Sentinel

Signal Detection and Refinement Activities within FDA's Sentinel System

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June 28, 2023

Disclaimers

- The views expressed in this presentation represent those of the presenter and do not necessarily represent the official views of the U.S. Food and Drug Administration (FDA).
- This Sentinel Operations Center is funded by the U.S. FDA through the Department of Health and Human Services (HHS) contract number 75F40119D10037.

Proposed Sentinel Signal Identification Process

Integrated Safety Summary

Clinical Trial Data | **Prescribing Information**

Signal identification led by **Divisions of Pharmacovigilance** and Sentinel Program Team

Follow up investigations to be conducted by **Divisions of Epidemiology**

1. Select 1 product
2. Choose study design(s) or tool
3. Conduct analysis
4. Review and classify statistical alerts
5. Integrate results with other sources of information

Identify Outcome for Further Evaluation (if any)

https://healthpolicy.duke.edu/events/implementation-signal-detection-capabilities-sentinel-system

Choosing between Self-Controlled and Cohort Design

- Self-Control
  - Used often in vaccines
  - Advantage is control for time-invariant characteristics by design
  - Asks the question: WHEN is there an etiological risk window for a particular outcome following medical exposure? It cannot detect if there is a sustained increase in an outcome over time.
  - Vulnerable to time-varying confounding and a poor choice for when there is a rapidly changing health state (or people who are truly acutely ill)
- Cohort (Usually Active Concurrent Comparator but Historical Comparators are possible)
  - Used more often in drugs to create a condition of clinical equipoise provided an appropriate comparator can be identified.
  - Mitigates (but does not eliminate) concerns about time-varying confounding, latent coding, confounding by indication
  - Conventional Propensity Score or Conventional+High dimensional Propensity Score (hdPS) adjustment? Use hdPS adjustment when clinical equipoise is not necessarily present.
    - Covariates can simultaneously be playing the role of confounder (for particular outcomes) AND instruments (for other outcomes)

Design: Single Outcome Study → Multiple Outcome Study

Steps for an observational single outcome study in claims data:		Steps for an observational multiple outcome study in claims data:	
Identify a cohort	→	Identify a cohort	✓
Classify exposure based on records of medication dispensings	→	Classify exposure based on records of medication dispensings	✓
Identify the outcome using a validated algorithm	→	**Create an outcome tree with multiple outcomes of interest**	
Control for confounding using propensity score methods	→	Control for confounding using propensity score methods	✓
Calculate a point estimate for the exposure-outcome association	→	**Calculate test statistics for each outcome using TreeScan**	

Tree-Based Scan Statistics Enabled by:

- A signal detection / data-mining method
- Automatically adjusts for multiple scenarios
- Scans electronic health data that are grouped into hierarchical tree structures

TreeScan Statistics and P-values for Alerting

- Hypothesis testing:
  - Composite Null: there is no increase in risk across any outcome in the tree in the exposed group
  - Alternative: there is an increase in risk for at least 1 outcome in the exposed group across the tree
- Formal adjustment for multiple scenarios to limit false positives
  - This is done via data perturbation and Monte Carlo simulation using a maximum likelihood ratio
- A statistical alert occurs when an outcome meets a pre-specified cutoff, i.e. it has a log-likelihood ratio that indicates that there is a departure from the expectation under the null hypothesis.
  - Log likelihood ratios are scaled differently for each analysis so this is plotted against a p-value (the percentile distribution against the test statistic). Large LLRs == small test statistics. We typically use a conventional cutoff of p-value <=0.05.
  - A log likelihood ratio is driven by 2 things: a) distance between observed and expected values, i.e. clinical imbalance in outcome occurrence between the two groups, b) overall counts or sample information

Alert Triage

1. Check the labeled conditions, commonly reported adverse reactions in the literature and in patent-facing medical materials (e.g., Cleveland Clinic, Mayo Clinic, etc.)
2. Check for late indications or infrequently coded comorbidities (i.e., Table 1 data) that are co-coded upon occurrence of another adverse event

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZARXIO safely and effectively. See full prescribing information for ZARXIO.
ZARXIO®(filgrastim-sndz) injection, for subcutaneous or intravenous use
Initial U.S. Approval: 2015
ZARXIO **(FILGRASTIM-SNDZ) IS BIOSIMILAR* TO NEUPOGEN (FILGRASTIM).**

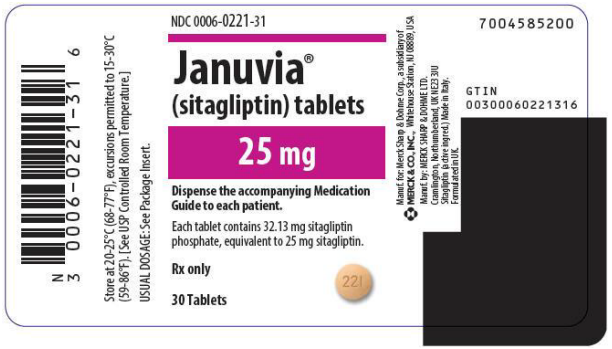
---------- **RECENT MAJOR CHANGES** ----------
Warnings and Precautions: Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) (5.8) 03/2021

---------- **CONTRAINDICATIONS** ----------
Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim products or pegfilgrastim products. (4)

---------- **WARNINGS AND PRECAUTIONS** ----------
- Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. (5.1)
- Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS. Discontinue ZARXIO in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis: Permanently discontinue ZARXIO in patients with serious allergic reactions. (5.3)
- Fatal sickle cell crises: Discontinue ZARXIO if sickle cell crisis occurs. (5.4)
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption of ZARXIO if causality is likely. (5.5)
- Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML): Monitor patients with breast and lung cancer using ZARXIO in conjunction with chemotherapy and/or radiotherapy for signs and symptoms of MDS/AML. (5.8)
- Thrombocytopenia: Monitor platelet counts. (5.9)

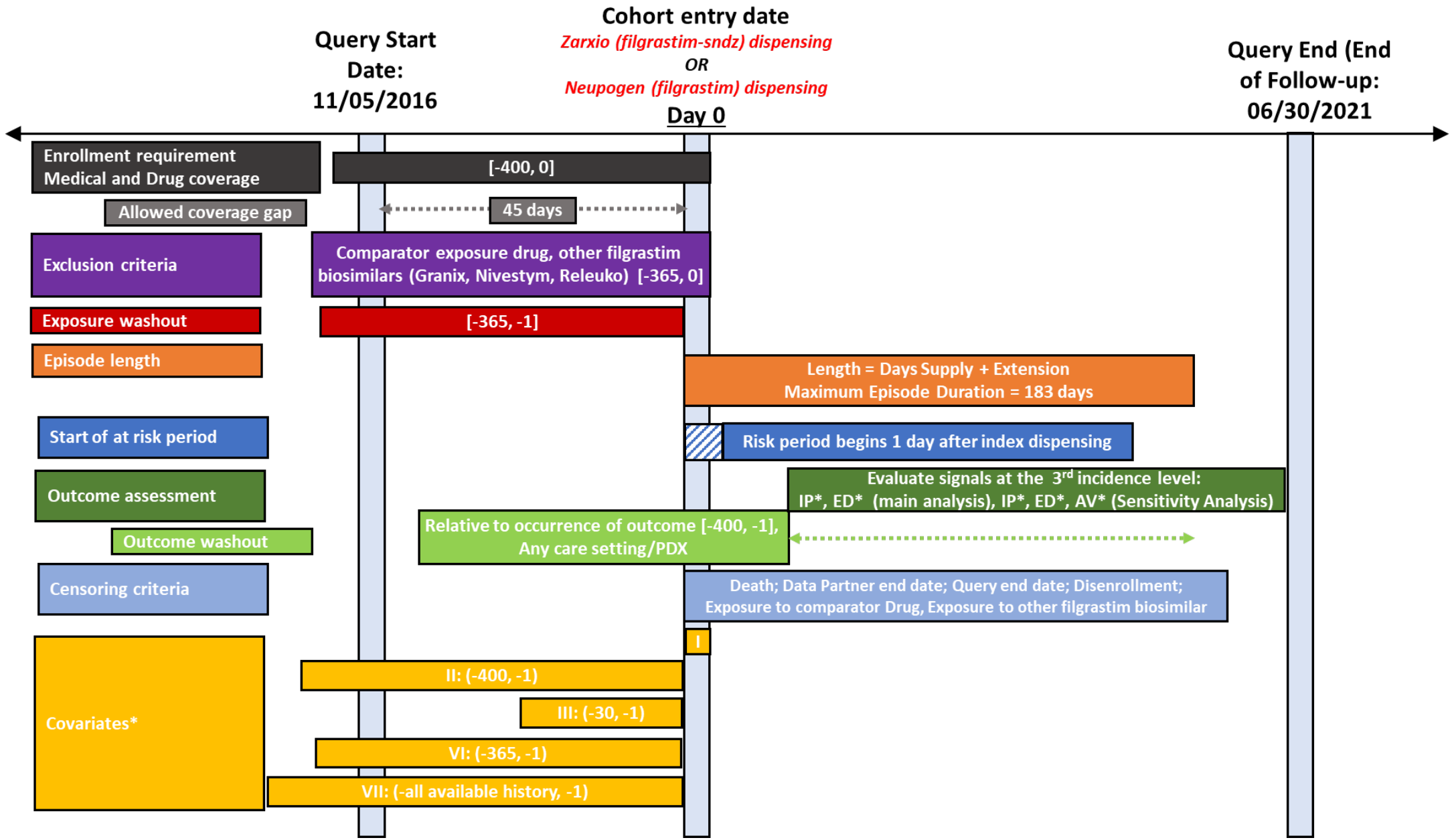
Initial Pilot Projects Selected: Ozempic and Zarxio

1. Anti-diabetic Drugs



2. Biosimilars

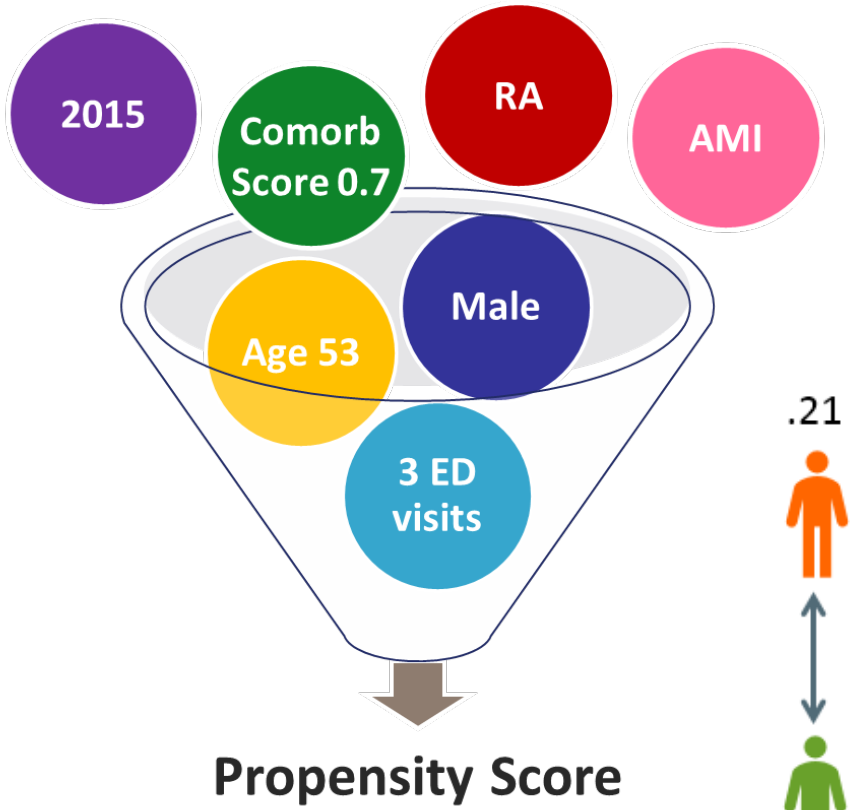
https://sentinelinitiative.org/studies/drugs/individual-drug-analyses/outcome-monitoring-following-ozempic-use-patients-type-2
https://sentinelinitiative.org/studies/drugs/individual-drug-analyses/outcome-monitoring-following-zarxio-use-signal

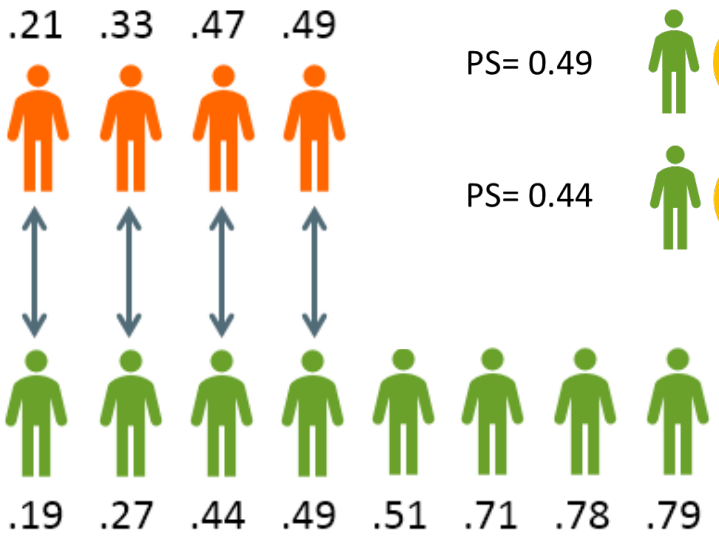


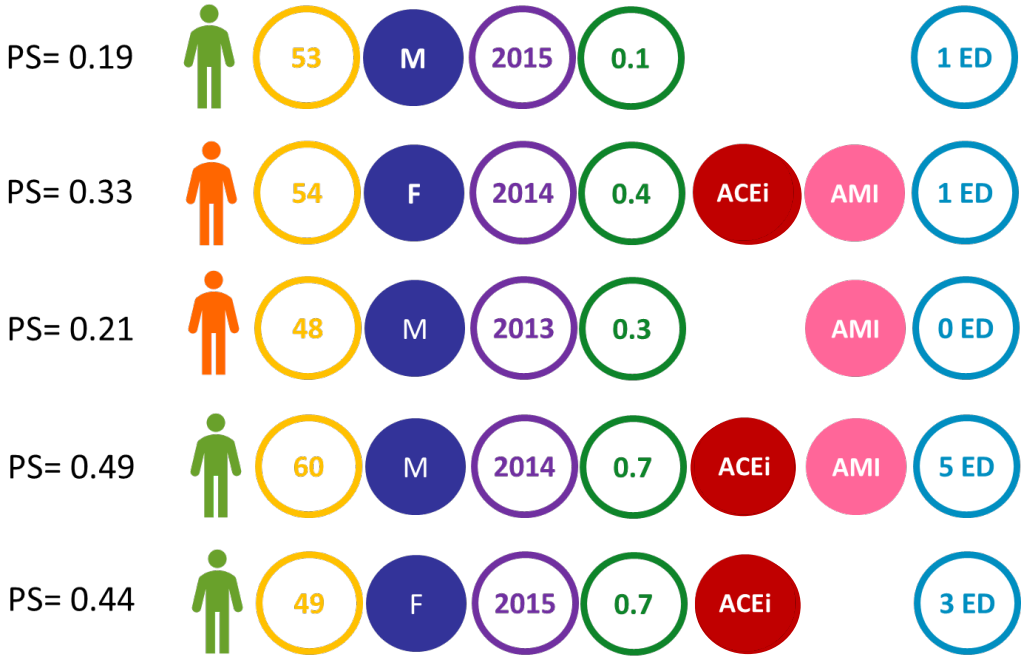
*Window I: age; race; ethnicity; sex; calendar year

*Window II: Charlson/Elixhauser combined comorbidity index; acute myocardial infarction; attention-deficit/hyperactivity disorder (ADHD), conduct disorders, hyperkinetic syndrome; alcohol use disorders; Alzheimer's disease; anemia; anxiety disorders; arrhythmia; asthma; atrial fibrillation and flutter; autism spectrum disorders; autoimmune disease; bacterial infection; benign prostatic hyperplasia; bipolar disorder; breast cancer; colorectal cancer; endometrial cancer; lung cancer; prostate cancer, urologic cancer; any of the above cancers (breast, colorectal, endometrial, lung, prostate, urologic); all cancers; cataracts; cerebral palsy; chemotherapy; all cancers or chemotherapy; chronic kidney disease (CKD); end-stage renal disease (ESRD) or dialysis; CKD, ESRD or dialysis; coagulopathy, colonoscopy; chronic obstructive pulmonary disease (COPD); cystic fibrosis and other metabolic developmental disorders; degenerative disease of central nervous system (CNS); depression, bipolar or other depressive mood disorders; depressive disorders; diabetes; insulin; anti-diabetics; diabetes or

1:1 Propensity Score Matching

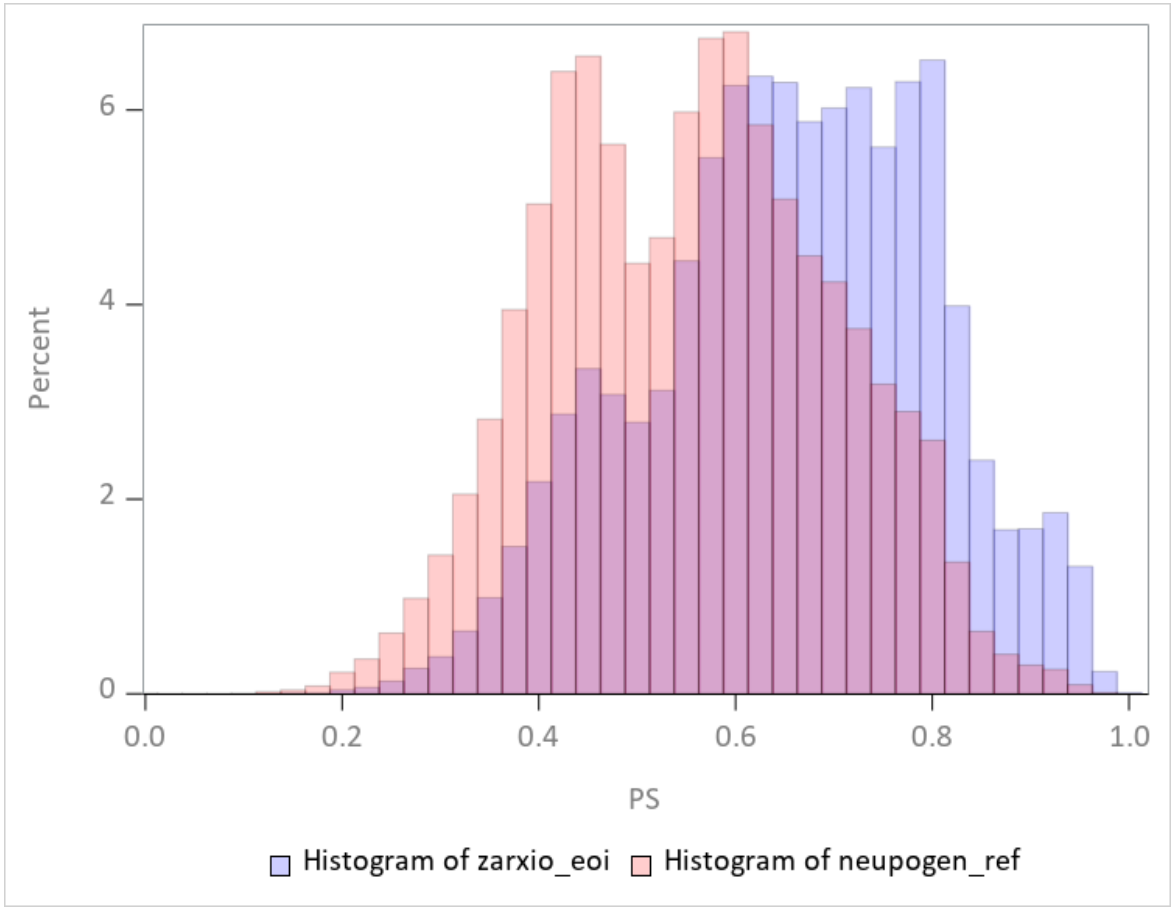


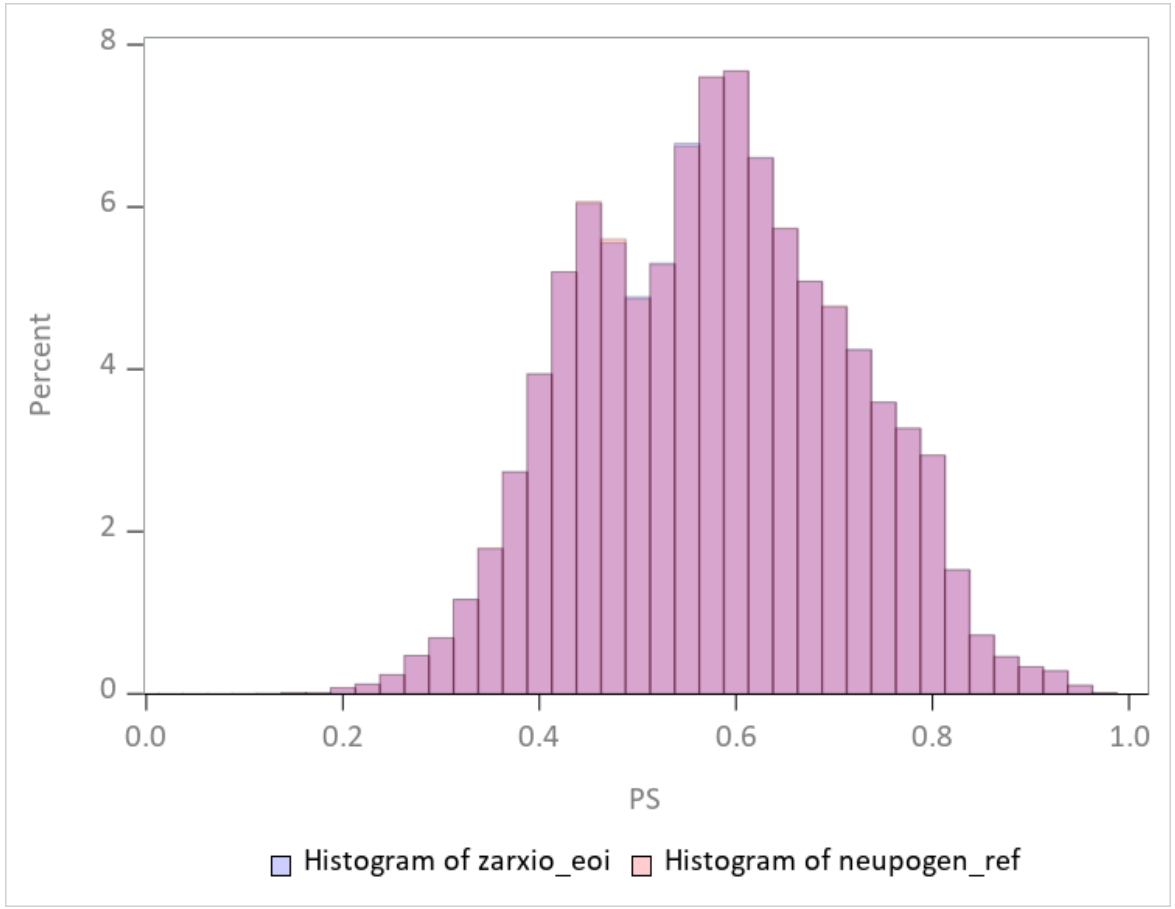




https://www.sentinelinitiative.org/communications/sentinel-initiative-events/sentinel-initiative-public-workshop-tenth-annual-day-2

Histograms Depicting Propensity Score Distribution





Histogram Depicting Propensity Score Distributions Before (Left) and After (Right) Matching, ZARXIO in BLUE and NEUPOGEN in PEACH, Ratio: 1:1, Caliper: 0.025

Patient Characteristics	Zarxio (filgrastim-sndz) Number/Mean	Zarxio (filgrastim-sndz) Percent/ Standard Deviation	Neupogen (filgrastim) Number/Mean	Neupogen (filgrastim) Percent/ Standard Deviation	Absolute Difference	Standardized Difference
Unique patients	77,804	100.00%	48,547	100.00%	N/A	N/A
Demographic Characteristics						
Age (years)	68.7	10.4	68.5	11.1	0.249	0.023
Age						
18-39 years	*2,617*	*3.4%*	*1,835*	*3.8%*	*-0.416*	*-0.022*
40-64 years	*17,974*	*23.1%*	*11,008*	*22.7%*	*0.427*	*0.010*
≥ 65 years	*57,213*	*73.5%*	*35,704*	*73.5%*	*-0.010*	*0.000*
Sex						
Female	43,022	55.3%	26,521	54.6%	0.666	0.013
Male	34,782	44.7%	22,026	45.4%	-0.666	-0.013
Race[4]						
American Indian or Alaska Native	186	0.2%	155	0.3%	-0.080	-0.015
Asian	1,400	1.8%	941	1.9%	-0.139	-0.010
Black or African American	5,714	7.3%	4,206	8.7%	-1.320	-0.049
NHOPI	102	0.1%	47	0.1%	0.034	0.010
Unknown	20,241	26.0%	11,196	23.1%	2.953	0.069
White	50,161	64.5%	32,002	65.9%	-1.449	-0.030
Hispanic origin						
Yes	1,604	2.1%	1,151	2.4%	-0.309	-0.021
No	54,402	69.9%	36,198	74.6%	-4.641	-0.104
Unknown	21,798	28.0%	11,198	23.1%	4.950	0.114
Year						
2016	1,359	1.7%	2,483	5.1%	-3.368	-0.186
2017	11,151	14.3%	14,353	29.6%	-15.233	-0.374
2018	13,947	17.9%	10,996	22.7%	-4.724	-0.118
2019	15,542	20.0%	9,092	18.7%	1.248	0.032
2020	15,533	20.0%	6,514	13.4%	6.546	0.176
2021	16,607	21.3%	4,358	9.0%	12.368	0.350
2022	3,665	5.0%	751	1.6%	3.414	0.192

https://sentinelinitiative.org/studies/drugs/zarxio-filgrastim-sndz, NHOPI = Native Hawaiian and Other Pacific Islander;
Italics indicates variable not included in Propensity Score Model, Blue font indicates imbalance

New Initiators of Zarxio and Neupogen

After 1:1 Matching, 43,009 pairs were available for analysis.

Unmatched New Initiators of Zarxio and Neupogen

Patient Characteristics	Zarxio (filgrastim-sndz) Number/Mean	Zarxio (filgrastim-sndz) Percent/ Standard Deviation	Neupogen (filgrastim) Number/Mean	Neupogen (filgrastim) Percent/ Standard Deviation	Absolute Difference	Standardized Difference
Health Characteristics						
Combined comorbidity score	7.7	3.9	7.8	3.9	-0.1	-0.026
Anemia	52,246	67.2%	33,798	69.6%	-2.468	-0.053
Chemotherapy (prior 30 days)	51,787	66.6%	29,400	60.6%	6.001	0.125
Chemotherapy (prior 400 days)	59,979	77.1%	34,849	71.8%	5.306	0.122
Degenerative diseases of CNS	34,154	43.9%	21,580	44.5%	-0.554	-0.011
Fluid and electrolyte disorder	39,618	50.9%	25,547	52.6%	-1.703	-0.034
Hyperlipidemia	52,768	67.8%	32,889	67.7%	0.075	0.002
Hypertension	58,196	74.8%	37,248	76.7%	-1.927	-0.045
NSAIDs	59,439	76.4%	37,675	77.6%	-1.209	-0.029
Organ transplant	13,168	16.9%	10,200	21.0%	-4.086	-0.104
Rheumatoid arthritis/osteoarthritis	34,043	43.8%	21,844	45.0%	-1.241	-0.025
Acute myeloid leukemia	3,283	4.2%	2,069	4.3%	-0.042	-0.002
Bone marrow harvest	138	0.2%	77	0.2%	0.019	0.005
Bone marrow transplant	462	0.6%	240	0.5%	0.099	0.014
Neutropenia	23,503	30.2%	15,999	33.0%	-2.748	-0.059
Non-myeloid malignancy	72,022	92.6%	43,351	89.3%	3.272	0.114
Myelodysplastic syndrome	5,438	7.0%	3,792	7.8%	-0.822	-0.031
Neupogen (all history)	*2,573*	*3.3%*	*2,773*	*5.7%*	*-2.405*	*-0.116*
Zarxio (all history)	*1,208*	*1.6%*	*196*	*0.4%*	*1.149*	*0.117*
Pegfilgrastim, biosimilars (all history)	*17,645*	*22.7%*	*11,493*	*23.7%*	*-0.995*	*-0.024*

https://sentinelinitiative.org/studies/drugs/zarxio-filgrastim-sndz, CNS = Central Nervous System; NSAIDS = Non-steroidal anti-inflammatory drugs
Italics indicates variable not included in Propensity Score Model, Blue font indicates imbalance

We observed 892,259 outcomes; 443,041 were among Zarxio-exposed patients.

Table 3. Signal Identification Outcome Assessment[1] in Inpatient and Emergency Department Settings, via Unconditional Bernoulli Tree-Based Scan Statistic[2] among Filgrastim-sndz (Zarxio) Initiators Matched to Filgrastim (Neupogen) Initiators in a Propensity Score Model Adjusting for Calendar Year of Index Date, Ratio 1:1, P-Value ≤ 0.05

Node Name	Node ID	Node Level	Total Node Outcomes among Filgrastim-sndz and Filgrastim Initiators	Node Outcomes among Filgrastim-sndz Initiators	Expected Node Outcomes among Filgrastim-sndz Initiators	Relative Risk	Test Statistic[2]	P-Value
Polyarthritis, unspecified	M130grp	4	32	28	16	1.75	10.12	0.0174

[1]Outcomes were assessed at the 3,4,5, and 6th level with a 400-day washout using the hierarchical ICD-10-CM tree structure.

[2]See Appendix H for details calculating the unconditional Bernoulli log likelihood ratio (LLR) based test statistic.

Table 5. Signal Identification Outcome Assessment[1] in Inpatient, Emergency Department, and Outpatient Settings, via Unconditional Bernoulli Tree-Based Scan Statistic[2] among Filgrastim-sndz (Zarxio) Initiators Matched to Filgrastim (Neupogen) in a Propensity Score Model Adjusting for Calendar Year of Index Date, Ratio 1:1, P-Value ≤ 0.05

Node Name	Node ID	Node Level	Total Node Outcomes among Filgrastim-sndz and Filgrastim Initiators	Node Outcomes among Filgrastim-sndz	Expected Node Outcomes among Filgrastim-sndz Initiators	Relative Risk	Test Statistic[2]	P-Value
Pain in right leg	M79604grp	6	619	393	309.5	1.27	22.81	0.0001
Pain in right lower leg	M79661grp	6	233	151	116.5	1.30	10.37	0.0231
Other disorders of peripheral nervous system	G64grp	3	191	126	95.5	1.32	9.91	0.0311

[1]Outcomes were assessed at the 3,4,5, and 6th level with a 400-day washout using the hierarchical ICD-10-CM tree structure.

[2]See Appendix H for details calculating the unconditional Bernoulli log likelihood ratio (LLR) based test statistic.

https://sentinelinitiative.org/sites/default/files/documents/Final_Report_cder_sir_wp005_v3.0.pdf

Signal Identification Takeaways

- Zarxio and Neupogen had very similar outcome occurrence; TreeScan identified few statistically significant imbalances/alerts.
- After review of alerts, FDA determined no further action was required.
- This analysis provides some reassurance regarding the safety profile of originator products and their biosimilars.
  - Analysis is subject to typical limitations, common to observational data studies
  - Signal identification, by nature, is designed for broad screening, not specific confounding control for targeted outcomes.

- FDA is beginning routine use of signal identification in non-pregnant populations to complement its existing surveillance activities.
- All analytic packages and results are publicly available.

https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_sir_wp005

Acknowledgements

Zarxio

U.S. Food and Drug Administration
Dutcher, Sarah
Eworuke, Efe
Herity, Leah
Hernandez, Jose
Kidd, James
Moeny, David
Mundkur, Mallika
Munoz, Monica
Ryan, Qin
Setse, Rosanna

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Marshall, Jim
Siranosian, Liz
Whited, Emma

Sentinel Data Partners
- CVS Health Clinical Trial Services, an affiliate of Aetna, a CVS Health Company, Blue Bell, PA
- Duke University School of Medicine, Department of Population Health Sciences, Durham, NC
- Carelon Research/Elevance Health, Wilmington, DE
- Humana Healthcare Research Inc., Louisville, KY
- OptumInsight Life Sciences Inc., Boston, MA

Ozempic

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- OptumInsight Life Sciences Inc., Boston, MA
- Vanderbilt University Medical Center, Department of Health Policy, Nashville, TN

Thank You