Zarxio™ (filgrastim)

Sandoz, a Novartis Company
Presentation to the Oncologic Drugs Advisory Committee
January 7, 2015

Introduction

Mark McCamish, MD, PhD
Global Head Biopharm. & Oncology Injectables Development
Sandoz
## Agenda

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<th>Affiliation</th>
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<td>Global Head Biopharm. &amp; Oncology Injectables Development, Sandoz</td>
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<td>Mark McCamish, MD, PhD</td>
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</tbody>
</table>

## Additional External Consultants

- **Kimberly Blackwell, MD**
  - Professor of Medicine, Duke University Medical Center

- **Paul Cornes, BM, BCh**
  - Clinical Oncologist, Bristol Haematology and Oncology Centre, UK

- **Nadia Harbeck, MD**
  - Professor of Medicine, University of Munich, Germany
Evolution of the Concept of Sameness/Biosimilarity

- Generic small molecule drugs introduced “sameness” as a regulatory matter (1984)
  - Complex generics, e.g. Enoxaparin (2010) - FDA’s 5 principles

- Comparability for manufacturing changes to currently approved drugs and biologics (FDA 1996), became ICH Q5E (2005)
  Comparable: A conclusion that products have highly similar quality attributes before and after manufacturing process changes …


Biosimilar Development

**HIGH SIMILARITY IS THE BASIS OF BIOSIMILAR DEVELOPMENT**

- **351(a) Reference Product**
  - Analytics establish “High Similarity” and therefore **support** this conclusion

- **351(k) Biosimilar Product**
  - Clinical trials **confirm** biosimilarity / Address residual uncertainty
  - PK/PD + Immunogenicity
  - Confirm similarity in one indication

**TOTALITY OF THE EVIDENCE**

- Multiple Indications - clinical studies in each indication
- Multiple Indications (clinical studies in each not required)
Overview of Zarxio (filgrastim)

- Zarxio is a biosimilar of the reference product Neupogen® (filgrastim)
  - Filgrastim (recombinant granulocyte-colony stimulating factor (G-CSF)), which stimulates the proliferation of white blood cells
- Was first approved in the EU in 2009\(^1\) and subsequently developed for US marketing authorization
- Since approval, has become the volume leader in Europe

\(^1\) Marketed as “Zarzio®” ex-US

Zarxio Dose, Route of Administration, and Indications

- The BLA is for Zarxio pre-filled syringes containing 300 mcg/0.5 mL or 480 mcg/0.8 mL intended for subcutaneous and intravenous injection
- The proposed indications for Zarxio are identical to those of the reference product:
  - Cancer patients receiving myelosuppressive chemotherapy
  - Patients with acute myeloid leukemia receiving induction or consolidation chemotherapy
  - Cancer patients receiving bone marrow transplant
  - Patients undergoing peripheral blood progenitor cell collection and therapy
  - Patients with severe chronic neutropenia
Zarxio US Development Program

- **Analytical**
  - Battery of structural and functional analyses
- **Nonclinical**
  - 5 animal studies to assess pharmacodynamics, toxicity, toxicokinetics, and local tolerance
- **Clinical (confirming similarity)**
  - 1 pivotal and 4 supportive PK/PD studies to demonstrate similar PK/PD
  - Comparative safety and efficacy clinical study to assess comparative efficacy

Biosimilar Requirements and Zarxio Alignment

<table>
<thead>
<tr>
<th>Statutory requirement</th>
<th>Statute language</th>
<th>Zarxio fulfillment of requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference product</td>
<td><em>One reference product per application</em></td>
<td><em>Single reference product</em> (US-licensed Neupogen)</td>
</tr>
<tr>
<td>Analytical data</td>
<td><em>Analytical studies</em> that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components*</td>
<td><em>Analytical data demonstrate that Zarxio is highly similar</em> to the reference product from a physiochemical and functional standpoint</td>
</tr>
<tr>
<td>Animal studies</td>
<td><em>Animal studies</em> (including the assessment of toxicity)*</td>
<td><em>Five animal studies assessed the pharmacodynamics, toxicity, toxicokinetics, and local tolerance of Zarxio compared to Neupogen and confirmed that the pharmacologic and toxicological profiles of the two products are similar</em></td>
</tr>
</tbody>
</table>
### Biosimilar Requirements and Zarxio Alignment

<table>
<thead>
<tr>
<th>Statutory requirement</th>
<th>Statute language</th>
<th>Zarxio fulfillment of requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical studies</td>
<td>A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product)</td>
<td>Relevant clinical data were collected in 174 healthy volunteers, 388 breast cancer patients receiving myelosuppressive chemotherapy, and 121 healthy stem cell donors.</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>The biological product and reference product utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism or mechanisms of action are known for the reference product</td>
<td>The mechanism of action of filgrastim as an rhG-CSF product is mediated by the selective binding to the G-CSF receptor and is similar across all indications. There are apparently no qualitative differences in the mechanism of action in neutropenia of different origins.</td>
</tr>
</tbody>
</table>

### Biosimilar Requirements and Zarxio Alignment

<table>
<thead>
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<th>Statutory requirement</th>
<th>Statute language</th>
<th>Zarxio fulfillment of requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditions of use</td>
<td>The condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product</td>
<td>Zarxio seeks licensure for the same indications for which the reference product is approved.</td>
</tr>
<tr>
<td>Route of administration, dosage form, and strength</td>
<td>The route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product</td>
<td>Zarxio has the same route of administration, dosage form, and strengths as the reference product.</td>
</tr>
</tbody>
</table>
Agenda

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Global Head Biopharm. & Oncology Injectables Development
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Analytical Demonstration of Similarity

Hansjoerg Toll, PhD
Head Analytical Characterization
Sandoz
Filgrastim is a Relatively Simple Biologic

- Protein only (non-glycosylated)
- Single main substance
- 1 chain
- 175 amino acids
- 18,799 Da

- Glycoprotein
- Mixture of variants
- 4 chains
- 1330 amino acids
- 144,000 Da

Biosimilars are Systematically Developed to Match the Reference Product

Adapted from McCamish M & Wootlett G. MAbs 2011; 3(2): 209–17
A Large Number of Zarxio and Neupogen Batches was Used for Assessing Similarity

<table>
<thead>
<tr>
<th>Zarxio</th>
<th>Neupogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>A00675111G V200001</td>
<td>1009162 1025275 1020167 1024506 1029572 N0792AB N1179AB</td>
</tr>
<tr>
<td>00657409G V201002</td>
<td>1014928 1025872 1021955 1024772 1029837 N0839AA N1179AB</td>
</tr>
<tr>
<td>006575011G V201102</td>
<td>1020649 1026358 1024050 1025051 1029883 N0875AA N1204AJ</td>
</tr>
<tr>
<td>030806 V201001</td>
<td>1021957 1026361 1000197 1025222 1032557 N0911AA N1213AH</td>
</tr>
<tr>
<td>040906 V201101</td>
<td>1023892 1026689 1000539 1026494 1036993 N0996AD</td>
</tr>
<tr>
<td>050906 V200201</td>
<td>1025266 1027991 1001143 1026519 1031133A N0999AF</td>
</tr>
<tr>
<td>111007</td>
<td>1027491 1031121 1003784 1026606 1032549A N1005AA</td>
</tr>
<tr>
<td>050409</td>
<td>1027493 1021952 1003865 1026690 N0512AA N1014AB</td>
</tr>
<tr>
<td>150210</td>
<td>1035682 1025277 1003937 1027142 N0527AA N1062AA</td>
</tr>
<tr>
<td>140210</td>
<td>1036971 1028687 1004154 1028082 N0577AA N1113AG</td>
</tr>
<tr>
<td>220810</td>
<td>1038184 1012002 1018725 1028497 N0586AA N1114AA</td>
</tr>
<tr>
<td></td>
<td>P104490 1013453 1023368 1029228 N0715AF N1114AJ</td>
</tr>
<tr>
<td></td>
<td>1022878 1017557 1023377 1029442 N0715AH N1144AE</td>
</tr>
</tbody>
</table>

Neupogen lots analyzed over a time frame of 10 years

Filgrastim Exerts its Biological Activity by Receptor Activation

Source table: Sandoz

Source images: Sandoz
## What Matters for Filgrastim Safety and Efficacy

<table>
<thead>
<tr>
<th>Quality Attribute</th>
<th>Criticality</th>
<th>Relevant for</th>
<th>Methods Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acid sequence</td>
<td>Very High</td>
<td>Efficacy, Safety, Immunogenicity</td>
<td>Edman, peptide mapping, MS</td>
</tr>
<tr>
<td>Potency</td>
<td>Very High</td>
<td>Efficacy, Safety</td>
<td>Bioassay</td>
</tr>
<tr>
<td>Target binding</td>
<td>Very High</td>
<td>Efficacy, Safety</td>
<td>Surface plasmon resonance</td>
</tr>
<tr>
<td>Protein concentration</td>
<td>Very High</td>
<td>Efficacy</td>
<td>Content determination</td>
</tr>
<tr>
<td>Higher order structure</td>
<td>High</td>
<td>Efficacy, Immunogenicity</td>
<td>CD and NMR spectroscopy</td>
</tr>
<tr>
<td>High-molecular weight variants/aggregates</td>
<td>High</td>
<td>Immunogenicity</td>
<td>Size exclusion chromatography</td>
</tr>
<tr>
<td>Oxidized variants</td>
<td>High</td>
<td>Efficacy</td>
<td>Reversed phase chromatography</td>
</tr>
<tr>
<td>Subvisible particles</td>
<td>High</td>
<td>Immunogenicity</td>
<td>Light obscuration</td>
</tr>
<tr>
<td>Truncated variants</td>
<td>Low</td>
<td>None</td>
<td>RP-HPLC-MS</td>
</tr>
<tr>
<td>Norleucine</td>
<td>Very Low</td>
<td>None</td>
<td>Reversed phase chromatography</td>
</tr>
<tr>
<td>Deamidation</td>
<td>Very Low</td>
<td>None</td>
<td>Cation exchange chromatography</td>
</tr>
</tbody>
</table>

## Today, Protein Analytics are Extremely Sensitive

**Example: mass spectrometry**

<table>
<thead>
<tr>
<th>Year</th>
<th>Detection limit for peptides (pmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>100</td>
</tr>
<tr>
<td>1993</td>
<td>10</td>
</tr>
<tr>
<td>1997</td>
<td>1</td>
</tr>
<tr>
<td>2000</td>
<td>0.1</td>
</tr>
<tr>
<td>2003</td>
<td>0.01</td>
</tr>
<tr>
<td>2005</td>
<td>0.001</td>
</tr>
<tr>
<td>2008</td>
<td>0.0001</td>
</tr>
<tr>
<td>2011</td>
<td>0.00001</td>
</tr>
</tbody>
</table>

Amino Acid Sequence and Folding

Primary structure
is the amino acid sequence

Secondary structure
occurs when the sequence of amino acids are linked by hydrogen bonds

Tertiary structure
is the final folding which occurs when certain attractions are present between alpha helices and beta sheets

Amino Acid Sequence of Filgrastim is Determined by Several Methods

- Edman Sequencing
- Peptide Map
- Mass Spectrometry
- Amino Acid Analysis
Peptide Map Confirms Identical Primary Structures of Zarxio and Neupogen

Folding of Filgrastim is Determined by Several Methods

Secondary structure
- Circular dichroism spectroscopy (CD)

Tertiary structure
- 1D NMR
- 2D NMR
Circular Dichroism of Proteins

Left and right circularly polarized light is absorbed differently by secondary structural elements, e.g. α-helix, β-sheet and random coil/unfolded, CD is a tool to analyze the higher order structure.

CD Confirms Highly Similar Secondary Structures of Zarxio and Neupogen

Source graph: Sandoz
2D NMR is Highly Sensitive in Detecting Differences in Structure

Single amino acid change can easily be detected

Example: Asn→Asp (N17D) in GM-CSF

2D NMR Confirms Highly Similar Tertiary Structures of Zarxio and Neupogen
Highly Sensitive HPLC Detects Even Very Low Levels of Product Variants

RP-HPLC analytics can detect product-related variants with high sensitivity.

Oxidized Variants and Purity are Highly Similar Between Zarxio and Neupogen

Reversed Phase HPLC
Both Zarxio and Neupogen Have Very Low Aggregate Levels

Size Exclusion HPLC

Surface Plasmon Resonance Confirms Highly Similar Receptor Binding

<table>
<thead>
<tr>
<th>Product</th>
<th>$k_{on}$ [M$^{-1}$ s$^{-1}$]</th>
<th>$k_{off}$ [µs$^{-1}$]</th>
<th>$K_D$ [pM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZARXIO n=6</td>
<td>1.1</td>
<td>9.6</td>
<td>87.5</td>
</tr>
<tr>
<td>Neupogen US n=6</td>
<td>1.2</td>
<td>9.4</td>
<td>80.1</td>
</tr>
</tbody>
</table>
Sensitive Biological Assay Confirms Highly Similar Biological Activity

<table>
<thead>
<tr>
<th>Product</th>
<th>Zarxio</th>
<th>Neupogen US</th>
<th>Neupogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific activity</td>
<td>1.0–1.1</td>
<td>1.0–1.2</td>
<td>0.4–1.6</td>
</tr>
</tbody>
</table>

Source image: Sandoz

Zarxio Matches Neupogen in Content

Source graph: Sandoz
Zarxio and Neupogen Formulations are Highly Similar

<table>
<thead>
<tr>
<th>Function</th>
<th>Zarxio</th>
<th>Neupogen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active Ingredient</strong></td>
<td>Filgrastim 0.600 mg/mL</td>
<td>Filgrastim 0.600 mg/mL</td>
</tr>
<tr>
<td><strong>Other Ingredients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffer</td>
<td>Glutamate pH 4.4 10 mM</td>
<td>Acetate pH 4.0 10 mM</td>
</tr>
<tr>
<td>Tonifying agent</td>
<td>Sorbitol 50 mg/mL</td>
<td>Sorbitol 50 mg/mL</td>
</tr>
<tr>
<td>Surfactant</td>
<td>Polysorbate 80 0.004%</td>
<td>Polysorbate 80 0.004%</td>
</tr>
<tr>
<td>Solvent</td>
<td>Water for Injection ad 0.5 mL or 0.8 mL</td>
<td>Water for Injection ad 0.5 mL or 0.8 mL</td>
</tr>
</tbody>
</table>

Zarxio and Neupogen are Highly Similar Regarding All Molecular Attributes

**Structure**
- Amino acid sequence
- Secondary structure
- Tertiary structure

**Function**
- Receptor binding
- Biological activity

**Heterogeneity**
- Product variants
  - Aggregated
  - Oxidized
  - Truncated
  - Deamidated
  - Norleucine
  - Minor variants

**Process impurities**

**Pharmaceutical properties**
- Concentration
- Particles
- Stability
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Biosimilar Clinical Development Program

Sigrid Balser, PhD  Global Clinical Development  Sandoz
### Overview of Clinical Program

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>N</th>
<th>Origin Neupogen</th>
<th>Dose</th>
<th>PK</th>
<th>PD</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Immuno-</th>
<th>genicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>109</td>
<td>Healthy volunteers</td>
<td>28 US</td>
<td>10 mcg/kg, s.c.</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>302</td>
<td>Breast cancer patients</td>
<td>218 US</td>
<td>5 mcg/kg, s.c.</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>101</td>
<td>Healthy volunteers</td>
<td>40 EU</td>
<td>10 mcg/kg, s.c.</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>102</td>
<td>Healthy volunteers</td>
<td>26 EU</td>
<td>5 mcg/kg, i.v.</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>103</td>
<td>Healthy volunteers</td>
<td>56 EU</td>
<td>2.5 mcg/kg, s.c. &amp; 5 mcg/kg, s.c.</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>Healthy volunteers</td>
<td>24 EU</td>
<td>1 mcg/kg, s.c.</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>301</td>
<td>Breast cancer patients</td>
<td>170 Single-arm</td>
<td>300 mcg if &lt; 60kg 480 mcg if ≥ 60kg</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>501</td>
<td>Healthy donors</td>
<td>240 Single-arm</td>
<td>10 mcg/kg, s.c.</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Plus extensive post-marketing pharmacovigilance data outside of the US

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### Study 109

Pharmacokinetic and Pharmacodynamic Equivalence Established in Healthy Volunteers
Healthy Volunteers as a Sensitive Model to Establish Biosimilarity

- Healthy volunteers provide the most sensitive setting to confirm high similarity
  - Same clinically relevant markers (ANC and CD34+ cells) and mode of action as in patient populations
  - Bone marrow is fully responsive to evaluate PD response
  - No confounding factors
  - Cross-over design reduces variability
  - Fully immunocompetent to assess immunogenicity

Study 109 – Design

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Blood Sampling</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 109</td>
<td>Zarxio 10 mcg/kg, s.c. (N = 14)</td>
<td>Neupogen 10 mcg/kg, s.c. (N = 14)</td>
<td>D1</td>
<td>Single dose</td>
</tr>
<tr>
<td>Study 109</td>
<td>Neupogen 10 mcg/kg, s.c. (N = 14)</td>
<td>Zarxio 10 mcg/kg, s.c. (N = 13)</td>
<td>D15</td>
<td>Blood sampling</td>
</tr>
<tr>
<td>Study 109</td>
<td>Zarxio 10 mcg/kg, s.c. (N = 13)</td>
<td>Neupogen 10 mcg/kg, s.c. (N = 13)</td>
<td>D15</td>
<td>Blood sampling</td>
</tr>
</tbody>
</table>

**Primary objectives (hierarchical test):**
- PD equivalence*: $E_{max}$, $AUEC_{0-120h}$ of absolute neutrophil count (ANC)
- PK equivalence*: $C_{max}$, $AUC_{last}$

**Secondary objectives:**
- CD34+ cell count
- Safety, immunogenicity and local tolerance

*Equivalence was assessed according to FDA endorsed bioequivalence margins of 80-125%

➢ Design was pre-discussed with FDA
Study 109 – PK Results (Primary Endpoint) 
Demonstrated PK Equivalence

Arithmetic mean ± SD - time profiles

Equivalence assessment with respect to FDA equivalence margins

Parameter | AUC₀⁻last | C₀ₓₜₘₐₓ |
--- | --- | --- |
Ratio [%] | Zarxio/Neupogen | 87.65 | 88.13 |
90% CI [%] | Zarxio/Neupogen | 84.39 – 91.04 | 84.00 – 92.46 |

Study 109 – PD Results (Primary Endpoint) 
Demonstrated PD Equivalence for ANC Response

Arithmetic mean ± SD - time profiles

Equivalence assessment with respect to FDA equivalence margins

Parameter | AUEC₀⁻120h | E₀₉₅ |
--- | --- | --- |
Ratio [%] | Zarxio/Neupogen | 103.07 | 100.33 |
95% CI [%] | Zarxio/Neupogen | 100.42 – 105.78 | 96.13 – 104.70 |
Study 109 – PD Results (Secondary Endpoint)
Demonstrated High PD Similarity for CD34+ Response

Arithmetic mean ± SD - time profiles

Similarity assessment with respect to FDA equivalence margins

Parameter | AUEC<sub>0-336h</sub> | E<sub>max</sub>
--- | --- | ---
Ratio [%] | Zarxio/Neupogen | 102.29 | 104.96
95% CI [%] | 93.80 – 111.55 | 92.11 – 119.64

Overall Highly Similar ANC and CD34+ Responses

- Superimposable dose-dependent profiles
- All point estimates close to 100% with confidence intervals well within margins
- Equivalent responses in both PD markers relevant for all approved indications
Similar Dose-Response Relationships
Multiple-Dose Studies (2.5/5/10 mcg/kg s.c.)

Absolute neutrophil count (ANC)  
CD34+ cell count

Study 302  
(NCT01519700)

Final Confirmation of Similarity in Breast Cancer Patients Treated with Myelosuppressive Chemotherapy
Study 302 - Breast Cancer as a Sensitive Setting to Confirm Biosimilarity

Breast cancer, TAC chemotherapy, primary endpoint:
- Homogenous population
- Treatment guidelines support use of TAC chemotherapy as a standard curative treatment in early breast cancer patients
- TAC chemotherapy has a proven dose-limiting hematological toxicity with grade 3-4 neutropenia in approx. 65.5% patients and a median duration of grade 4 neutropenia of 7 days without G-CSF support
- Treatment guidelines require primary prophylaxis with G-CSF as supportive care for TAC chemotherapy with a proven substantial effect in this setting
- The duration of severe neutropenia has become a well-established, objective measure of efficacy (risk of infection is directly proportional to severity and duration of neutropenia)
- Well-established model to study and compare products in the G-CSF class

- All study design aspects were pre-discussed with FDA

---

Study 302 - Study Objectives

Primary objective:
- Assess non-inferiority in the mean duration of severe neutropenia (DSN) during Cycle 1 in breast cancer patients receiving TAC chemotherapy

DSN is defined as the number of consecutive days with grade 4 neutropenia (absolute neutrophil count [ANC] less than 0.5 × 10^9/L)

Secondary efficacy endpoints:
- Incidence of febrile neutropenia (FN), defined as oral temperature ≥ 38.3°C while having an ANC < 0.5 × 10^9/L, by cycles and across all cycles
- Number of days of fever, defined as orally temperature ≥ 38.3°C, by cycles and across all cycles
- Depth of ANC nadir in Cycle 1
- Time to ANC recovery in Cycle 1
- Frequency of infections by cycle and across all cycles
- Incidence and duration of hospitalization due to FN

Safety endpoints:
- Incidence, occurrence, and severity of (serious) adverse events
- Local tolerability at the injection site
- Systemic tolerance

Objective of special interest:
- Immunogenicity (anti-rhG-CSF antibody formation)
Study 302 – Treatment Regimen per Cycle

- TAC is applied according to the label as approved by FDA
- G-CSF is applied daily starting on Day 2 at a dose of 5 mcg/kg until ANC has recovered to 10x10^9/L or until Day 15, whichever occurs first

Treatment regimen in each cycle

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Days 2-15</th>
<th>Days 16-21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel&lt;sup&gt;1&lt;/sup&gt;&lt;br&gt;75 mg/m²</td>
<td>5 mcg/kg for up to 14 days&lt;br&gt;Zarxio</td>
<td>No treatment</td>
</tr>
<tr>
<td>Doxorubicin&lt;sup&gt;2&lt;/sup&gt;&lt;br&gt;50 mg/m²</td>
<td>5 mcg/kg for up to 14 days&lt;br&gt;Neupogen</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide&lt;sup&gt;3&lt;/sup&gt;&lt;br&gt;500 mg/m²</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Taxotere
2. Adriamycin
3. Cytoxan

Study 302 – Primary Analysis of Zarxio vs. Neupogen

218 patients were included in 25 sites between 12/2011 and 09/2012

Primary endpoint analysis: Non-inferiority assessment in DSN between Zarxio and Neupogen with respect to a non-inferiority margin of 1 day
Study 302 - Baseline Characteristics
For Patients Treated with Zarxio or Neupogen in Cycle 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Zarxio N=107</th>
<th>Neupogen N=107</th>
<th>Total N=214</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [Mean ± SD]</td>
<td>49.5 ± 11.52</td>
<td>48.4 ± 11.02</td>
<td>49.0 ± 11.34</td>
</tr>
<tr>
<td>Time since initial diagnosis in months [Median (min, max)]</td>
<td>1.0 (0.171*)</td>
<td>1.0 (0.16)</td>
<td>1.0 (0.171*)</td>
</tr>
<tr>
<td>Clinical stage n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>7 (6.5)</td>
<td>8 (7.5)</td>
<td>15 (7.0)</td>
</tr>
<tr>
<td>II</td>
<td>57 (53.3)</td>
<td>53 (49.5)</td>
<td>110 (51.4)</td>
</tr>
<tr>
<td>III</td>
<td>43 (40.2)</td>
<td>46 (43.0)</td>
<td>89 (41.6)</td>
</tr>
<tr>
<td>IV</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Adjuvant chemotherapy n (%)</td>
<td>63 (58.9)</td>
<td>61 (57.0)</td>
<td>124 (57.9)</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy n (%)</td>
<td>44 (41.1)</td>
<td>46 (43.0)</td>
<td>90 (42.1)</td>
</tr>
</tbody>
</table>

*patient 711-32 was enrolled in the study with contralateral breast cancer diagnosed 1 month prior to enrolment; the initial diagnosis was 171 month before randomization.

Study 302: Cycle 1 – Superimposable ANC Profiles
**Study 302: Cycle 1 - Primary Endpoint**

**Equivalence in Duration of Severe Neutropenia**

Mean DSN on Cycle 1 with 95% CI

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Zarxio (N=101)</th>
<th>Neupogen (N=103)</th>
<th>Comparison Zarxio-Neupogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depth of nadir (10^9/L) (mean ± SD)</td>
<td>0.734 ± 1.1388</td>
<td>0.757 ± 1.3131</td>
<td></td>
</tr>
<tr>
<td>Time to ANC recovery [days] (mean ± SD)</td>
<td>1.8 ± 0.97</td>
<td>1.7 ± 0.81</td>
<td></td>
</tr>
<tr>
<td>Incidence of FN (n (%))</td>
<td>4 (4.0%)</td>
<td>2 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>Incidence of hospitalizations due to FN (n (%))</td>
<td>1 (1.0%)</td>
<td>1 (1.0%)</td>
<td></td>
</tr>
<tr>
<td>Incidence of infections (n (%))</td>
<td>2 (2.0%)</td>
<td>2 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>Number of days of fever [days] (median, range)</td>
<td>0 (0 – 2)</td>
<td>0 (0 – 2)</td>
<td></td>
</tr>
</tbody>
</table>

**Definitions:**
- **Time to ANC recovery:** number of days until ANC increases to \(\geq 2 \times 10^9/L\) after nadir
- **Febrile Neutropenia (FN):** oral temperature \(\geq 38.3^\circ C\) and ANC \(\leq 0.5 \times 10^9/L\) on the same day
- **Fever episode:** oral body temperature of \(\geq 38.3^\circ C\)
- **Incidence:** number of patients with at least one such event

✓ Lower bound of the confidence interval is above the non-inferiority margin of -1 day
✓ Non-inferiority between Zarxio and Neupogen established
✓ Two-sided confidence interval supports equivalence conclusion

---

**Study 302: Cycle 1 – Similarity in Secondary Efficacy Endpoints**

<table>
<thead>
<tr>
<th>Parameter (Cycle 1)</th>
<th>Zarxio</th>
<th>Neupogen</th>
<th>Comparison Zarxio-Neupogen</th>
</tr>
</thead>
</table>

-10% -5% 0% 5% 10%

-0.4 -0.2 0.0 0.2 0.4

-10% -5% 0% 5% 10%

-0.4 -0.2 0.0 0.2 0.4
### Study 302: Similar Overall Safety Profiles
**All Six Cycles with Continuous Treatment**

<table>
<thead>
<tr>
<th>Event category</th>
<th>Zarxio N=53</th>
<th>Neupogen N=52</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any AE</strong></td>
<td>52 (98.1%)</td>
<td>50 (96.2%)</td>
</tr>
<tr>
<td><strong>Study drug-related AEs</strong></td>
<td>19 (35.8%)</td>
<td>20 (38.5%)</td>
</tr>
<tr>
<td><strong>Chemotherapy-related AEs</strong></td>
<td>49 (92.5%)</td>
<td>50 (96.2%)</td>
</tr>
<tr>
<td><strong>Any SAE</strong></td>
<td>5 (9.4%)</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td><strong>Study drug-related SAEs</strong></td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>Chemotherapy-related SAEs</strong></td>
<td>3 (5.7%)</td>
<td>2 (3.8%)</td>
</tr>
</tbody>
</table>

### Most Frequent (> 5%) AEs by Preferred Term
**All Cycles – Continuous Treatment**

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Zarxio N=53</th>
<th>Neupogen N=52</th>
<th>Comparison Zarxio-Neupogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>41 (77.4%)</td>
<td>43 (82.7%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>29 (54.7%)</td>
<td>37 (71.2%)</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>20 (37.7%)</td>
<td>28 (53.8%)</td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>13 (24.5%)</td>
<td>19 (36.5%)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (32.1%)</td>
<td>13 (25.0%)</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>8 (15.1%)</td>
<td>13 (25.0%)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (17.0%)</td>
<td>9 (17.3%)</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (11.3%)</td>
<td>11 (21.2%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (9.4%)</td>
<td>8 (15.4%)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5 (9.4%)</td>
<td>6 (11.5%)</td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>5 (9.4%)</td>
<td>6 (11.5%)</td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>4 (7.5%)</td>
<td>3 (5.8%)</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6 (11.3%)</td>
<td>1 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (5.7%)</td>
<td>3 (5.8%)</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (5.7%)</td>
<td>3 (5.8%)</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>5 (9.4%)</td>
<td>1 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>3 (5.7%)</td>
<td>2 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>2 (3.8%)</td>
<td>3 (5.8%)</td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3 (5.7%)</td>
<td>1 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (5.7%)</td>
<td>1 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3 (5.7%)</td>
<td>1 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>3 (5.7%)</td>
<td>1 (1.9%)</td>
<td></td>
</tr>
</tbody>
</table>
Overall Immunogenicity in Breast Cancer Patients and in Healthy Volunteers

No Signs of Induced Immunogenicity in over 3300 Samples Tested

No Signs of Immunogenicity in Breast Cancer Patients and Healthy Volunteers

<table>
<thead>
<tr>
<th>Study</th>
<th>Cycles</th>
<th>Dose</th>
<th>Subjects</th>
<th>Samples</th>
<th>RIP positive</th>
<th>NAB positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>302</td>
<td>Up to 6</td>
<td>5 mcg/kg</td>
<td>214</td>
<td>1583</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>301</td>
<td>Up to 4</td>
<td>300 mcg if &lt; 60kg 480 mcg if ≥ 60kg</td>
<td>170</td>
<td>643</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>384</td>
<td>2226</td>
<td>0</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**Breast cancer patients:**

**Healthy volunteers:**

<table>
<thead>
<tr>
<th>Applications</th>
<th>Dose</th>
<th>Subjects</th>
<th>Samples</th>
<th>RIP positive</th>
<th>NAB positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-dose</td>
<td>1 – 10 mcg/kg</td>
<td>156</td>
<td>486</td>
<td>3*</td>
<td>0</td>
</tr>
<tr>
<td>Multiple-dose</td>
<td>2.5 – 10 mcg/kg</td>
<td>208</td>
<td>597</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>364</td>
<td>1083</td>
<td>3*</td>
<td>0</td>
</tr>
</tbody>
</table>

* All three confirmed positive samples derive from the same subject; subject was already showed a signal at baseline, with no increase in titer after treatment, i.e. likely not driven by a response to G-CSF

RIP: radioimmunoprecipitation assay to assess binding antibodies; NAB: assesses neutralizing antibodies
Post-marketing Experience with Zarxio

Marketed as Zarzio and as Filgrastim Hexal Outside the US

Summary of Experience Outside US

- Zarzio was first approved by EMA in 2009 and is now approved in over 60 countries worldwide
- Over 7.5 million patient-days of exposure (currently the most prescribed daily filgrastim in Europe)
- Safety is monitored in several post-marketing studies as well as by routine pharmacovigilance
  - To date, more than 3800 patients treated with Zarzio have been observed in post-marketing studies in a wide range of indications covering Chemotherapy Induced Neutropenia, Hematopoietic Stem Cell Mobilization, and Severe Chronic Neutropenia
- No signals of a potential difference in the safety profile as compared to Neupogen
- No cases of immunogenicity reported to date
- No additional risk minimization activities are required beyond those included in the product information
  - Safety and effectiveness confirmed in clinical practice
Stem Cell Mobilization Study (501)
Non-interventional Study in Healthy Unrelated Stem Cell Donors

Study objectives:
- Efficacy of stem cell mobilization with Zarzio
- (Long-term) Safety assessment

Treatment:
- s.c. injections of 10 mcg/kg per day
- Apheresis starts at Day 5 of mobilization
- Target of mobilization: harvest of $4 \times 10^6$ CD34+ cells/kg recipient body weight

- CD34+ yield in all donors exceeded minimum target harvest of $4 \times 10^6$ per kg bodyweight of the recipient
- Confirms results seen for CD34+ cell count in healthy volunteer PK/PD studies

*Interim Analysis Based on Data Cut-off Aug 2013

Overall Conclusions Based on Human Experience with Zarxio
Summary of Human Efficacy and Safety Data

• PK equivalence established in healthy volunteers
• Equivalent ANC response across different treatment regimens in breast cancer patients and in healthy volunteers
• Similar CD34⁺ cell response in healthy volunteers and proven effectiveness in healthy donors (post-marketing study)
• Similar response profile as compared to Neupogen in all indications evaluated in clinical trials as well as post-marketing outside the US

Summary of Human Efficacy and Safety Data

• Incidence and nature of AEs were similar for Zarxio and Neupogen in all populations studied
• No signs of immunogenicity
• No concerning or unexpected safety findings for Zarxio throughout entire clinical program as well as through post-marketing surveillance
  ➢ No clinically meaningful differences between Zarxio and Neupogen
# Agenda

<table>
<thead>
<tr>
<th>Section</th>
<th>Presenter</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>Mark McCamish, MD, PhD</td>
<td>Global Head Biopharm. &amp; Oncology Injectables Development Sandoz</td>
</tr>
<tr>
<td>Analytical Demonstration of Biosimilarity</td>
<td>Hansjoerg Toll, PhD</td>
<td>Head Analytical Characterization Sandoz</td>
</tr>
<tr>
<td>Biosimilar Clinical Development Program</td>
<td>Sigrid Balser, PhD</td>
<td>Global Clinical Development Sandoz</td>
</tr>
<tr>
<td>A Clinical Perspective on Biosimilarity</td>
<td>Louis Weiner, MD</td>
<td>Professor and Director of Lombardi Comprehensive Cancer Center Georgetown University</td>
</tr>
<tr>
<td>Totality of the Evidence and Concluding Remarks</td>
<td>Mark McCamish, MD, PhD</td>
<td>Global Head Biopharm. &amp; Oncology Injectables Development Sandoz</td>
</tr>
</tbody>
</table>

---

# A Clinical Perspective on Biosimilarity

Louis M. Weiner, MD  
Director, Lombardi Comprehensive Cancer Center  
Francis L and Charlotte G Gragnani Professor  
Chairman, Department of Oncology  
Georgetown University Medical Center
Conflicts of Interest

- Sandoz (Consultant)*
- Merrimack Pharmaceuticals (Scientific Advisory Board, Stock Options)
- Cellflex Pharmaceuticals (Scientific Advisory Board, Stock Options)
- TDT Therapeutics (Stock)
- Jounce Therapeutics (Scientific Advisory Board, Stock Options)
- AbbVie (Scientific and Clinical Advisory Boards)
- Immunome (Scientific Advisory Board)
- CytoMx (Scientific Advisory Board)

* Relevant to this presentation

What criteria need to be met for me to treat a patient with this biosimilar?

- Does the originator molecule have meaningful clinical value?
- Does the biosimilar have equivalent properties as the originator?
- Does the biosimilar have efficacy and toxicity profiles that are consistent with those of the originator?
- Is extrapolation reasonable if biosimilarity is demonstrated?
- Will use of the biosimilar lower costs?
Does the originator molecule filgrastim have meaningful clinical value?

- G-CSF has been widely used around the world for more than 20 years

- Indications in the US include:
  - Cancer patients receiving myelosuppressive chemotherapy
  - Patients with acute myeloid leukemia receiving induction or consolidation chemotherapy
  - Cancer patients receiving bone marrow transplant
  - Patients undergoing peripheral blood progenitor cell collection and therapy
  - Patients with severe chronic neutropenia

Unquestioned clinical value helps patients

---

G-CSF is Underused and Badly Used


**Design:**
- US Medicare database used to link 12,707 courses of chemotherapy for 5 common cancers to G-CSF use in patients receiving high-risk chemotherapy regimens

**Results:**
- G-CSF given to less than 50% of eligible patients receiving a high-risk chemotherapy regimen
- Depending upon tumor type, 4.8-22.6% of patients receiving a high-risk regimen experienced chemotherapy-induced neutropenic complication (CINC) requiring hospitalization

- G-CSF compliance reduces emergency room admission rate from 25.9% to 10.5% (OR 0.34; p<0.001) and patient care cost savings

---
Proper Use of G-CSF Benefits Patients and Reduces Costs

Weycker, et al. BMC Health Services Research 2014; 14:189

Design:
- Retrospective cohort design using US healthcare claims data from 2001-2010 – 135,921 patients, 5,577 received daily filgrastim
- Included all patients who initiated ≥ 1 course myelosuppressive chemo and received daily filgrastim ≥ 1 cycle
- Followed for CINC, mortality, costs

Results:

<table>
<thead>
<tr>
<th>Days of Filgrastim (n)</th>
<th>CINC Risk</th>
<th>Mortality (%)</th>
<th>Mean Expenditures ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 (8,371)</td>
<td>2.4</td>
<td>8.4</td>
<td>18,912</td>
</tr>
<tr>
<td>4-6 (3,691)</td>
<td>1.9</td>
<td>4.0</td>
<td>14,907</td>
</tr>
<tr>
<td>≥7 (2,226)</td>
<td>1.0</td>
<td>0</td>
<td>13,165</td>
</tr>
</tbody>
</table>

Does the biosimilar have equivalent properties as the originator?

- Identical properties not necessary
  - Structure, function and bioactivity are all identical or similar to originator G-CSF
- At most, minor differences in formulation
  - e.g., glutamate as opposed to acetate buffer

**The preponderant evidence supports biosimilarity**
Do Neupogen and Zarxio have similar efficacy and toxicity profiles?

- Proof of biosimilarity does not require comprehensive clinical testing per FDA, but thorough analysis of the available clinical data is essential
  - Clinical trial results possess more intrinsic variability than detailed molecular analysis when analyzing biosimilarity
    • e.g., patient selection, study size, trial design

Analysis of the clinical trial results supports the similarity of originator and biosimilar efficacy and toxicity profiles

Do Neupogen and Zarxio have similar efficacy and toxicity profiles?

- Vast world-wide experience with Zarzio
  - 7.5 million treatment days analyzed since 2009 across many indications
  - Not rigorously collected data from randomized, controlled clinical trials, BUT
  - Large body of relevant information of interest
  - No obvious signs of unexpected toxicities or ineffectiveness

Comforting context for a prescribing physician
### The Introduction of Filgrastim Biosimilars Coincided with More G-CSF Use in Europe

<table>
<thead>
<tr>
<th>Year</th>
<th>Total G-CSF Market Volume in Europe by Year (thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>5,954</td>
</tr>
<tr>
<td>2008</td>
<td>6,208</td>
</tr>
<tr>
<td>2009</td>
<td>6,417</td>
</tr>
<tr>
<td>2010</td>
<td>6,827</td>
</tr>
<tr>
<td>2011</td>
<td>7,361</td>
</tr>
<tr>
<td>2012</td>
<td>7,861</td>
</tr>
</tbody>
</table>

Note: Data covers full year sales. Source: IMS

After introduction of biosimilars in Sep 2008, there was a +30% increase in the total G-CSF market volume.


---

### Is extrapolation reasonable if biosimilarity is demonstrated?

- **Paradigm shift of biosimilars** – “where the rubber meets the road”
- If the molecule is biosimilar then it stands to reason that extrapolation to the originator’s indications is warranted
  - Additional safety and efficacy context provided by Zarzio worldwide experience adds confidence
Will the use of biosimilar lower costs?

- Introduction of the biosimilar will lower drug costs and spur competition

- Data from Europe suggest that introduction of biosimilars has:
  - Increased utilization of guidelines
  - Improved clinical outcomes
  - Reduction of drug costs

What criteria need to be met for me to treat a patient with this biosimilar?

- The originator molecule has meaningful clinical value
- The biosimilar possesses equivalent properties as the originator
- The biosimilar’s efficacy and toxicity profiles are consistent with those of the originator
- Extrapolation is reasonable if FDA agrees that biosimilarity has been demonstrated
- Use of the biosimilar is likely to lower costs
## Agenda

<table>
<thead>
<tr>
<th>Introduction</th>
<th>Mark McCamish, MD, PhD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Global Head Biopharm. &amp; Oncology Injectables Development</td>
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<tr>
<td></td>
<td>Global Clinical Development</td>
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<td>Professor and Director of Lombardi Comprehensive Cancer Center</td>
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<td>Totality of the Evidence and Concluding Remarks</td>
<td>Mark McCamish, MD, PhD</td>
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<td>Global Head Biopharm. &amp; Oncology Injectables Development</td>
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## Totality of the Evidence and Concluding Remarks

Mark McCamish, MD, PhD
Global Head Biopharm. & Oncology Injectables Development
Sandoz
Findings from the Analytical Program

- Zarxio is highly similar to Neupogen
  - Identical primary structure
  - Highly similar secondary and tertiary structure
  - Highly similar purity and stability profiles
  - Highly similar receptor binding and biological activity

Summary of Clinical Evidence

- Efficacy data confirm similarity
  - PK/PD with ANC and CD34+ cells confirm similarity
  - DSN in the range of what is reported for Neupogen in this setting
  - Tight confidence interval with lower boundary of approx. ¼ day
  - Data would also support equivalence within tight limits (-0.21; 0.28)
  - Extrapolation justified by totality of data
Summary of Safety Data

• Incidence and nature of AEs were similar for Zarxio and Neupogen
  – In cancer patients receiving myelosuppressive chemotherapy (Study 302)
  – In healthy volunteers (PK/PD Studies)
• No concerning or unexpected safety findings for Zarxio throughout entire clinical program
  – Repeated switching did not an negative impact on safety profiles
• Incidence and nature of AEs similar throughout post-marketing experience

Summary

• Biologic drugs are important therapeutic agents that are very costly and access may be limited
• Modern technology and analytics allow full characterization and creation of biosimilars
• Zarxio has been demonstrated both analytically and clinically to be highly similar to the reference product, Neupogen
• This high similarity justifies extrapolation to all indications for the reference product
• Approval of Zarxio will expand options available to healthcare providers and patients
Zarxio™ (filgrastim)

Sandoz, a Novartis Company
Presentation to the Oncologic Drugs Advisory Committee
January 7, 2015

Backup Slides
Figure 22
Arithmetic Mean of Serum Concentrations of ZARXIO Glutamate, ZARXIO Acetate, and Neupogen
PP Population, n = 28

![Graph showing serum concentrations over time](image)

Intended Storage Condition (2-8 °C)

![Graph showing sum of degradation products over time](image)

Rate of degradation:
Zarxio: 0.07 %/month
Neupogen: 0.06 %/month
Regulatory History and FDA Communications (1/2)

- **October 1<sup>st</sup> 2009: PDUFA Type B PreIND meeting**
  - Discussed the development program of Zarxio under 351(a) pathway

- **March 23<sup>rd</sup> 2010: Biosimilar 351(k) pathway** was established under BPCI Act

- **October 11<sup>th</sup> 2010: PreIND meeting**
  - Determined the path forward for the development of Zarxio using the biosimilar 351(k) pathway

- **November 1<sup>st</sup> 2010: Submitted study designs** of pivotal Study 302 and Study 109 for FDA’s feedback

- **April 4<sup>th</sup> 2011: Received FDA’s feedback on the study designs**

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Zarxio can be Manufactured to Match Neupogen in Content

![Graph showing content match between Zarxio and Neupogen]
Autologous Stem Cell Transplant in Pediatric Patients – Physician Led Report

- A retrospective study on cases treated at three Italian pediatric transplant centers, from January 2011 to October 2013
- Data were collected on 29 children (mean age 4.6 years) with solid tumor or non-Hodgkin’s lymphoma undergoing first peripheral blood stem cell (PBSC) mobilization with Zarzio and chemotherapy and compared with a case-matched historical control group (n=29)
- No major and/or unexpected side effects were reported; mild bone pain and headache each in one patient
- Peak peripheral blood CD34+ cell count of $20 \times 10^6/L$ was achieved in 90% of patients, with a median value of $71 \times 10^6/L$; 83% of patients reached the desired target (CD34+/kg) dose.
- No differences were observed in comparison with historical control group mobilized with originator filgrastim.