Baricitinib for Treatment of Moderate to Severe Rheumatoid Arthritis

April 23, 2018
Arthritis Advisory Committee
Eli Lilly and Company
Introduction

Robin Wojcieszek, RPh
Senior Director, Global Regulatory Affairs
Eli Lilly and Company
Effective Treatments Needed for Patients Who Tried Therapies, but Have Persistent, Active Disease

- Patients continue to experience associated pain, disability, irreversible joint damage, risk of early mortality\(^1,2\)
- Many patients inadequately treated with current therapies
  - 75-90% of patients do not reach the target of remission\(^3\)

Baricitinib: Once Daily, Small Molecule, JAK Inhibitor that Reduces Inflammation

- Codeveloped by Lilly and Incyte
- Inhibits activity of Janus Kinase (JAK) inside the cell
  - Selectivity for JAK1 and JAK2
- Oral tablet
- Modulates JAK-STAT pathway
  - Disrupts signaling of multiple pro-inflammatory cytokines involved in RA pathogenesis
    - e.g. IL-6, GM-CSF
Comprehensive Clinical Program Studied Patients Across Rheumatoid Arthritis (RA) Continuum

- RA program includes 27 studies
  - 19 clinical pharmacology studies (N=610)
  - 3 Phase 2 studies (N=571)
  - 4 Phase 3 controlled studies (N=3100)
  - 1 Long-term extension study – ongoing (N=2871; April 2017 cutoff)
Dataset for Today’s Presentation

- Efficacy: 4 pivotal, Phase 3 studies
  - Enrolled 3100 patients
  - Each study met primary endpoint

- Safety: data from completed and ongoing RA studies
Regulatory Pathway Leading to Advisory Committee

2016

Global submissions included 4 mg and 2mg

2017

NDA submitted Jan 2016

FDA Complete Response Letter (CR)

Baricitinib 2 mg and 4 mg approved in more than 40 countries, including European Union and Japan
CR FDA Review Issues

- Inconsistent efficacy advantages of 4 mg over 2 mg
  - Dose ranging considerations
- Inadequate safety exposure at baricitinib 2 mg
- Potential venous thrombotic risk
- Inability to conclude a favorable benefit-risk profile
Agreement on Contents of Resubmission

- Updates RA safety database: 7860 patient years of exposure (PYE)
  - Increase in 2 mg exposure to: 1275 PYE
  - Nearly 90% increase in PYE since initial submission
  - No new safety signal identified
- Evaluates safety in context of approved RA treatments
  - Including potential thrombotic risk
- Risk management plan
- Consistent added benefit of 4 mg for some, not all patients
- Proposed dosing recommendation
Proposed Indication

Baricitinib is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate.
Within Indicated Population, Baricitinib Can Address Patient Needs Across RA Continuum

- Both doses provide flexibility for physicians to meet patients where they are on continuum
- Some with more treatment-refractory disease need 4 mg
- Other patients will be successful on 2 mg
Benefit-Risk Questions for Advisory Committee Discussion

- Benefit – Risk: Each Dose Independently
  - Benefit – Risk 2 mg Dose
  - Benefit – Risk 4 mg Dose

- Benefit – Risk: Other Comparisons
  - Benefit – Risk 2 mg vs. 4 mg
  - Benefit – Risk Baricitinib vs. SOC
Agenda

Unmet Need

**Mark Genovese, MD**
Director of the Rheumatology Clinic in the Division of Immunology and Rheumatology
*Stanford University Medical Center, USA*

Clinical Design and Efficacy

**Terence Rooney, MD**
Senior Medical Director, Immunology
*Eli Lilly and Company, USA*

Safety

**Melissa Veenhuizen, DVM, MS**
Senior Medical Director, Global Patient Safety
*Eli Lilly and Company, USA*

Clinical Perspective

**Josef Smolen, MD**
Professor of Medicine & Chairman of the Department of Medicine III & Division of Rheumatology
*Medical University of Vienna, Austria*

Conclusion

**James McGill, MD**
Global Development Leader, Immunology
*Eli Lilly and Company, USA*
Additional Experts

Biostatistics

Scott D. Beattie, PhD
Senior Research Advisor, Global Statistical Sciences
Eli Lilly and Company, USA

Gary G. Koch, PhD
Professor – Department of Biostatistics
Gillings School of Global Public Health
University of North Carolina at Chapel Hill, USA

Safety

Robert Baker, MD
Vice President, Global Patient Safety
Eli Lilly and Company, USA

Venous Thrombotic Events

Thomas Dörner, MD
Professor of Rheumatology, Clinical Immunology & Hemostaseology; Department of Medicine/Rheumatology & Clinical Immunology
Charité University Hospitals, Germany

Regulatory

Carl Garner, PhD
Vice President, Global Regulatory Affairs
Eli Lilly and Company, USA

Biology

Venkatesh Krishnan, PhD
Senior Research Fellow, Lilly Research Laboratories
Eli Lilly and Company, USA
**Additional Experts**

**PK/PD**
Donald E. Mager, PharmD, PhD, FCP  
Professor & Vice Chair of Pharmaceutical Sciences  
*University at Buffalo, SUNY, USA*

**Epidemiology**
Xin Zhang, PhD  
Principal Research Scientist, Global PK/PD & Pharmacometrics  
*Eli Lilly and Company, USA*

**Musculoskeletal Science**
Stephen Motsko, PhD  
Senior Director, Pharmacoepidemiology  
*Eli Lilly and Company, USA*

**Infectious Diseases**
Peter Taylor, MA, PhD, FRCP, FRCPE  
Norman Collisson Professor of Musculoskeletal Sciences  
Head of Clinical Sciences, Botnar Research Centre  
Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Sciences  
*University of Oxford, UK*

**Infectious Diseases**
Kevin Winthrop, MD, MPH  
Professor, School of Public Health  
Associate Professor, School of Medicine  
Division of Infectious Diseases  
*Oregon Health & Sciences University, USA*
Unmet Need for Patients with Rheumatoid Arthritis

Mark Genovese, MD
James W. Raitt Endowed Professor of Medicine
Director of the Rheumatology Clinic
Division of Immunology and Rheumatology
Stanford University Medical Center
Rheumatoid Arthritis: Chronic, Progressive, Inflammatory Autoimmune Disease

- Patients with moderately-to-severely active disease experience systemic inflammation
- Symptoms can result in significant restrictions to daily living\(^1\)
  - Pain, fatigue, functional impairment at work and home
- Affects ~1.3 million in US\(^2\)
  - About three-quarters of patients are women
- Can present at any age, average onset 55 years\(^3\)

Patients with RA Suffer from Increased Disability, Morbidity and Mortality

- Reduced levels of physical function and quality of life\(^1\)
  - Comparable or worse than type 2 diabetes, heart failure, myocardial infarction

- Increased rates of mortality\(^2\)
  - High disease activity associated with loss of 10 years of life

- Increased morbidity comes from multiple organ systems:
  - Cardiovascular disease most prevalent morbidity and leading cause of death\(^3\)
  - Serious infections\(^4\)
  - Malignancies are more frequent than in general population
    - e.g., lymphomas and lung cancer\(^5\)

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Treatment Goal: Achieve Disease Remission or Low Disease Activity in Every Patient

- RA treatment goals$^{1,2,3}$
  - Stop/reduce inflammation
  - Prevent joint and organ damage
  - Relieve pain
  - Improve physical function
  - Reduce long-term complications

- Routinely monitor status

- Modify therapy if no improvement by 3 months, or if target not reached by 6 months$^4$

Current Treatment Approach for Achieving Goals\textsuperscript{1,2}

- Important to start treatment early and adjust therapy to treat to target to reduce risks of disability, irreversible joint damage, early mortality

- RA Diagnosis

- Disease-Modifying Antirheumatic Drug (DMARD)
  - Usually non-biologic
  - Methotrexate (MTX) often first
  - Monotherapy or combination

- Biologic DMARD or JAK inhibitor
  - Usually TNF-\(\alpha\) inhibitor w/ MTX
  - Other biologic DMARDs or JAKi w/ MTX are options
  - Patients who fail often switched
  - Dose tapering but not discontinuation for sustained remission

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Room for Improvement with Current RA Therapies

MTX-Inadequate Response Patients

ACR 70 Response in MTX-IR Patients at Week 24 (%)

- 75% to 80% do not achieve an ACR70 response

+Background Methotrexate

Room for Improvement with Current RA Therapies More Pronounced in bDMARD-IR Patients

ACR 70 Response in bDMARD-IR Patients at Week 24 (%)

80% to 90% do not achieve an ACR70 response

+Background Methotrexate

a. Placebo data is from Week 12
Rheumatologists Diagnose and Manage Safety Issues with RA Therapies$^1,^2$

- Serious infections
- Immune reactions
- Malignancies
- Laboratory changes
  - e.g. liver function tests, cell counts and lipid changes

Unmet Need in Patients Inadequately Treated or Intolerant of Current Therapy Options

- Minority of patients achieve remission\textsuperscript{1,2}
  - Many have partial response, lose efficacy
  - Others do not tolerate, experience side effects

- Want all patients with RA to:
  - Reduce symptoms, improve functioning, quality of life

- Patients need options that:
  - Increase chance for disease control over standard of care
  - Help attain and maintain treatment goals

Clinical Design and Efficacy

Terence Rooney, MD
Senior Medical Director
Eli Lilly and Company
Efficacy Results Overview

- Four positive pivotal trials
  - 2 mg and 4 mg doses superior to placebo
  - 4 mg superior to standards of care (MTX and adalimumab)

- Randomized dose taper maintenance study
  - Taper from 4 mg to 2 mg successful for majority of patients

- Data support a valuable role in therapy for both doses
  - Some patients will need 4 mg, 2 mg will be appropriate for others
  - Dose flexibility allows for optimal patient management
Phase 2 Dose-Ranging: Baricitinib 2 mg and 4 mg Advanced to Phase 3

- Phase 2 studies evaluated Bari 1 mg to 10 mg / day vs. placebo
- Observed data: optimal effects seen with 4 mg daily
- Exposure / response:

\[ \text{DAS28-CRP} \leq 3.2 \text{ in cDMARD-IR at Week 12, Proportion of Patients} \]

\[ \text{Baricitinib Average Concentration in Plasma at Steady-State (Cav, ss), ng/ml} \]

\text{cDMARD} = \text{conventional disease-modifying antirheumatic drug; CRP = C-reactive protein; DAS28 = Disease Activity Score based on the 28 joint count; IR = inadequate responder} \]

Exposure / response data from Phase 2 Study JADA. Shaded areas indicate the range (5th-85th percentile) of Cav, ss for the corresponding doses.
Phase 3 Program Overview

DMARD = disease-modifying antirheumatic drug; cDMARD = conventional DMARD; bDMARD = biologic DMARD; IR = inadequate responder; MTX = methotrexate
Phase 3 Program Overview

DMARD = disease-modifying antirheumatic drug; cDMARD = conventional DMARD; bDMARD = biologic DMARD; IR = inadequate responder; MTX = methotrexate
Placebo-Controlled Trials of 2 mg and 4 mg JADW (bDMARD-IR) and JADX (cDMARD-IR)

DMARD = disease-modifying antirheumatic drug; cDMARD = conventional DMARD; bDMARD = biologic DMARD; IR = inadequate responder; MTX = methotrexate
Study Design
JADW (bDMARD-IR) and JADX (cDMARD-IR)

- JADW (N=527 bDMARD-IR): inadequate response or intolerance to ≥ 1 injectable, bDMARDs
- JADX (N=684 cDMARD-IR, bDMARD-naïve): inadequate response or intolerance to ≥ 1 cDMARDs, and bDMARD naïve
Placebo-Controlled Trials of 2 mg and 4 mg JADW (bDMARD-IR)

DMARD = disease-modifying antirheumatic drug; cDMARD = conventional DMARD; bDMARD = biologic DMARD; IR = inadequate responder; MTX = methotrexate
## JADW (bDMARD-IR) 
### 2 mg and 4 mg Superior to Placebo

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>PBO (N=176)</th>
<th>2 mg (N=174)</th>
<th>4 mg (N=177)</th>
<th>2 mg vs. PBO</th>
<th>4 mg vs. PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>27.3%</td>
<td>48.9%</td>
<td>55.4%</td>
<td>YES (p≤0.001)</td>
<td>YES (p≤0.001)</td>
</tr>
<tr>
<td>Δ DAS28-CRP</td>
<td>-0.8</td>
<td>-1.5</td>
<td>-1.8</td>
<td>YES (p≤0.001)</td>
<td>YES (p≤0.001)</td>
</tr>
<tr>
<td>Δ HAQ-DI</td>
<td>-0.17</td>
<td>-0.37</td>
<td>-0.40</td>
<td>YES (p≤0.001)</td>
<td>YES (p≤0.001)</td>
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<tr>
<td>SDAI Remission</td>
<td>1.7%</td>
<td>2.3%</td>
<td>5.1%</td>
<td>NO (p=0.723)</td>
<td>NO (p=0.140)</td>
</tr>
<tr>
<td>SDAI LDA</td>
<td>9.1%</td>
<td>22.4%</td>
<td>28.2%</td>
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<td>YES</td>
</tr>
<tr>
<td>ACR50</td>
<td>8.0%</td>
<td>20.1%</td>
<td>28.2%</td>
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<td>YES</td>
</tr>
<tr>
<td>ACR70</td>
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<td>12.6%</td>
<td>11.3%</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>

Values shown are Week 12

Δ = least squares mean change from baseline

Colored cells = key objectives, i.e. those included in the multiplicity control plan.

- **Green** = significant with multiplicity control.
- **Light Green** = significant but without multiplicity control.
- **Orange** = not significant. No highlighting indicates secondary endpoints not included in multiplicity control plan.
JADW (bDMARD-IR)
Dose-Dependent Improvements in Disease Activity

**Δ DAS28-CRP**

**Δ SDAI**

*Placebo (N=176)*

*Bari 2 mg (N=174)*

*Bari 4 mg (N=177)*

\[Δ = \text{least squares mean change from baseline.} \ P\text{-value vs. Placebo: } ^*p \leq 0.05; ^{**}p \leq 0.01; ^{***}p \leq 0.001 \]

P-value 4 mg vs. 2 mg: +p \leq 0.05; ++p \leq 0.01 (between-dose statistical comparisons are post hoc)
JADW (bDMARD-IR): Dose-Dependent Improvements in SDAI Low Disease Activity and Remission Rates

- **LDA (SDAI > 3.3, ≤ 11)**
- **Remission (SDAI ≤ 3.3)**

**NNT ~ 6**

**NNT ~ 12/13**

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**Total height of each bar = SDAI ≤ 11 (LDA or remission)**

**P-value vs. placebo:** ^ * p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001
JADX (cDMARD-IR) Placebo-Controlled Trials of 2 mg and 4 mg

DMARD = disease-modifying antirheumatic drug; cDMARD = conventional DMARD; bDMARD = biologic DMARD; IR = inadequate responder; MTX = methotrexate
# JADX (cDMARD-IR)
## 2 mg and 4 mg Superior to Placebo

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>PBO (N=228)</th>
<th>2 mg (N=229)</th>
<th>4 mg (N=227)</th>
<th>2 mg vs PBO</th>
<th>4 mg vs PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>39.5%</td>
<td>65.9%</td>
<td>61.7%</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Δ DAS28-CRP</td>
<td>-1.1</td>
<td>-1.8</td>
<td>-1.9</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Δ HAQ-DI</td>
<td>-0.34</td>
<td>-0.54</td>
<td>-0.53</td>
<td>YES</td>
<td>YES</td>
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<tr>
<td>SDAI Remission</td>
<td>0.9%</td>
<td>9.2%</td>
<td>8.8%</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>MJS Duration, mins</td>
<td>60.0</td>
<td>44.4</td>
<td>34.6</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>MJS Severity NRS</td>
<td>4.1</td>
<td>3.5</td>
<td>3.4</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Worst Joint Pain NRS</td>
<td>4.7</td>
<td>3.8</td>
<td>3.8</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Worst Tiredness NRS</td>
<td>4.5</td>
<td>4.1</td>
<td>4.0</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>SDAI LDA</td>
<td>19.7%</td>
<td>33.2%</td>
<td>34.8%</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>ACR50</td>
<td>12.7%</td>
<td>33.6%</td>
<td>33.5%</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>ACR70</td>
<td>3.1%</td>
<td>17.9%</td>
<td>18.1%</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>

Values shown are Week 12
Δ = least squares mean change from baseline
MJS duration values = median
Other diary values = LS mean

**Colored cells = key objectives**, i.e. those included in the multiplicity control plan.
**Green = significant with multiplicity control.**
Cells without highlighting indicate secondary endpoints not included in multiplicity control plan.
JADX (cDMARD-IR): Improvements in Disease Activity Less Dose-Dependent than JADW (bDMARD-IR)

\[\Delta \text{DAS28-CRP}\]

\[\Delta \text{SDAI}\]

\[\Delta = \text{least squares mean change from baseline. P-value vs. placebo: } ^* p \leq 0.05; ^{**} p \leq 0.01; ^{***} p \leq 0.001\]
JADX (cDMARD-IR): Improvements in Disease Activity More Dose-Dependent where ≥ 2 DMARDs Failed

**Δ SDAI**

Single DMARD-IR N=298 (Less Refractory)

≥ 2 DMARD-IR N=381 (More Refractory)

△ = least squares mean change from baseline. P-value vs. placebo: * p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001. P-value 4 mg vs. 2 mg: +p ≤ 0.05; ++p ≤ 0.01

Post hoc analyses
JADX (cDMARD-IR) 
Reduction in Progressive Radiographic Joint Damage

Δ mTSS Week 24

<table>
<thead>
<tr>
<th>Group</th>
<th>LS Mean Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.70</td>
</tr>
<tr>
<td>Bari 2 mg</td>
<td>0.33</td>
</tr>
<tr>
<td>Bari 4 mg</td>
<td>0.15</td>
</tr>
</tbody>
</table>

P-value vs. placebo: * p ≤ 0.05; ** p ≤ 0.01
Δ mTSS = least squares mean change from baseline in modified Total Sharp Score. Linear extrapolation used to impute after rescue or discontinuation
JADW (bDMARD-IR) and JADX (cDMARD-IR)
Conclusions

- Bari 2 mg and 4 mg superior to placebo

- Both doses of value
  - Some patients need 4 mg, including more refractory
  - 2 mg appropriate for others
Pooled Exposure/Response: Higher Baricitinib Concentrations Needed in More DMARD-Refractory Disease

Subgroup analysis is post hoc based on integrated population PK/PD analysis from 6 Phase 2 and 3 studies. Baricitinib plasma concentration is based on average daily concentration at steady state.
Active Comparator Trials – JADZ (DMARD-naïve)

DMARD = disease-modifying antirheumatic drug; cDMARD = conventional DMARD; bDMARD = biologic DMARD; IR = inadequate responder; MTX = methotrexate
Study Design JADZ (DMARD-naïve)

Patients with no prior DMARD therapy (other than limited use of methotrexate)

- MTX QW (N=210)
- Baricitinib 4 mg QD (N=159)
- Baricitinib 4 mg QD + MTX QW (N=215)

ACR = American College of Rheumatology; QD = once daily; W = week
Treatment did not include a background cDMARD
# JADZ (DMARD-naïve)

Baricitinib 4 mg Superior to MTX Active Comparator

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>MTX (N=210)</th>
<th>4 mg (N=159)</th>
<th>4 mg + MTX (N=215)</th>
<th>4 mg vs MTX</th>
<th>4 mg + MTX vs MTX</th>
</tr>
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<tbody>
<tr>
<td>ACR20</td>
<td>61.9%</td>
<td>76.7%</td>
<td>78.1%</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>△ DAS28-CRP</td>
<td>-2.1</td>
<td>-2.8</td>
<td>-2.8</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>△ HAQ-DI</td>
<td>-0.72</td>
<td>-1.00</td>
<td>-0.95</td>
<td>YES</td>
<td>YES</td>
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<tr>
<td>SDAI Remission</td>
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<td>22.0%</td>
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<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>△ mTSS</td>
<td>0.6</td>
<td>0.4</td>
<td>0.3</td>
<td>NO</td>
<td>YES</td>
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<tr>
<td>ACR50</td>
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<tr>
<td>ACR70</td>
<td>21.4%</td>
<td>42.1%</td>
<td>39.5%</td>
<td>YES</td>
<td>YES</td>
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</tbody>
</table>

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Active Comparator Trials
JADV (cDMARD-IR, Adalimumab Comparator)

DMARD = disease-modifying antirheumatic drug; cDMARD = conventional DMARD; bDMARD = biologic DMARD; IR = inadequate responder; MTX = methotrexate
Study Design
JADV (cDMARD-IR, Adalimumab Comparator)

Patients with inadequate response to methotrexate, naïve to biologic DMARDs

- Placebo (N=488) (Background MTX)
- Baricitinib 4 mg QD (N=487) (Background MTX)
- Adalimumab 40 mg Q2W (N=330) (Background MTX)

Randomization: W0
Primary (ACR20): W12
Rescue Available (Baricitinib 4 mg): W16
Follow-up: W56
## JADV (cDMARD-IR): Baricitinib 4 mg Superior to Placebo and to Adalimumab Active Comparator

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>PBO (N=488)</th>
<th>4 mg (N=487)</th>
<th>ADA (N=330)</th>
<th>4 mg vs PBO</th>
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<td>40.2%</td>
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<td>YES</td>
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<td>(\Delta) DAS28-CRP</td>
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<td>-1.9</td>
<td>YES</td>
<td>YES</td>
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<tr>
<td>HAQ-DI</td>
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<td>-0.65</td>
<td>-0.55</td>
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<td>YES</td>
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<tr>
<td>SDAI Remission</td>
<td>1.8%</td>
<td>8.4%</td>
<td>7.3%</td>
<td>YES</td>
<td>NO</td>
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<tr>
<td>MJS Duration, mins</td>
<td>60.0</td>
<td>27.1</td>
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<td>YES</td>
<td>YES</td>
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<tr>
<td>MJS Severity NRS</td>
<td>4.1</td>
<td>3.0</td>
<td>3.5</td>
<td>YES</td>
<td>YES</td>
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<tr>
<td>Worst Joint Pain NRS</td>
<td>4.6</td>
<td>3.4</td>
<td>4.0</td>
<td>YES</td>
<td>YES</td>
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<tr>
<td>Worst Tiredness NRS</td>
<td>4.3</td>
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<td>3.9</td>
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<tr>
<td>(\Delta) mTSS (Wk 24)</td>
<td>0.9</td>
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<td>18.9%</td>
<td>12.7%</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>

Values shown are Week 12 unless otherwise stated.
\(\Delta\) = least squares mean change from baseline.
MJS duration values = median.
Other diary values = LS mean.

Colored cells = key objectives, i.e., those included in the multiplicity control plan.
Green = significant with multiplicity control.
Cells without highlighting indicate secondary endpoints not included in multiplicity control plan.
JADV (cDMARD-IR): Significant Improvements in Disease Activity for Baricitinib 4 mg

\[ \Delta \text{DAS28-CRP} \]

\[ \Delta \text{SDAI} \]

- Placebo (N=488)
- Adalimumab (N=330)
- Baricitinib 4 mg (N=487)

\( \Delta = \) least squares mean change from baseline. P-value vs. placebo: * \( p \leq 0.05 \); ** \( p \leq 0.01 \); *** \( p \leq 0.001 \). P-value vs. ADA: + \( p \leq 0.05 \); ++ \( p \leq 0.01 \); +++ \( p \leq 0.001 \)
JADV (cDMARD-IR): Significant Improvements in PROs for Joint Stiffness, Joint Pain, Tiredness

**Duration of Morning Joint Stiffness**
- Placebo
- Adalimumab
- Bari 4 mg

**Severity of Morning Joint Stiffness**
- Placebo
- Adalimumab
- Bari 4 mg

**Worst Joint Pain**
- LS Mean (NRS 0-10)

**Worst Tiredness**
- LS Mean (NRS 0-10)

P-value vs. placebo: * p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001. P-value vs. ADA: ++p ≤ 0.05; +++p ≤ 0.01; ++++p ≤ 0.001
Study JADY

2 mg, 4 mg
Long-term Extension with Dose Taper Sub-study
Study Design – JADY Dose Taper Sub-Study

Non-rescued 4 mg patients who achieved sustained (≥ 12 weeks) CDAI LDA or remission

Baricitinib 4 mg QD (N=874)

Continue Baricitinib 4 mg QD (N=435)

Taper to Baricitinib 2 mg QD (N=439)

Double blind randomization occurs once eligibility criteria met, without revealing that randomization has occurred
JADY Dose Taper: 4 mg Superior to 2 mg But Most Patients Maintain Control (CDAI) with Taper

% Patients Achieving CDAI State

Total height of each bar = CDAI ≤ 10 (LDA or remission)

LDA (CDAI > 2.8, ≤ 10)
Remission (CDAI ≤ 2.8)
Bari 4 mg → 2 mg
Bari 4 mg → 4 mg

< 1/5 tapered patients required rescue back to 4 mg

24 weeks post-rescue, ~ 2/3 of these recaptured their prior level of disease control

Of the remainder, ~ 2/3 did so subsequently

Data from DMARD-IR patients from Studies JADW, JADX, JADV. DMARD-naive patients (JADZ) had a different randomization criterion (remission)
P-value between groups: * p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001
Two Efficacious Doses, One Superior To Conventional and Biologic Standards of Care, with Option to Dose Taper

- Four positive pivotal trials
  - 2 mg and 4 mg doses superior to placebo
  - 4 mg superior to standards of care (MTX and adalimumab)

- Randomized dose taper maintenance study
  - Taper from 4 mg to 2 mg successful for majority of patients

- Data support a valuable role in therapy for both doses
  - Some patients will need 4 mg, 2 mg will be appropriate for others
  - Dose flexibility allows for optimal patient management
Safety

Melissa Veenhuizen, DVM, MS
Senior Medical Director, Global Patient Safety
Autoimmune and Pain
Eli Lilly and Company
Safety Outline

- RA Exposure to Baricitinib
- Safety Results Overview
  - Infection
  - Malignancy
  - Major Adverse Cardiovascular Events (MACE)
  - Laboratory Findings
  - Thrombotic Events – focusing on venous thromboembolism (VTE)
- Risk Management
- Post-approval Safety Data, outside US
# Substantial Safety Data Support Baricitinib for RA

<table>
<thead>
<tr>
<th></th>
<th>Initial Submission</th>
<th>Resubmission</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bari All Doses</strong></td>
<td>3464</td>
<td>3492</td>
</tr>
<tr>
<td><strong>Bari 2 mg</strong></td>
<td>723</td>
<td>1005</td>
</tr>
<tr>
<td><strong>Bari 4 mg</strong></td>
<td>2997</td>
<td>3107</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Number of patients*</th>
<th>Patient-years of exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bari All Doses</strong></td>
<td>3464</td>
<td>4214</td>
</tr>
<tr>
<td><strong>Bari 2 mg</strong></td>
<td>723</td>
<td>537</td>
</tr>
<tr>
<td><strong>Bari 4 mg</strong></td>
<td>2997</td>
<td>3509</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Bari All Doses</th>
<th>Bari 2 mg</th>
<th>Bari 4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resubmission</strong></td>
<td>3492</td>
<td>1005</td>
<td>3107</td>
</tr>
<tr>
<td><strong>Bari All Doses</strong></td>
<td>7860</td>
<td>1275</td>
<td>6392</td>
</tr>
</tbody>
</table>

*Number of patients ever exposed to a dose, without regard to censoring; some patients are counted in both dose columns
## Baricitinib Safety Data Sets

<table>
<thead>
<tr>
<th>Analysis Purpose</th>
<th>Dataset Name</th>
<th>Data Pool</th>
<th>N</th>
<th>Patient Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term Safety vs Placebo</td>
<td>Placebo Controlled (PC)</td>
<td>Two Phase II Studies Two Phase III Studies 16 Weeks</td>
<td>1509</td>
<td>425</td>
</tr>
<tr>
<td>Long-term Safety 2 mg vs 4 mg</td>
<td>Extended</td>
<td>All Phase II Studies All Phase III Studies including Extension*</td>
<td>1850</td>
<td>3568</td>
</tr>
<tr>
<td>Safety Across All Exposure</td>
<td>All Bari RA</td>
<td>1 Phase 1 RA Study All Phase II Studies All Phase III Studies including Extension**</td>
<td>3492</td>
<td>7860</td>
</tr>
</tbody>
</table>

*Data censored at dose switch or rescue
**Patients completing any Phase 3 study and Phase 2 study JADA
Overview of Safety

Placebo-Controlled

% Patients With Event

- Any TEAE
  - Placebo (N=551): 59%
  - Bari 2 mg (N=479): 61%
  - Bari 4 mg (N=479): 66%

- SAE
  - Placebo (N=551): 4%
  - Bari 2 mg (N=479): 3%
  - Bari 4 mg (N=479): 5%

- AE - Permanent D/C
  - Placebo (N=551): 3%
  - Bari 2 mg (N=479): 4%
  - Bari 4 mg (N=479): 5%

- Deaths
  - Placebo (N=551): 0.4%
  - Bari 2 mg (N=479): 0.2%
  - Bari 4 mg (N=479): 0.0%

TEAE = Treatment Emergent Adverse Event; SAE = Serious Adverse Event; D/C = Discontinuation
Overview of Safety – Deaths

All Bari RA & Extended

- **All Bari RA** (N=3492)
  - PYE=7993*
  - Incidence Rate: 0.35

- **Bari 2 mg** (N=479)
  - PYE=617
  - Incidence Rate: 0.16

- **Bari 4 mg** (N=1371)
  - PYE=2951
  - Incidence Rate: 0.34

Other RA Clinical Programs

- **ABA** (N=2760)
  - PYE=1688
  - Incidence Rate: 0.53

- **TCZ** (N=4009)
  - PYE=8580
  - Incidence Rate: 0.60

- **ADA** (N=2468)
  - PYE=4870
  - Incidence Rate: 0.90

- **TOF** (N=4791)
  - PYE=6922
  - Incidence Rate: 0.35

* Includes follow up time. 
1. ABA = Abatacept (FDA Medical Review, 2005); 
2. TCZ = Tocilizumab (FDA Medical Review Complete Response, 2009); 
3. ADA = Adalimumab (FDA Update on TNF blocking agents); 
4. TOF = Tofacitinib (FDA Advisory Briefing Document, 2012)
Overview of Safety – Serious Adverse Events (SAEs)

Incidence Rates per 100 PYE

<table>
<thead>
<tr>
<th>All Bari RA &amp; Extended</th>
<th>Other RA Clinical Programs</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Bari RA (N=3492)</td>
<td>ABA¹ (N=2760)</td>
</tr>
<tr>
<td>(PYE=7993*)</td>
<td>TCZ² (N=4009)</td>
</tr>
<tr>
<td>Bari 2 mg (N=479)</td>
<td>ADA³ (N=2468)</td>
</tr>
<tr>
<td>PYE=617</td>
<td>TOF⁴ (N=4791)</td>
</tr>
<tr>
<td>Bari 4 mg (N=1371)</td>
<td></td>
</tr>
<tr>
<td>PYE=2951</td>
<td></td>
</tr>
<tr>
<td>8.9</td>
<td>15.8</td>
</tr>
<tr>
<td>10.1</td>
<td>16.4</td>
</tr>
<tr>
<td>9.2</td>
<td>19.0</td>
</tr>
<tr>
<td>10.3</td>
<td></td>
</tr>
</tbody>
</table>

Frequency of Infections in Placebo-Controlled Period

- **Placebo-Controlled**

  - **Infectious TEAEs**
    - Placebo (N=551): 24
    - Bari 2 mg (N=479): 29
    - Bari 4 mg (N=479): 32

  - **SIEs**
    - Placebo (N=551): 1
    - Bari 2 mg (N=479): 1
    - Bari 4 mg (N=479): 2

  - **D/C due to infection**
    - Placebo (N=551): 0
    - Bari 2 mg (N=479): 1
    - Bari 4 mg (N=479): 2

TEAE = treatment-emergent adverse event; SIE = serious infectious adverse event; D/C = discontinuation
Serious Infection Rates For All Baricitinib RA, by Dose, and Across Therapies

- **All Bari RA & Extended**
  - All Bari RA (N=3492)
    - PYE=7766
  - Bari 2 mg (N=479)
    - PYE=600
  - Bari 4 mg (N=1371)
    - PYE=2867
  - ABA¹ (N=2760)
    - PYE=1688
  - TCZ² (N=4009)
    - PYE=8580
  - ADA³ (N=2468)
    - PYE=4870
  - TOF⁴ (N=4791)
    - PYE=6922

- **Other RA Clinical Programs**
  - Incidence Rate (95% CI) per 100 PYE
  - 3.0
  - 3.3
  - 3.2
  - 2.9
  - 5.1
  - 4.6
  - 3.0

Proportion and Incidence Rate of Herpes Zoster

**Placebo-Controlled**

<table>
<thead>
<tr>
<th>Group</th>
<th>Incidence Rate (95% CI) per 100 PYE</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N=551)</td>
<td>0.4</td>
<td>2</td>
</tr>
<tr>
<td>Bari 2 mg (N=479)</td>
<td>1.0</td>
<td>5</td>
</tr>
<tr>
<td>Bari 4 mg (N=479)</td>
<td>1.9</td>
<td>9</td>
</tr>
</tbody>
</table>

**All Bari RA & Extended**

<table>
<thead>
<tr>
<th>Group</th>
<th>Incidence Rate (95% CI) per 100 PYE</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Bari RA (N=3492)</td>
<td>3.3</td>
</tr>
<tr>
<td>Bari 2 mg (N=479)</td>
<td>2.8</td>
</tr>
<tr>
<td>Bari 4 mg (N=1371)</td>
<td>3.3</td>
</tr>
</tbody>
</table>

**Other RA Clinical Programs**

<table>
<thead>
<tr>
<th>Group</th>
<th>Incidence Rate (95% CI) per 100 PYE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCZ(^1) (N=3778)</td>
<td>1.6</td>
</tr>
<tr>
<td>TOF(^2) (N=4789)</td>
<td>4.3</td>
</tr>
</tbody>
</table>

1. TCZ = Tocilizumab (FDA Advisory Committee Slides, 2008); 2. TOF = Tofacitinib; Winthrop et al. 2014
Opportunistic Infections Infrequent

- **Tuberculosis** – 11 cases reported
  - IR = 0.14 for All Bari RA group, IR = 0.24 for 4 mg

- **Multidermatomal Herpes Zoster**
  - IR = 0.28 for the All Bari RA group, IR = 0.27 for 4 mg

- **Other Opportunistic Infections**
  - IR = 0.3 for All Bari RA, 2 mg and 4 mg
  - Events included:
    - Esophageal candidiasis (7); Pneumocystis (3); Cytomegalovirus (3); Other systemic fungal infections - single events
Malignancy Incidence Rates For All Baricitinib RA, by Dose, and Across Therapies

Malignancies, excluding NMSC

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence Rate (95% CI) per 100 PYE</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Bari RA</td>
<td>0.80</td>
</tr>
<tr>
<td>Bari 2 mg</td>
<td>0.49</td>
</tr>
<tr>
<td>Bari 4 mg</td>
<td>0.75</td>
</tr>
<tr>
<td>ABA(^1)</td>
<td>0.67</td>
</tr>
<tr>
<td>TCZ(^2)</td>
<td>1.3</td>
</tr>
<tr>
<td>ADA(^3)</td>
<td>0.95</td>
</tr>
<tr>
<td>TOF(^4)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Includes follow up time. 1. ABA = Abatacept (FDA ABA Briefing Document 2006); 2. TCZ = Tocilizumab (FDA TCZ Clinical Review of Complete Response, 2009); 3. ADA = Adalimumab (FDA ADA Advisory Committee Briefing Document, 2003); 4. TOF = Tofacitinib (FDA TOF Advisory Committee Briefing Document, 2012)
MACE In Placebo-Controlled Period

- Few events
  - 2 events in placebo
    - 1 myocardial infarction
    - 1 stroke
  - 2 events in 4 mg
    - 1 myocardial infarction
    - 1 stroke
MACE Incidence Rates For All Bari RA, by Dose and Across Therapies

![Incidence Rate Chart]

- **All Bari RA & Extended**
  - **All Bari RA** (N=3492)
    - PYE=7232
    - Incidence Rate: 0.52
  - **Bari 2 mg** (N=479)
    - PYE=617
    - Incidence Rate: 0.16
  - **Bari 4 mg** (N=1371)
    - PYE=2935
    - Incidence Rate: 0.54

- **Other RA Clinical Programs**
  - **ABA** (N=2760)
    - PYE=1688
    - Incidence Rate: 1.1
  - **TCZ** (N=4009)
    - PYE=8580
    - Incidence Rate: 0.34
  - **ADA** (N=204)
    - PYE=178.9
    - Incidence Rate: 1.7
  - **TOF** (N=4791)
    - PYE=6922
    - Incidence Rate: 0.57

---

^ Total exposure time including follow up
3. ADA = Adalimumab (FDA ADA Advisory Committee Briefing Document, 2003); 4. TOF = Tofacitinib (FDA TOF Advisory Committee Briefing Document, 2012)
Evaluation of Laboratory Findings
Placebo-Controlled Data

- Frequency of CTCAE* grade 3 changes in hematology and clinical chemistry
- Mean change from baseline over time

*CTCAE = Common Terminology Criteria for Adverse Events
### Summary of Laboratory Changes
**Placebo-Controlled Time Period**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Impact</th>
<th>Placebo (N=551) n (%)</th>
<th>2 mg (N=479) n (%)</th>
<th>4 mg (N=479) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platelets</strong></td>
<td>Increased to (&gt; 600 x10³/L)</td>
<td>7 (1.3)</td>
<td>5 (1.1)</td>
<td>11 (2.3)</td>
</tr>
<tr>
<td><strong>Hemoglobin</strong></td>
<td>CTCAE Grade 3+ (&lt; 8.0 g/dL)</td>
<td>1 (0.2)</td>
<td>2 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Neutrophils (neutropenia)</strong></td>
<td>CTCAE Grade 3 (&lt; 1,000/mm³)</td>
<td>0</td>
<td>3 (0.6)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td><strong>Lymphocytes (lymphopenia)</strong></td>
<td>Grade 3 (&lt; 500/mm³)</td>
<td>2 (0.4)</td>
<td>4 (0.8)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td><strong>ALT</strong></td>
<td>&gt; 3x ULN</td>
<td>2 (0.4)</td>
<td>8 (1.7)</td>
<td>6 (1.3)</td>
</tr>
<tr>
<td><strong>Creatine Phosphokinase (increased)</strong></td>
<td>CTCAE Grade 3+ (&gt; 5x ULN)</td>
<td>3 (0.6)</td>
<td>4 (0.8)</td>
<td>7 (1.5)</td>
</tr>
<tr>
<td><strong>LDL (NCEP Criteria)</strong></td>
<td>≥ 160 mg/dL; High+</td>
<td>24 (7.8)</td>
<td>38 (11.3)</td>
<td>44 (13.6)</td>
</tr>
</tbody>
</table>

*Includes all patients with post-baseline values > 3xULN regardless of baseline value; NCEP = National Cholesterol Education Program*
Mean Platelet Counts Over 52 Weeks

Mean Platelets Count (10^9/L)

- **Placebo (N=1,009)**
- **Bari 2 mg (N=458)**
- **Bari 4 mg (N=964)**

ULN (450 x 10^9)

LLN (140 x 10^9)

Mean Platelets (SE)

Week
Potential Hypotheses for Increased Platelet Count

Increased Platelet Production

- Increased production from Bone Marrow
- Young, large platelets: Sialylated
- MPV increased

Reduced Platelet Clearance

- Old, small platelets: Desialylated
- Clearance
- MPV decreased

Baricitinib decreased mean platelet volume


Grozovsky, et al. Nature Medicine, 2015; ASM=Ashwell Morrell Receptor
Mean Neutrophil Counts Over 52 Weeks

- **Placebo (N=995)**
- **Bari 2 mg (N=458)**
- **Bari 4 mg (N=942)**

**ULN (8.36 x 10^9)**

**LLN (2.0 x 10^9)**
Mean Lymphocyte Counts Over 52 Weeks

Mean Lymphocytes ($10^9$/L)

- Placebo ($N=1025$)
- Bari 2 mg ($N=458$)
- Bari 4 mg ($N=973$)

ULN ($3.36 \times 10^9$)

LLN ($1.0 \times 10^9$)

Week
LDL-c Shows Dose-Dependent Increase That Stabilizes
HDL-c Shows Dose-Dependent Increase That Stabilizes

![Mean HDL Cholesterol (mg/dL) vs. Week graph]

- **Placebo (N=875)**
- **Bari 2 mg (N=390)**
- **Bari 4 mg (N=878)**
No Change in LDL/HDL Ratio
Potential Thrombotic Risk
# Arterial Thrombotic Event (ATE) Incidence Rates, By Analysis Sets

<table>
<thead>
<tr>
<th></th>
<th>PC Dataset (week 0-24)</th>
<th>PC 4 mg (week 0-24)</th>
<th>Extended Set</th>
<th>All Bari RA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n [IR]</strong></td>
<td></td>
<td></td>
<td></td>
<td>N=3492</td>
</tr>
<tr>
<td>PBO N=551</td>
<td>1 [0.51]</td>
<td>2 [1.04]</td>
<td>2 [1.03]</td>
<td></td>
</tr>
<tr>
<td>2 mg N=479</td>
<td></td>
<td></td>
<td>2 [0.2]</td>
<td>3 [0.49]</td>
</tr>
<tr>
<td>4 mg N=479</td>
<td></td>
<td></td>
<td>2 [0.2]</td>
<td>14 [0.48]</td>
</tr>
<tr>
<td>PBO N=1070</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 mg N=997</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mg N=479</td>
<td></td>
<td></td>
<td>3 [0.49]</td>
<td></td>
</tr>
<tr>
<td>4 mg N=1371</td>
<td></td>
<td></td>
<td>14 [0.48]</td>
<td></td>
</tr>
<tr>
<td><em>(95% CI)</em></td>
<td>(0.01, 2.8)</td>
<td>(0.1, 3.7)</td>
<td>(0.06, 1.8)</td>
<td>(0.31, 0.61)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.1, 3.7)</td>
<td>(0.06, 1.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.1, 1.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.26, 0.8)</td>
<td></td>
</tr>
</tbody>
</table>

ATE primarily defined as myocardial infarction, ischemic stroke, peripheral artery thrombosis, embolism, cerebral infarction, cerebral vascular accident, transient ischemic attack along with other specific terms.
Venous Thromboembolism Potential Risk
Imbalance in Venous Thromboembolic Events (VTE) Placebo-Controlled Period, Weeks 0-24

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PBO</th>
<th>Bari 4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subset</td>
<td>4 mg PC Dataset</td>
<td></td>
</tr>
<tr>
<td>All Patients</td>
<td>1070</td>
<td>997</td>
</tr>
<tr>
<td>With Events</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Patient Years</td>
<td>406</td>
<td>418</td>
</tr>
</tbody>
</table>
# VTE Cases – Placebo-Controlled Period, 0-24 Weeks

<table>
<thead>
<tr>
<th>Patient</th>
<th>Event days</th>
<th>Event</th>
<th>Serious</th>
<th>Age/Sex</th>
<th>BMI kg/m²</th>
<th>Relevant Medical History</th>
<th>MTX/Steroid</th>
<th>Baricitinib Status</th>
<th>Treated with Anti-Coagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>PE</td>
<td>N</td>
<td>62/F</td>
<td>37</td>
<td>Hypertension, COPD, pulmonary fibrosis, varicose veins</td>
<td>Y/Y</td>
<td>Continued</td>
<td>Y</td>
</tr>
<tr>
<td>2*</td>
<td>49</td>
<td>DVT</td>
<td>Y</td>
<td>38/F</td>
<td>20</td>
<td>OCP use</td>
<td>Y/N</td>
<td>Interrupted 36 days and resumed</td>
<td>Y</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>PE</td>
<td>Y</td>
<td>66/F</td>
<td>45</td>
<td>Hypertension, peripheral edema, family history of PE</td>
<td>Y/Y</td>
<td>Bari. admin for 3 weeks; DC ~1 month prior to PE due to AE of hypersensitivity</td>
<td>Y</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>PE</td>
<td>Y</td>
<td>65/F</td>
<td>52</td>
<td>Hypertension, history trauma/rib fracture</td>
<td>Y/Y</td>
<td>Interrupted for 3 weeks and resumed</td>
<td>Y</td>
</tr>
<tr>
<td>5</td>
<td>113</td>
<td>DVT</td>
<td>N</td>
<td>53/F</td>
<td>36</td>
<td>Peripheral edema, smoker</td>
<td>Y/Y</td>
<td>Continued</td>
<td>N</td>
</tr>
<tr>
<td>6</td>
<td>150</td>
<td>DVT</td>
<td>N</td>
<td>58/F</td>
<td>39</td>
<td>Prior DVT, peripheral edema</td>
<td>Y/N</td>
<td>Interrupted for 4 days and resumed</td>
<td>Y</td>
</tr>
</tbody>
</table>

*Reported as thrombophlebitis by the investigator; BMI = body mass index; COPD = chronic obstructive pulmonary disease; DC = discontinued; OCP = oral contraceptive pill
Univariable Risk Assessment for VTE

- Originating study
- Geographic region
- Treatment history
  - DMARD-naïve, cDMARD-IR, bDMARD-IR
- Initial baricitinib dose
  - 2 mg
  - 4 mg
  - Other
- RA history
  - Time from symptom onset
  - Time from diagnosis
- RA characteristics at baseline
  - DAS28-CRP
  - HAQ-DI
  - RF(+) or ACPA(+)
- Platelet Counts
  - Baseline
  - 2-week change from baseline
  - Maximum change from baseline
- Demographic characteristics
  - Age
  - BMI
  - Gender
  - Smoker
- AE History
  - Prior DVT/PE
  - History of thrombosis
  - History of hypertension
  - History of CHF or resp. failure
  - History of cancer
- Concomitant Medications
  - COX-2 inhibitor use
  - MTX
  - Glucocorticoid
  - Anti-platelet
  - Anti-thrombotics
  - Oral contraceptives / SERM
  - NSAID
  - Folate
Multivariable Risk Assessment for VTE

- Originating study
- Geographic region
- Treatment history
  - DMARD-naïve, cDMARD-IR, bDMARD-IR
- Initial baricitinib dose
  - 2 mg
  - 4 mg
  - Other
- RA history
  - Time from symptom onset
  - Time from diagnosis
- RA characteristics at baseline
  - DAS28-CRP
  - HAQ-DI
  - RF(+) or ACPA(+)
- Platelet Counts
  - Baseline
  - 2-week change from baseline
  - Maximum change from baseline
- Demographic characteristics
  - Age
  - BMI
  - Gender
  - Smoker
- AE History
  - Prior DVT/PE
  - History of thrombosis
  - History of hypertension
  - History of CHF or resp. failure
  - History of cancer
- Concomitant Medications
  - COX-2 inhibitor use
  - MTX
  - Glucocorticoid
  - Anti-platelet
  - Anti-thrombotics
  - Oral contraceptives / SERM
  - NSAID
  - Folate
Imbalance in VTE – Placebo-Controlled and Switched/Rescued Data

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PBO</th>
<th>Bari 4 mg</th>
<th>PBO → Bari 4 mg</th>
<th>Active → Bari 4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subset</td>
<td>4 mg PC Dataset</td>
<td>24 wks post-switch</td>
<td>24 wks post-switch</td>
<td></td>
</tr>
<tr>
<td>All Patients</td>
<td>1070</td>
<td>997</td>
<td>928</td>
<td>451</td>
</tr>
<tr>
<td>With Events</td>
<td>0</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Patient Years</td>
<td>406</td>
<td>418</td>
<td>410</td>
<td>203</td>
</tr>
</tbody>
</table>
VTE Not Clustered – Accrued ~ 0.5% Annually

For patients with an event, data was censored at the event start date; data was censored at last observation or data cut-off date for patients without an event.
VTE Incidence Rates by Dose and All Bari RA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>All Bari RA</th>
<th>Bari 2 mg</th>
<th>Bari 4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subset</strong></td>
<td><strong>Overall</strong></td>
<td><strong>Extended</strong></td>
<td></td>
</tr>
<tr>
<td>All Patients</td>
<td>3492</td>
<td>479</td>
<td>1371</td>
</tr>
<tr>
<td>With Events</td>
<td>42</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Patient Years*</td>
<td>7949</td>
<td>615</td>
<td>2936</td>
</tr>
</tbody>
</table>

* Includes follow up time
# Serious VTE Incidence Rates for Sarilumab and Baricitinib

<table>
<thead>
<tr>
<th></th>
<th>Sarilumab + DMARD&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>All Bari RA&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PYE=5845</td>
<td>PE PYE=7977</td>
</tr>
<tr>
<td>Serious PE, n</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>[IR] (95% CI)</td>
<td>[0.17] (0.08, 0.31)</td>
<td>[0.21] (0.12, 0.34)</td>
</tr>
<tr>
<td>Serious DVT, n</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>[IR] (95% CI)</td>
<td>[0.15] (0.07, 0.29)</td>
<td>[0.21] (0.12, 0.34)</td>
</tr>
</tbody>
</table>

1. Sarilumab Clinical Summary of Safety, obtained from EMA via FOI request; 2. 10 patients with 11 events; 3. Events through April 1, 2017
External Databases and Literature Demonstrate VTE Incidence Rate in RA Patients

Crude Incidence Rate per 100 Person-years

- **Tofacitinib**
  - Sentinel¹: 0.93 (N=1846)
  - Truven²: 1.23 (N=3783)

- **cDMARDs**
  - Sentinel¹: 1.49 (N=19,001)
  - Truven²: 1.07 (N=71,552)

- **bDMARDs**
  - Sentinel¹: 0.98 (N=19,146)
  - Truven²: 0.95 (N=77,086)

Range from published literature³: 0.79 to 0.33

---

1. Five Sentinel data partners  
2. Truven Marketscan database  
3. Choi 2013, Kim 2013, Ogdie 2017 and others
Venous Thromboembolism Summary

- Imbalance in Placebo-Controlled period
- Patients had one or multiple risk factors
  - History of VTE, older age, higher BMI, COX-2 inhibitor use
- Increased risk not found for patients switched to baricitinib
- Lack of temporal relationship
- Lack of association with platelet counts
- Lack of dose response in Extended dataset
- Overall IR = 0.53; 95% CI (0.38, 0.71)
- Venous thromboembolism is an important potential risk
- Label warning proposed
Overall Risk Management

- Identified and potential risks in label warnings
  - Inform, consider appropriate monitoring, interrupt if needed and treat

- Post-approval risk management will further characterize potential risks of serious infections, malignancy, MACE, VTE
  - Ongoing and planned post-approval observational studies
  - Evaluation of post-approval spontaneous reports

- Continue to gather adverse event information from RA studies and other indications
Risk Management – Post-Approval Studies Evaluate Long-Term Safety from ~13,000 Baricitinib RA Patients

- Prospective observational study (n=4000/arm)
  - 80% power to detect 2x relative risk at target enrollment
- Retrospective database cohort study (n~4000)
- Registries in Sweden, Denmark, Germany and UK (n~2000)
- Japan – prospective baricitinib cohort (n=3000)
Post-Approval Safety Data
Outside of US

~12,900 patients with 3500 PYE
# Spontaneous Post-Approval Serious and All Reported Adverse Events of Special Interest

<table>
<thead>
<tr>
<th>Events of Special Interest</th>
<th>Serious AESIs n=48</th>
<th>All Reported AESIs n=193</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Infection</td>
<td>35</td>
<td>161</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>Malignancies, excluding NMSC</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>NMSC</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>MACE</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Arterial thrombotic event (ATE)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Data through 13 February 2018

MACE and ATE are same event of MI
# Postmarketing Safety from EU Registries and Japan PMSS

<table>
<thead>
<tr>
<th>Registry</th>
<th>Current Enrollment</th>
<th>SAEs</th>
<th>All AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARTIS (Sweden)¹</td>
<td>175</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>BSRBR (United Kingdom)²</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DANBIO (Denmark)³</td>
<td>21</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>RABBIT (Germany)⁴</td>
<td>191</td>
<td>7</td>
<td>41</td>
</tr>
<tr>
<td>Japan PMSS⁵</td>
<td>503</td>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>899</strong></td>
<td><strong>11</strong></td>
<td><strong>102</strong></td>
</tr>
</tbody>
</table>

No Death, MACE or VTE reported

---


PMSS = Post Marketing Safety Study
Safety Conclusions

- Acceptable safety profile with 2 mg and 4 mg doses
  - More precise risk estimates within range of approved RA medicines
- AEs of Special Interest and laboratory changes in draft labeling
- IR of serious infection, malignancy and MACE similar to other RA therapies
  - Some dose-related differences
- VTE important potential risk
- Risk management plans to characterize long-term risks by dose
Clinical Perspective

Josef Smolen, MD
Professor of Internal Medicine and
Chairman of the Department of Medicine III
and Division of Rheumatology

Medical University of Vienna, Austria
Despite Many Approved Options, Many Patients Do Not Respond Sufficiently

- 5 TNF-inhibitors
  - Adalimumab, certolizumab, etanercept, golimumab, infliximab
- 2 Anti-IL-6R
  - Sarilumab, tocilizumab
- 2 Biologics with other MOA
  - Abatacept, rituximab
- 1 JAK-inhibitor
  - Tofacitinib
How Baricitinib Fits into Treatment Landscape of Methotrexate-IR Population (cDMARD-IR)

- Adalimumab achieved response rates comparable to other treatment options
- Baricitinib is first RA treatment to demonstrate superiority to SOC biologic with methotrexate

* *p < 0.05


SAR = Sarilumab (200 mg); TCZ = Tocilizumab (8 mg); ABA = Abatacept (10 mg); GOL = Golimumab (50 mg); RTX = Rituximab (1,000 mg); TOF = Tofacitinib (5 mg BID)
How Baricitinib Fits into Treatment Landscape of TNFi-IR Population (bDMARD-IR)

- Baricitinib 2 mg achieved response rates comparable to other treatment options for TNFi-IR patients
- Baricitinib 4 mg achieved highest response rate
- Patients in JADW failed multiple biologic therapies, both in number and class


SAR = Sarilumab (200 mg); TCZ = Tocilizumab (8 mg); ABA = Abatacept (10 mg); GOL = Golimumab (50 mg); RTX = Rituximab (1,000 mg); TOF = Tofacitinib (5 mg BID)
Both Baricitinib Doses Demonstrated Efficacy: Some Patients Need 4 mg, 2 mg Appropriate for Others

SDAI
LS Mean Δ from baseline

bDMARD-IR (JADW) N=527

≥ 2 cDMARD-IR (JADX) N=381

P-value vs. Placebo: * p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001

post-hoc analysis
Baricitinib 4 mg Delivers Rapid Patient-Focused Outcomes for Highly-Refractory Patients

Pain

bDMARD-IR (JADW)

Swollen Joint Count

bDMARD-IR (JADW)

Δ = Change; P-value vs. Placebo: * p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001
Reduction in Progressive Radiographic Joint Damage

**JADX ≥ 2 cDMARD-IR**

<table>
<thead>
<tr>
<th>Δ mTSS</th>
<th>Week 24 (N=388)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS Mean Δ from Baseline to Week 24</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.92</td>
</tr>
<tr>
<td>Bari 2 mg</td>
<td>0.33 *</td>
</tr>
<tr>
<td>Bari 4 mg</td>
<td>0.05 **</td>
</tr>
</tbody>
</table>

**JADV (MTX-IR)**

<table>
<thead>
<tr>
<th>Δ mTSS</th>
<th>Week 24 (N=1234)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS Mean Δ from Baseline to Week 24</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.90</td>
</tr>
<tr>
<td>Bari 4 mg</td>
<td>0.41 ***</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>0.33 ***</td>
</tr>
</tbody>
</table>

Δ P-value vs. placebo: * p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001

Δ mTSS = least squares mean change from baseline in modified Total Sharp Score. Linear extrapolation used to impute after rescue or discontinuation.
Baricitinib Demonstrates Continued Clinical Effectiveness Following Dose Tapering in Most Patients

- Patients with inadequate response to cDMARDs or bDMARDs
  - Start on baricitinib 4 mg
    - Once control is achieved, consider dose tapering to 2 mg
  - Dose tapering study
    - Large majority of patients maintained control on 2 mg or recaptured control after returning to 4 mg

- Dose tapering aligns with ACR and EULAR guidelines
Safety Profile

**Incidence Rate (95% CI) Per 100 PYE**

- **Serious Infection**
  - All Bari RA*: 3.0
  - Bari 2 mg: 3.3
  - Bari 4 mg: 3.2
  - ABA: 2.9
  - TCZ: 5.1
  - ADA: 4.6
  - TOF: 3.0

- **Malignancy**
  - All Bari RA & Extended: 0.80
  - Other RA Therapies: 0.49
  - ABA: 0.75
  - TCZ: 1.3
  - ADA: 0.67
  - TOF: 0.95
  - TOF: 0.94

- **Herpes Zoster**
  - All Bari RA & Extended: 3.3
  - Other RA Therapies: 2.8
  - ABA: 3.3
  - TCZ: 4.3
  - ADA: 1.6

- **MACE**
  - All Bari RA & Extended: 0.52
  - Other RA Therapies: 0.16
  - ABA: 0.54
  - TCZ: 1.1
  - ADA: 0.34
  - TOF: 0.57

Safety Profile – Potential Risk of VTE

- VTEs require additional consideration, thorough follow-up
  - In clinical practice
  - Ongoing studies
  - Post-approval surveillance studies
- Rheumatologists familiar with risk assessment, diagnosis and management of VTEs
Baricitinib Expands RA Treatment Armamentarium; Consistent and Significant Benefits Across Domains

- Baricitinib 2 mg and 4 mg achieved consistent, significant benefits across domains of DMARDs:
  - Signs and symptoms, physical function, structural damage and Patient Reported Outcomes
- Benefits achieved rapidly; outweigh risks
- Baricitinib 4 mg superior compared with standards of care
  - Adalimumab, methotrexate
- Dosing regimen - provides flexibility for patients and physicians
Conclusion

James McGill, MD
Global Development Leader
Eli Lilly and Company
Update Since Original Baricitinib Submission

- Baricitinib approved in > 40 countries – no new safety signal
- ~90% increase in patient years safety exposure
  - Better characterization of 2 mg dose
- More precise point estimate of VTE incidence rate
  - Continue to study this and other rare events
- Use of two dosing options driven by patient need
  - Many still struggle to manage RA despite availability of other therapies
- Provide physicians flexibility to balance benefits and risks
Baricitinib for Treatment of Moderate to Severe Rheumatoid Arthritis

April 23, 2018
Arthritis Advisory Committee
Eli Lilly and Company
BACK UP SLIDES

April 23, 2018
Arthritis Advisory Committee
Eli Lilly and Company
### Evidence of Heterogeneity in Study JADX by DMARD History

<table>
<thead>
<tr>
<th>Week 12</th>
<th>SDAI (improvement from baseline)</th>
<th>DAS28-CRP (improvement from baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baricitinib 4 mg vs 2 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 DMARD-IR</td>
<td></td>
<td>Interaction Test p=0.068</td>
</tr>
<tr>
<td>2+DMARD-IR</td>
<td></td>
<td>Interaction Test p=0.104</td>
</tr>
<tr>
<td>Baricitinib 4 mg vs 2 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 DMARD-IR</td>
<td>Interaction Test p=0.125</td>
<td></td>
</tr>
<tr>
<td>2+DMARD-IR</td>
<td>Interaction Test p=0.081</td>
<td></td>
</tr>
</tbody>
</table>

**Least Squares Mean Difference**

- Favor Bari 4 mg
JADZ ACR Components (mLOCF)

Pain, 0-100mm VAS

hsCRP, mg/L

HAQ-DI, range 0-3

ESR, mm/h

P-value vs. MTX: *** p ≤ 0.001, ** p ≤ 0.01, * p ≤ 0.05
Comparable Exposures between Patients with and without DVTs

Note: Event = patients with reported DVT/PE.
# JADX Concomitant cDMARD

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=228)</th>
<th>Baricitinib 2 mg (N=229)</th>
<th>Baricitinib 4 mg (N=227)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX</td>
<td>168 (73.7)</td>
<td>171 (74.7)</td>
<td>173 (76.2)</td>
</tr>
<tr>
<td>Mean (SD) MTX dose, mg/week</td>
<td>16.0 (4.8)</td>
<td>16.4 (4.7)</td>
<td>16.1 (5.0)</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>54 (23.7)</td>
<td>63 (27.5)</td>
<td>54 (23.8)</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>28 (12.3)</td>
<td>21 (9.2)</td>
<td>29 (12.8)</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>23 (10.1)</td>
<td>28 (12.2)</td>
<td>22 (9.7)</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>3 (1.3)</td>
<td>2 (0.9)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>1 (0.4)</td>
<td>0</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Bucillamine</td>
<td>0</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>1 (0.4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Minocycline</td>
<td>1 (0.4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mizoridine</td>
<td>0</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>1 (0.4)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
# Deaths As-Treated Pbo, 2-mg, 4-mg and All Bari RA

<table>
<thead>
<tr>
<th>SOC</th>
<th>PBO N = 1070 PYE=405.8</th>
<th>As-Treated 2-mg N=1005 PYE=1275</th>
<th>As-Treated 4-mg N=3107 PYE=6392</th>
<th>All N=3492 PYE=7860</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>-</td>
<td>1</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Infection</td>
<td>-</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Malignancies</td>
<td>-</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory</td>
<td>-</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Others</td>
<td>-</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total, n [IR] {95%CI}</strong></td>
<td><strong>2 [0.49]</strong> {0.06,1.78}</td>
<td><strong>2 [0.16]</strong> {0.02,0.57}</td>
<td><strong>25 [0.39]</strong> {0.25, 0.58}</td>
<td><strong>28 [0.36]</strong> {0.24, 0.51}</td>
</tr>
</tbody>
</table>

Data as of Apr. 1, 2017
# Patient Demographics and VTE Risk Factors at Baseline – 6 Study Data Set

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=1,070</th>
<th>Bari 4 mg N=997</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age Categories</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50</td>
<td>692 (64.7)</td>
<td>661 (66.3)</td>
<td>0.572</td>
</tr>
<tr>
<td>≥ 60</td>
<td>339 (31.7)</td>
<td>327 (32.8)</td>
<td>0.783</td>
</tr>
<tr>
<td>≥ 65</td>
<td>173 (16.2)</td>
<td>199 (20.0)</td>
<td>0.043*</td>
</tr>
<tr>
<td><strong>BMI Categories</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30 kg/m²</td>
<td>333 (31.1)</td>
<td>301 (30.2)</td>
<td>0.377</td>
</tr>
<tr>
<td>≥ 35 kg/m²</td>
<td>154 (14.4)</td>
<td>146 (14.6)</td>
<td>0.841</td>
</tr>
<tr>
<td>≥ 40 kg/m²</td>
<td>61 (5.7)</td>
<td>60 (6.0)</td>
<td>0.996</td>
</tr>
<tr>
<td><strong>Cigarette Smoking</strong></td>
<td>166 (18.6)</td>
<td>182 (20.4)</td>
<td>0.333</td>
</tr>
<tr>
<td><strong>Time from RA Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 5 years</td>
<td>515 (48.1)</td>
<td>510 (51.2)</td>
<td>0.812</td>
</tr>
<tr>
<td>≥ 10 years</td>
<td>298 (27.9)</td>
<td>289 (29.0)</td>
<td>0.643</td>
</tr>
<tr>
<td><strong>Time from Symptom Onset of RA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 5 years</td>
<td>649 (60.7)</td>
<td>621 (62.3)</td>
<td>0.884</td>
</tr>
<tr>
<td>≥ 10 years</td>
<td>383 (35.8)</td>
<td>386 (38.7)</td>
<td>0.469</td>
</tr>
<tr>
<td><strong>Seropositive Status: RF or ACPA Positive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>891 (83.3)</td>
<td>842 (84.5)</td>
<td>0.649</td>
</tr>
<tr>
<td><strong>Glucocorticoid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>610 (57.0)</td>
<td>538 (54.0)</td>
<td>0.133</td>
</tr>
<tr>
<td><strong>MTX</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>967 (90.4)</td>
<td>903 (90.6)</td>
<td>0.523</td>
</tr>
<tr>
<td><strong>Cancer History</strong></td>
<td>17 (1.6)</td>
<td>27 (2.7)</td>
<td>0.060</td>
</tr>
<tr>
<td><strong>History of DVT/PE</strong></td>
<td>13 (1.2)</td>
<td>12 (1.2)</td>
<td>0.945</td>
</tr>
<tr>
<td><strong>History of Venous Thrombosis</strong></td>
<td>19 (1.8)</td>
<td>19 (1.9)</td>
<td>0.913</td>
</tr>
</tbody>
</table>

*Statistically significant
Placebo Response Rate in Baricitinib Program was Consistent with Other Contemporary Phase 3 Trials

- Placebo response rates in Baricitinib phase 3 program consistent with other contemporary trials
- Data from tofacitinib ORAL Standard, upadacitinib, cDMARD IR and Sarilumab Mobility study (MTX-IR) are shown here
Regional Distribution of PCP

- PCP (4)
  - 3 from Japan (Bari 4mg + MTX, Bari 4mg and Bari 8mg each) modest $\uparrow_{\beta}$-d glucan
    - abnormal chest CT
    - no microbiology confirmation
    - treated and recovered
  - 1 from South Korea (Bari 4mg), BAL PCR + for PCP and CMV, Died of CMV and PCP pneumonia
JADW ACR Components (mLOCF)

LS mean Δ from baseline (mLOCF)

SJC, 0-66

Physician Global

TJC, 0-68

Patient Global

Placebo (N=176)
Bari 2 mg (N=174)
Bari 4 mg (N=177)

P-value vs. pbo: ***p≤.001; **p≤.01; *p≤.05.
JADW ACR Components and ESR (mLOCF)

**P-value vs. pbo:** ***p≤0.001; **p≤0.01; *p≤0.05.**
Evidence of Heterogeneity in JADX by DMARD History: Baricitinib 4 mg vs 2 mg (Time-Averaged AUC)

AUC Through Week 24

- Baricitinib 4 mg vs 2 mg
  - 1 DMARD-IR
  - 2+DMARD-IR

Interaction test positive (p≤0.1)
* 4 mg superior to 2 mg (p≤0.05)
Changes in Mean Platelet Count and Platelet Volume

Mean Platelet Count

Mean $\Delta$ from Baseline (95% CI)

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>14</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>263</td>
<td>266</td>
<td>253</td>
<td>236</td>
<td>248</td>
<td>237</td>
<td>237</td>
</tr>
</tbody>
</table>

Within group *p ≤ 0.05

Mean Platelet Volume

Mean $\Delta$ from Baseline (95% CI)

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>14</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bari 4 mg
Lack of Correlation Between Platelet Counts and VTE Time to Event

- Baseline platelet count (1e9/L) with correlation coefficient $r=0.0587$; $p=0.7118$
- Prior to event platelet count (1e9/L) with correlation coefficient $r=0.1416$; $p=0.3711$
- Change in platelet count (1e9/L) with correlation coefficient $r=0.1714$; $p=0.2609$
ACR20, DAS28 & HAQ-DI at Week 12 Across Studies: Bari 2 mg Consistently Superior to Placebo

<table>
<thead>
<tr>
<th>Study JADX (cDMARD-IR)</th>
<th>ACR20</th>
<th>p&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p=0.00002</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study JADW (bDMARD-IR)</th>
<th>DAS28-CRP</th>
<th>p&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p=0.000002</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>HAQ-DI</th>
<th>p&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p=0.00015</td>
<td></td>
</tr>
</tbody>
</table>

Least Squares Mean Difference

Favors Bari 2 mg
Patients with History 2+DMARD-IR Show Similar Response After Dose Tapering

All patients from studies JADV, JADX, and JADW

2+ DMARD-IR patients from JADV, JADX, and JADW
## Similar Safety in DMARD Refractory Patients, Controlled Portion

<table>
<thead>
<tr>
<th></th>
<th>1 Prior DMARD</th>
<th>2 or more prior DMARDs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO N=172 PYE=45.4 n [IR]</td>
<td>PBO N=378 PYE=104.6 n [IR]</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>0</td>
<td>2 [1.9]</td>
</tr>
<tr>
<td><strong>VTE</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Malignancies (excl NMSC)</strong></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
# Safety in DMARD Refractory Patients, Extended

<table>
<thead>
<tr>
<th></th>
<th>EXT Period</th>
<th>1 Prior DMARD</th>
<th>2 or more prior DMARDs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2-mg N=141 PYE=175.5</td>
<td>4-mg N=143 PYE=198</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td>1 [0.6]</td>
<td>1 [0.5]</td>
</tr>
<tr>
<td><strong>TEAEs</strong></td>
<td></td>
<td>99 [56.4]</td>
<td>118 [59.6]</td>
</tr>
<tr>
<td><strong>Serious infections</strong></td>
<td></td>
<td>2 [1.1]</td>
<td>8 [4.0]</td>
</tr>
<tr>
<td><strong>VTE</strong></td>
<td></td>
<td>1 [0.6]</td>
<td>4 [2.0]</td>
</tr>
<tr>
<td><strong>Malignancies (excl NMSC)</strong></td>
<td></td>
<td>1 [0.6]</td>
<td>4 [2.0]</td>
</tr>
</tbody>
</table>
Mechanism of Action of Baricitinib and Causal Link to Thromboembolic Risk

- No Mechanistic Link to Risk Factors
  - Activated platelets, clotting cascade & endothelial function
- 2 year carcinogenicity study in rodents
  - Normal vascular histopathology
  - No histological observations after 2 years of baricitinib treatment
    - No evidence of thrombus or infarcts in vasculature
# Details of MTX - PE Death Case

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina/79/Female</td>
<td>234 days after first dose of methotrexate</td>
</tr>
<tr>
<td>MTX - JADZ</td>
<td>Relevant history: osteoporosis</td>
</tr>
<tr>
<td>BMI - 20</td>
<td>Other risk factors: None.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concurrent Meds</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX Y</td>
<td>Patient hospitalized with heart failure and arrhythmia, and died 3 days later due to PE</td>
</tr>
<tr>
<td>Glucocorticoid N</td>
<td>Diagnosis clinically- no imaging</td>
</tr>
<tr>
<td>Cox-2 Inhibitor Y</td>
<td>Serious: Y (fatal)</td>
</tr>
<tr>
<td>NSAID N</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Platelets</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline: 204</td>
<td>Severity: Severe</td>
</tr>
<tr>
<td>Highest prior to event: 212</td>
<td>Outcome: Supportive treatment administered; event was fatal.</td>
</tr>
</tbody>
</table>
Arterial Thromboembolic Event Identification

- ATE identified through adjudicated MI and ischemic stroke events where applicable, in conjunction with MedDRA preferred term search

- Search terms include

<table>
<thead>
<tr>
<th>Acute Myocardial Infarction</th>
<th>Transient Ischemic Attack</th>
</tr>
</thead>
</table>
- acute myocardial infarction | transient ischemic attack |
- amaurosis                   | vertebral artery thrombosis|
- basilar artery thrombosis  | cardiac ventricular thrombosis (arterial event based on case review) |
- coronary artery occlusion   | cerebral infarction        |
- ischemic stroke             | cerebrovascular accident   |
- myocardial infarction       | retinal vascular thrombosis (arterial event based on case review) |
- peripheral artery thrombosis| thrombectomy (arterial event based on case review) |
- peripheral embolism         |                           |
- retinal artery embolism     |                           |
Management of 42 VTE Cases

- 40 treated with anticoagulant therapy
  - 2 did not receive anticoagulant therapy
    - Both patients continued treatment with baricitinib
      - 1 patient recovered
      - No worsening and no further DVT
- 28 of 42 were serious events
- 5 of 42 permanently discontinued
- 28 continued therapy - 2 had recurrence
DVT/PE Events Not Clustered; Accrued ~ 0.5% or less Annually, by Dose

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Bari 2 mg; n=2</th>
<th>Bari 4 mg; n=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>479</td>
<td>1371</td>
</tr>
<tr>
<td>12</td>
<td>439</td>
<td>1271</td>
</tr>
<tr>
<td>24</td>
<td>386</td>
<td>1140</td>
</tr>
<tr>
<td>36</td>
<td>341</td>
<td>1021</td>
</tr>
<tr>
<td>48</td>
<td>320</td>
<td>965</td>
</tr>
<tr>
<td>60</td>
<td>300</td>
<td>935</td>
</tr>
<tr>
<td>72</td>
<td>281</td>
<td>789</td>
</tr>
<tr>
<td>84</td>
<td>184</td>
<td>441</td>
</tr>
<tr>
<td>96</td>
<td>85</td>
<td>180</td>
</tr>
</tbody>
</table>