Investigating Potential Differences in the Safety Profiles of Biosimilars Relative to Originator Products Using a Tree-Based Scan Statistic

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Disclosures

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Biosimilars and Postmarketing Surveillance

- Biological products that are ***highly similar*** to FDA-licensed biological reference products
  - Highly similar, not identical
  - Abbreviated licensure pathway intended to reduce costs
- Biosimilarity assumes no clinically meaningful differences from the reference product in terms of safety, purity, and potency
  - Complex manufacturing processes may lead to product variability
  - Potential for differences in immunogenicity
- Postmarketing surveillance for differences in safety profiles is critical

FDA [Internet]. Biosimilars Action Plan: Balancing Innovation and Competition [2018 July; cited 2023 April 28] Available from: https://www.fda.gov/media/114574/download.

Biosimilars and Postmarketing Surveillance: Limitations of FAERS

- Adverse event reports for biosimilars inadvertently submitted under the reference product
- Inability to control for multiple confounding variables in medically complex patient populations
  - Rheumatology
  - Oncology
- Challenges with detecting differences in adverse event frequency between biosimilars and their reference products
  - Particularly for commonly reported adverse events
    - Immunogenicity
    - Lack of drug effect

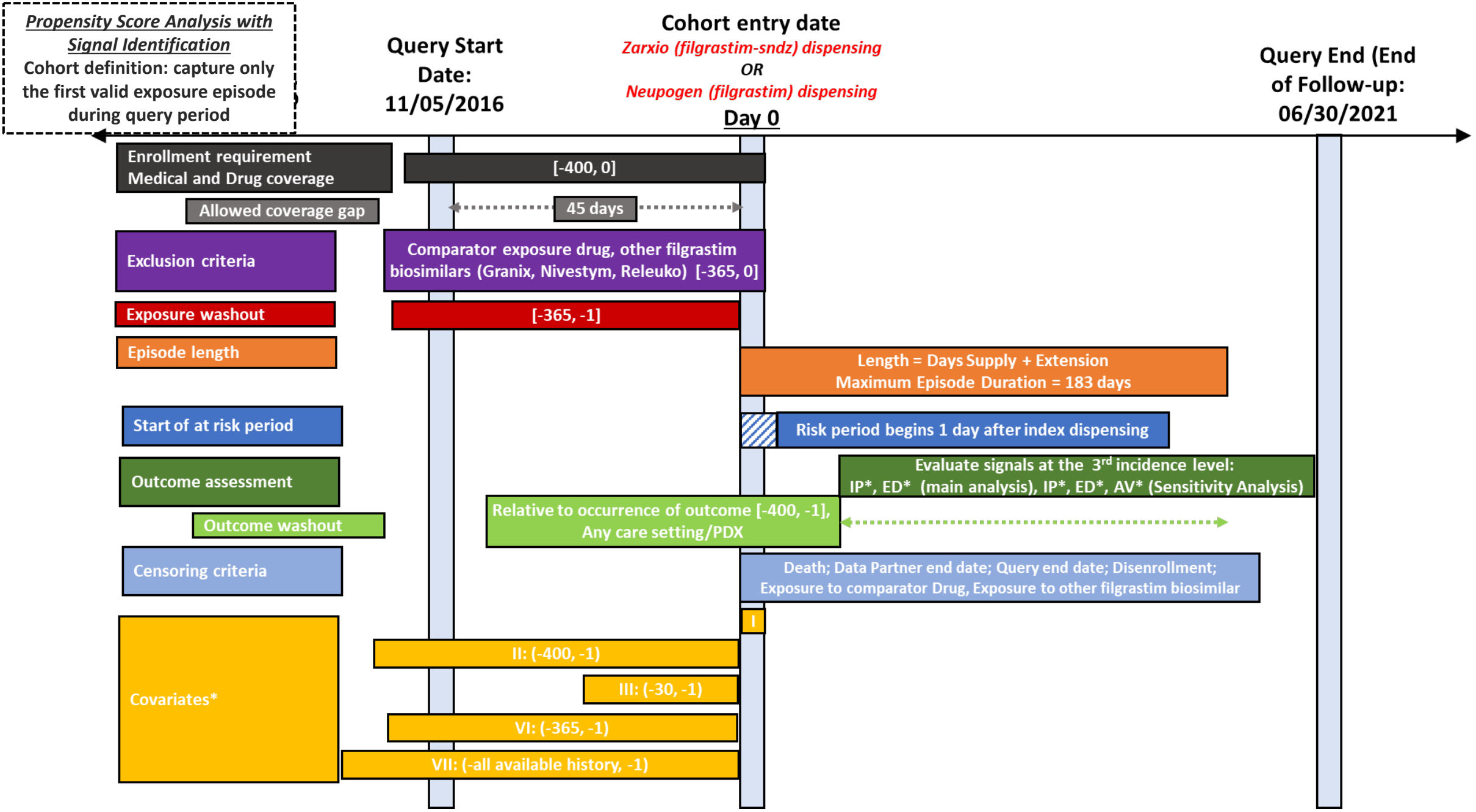
Biosimilar Product Selection

- Approval dates
  - Neupogen: February 20, 1991
  - Zarxio: March 6, 2015
- Human granulocyte colony-stimulating factor (G-CSF) approved for a variety of indications related to:
  - Reduced duration of neutropenia after chemotherapy
  - Reduced incidence of sequelae of neutropenia
  - Mobilization of autologous hematopoietic progenitor cells
  - Hematopoietic Syndrome of Acute Radiation Syndrome (Neupogen only)
- Similar safety labeling between biosimilar and reference product

Methods

Steps:

1. Identify new user cohorts using an active comparator design
2. Classify exposure based on records of medication dispensings
3. Create an outcome tree with multiple outcomes of interest
4. Control for confounding using propensity score methods
5. Calculate test statistics for each outcome using TreeScan



*See Appendix K in the report for details on covariates in this analysis:
https://www.sentinelinitiative.org/studies/drugs/individual-drug-analyses/outcome-monitoring-following-zarxio-use-signal

Methods

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

http://www.treescan.org

Methods

Alert Triage

1. Check the labeled conditions, commonly reported adverse reactions in the literature and in patent-facing medical materials
2. Check for late coding of indications or infrequently coded comorbidities 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)

Results

Data Partners	• Five large national health plans (69% CMS)
Sample Size	• 43,009 1:1 matched pairs
Primary Analysis Alerts (IP/ED)	• One alert
Secondary Analysis Alerts (IP/ED/AV)	• Three alerts

Results

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

Conclusions

- TreeScan identified few statistically significant imbalances/alerts for Zarxio
- 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
- Temporal substitution effects may occur
  - Trend toward biosimilar substitution over the query period
  - YEAR variable may act as a treatment indicator

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