THE NEW BIOLOGICS
IN THE RHEUMATIC DISEASES

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Disclosures

• None
Topics

• The Biologics Era
• Mechanisms of Action
• Biologics and the Diseases Treated
• Use and Precautions
• Biosimilars: A New Era?
The Biologics Era

• A new period of “molecular medicine”: the therapeutic use of directed macromolecules
• The first commercial biologic: human insulin (1982, Eli Lilly and Genentech)
• Other early drugs: tissue plasminogen activator (1987, Genentech), erythropoietin (1983, Amgen)
• First biologics in arthritis:
  • Remicade® (infliximab) [Centocor, Aug. 24, 1998]
  • Enbrel® (etanercept) [Immunex, Nov. 2, 1998]
  • Humira® (adalimumab) [Abbot, Dec. 31, 2002]
The result of understanding molecular targets
The result of advances in manufacturing

- Four 3,000-liter bioreactors
  - Batch sizes > 1 kg purified bulk
- Two 6,000-liter bioreactors
  - >100 kg annual capacity
  - >100,000 patient-years
- Second plant (PR; $350 M investment) in construction
Advanced Biotechnology

Selection of Phage Antibodies for Antigen Binding

Phage library

1,000 fold enrichment

growth of phage in bacterium

a further 1,000 fold enrichment = 1,000,000 fold

TNF affinity selection

TNF affinity selection
Advanced Biotechnology

Generation of Fully Human Anti-huTNF MAb adalimumab (D2E7) by Guided Selection

Heavy Chain/Light Chain Pairing

- Mu/Mu
- Mu/Hu
- Hu/Mu
- Hu/Hu

MAK 195 Segard™

random huVL phage library

random huVH phage library

iterative optimization by chain shuffling and mutagenesis

D2E7
Available Anti-TNF Biologic Drugs

The Origin of Species (of mAbs)
I'm Talking to You-Mab—How to Pronounce the New, Unpronounceable Pharmaceuticals

Daniel S. Frank, MD
MedNorthwest,
Seattle, Washington.

The abundance of new pharmaceuticals has created an enormous challenge for clinicians: pronouncing the names of these drugs correctly. Having a uniform pronunciation is beneficial on many fronts, including patient safety, and as physicians we are embarrassed when we don't know how to say a drug's name properly. To avoid appearing incompetent, we skirt the issue by using trade names or, worse, therapeutic classes. Sure, it is more informative to say your psoriasis patient is on "secukinumab" than on "biologics," but this means tackling, in front of your peers, an invented monstrosity of a word that was never mentioned in medical school. As geustkinumab, which seems like a former Soviet Republic, or canagliflozin, which is not an extremely rich Italian dessert but a sodium-glucose cotransporter-2 (SGLT2) inhibitor.

Many stems are simply not found in nature. Given that the Queen's English has 0 words ending in -nib or -mab, it's no wonder we have trouble with pronunciation. The naming system for monoclonal antibodies is particularly bad and seems to represent an effort by the USAN to teach the nation's physicians to speak Klingon.

Having a phonetic spelling is helpful, but that version must be translated into the correct spoken sounds. Your trusty Merriam-Webster has schwas (ə) and other inscrutable symbols like ə and ɔ that most of us gloss over. Imagine trying to pronounce "monoclonal" from this: mā-na-klo-nəl. The USAN Council uses a different phonetic spelling system which was revised in 2006 so that adalimumab from 2001, is given as ay da lim’ yoo mab, whereas bert,” not as the dictionary tells us, sure-bet, as in “it's a sure bet you'll order sherbet.”

The SGLT2 inhibitor empagliflozin is also in danger of being mispronounced emp-uh-GLIF-oh-zin, as I heard a diabetologist call it on a recent podcast, instead of emp-uh-gli-FLOW-zin, which USAN spells phonetically as em’ pagli floe’
The simple days are over…

ciprofloxacin $\rightarrow$ Cipro®

ixekizumab $\rightarrow$ Ick® (???)

Taltz®
Mechanisms of Action:
1) Bind the ligand (e.g. cytokine molecule)

- Etanercept (Enbrel)
- Infliximab (Remicade)
- Adalimumab (Humira)
- Certolizumab (Cimzia)
- Golimumab (Simponi)

- Ustekinumab (Stelara)
- Secukinumab (Cosentyx)

Mechanisms of Action:

2) Block the receptor (e.g. cytokine receptor)

- Anakinra (Kineret)
- Tocilizumab (Actemra)

Mechanisms of Action:
3) Inhibit cell-cell signaling and activation (e.g. T cell activation)

Abatacept (Orencia)
Mechanisms of Action:

4) Cellular lysis

Mechanisms of Action:
5) Block growth and differentiation factors

Belimumab (Benlysta)

Mechanisms of Action:
6) Block intracellular signaling (e.g. JAK-STAT)

Tofacitinib (Xeljanz)

### Abbreviations
- mAb: monoclonal antibody
- TCZ: tocilizumab
- RA: rheumatoid arthritis
- PSA: psoriatic arthritis
- JAK: Janus kinase

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**Table 1: Immune targets in RA including novel approaches**

<table>
<thead>
<tr>
<th>Target</th>
<th>Mechanism</th>
<th>Results</th>
<th>Comments</th>
<th>FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytokine targets</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-TNF inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stNF/TNFR1 blocking agents</td>
<td>TNF muteins form heterodimers with stNF-α incapable of activating TNFR1.</td>
<td>Mouse studies showed equal efficacy to etanercept.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-TNF vaccine</td>
<td>Inactivated TNF-α conjugated with KLH carrier protein, (TNFK) induces production of anti-TNF antibodies.</td>
<td>52-wk, human Phase IIa demonstrated improvement in outcomes.</td>
<td>Leads to tolerance of TNF-specific B cells, but not memory T cells.</td>
<td></td>
</tr>
<tr>
<td>Anti-IL6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mAbs against IL6-receptor (IL6R)</td>
<td>TCZ, an anti-IL-6R and sIL-6R humanized mAb.</td>
<td>Efficacy in human trials of RA is impressive.</td>
<td>Elevated liver function tests, low white blood cell count, gastrointestinal perforations and infectious risks, risks thought to be due to signaling inhibition.</td>
<td></td>
</tr>
<tr>
<td>Sarilumab anti-IL6R mAb. ALX-0061 nanobody.</td>
<td></td>
<td>Higher affinity for its ligand. Higher potency of trans-signaling blockade.</td>
<td>Side effects similar to TCZ.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: mAb-monoclonal antibody; TCZ-tocilizumab; RA-rheumatoid arthritis; PSA-psoriatic arthritis; JAK-Janus kinase

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Indicates FDA approved and commercially available as of March 2018

### Biologics in Rheumatic Diseases -- Reference

**Abbreviations:** mAb-monoclonal antibody; TCZ-tocilizumab; RA-rheumatoid arthritis; PSA-psoriatic arthritis; JAK-Janus kinase

#### Th-17 Pathway

<table>
<thead>
<tr>
<th>Targeting Th-17 differentiation</th>
<th>Ustekinumab and guselkumab block IL-23.</th>
<th>Human studies did not show benefit over placebo.¹⁹</th>
<th>IL-12 and IL-23 may not have benefit in RA, but show significant efficacy in psoriasis and PSA.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Th-17 cytokines, IL-17</td>
<td>Secukinumab fully human anti–IL-17A mAb</td>
<td>In RA-Phase II study did not show benefit over placebo,²⁰ being tested in Phase III.</td>
<td>Efficacy established in psoriasis, PSA, and AS.</td>
</tr>
<tr>
<td></td>
<td>Ixekizumab humanized anti–IL-17A mAb.</td>
<td>Phase II trial showed efficacy in RA and confirmed in open-label extension.²¹</td>
<td>Now being developed only in AS and psoriasis and PSA. FDA approved for psoriasis.</td>
</tr>
<tr>
<td></td>
<td>Brodalumab, inhibitor of human IL-17 receptor.</td>
<td>Failed clinical efficacy.²²</td>
<td>IL-17 inhibition may be relevant in RA, but efficacy may be lower compared with other inflammatory diseases.</td>
</tr>
<tr>
<td>B-cell targets</td>
<td>B cells have multiple roles in RA. Act as antigen-presenting cells to T cells; stimulate T-cell differentiation and cytokine production; secrete proinflammatory cytokines.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell-surface molecules</td>
<td>Rituximab (anti-CD20 chimeric mAb).</td>
<td>Depletes CD20-expressing B cells and CD4⁺ T cells and is FDA approved for RA.</td>
<td>Clinical development of ocrelizumab, humanized anti-CD20 mAb, was discontinued due to risk of serious infection.</td>
</tr>
<tr>
<td></td>
<td>Ofatumumab (human anti-CD20 mAb).</td>
<td>Recognizes a distinct and proximal epitope, both in long-term and early RA.</td>
<td>More efficient than predecessor, rituximab. Long-term safety data have shown acceptable tolerability.¹⁵</td>
</tr>
<tr>
<td></td>
<td>Alemtuzumab (anti-CD52 mAb).</td>
<td>Approved for B-cell chronic lymphocytic leukemia and multiple sclerosis.</td>
<td>Toxicity issues have stopped development for RA.</td>
</tr>
<tr>
<td></td>
<td>MDX-1342 (anti-CD19 human mAb).</td>
<td>Development halted, due to safety concerns.</td>
<td></td>
</tr>
</tbody>
</table>

### Biologics in Rheumatic Diseases -- Reference

<table>
<thead>
<tr>
<th>JAK inhibitors</th>
<th>JAK inhibitors appear to be the most successful target for RA, due to their predominant role in signaling.</th>
<th>Deletion of JAK1 and JAK2 in mice is lethal.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib.</td>
<td>Tofacitinib, first available JAK3 (and potentially JAK2) inhibitor. FDA approved for RA.</td>
<td>Linked to anemia and infection.</td>
</tr>
<tr>
<td>Filgotinib.</td>
<td>30-fold selectivity in the inhibition of JAK1&gt;&gt;JAK2, JAK3, and Tyk2.</td>
<td>4-wk treatment, increased hemoglobin levels in patients with RA.</td>
</tr>
<tr>
<td>ABT-494.</td>
<td>74-selective agent for JAK1&gt;&gt;JAK2.</td>
<td>Significant clinical response in Phase IIb trials.</td>
</tr>
<tr>
<td>Decernotinib</td>
<td>Specific inhibitor against JAK3.</td>
<td>Effective in Phase II trials; currently being tested in Phase III trials.</td>
</tr>
<tr>
<td>Baricitinib.</td>
<td>JAK1 and JAK2 selective inhibitor.</td>
<td>Successful Phase II trials, undergoing Phase III trials, undergoing Phase III trials and expected FDA approval.</td>
</tr>
</tbody>
</table>

- Abatacept (T cell signaling inhibitor) – RA, PSA
- Anakinra (IL-1 receptor antagonist) – RA
- Ustekinumab (IL-12/23 receptor antagonist) – Psoriasis, PSA
- Belimumab (B cell proliferation inhibitor) – SLE
- Gusekumab (IL-23 receptor antagonist) – Psoriasis, PSA
- Apremilast (Phosphodiesterase 4 inhibitor) – Psoriasis, PSA

Abbreviations: mAb-monoconal antibody; TCZ-tocilizumab; RA-rheumatoid arthritis; PSA-psoriatic arthritis; JAK-Janus kinase

# Approved Biologic Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Dose</th>
<th>Prescreen</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Remicade®</em> (infliximab)</td>
<td>TNF</td>
<td>3-10 mg/kg IV q4-8 wk</td>
<td>TB, HBV, HCV</td>
<td>with MTX</td>
</tr>
<tr>
<td><em>Enbrel®</em> (etanercept)</td>
<td>TNF</td>
<td>50 mg SQ qwk</td>
<td>TB, HBV, HCV</td>
<td></td>
</tr>
<tr>
<td><em>Humira®</em> (adalimumab)</td>
<td>TNF</td>
<td>40 mg SQ q2wk</td>
<td>TB, HBV, HCV</td>
<td>Also Uveitis</td>
</tr>
<tr>
<td><em>Cimzia®</em> (certolizumab)</td>
<td>TNF</td>
<td>200 mg SQ q2wk OR 400 mg SQ q4wk</td>
<td>TB, HBV, HCV</td>
<td>Load 400 mg SQ at week 0, 2, 4</td>
</tr>
<tr>
<td><em>Simponi®</em> (golimumab)</td>
<td>TNF</td>
<td>50 mg SQ q4wk</td>
<td>TB, HBV, HCV</td>
<td></td>
</tr>
<tr>
<td><em>Orencia®</em> (abatacept)</td>
<td>T cell</td>
<td>500-1000 mg IV q4wk OR 125 mg SQ qwk</td>
<td>TB</td>
<td></td>
</tr>
<tr>
<td><em>Rituxan®</em> (rituxumab)</td>
<td>B cell</td>
<td>1000 mg IV q2wk x 2</td>
<td>HBV</td>
<td></td>
</tr>
<tr>
<td><em>Actemra®</em> (tocilizumab)</td>
<td>IL-6</td>
<td>4-8 mg/kg IV q4wk OR 162.5 mg SQ q1-2wk</td>
<td>TB, HCV, HBV, lipids</td>
<td></td>
</tr>
<tr>
<td><em>Kineret®</em> (anakinra)</td>
<td>IL-1</td>
<td>100 mg SQ qD</td>
<td>CBC</td>
<td></td>
</tr>
<tr>
<td><em>Xeljanz®</em> (tofacitinib)</td>
<td>JAK 1,2</td>
<td>5 mg PO BID OR 11 mg PO qD</td>
<td>TB, HBV, HCV, lymphocyte count (&gt;500 cells/mm3) or abs neutrophil count (&gt;1000 cells/mm3), hemoglobin level greater than 9 g/dL</td>
<td></td>
</tr>
</tbody>
</table>
# Approved Biologic Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Dose</th>
<th>Prescreen</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriatic Arthritis: see also Enbrel, Remicade, Humira, Cimzia, Simponi, Orencia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stelara ® (ustekinumab)</td>
<td>IL-12/23</td>
<td>45-90 mg SQ q12wk</td>
<td>TB</td>
<td></td>
</tr>
<tr>
<td>Cosentyx ® (secukinumab)</td>
<td>IL-17A</td>
<td>150-300 SQ q4wk</td>
<td>TB</td>
<td></td>
</tr>
<tr>
<td>Taltz ® (ixekizumab)</td>
<td>IL-12</td>
<td>80 mg SQ q4wk</td>
<td>TB</td>
<td></td>
</tr>
<tr>
<td>Tremfya ® (guselkumab)</td>
<td>IL-23</td>
<td>100 mg SQ q8wk</td>
<td>TB</td>
<td></td>
</tr>
<tr>
<td>Otezla ® (apremilast)</td>
<td>PDE4</td>
<td>30 mg PO BID</td>
<td>TB, HBV</td>
<td></td>
</tr>
<tr>
<td>Ankylosing Spondylitis: see Enbrel, Remicade, Humira, Cimzia, Simponi, Cosentyx</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benlysta ® (belimumab)</td>
<td></td>
<td>10 mg/kg IV q4wk</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituxan ® (rituximab)</td>
<td>B cell</td>
<td>375 mg/m2 IV qwk x 4</td>
<td>ANCA vasculitis</td>
<td></td>
</tr>
<tr>
<td>Actemra ® (tocilizumab)</td>
<td>IL-6</td>
<td>162.5 mg SQ qwk</td>
<td>GCA</td>
<td></td>
</tr>
</tbody>
</table>
Side Effects

- **Actemra®** (tocilizumab): infections, increased liver function tests, neutropenia, thrombocytopenia, increase of lipid levels, and gastrointestinal perforation (rare)
- **Benlysta®** (belimumab): infection, hypersensitivity reactions, depression, progressive multifocal leukoencephalopathy (rare)
- **Orencia®** (abatacept): Side effects: infections, increased frequency of chronic obstructive pulmonary disease exacerbations, injection site reactions, hypersensitivity reaction
- **Otezla®** (apremilast): nausea, vlimiting, diarrhea, URTI
- **Rituxan®** (rituximab): infection, infusion reactions, cytopenias, hepatitis B reactivation. Rarely progressive multifocal leukoencephalopathy, cardiac arrhythmias, angina
- **Stelara®**: infections, tuberculosis and other mycobacterial conditions, anaphylaxis, reversible posterior leukoencephalopathy syndrome
- **Taltz®** (ixekizumab): Infections, tuberculosis reactivation, hypersensitivity, Inflammatory Bowel Disease exacerbation
- **TNF Inhibitors**: infections, including fungal infections and tuberculosis reactivation, hepatitis B reactivation, cytopenias, heart failure, lupus-like syndrome, non-melanoma skin cancer, demyelinating disease (rare)
- **Tremfya®** (guselkumab): upper respiratory infections, headache, injection site reactions, arthralgia, diarrhea, gastroenteritis, tinea infections, herpes simplex infections
- **Xeljanz®** (tofacitinib): infections, monitor labs (lymphocytes, neutrophils, hemoglobin, liver enzymes, lipids). Rarely GI perforation

Adapted from Wolfe and Ang. Immunol Allergy Clin N Am 37 (2017) 283–299
Biosimilars in Rheumatology

- Biopharmaceuticals that replicate originator molecules using similar, but not identical biomanufacturing processes
- Biosimilar must demonstrate no significant difference from its reference product
  - Robust analytical, toxicologic, PK/PD, and immunogenicity studies in comparison to reference product
  - Smaller comparative effectiveness clinical trial(s), which must be conducted in pts with a disease for which the reference product is licensed
  - No need to demonstrate efficacy in all indications
- No differences in safety or efficacy are expected between an approved biosimilar and its reference product
- In Europe, the advent of biosimilars to infliximab, etanercept and rituximab has introduced more treatment choice and led to cost reduction
## Why Biosimilars Are NOT Generic Biologics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Biosimilar Products</th>
<th>Generic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthesis</td>
<td>In living systems, generally with recombinant DNA technology</td>
<td>Chemical synthesis</td>
</tr>
<tr>
<td>Structure vs reference product</td>
<td>Similar</td>
<td>Almost completely identical</td>
</tr>
<tr>
<td>Structural complexity</td>
<td>Many layers of structure, including posttranslational modification</td>
<td>Typically simple molecular structure</td>
</tr>
<tr>
<td>Immunogenic potential</td>
<td>Possible; requires testing and pharmacovigilance monitoring</td>
<td>Less likely; allergic reactions can occur</td>
</tr>
<tr>
<td>Interchangeability with reference product</td>
<td>Only when higher standard of “interchangeable” has been met</td>
<td>Allowed by legislation if standards of purity and bioequivalence have been met</td>
</tr>
<tr>
<td>Automatic substitution</td>
<td>Guidance pending</td>
<td>Generally allowed; depends on state law and physician preference</td>
</tr>
<tr>
<td>Nomenclature</td>
<td>FDA proposes unique INN (eg, reference product with a distinguishing 4-letter suffix that is devoid of meaning)</td>
<td>INN generally same as reference product</td>
</tr>
</tbody>
</table>

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Slide credit: clinicaloptions.com
Lot-to-lot variability of critical quality attributes must be assessed and controlled to ensure consistent product quality.
# Immunology Biosimilars in the United States

<table>
<thead>
<tr>
<th>Biosimilar</th>
<th>Approval Date</th>
<th>Reference Product</th>
<th>Rheumatologic Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab-dyyb</td>
<td>2016</td>
<td>Infliximab</td>
<td>Rheumatoid arthritis, Ankylosing spondylitis, Psoriatic arthritis, Plaque psoriasis</td>
</tr>
<tr>
<td>Infliximab-abda</td>
<td>2016</td>
<td>Infliximab</td>
<td></td>
</tr>
<tr>
<td>Adalimumab-atto</td>
<td>2016</td>
<td>Adalimumab</td>
<td>Rheumatoid arthritis, Juvenile idiopathic arthritis, Ankylosing spondylitis, Psoriatic arthritis, Plaque psoriasis</td>
</tr>
<tr>
<td>Etanercept-szzs</td>
<td>2016</td>
<td>Etanercept</td>
<td>Rheumatoid arthritis, Juvenile idiopathic arthritis, Ankylosing spondylitis, Psoriatic arthritis, Plaque psoriasis</td>
</tr>
</tbody>
</table>

NOR-SWITCH: Switch to Infliximab-dyyb for Multiple Indications

- 52-wk randomized, double-blind phase 4 trial in pts with RA, SpA, CD, Ps, PsA, or UC on stable infliximab for ≥ 6 mos
- Primary endpoint: disease worsening during 52-wk follow-up
  - Prespecified non-inferiority margin: 15%
- Result: Switching from infliximab to infliximab-dyyb noninferior to continued treatment with infliximab

VOLTAIRE-RA phase III randomised equivalence study of adalimumab biosimilar BI 695501 and Humira reference product

### Biosimilars Currently in the Pipeline for Rheumatologic Conditions

<table>
<thead>
<tr>
<th>Reference Biologic</th>
<th>Drug Class</th>
<th>~ Patent Exp. Date</th>
<th>Indication</th>
<th>Biosimilars With Phase III Clinical Trials</th>
</tr>
</thead>
</table>
| Rituximab<sup>[1-3]</sup> | CD20 inhibitor | 2016 | Lymphoma; RA | ▪ BCD-020 equivalent PK/PD, efficacy, safety in iNHL  
▪ CT-P10 equivalent PK/PD, efficacy, safety, immunogenicity in RA  
▪ RTXM83 equivalent PK, safety in DLBCL |
| Adalimumab<sup>[2-4]</sup> | TNF-α inhibitor | 2022* | Autoimmune diseases | ▪ BI695501 accepted for FDA review  
▪ Multiple others registered/under way |
| Infliximab<sup>[2-4]</sup> | TNF-α inhibitor | 2018* | Autoimmune diseases | ▪ Multiple registered/under way |

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Potential Scenarios: Incorporation of Biosimilars Into Clinical Practice

- Gradual introduction of biosimilars only in patients newly starting a biologic
- Instant switching to biosimilars for patients currently receiving a biologic
- Switching due to loss of response or adverse events with a biologic
- Switching between the biosimilar and the reference drug on an alternating basis, depending on pharmacy supply and drug product availability
- In the United States, the complexity of drug pricing and distribution through Pharmacy Benefit Managers does not guarantee easier access or significantly lower cost (Fleischmann, Arthritis Rheum 2018)
Summary

• Biologics are now a well-established form of drug therapy using a variety of targeting molecules based on the knowledge of the mechanisms of disease
• As molecular pathways become clearer, more directed treatments will emerge
• Biologics for diseases of immunity and inflammation are highly efficacious and share similar side effects
• Biosimilars are molecules manufactured in the same principle of their parent originator drugs – they hold the promise of providing greater access, equal efficacy and safety, and lower cost
Thank you

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