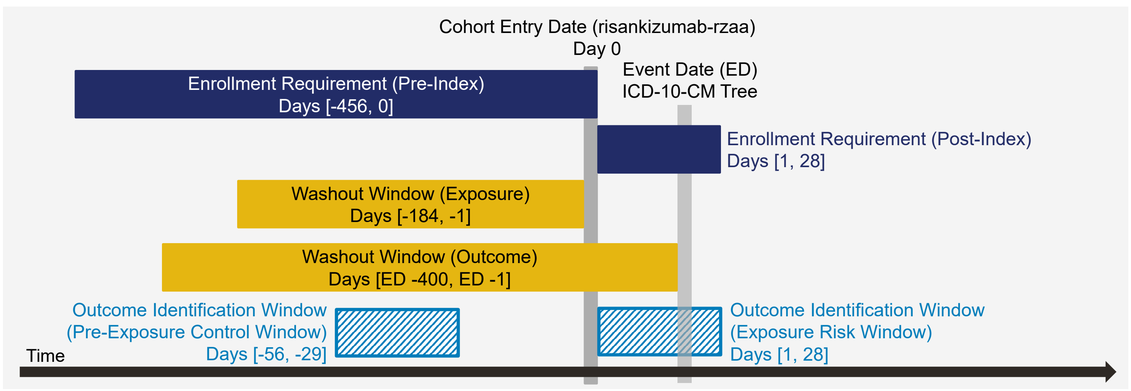

Figure 1. SCRI Design Diagram for the Fixed Risk Window Cohort

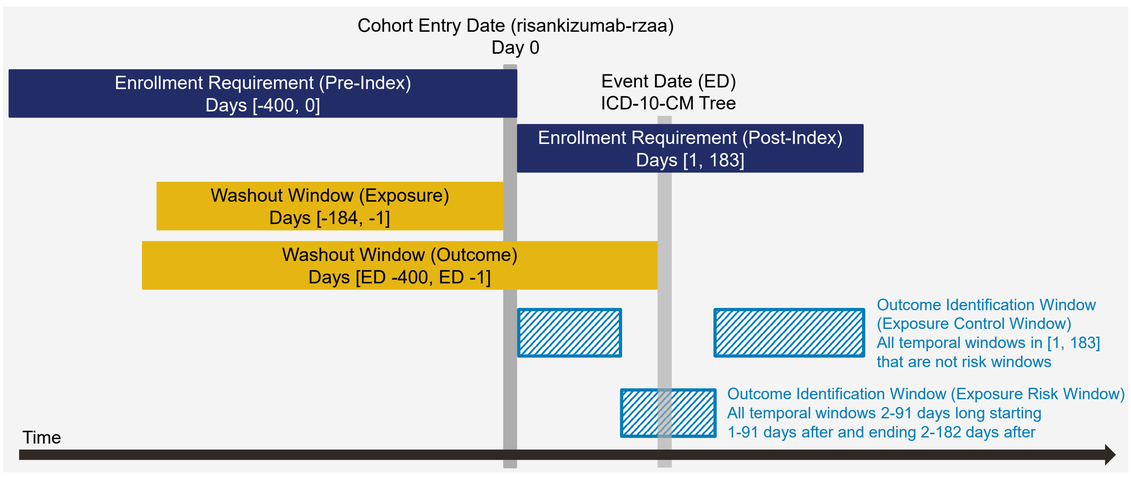

Figure 2. SCRI Design Diagram for the Variable Risk Window Cohort

AC Study Design

- We used high-dimensional propensity scores (hdPS) to match risankizumab-rzaa new users 1:1 to IL-23 inhibitor guselkumab new users, and an unconditional Bernoulli tree-based scan statistic to identify imbalances in incident outcome occurrence **(Figure 3)**.

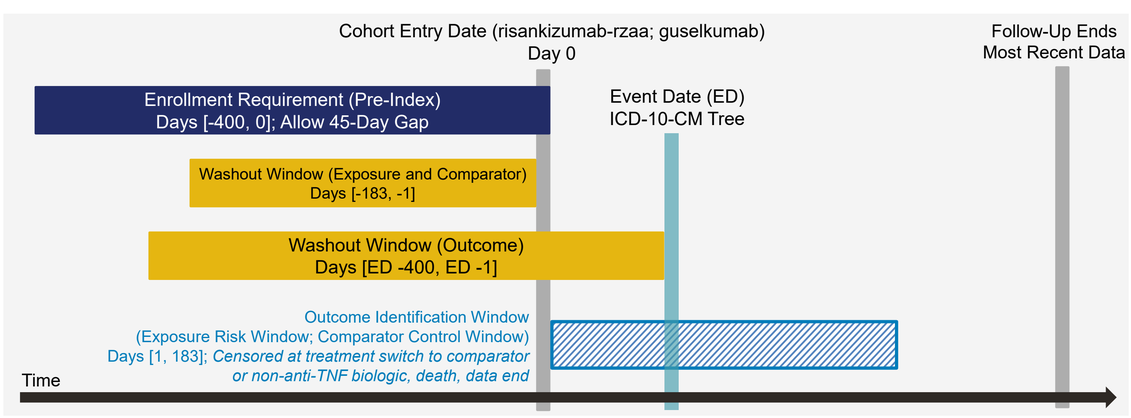

Figure 3. AC Design Diagram for hdPS-Matched Cohort

Results

SCRI Study

Table 1. Characteristics of Risankizumab-rzaa New Users in the SCRI Study

	Fixed Risk Window Cohort		Variable Risk Window Cohort	
Characteristic	**Number/Mean**	**Percent/Standard Deviation***	**Number/Mean**	**Percent/Standard Deviation***
Unique patients	28,684	N/A	20,345	N/A
Episodes	29,815	100%	21,095	100%
Age (years)	51.7	13.5	51.8	13.4
Sex				
Female	14,703	51.3%	10,264	50.4%
Male	13,981	48.7%	10,081	49.6%
Race†				
Black or African American	842	2.9%	587	2.9%
Unknown	17,066	59.5%	12,229	60.1%
White	9,797	34.2%	6,852	33.7%
Any risankizumab-rzaa indication‡ [-400,0] days	29,397	98.6%	20,808	98.6%
Plaque psoriasis	27,363	91.8%	20,301	96.2%
Psoriatic arthritis	6,452	21.6%	4,408	20.9%
Crohn's disease	1,936	6.5%	463	2.2%
Prior treatment [-400,0] days				
Any non-anti-TNF biologic§	8,457	28.4%	6,127	29.0%
Topical	21,180	71.0%	15,618	74.0%
Systemic non-biologic	6,713	22.5%	5,000	23.7%
Systemic anti-TNF biologic	5,248	17.6%	3,632	17.2%
Health service utilization [-400,-1] days				
Number of ambulatory encounters	21.4	22.4	20.7	21.6
Number of filled prescriptions	40.1	37.7	39.6	37.4

* Value represents standard deviation where no % follows the value.
† Represents the three most frequently coded races. Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.
‡ Risankizumab-rzaa was not FDA approved for the indication of ulcerative colitis until after the study period had ended.
§ Includes guselkumab, tildrakizumab, ustekinumab, secukinumab, ixekizumab, and brodalumab.

Table 2. Statistically Significant Alerts Among New Users of Risankizumab-rzaa in the SDD From Primary SCRI Analyses

Diagnosis Code Name (ICD-10-CM)*	Cohort (Risk Window)	Expected Outcomes in Risk Window†	Relative Risk	P-Value
Calculus of gallbladder without cholecystitis without obstruction (K80.20 node)	Variable risk window (9-11 days post-index)	0.59	15.16	0.0360
Calculus of gallbladder without cholecystitis (K80.2 node)	Variable risk window (9-11 days post-index)	0.61	14.60	0.0461

* Includes incident outcomes occurring in inpatient or emergency department settings. There were no alerts in the fixed risk window cohort that reached the statistically significant alert threshold in the primary analysis.
† Numbers of observed outcomes during the risk window are withheld to protect patient privacy.

AC Study

Table 3. Adjusted Characteristics of Risankizumab-rzaa and Guselkumab New Users in the hdPS-Matched Cohort

	Risankizumab-rzaa		Guselkumab		Covariate Balance
Characteristic	**Number/Mean**	**Percent/Standard Deviation***	**Number/Mean**	**Percent/Standard Deviation***	**Standardized Difference**
Unique patients	14,819	48.3%	14,819	80.7%	N/A
Age (years)	51.3	13.2	51.3	12.9	-0.000
Sex					
Female	7,635	51.5%	7,542	50.9%	0.013
Male	7,184	48.5%	7,277	49.1%	-0.013
Race†					
Black or African American	352	2.4%	323	2.2%	0.013
Unknown	9,779	66.0%	9,850	66.5%	-0.010
White	4,268	28.8%	4,232	28.6%	0.005
Any risankizumab-rzaa indication‡ [-400,0] days	14,560	98.3%	14,606	98.6%	-0.025
Plaque psoriasis	14,137	95.4%	14,102	95.2%	0.011
Psoriatic arthritis	4,544	30.7%	4,540	30.6%	0.001
Crohn's disease	113	0.8%	121	0.8%	-0.006
Prior treatment [-400,0] days					
Any non-anti-TNF biologic§	4,015	27.1%	3,943	26.6%	0.011
Topical	10,364	69.9%	10,276	69.3%	0.013
Systemic non-biologic	3,406	23.0%	3,393	22.9%	0.002
Systemic anti-TNF biologic	2,447	16.5%	2,419	16.3%	0.005
Most common health conditions [-400,-1] days					
Hypertension	6,639	44.8%	6,610	44.6%	0.004
Rheumatoid arthritis/osteoarthritis	6,467	43.6%	6,441	43.5%	0.004
Hyperlipidemia	6,464	43.6%	6,435	43.4%	0.004
Health service utilization [-400,-1] days					
Number of ambulatory encounters	20.2	19.9	20.1	20.5	0.005
Number of filled prescriptions	38.3	36.6	37.9	35.8	0.010

* Value represents standard deviation where no % follows the value.
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‡ Risankizumab-rzaa was not FDA approved for the indication of ulcerative colitis until after the study period had ended.
§ Includes tildrakizumab, ustekinumab, secukinumab, ixekizumab, and brodalumab.

- There were no alerts from the primary active comparator analysis that reached the predefined statistically significant alert threshold.

Conclusions

- We demonstrate the feasibility of using two different untargeted signal identification study designs to identify safety signals for risankizumab-rzaa.
- Monitoring tens of thousands of new users for thousands of outcomes, we found few statistical alerts in the SCRI study and no statistical alerts in the AC study.
- After further investigation of the patient episode data and clinical context, codes contributing to the statistical alert for calculus of the gallbladder appeared to be incidental to orders for imaging given by diagnostic radiology during the course of hospitalization for other events, mainly infections; therefore, the statistical alert was deemed not to represent a new safety signal.
- Although the analyses may be underpowered to detect rare adverse events, this evaluation provides additional reassurance beyond routine surveillance of risankizumab-rzaa's short-term safety profile.

References

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2. Skyrizi (risankizumab-rzaa) [package insert]. North Chicago, IL: AbbVie Inc.; 2024.

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