Tree-Based Mining of Real-World Data for Potential Safety Signals Associated with the Use of Dupilumab in the United States (2017-2023)

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OBJECTIVES

To conduct a broad screening assessment of the safety of dupilumab using tree-based scan statistics (TBSS).

BACKGROUND

- Dupilumab is a monoclonal antibody for management of atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis, and prurigo nodularis in the United States.
- Real-world data on the safety of dupilumab are limited.
- TBSS enables FDA to conduct signal identification to complement other pharmacovigilance approaches.

METHODS

Study Period: March 1, 2017 - June 30, 2023

Data Source: 13 sites including national insurers, regional integrated delivery systems, and Medicare and Medicaid.

Cohort: New users of dupilumab aged 12 and older, without evidence of pregnancy.

Study Design: Self-controlled risk interval design.

1. Pre/Post Analysis: compared outcome occurrence in the 4 weeks post-drug initiation (risk) to 4-weeks pre-initiation (control).
2. Temporal Cluster Analysis: evaluated temporal clusters of outcomes in the 6 months post-initiation.

Outcome Assessment: A hierarchical ICD-10-CM diagnosis code tree was used, excluding codes that were unlikely to be drug-related. Primary analyses evaluated outcomes in inpatient or emergency department settings; sensitivity analyses also included outcomes in the ambulatory setting.

Statistical Analysis: Computed TBSS from Pre/Post and Temporal Cluster analyses to observe elevated frequencies of outcomes; statistically significant alerts based on $p \leq 0.05$ (adjusted for multiple testing).

Figure 1. Pre/Post Analysis

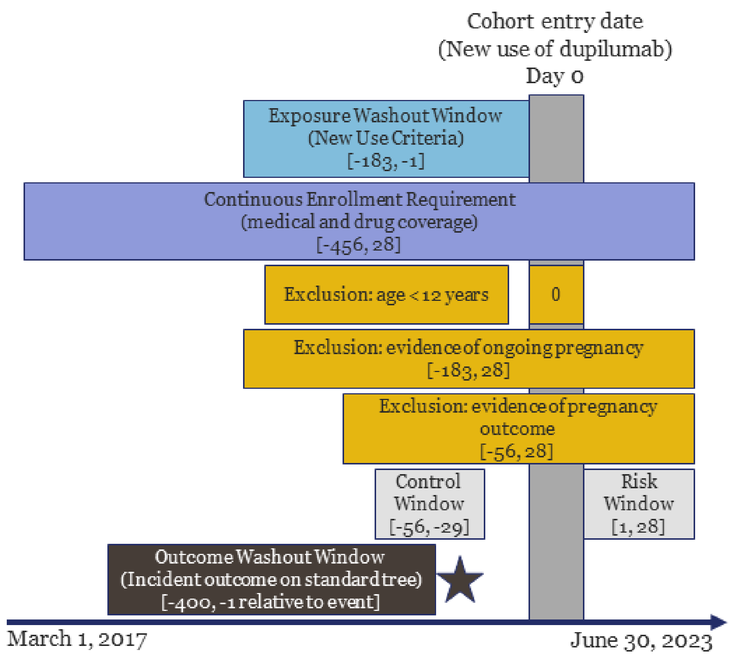
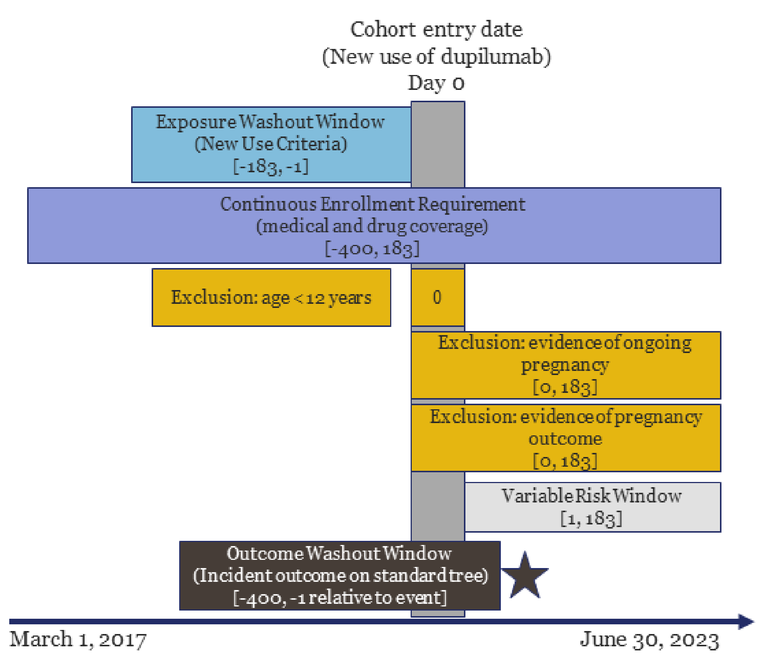


Figure 2. Temporal Cluster Analysis



RESULTS

Cohort Characterization:

- We identified 85,373 patients with 89,516 new dupilumab episodes for the pre/post analysis. There were 67,651 patients with 70,688 new dupilumab episodes in the temporal cluster analysis.
- The mean age of new users was 49 years in both analytic cohorts; more patients were female (56%) in both analytic cohorts.
- 90% of dupilumab episodes had a documented indication in the 183 days prior to treatment initiation, including 60% for atopic dermatitis, in both analytic cohorts; many had evidence of more than one indication.

Statistically Significant Alerts:

- Acute embolism and thrombosis of deep veins of lower extremity (code I82.4) was a statistically significant alert in the Pre/Post primary analysis.
  - Most of these outcomes (70%) were in Data Partners with older populations. A review of patient-level line listings in Medicare and Medicaid data partners (17/29 cases) revealed patients with multiple comorbidities and other risk factors for a deep vein thrombosis.
- Poisoning by, adverse effect of and underdosing of other drugs, medicaments and biological substances (T50.99) was a statistically significant alert in several analyses (Pre/Post and Temporal Cluster, primary and sensitivity analyses). This non-specific code is unlikely to represent a new safety signal and has been observed in TBSS analyses for other products.
- Many of the statistically significant alerts in the sensitivity analyses (including ambulatory setting) were either for indications (e.g., atopic dermatitis) or labeled adverse effects (e.g., conjunctivitis, pruritis, pain, nausea).

Figure 3. Distribution of Total Observed Events in Inpatient and Emergency Department Care Settings Among Dupilumab New Users in the Pre/Post Analysis

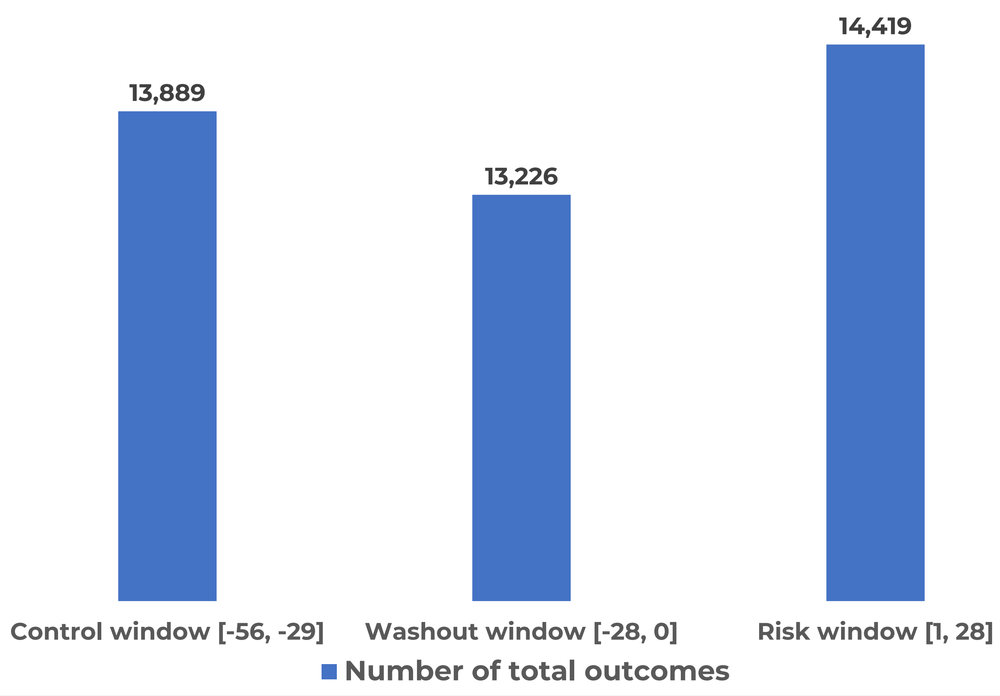


Table 1. Signal Identification Outcome Assessment in the Inpatient, Emergency Department Care Settings via Conditional Bernoulli Tree-Based Scan Statistic or Tree Temporal Scan Statistic Conditioned on Node and Time

Node Name	Node Outcomes/ Cases in Window	Expected Node Outcomes/ Cases	Relative Risk	Test Statistic	P-Value
Pre/Post Analysis					
Poisoning by, adverse effect of and underdosing of other drugs, medicaments and biological substances (T5099grp)	40	22.9	1.75	14.87	0.0001
Acute embolism and thrombosis of deep veins of lower extremity (I824grp)	29	17.3	1.68	8.94	0.0187
Temporal Cluster Analysis					
Poisoning by, adverse effect of and underdosing of other drugs, medicaments and biological substances (T5099grp)	26	8.0	4.58	12.62	0.0142

CONCLUSIONS

- Broad screening in real-world data provides a complementary view of dupilumab's safety profile to other data sources and methods.
- Statistical alerts generated by this analysis do not on their own represent safety signals.
- Statistical alerts will be evaluated in consideration of patient-level line lists of claims records, the study design, therapeutic context, treated population, potential public health impact, and other sources of information (e.g., postmarketing adverse event reports, clinical trial data) to determine if a statistical alert constitutes a newly identified safety signal.
- Alerts determined to be newly identified safety signals (NISS) will follow the FDA's policies and procedures for NISS.

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- The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the US Government.
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- SA, JB, AP, TNT, ERH, TCM are employees at HPHCI, an organization that conducts work for government and private organizations, including pharmaceutical companies.
- The authors have no conflicts of interest to disclose.

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