XELJANZ® (tofacitinib) for the Treatment of Psoriatic Arthritis (PsA)

Arthritis Advisory Committee (AAC)
August 3, 2017
FDA White Oak Campus
Silver Spring, MD
Introduction

Nancy McKay
Director, Regulatory Affairs
Pfizer Inc
# Overview of Presentation

<table>
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<tr>
<th>Topic</th>
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</table>
| Introduction                               | Nancy McKay  
Director, Regulatory Affairs  
Pfizer Inc                                     |
| Psoriatic Arthritis:                        | Philip Mease, MD, MACR  
Director, Rheumatology Research, Swedish-Providence-St.  
Joseph Health Systems  
Clinical Professor, University of Washington School of Medicine,  
Seattle, WA                              |
| PsA: A Physician’s Perspective/             | Keith Kanik, MD, FACP  
Senior Director, Global Clinical Lead PsA  
Inflammation and Immunology  
Pfizer Inc                                      |
| Unmet Medical Need                         | Daniela Graham, MD  
Clinician, PsA Development Program  
Inflammation and Immunology  
Pfizer Inc                                        |
| Tofacitinib PsA Development Program and Efficacy | Thomas Jones, MD  
Senior Director, Safety Risk Management  
Pfizer Inc                                           |
| Tofacitinib PsA Safety                      | Michael Corbo, PhD  
Senior VP, Chief Development Officer  
Inflammation and Immunology  
Pfizer Inc                                          |
Tofacitinib is an Oral, Small Molecule JAK Inhibitor

- JAK inhibition is partial and reversible and interferes with signaling of cytokines important in psoriatic arthritis
- Effective oral drug with manageable safety profile and efficacy similar to TNF-inhibitors
- Provides an oral option to address unmet needs for the treatment of patients with active PsA

JAK=Janus Kinase; TNF=Tumor Necrosis Factor
XELJANZ® (tofacitinib) Development Program and Clinical Experience

- Xeljanz studied extensively with Phase 3 clinical development programs
  - Including rheumatoid arthritis, psoriasis, psoriatic arthritis, and ulcerative colitis

- Cumulatively, 22,132 patients have participated in the tofacitinib clinical development program with patients exposed for up to 9 years

- The total estimated post-marketing exposure is in excess of 83,000 patient-years (PY)

- The safety of tofacitinib for the treatment of PsA is based on a clinical development program that consists of
  - 783 PsA patients that have been exposed to tofacitinib
  - 775 patient-years of tofacitinib exposure as of May 10, 2016
XELJANZ® (tofacitinib) Regulatory History

- Rheumatoid Arthritis (RA)
  - Adult RA 5 mg BID IR NDA Approved – November 6, 2012
  - Adult RA 11 mg QD XR NDA Approved – February 23, 2016
  - Tofacitinib tablets are approved for RA in more than 80 countries; including US, Canada, EU countries and Japan

- Other Indications
  - PsO sNDA CRL – October 9, 2015 / sNDA Withdrawn – July 26, 2016
  - PsA sNDAs (IR and XR) Submitted – February 22, 2017
  - UC sNDA Submitted – May 4, 2017

BID=twice daily; CRL=Complete Response Letter; IR=Immediate Release; mg=milligram; NDA=New Drug Application; PsO=Psoriasis; QD=once daily; sNDA=supplemental New Drug Application; UC=Ulcerative Colitis; XR=Extended Release
Tofacitinib for the Treatment of PsA

- 5 mg BID of tofacitinib in PsA has shown efficacy consistent with bDMARDs in TNFi-naïve patients, while also demonstrating similar efficacy in TNFi-Inadequate Responders (IR)

- The safety profile of tofacitinib, including that in PsA patients, is well characterized, stable and manageable. It is informed by a large and growing safety database, with consistency between real world and clinical safety data

- The benefit:risk profile of tofacitinib 5 mg BID for PsA is positive and is based on substantial clinical evidence

bDMARD=biologic Disease-Modifying Anti-Rheumatic Drug; TNFi=Tumor Necrosis Factor inhibitor
XELJANZ® (tofacitinib) for PsA
Proposed USPI: Indication and Dosage

Proposed Indication in sNDA
(1. INDICATIONS AND USAGE)

XELJANZ is indicated for the treatment of adult patients with active psoriatic arthritis

Proposed Dosage in sNDA
(2. DOSAGE AND ADMINISTRATION)

The recommended dose of XELJANZ is 5 mg twice daily used in combination with conventional synthetic DMARDs
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| Benefit:Risk and Conclusions                   |                                                                           |
Psoriatic Arthritis: A Physician’s Perspective/Unmet Medical Need

Philip Mease, MD, MACR

Director, Rheumatology Research, Swedish-Providence-St. Joseph Health Systems

Clinical Professor of Medicine, University of Washington School of Medicine, Seattle, WA
Disclosures for Philip Mease

- Research grants, consultation fees, and/or speaker honoraria: Abbvie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Crescendo, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, SUN, UCB
Professor Mease: Relevant Clinical, Research, and Education Experience

- **Clinical Practice**
  - Clinical rheumatologist for 35 years and Clinical Professor, University of Washington, Seattle
  - Clinical experience with tofacitinib in RA patients since approval in November 2012

- **Research experience**
  - Conducted the first trial of TNFi therapy in PsA and participated in most PsA development programs
  - Involvement in tofacitinib RA studies and in tofacitinib PsA clinical trial design and data interpretation

- **Relevant committees and working groups**
  - Founder and current executive committee member of Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)
  - OMERACT PsA working group, the National Psoriasis Foundation PsA task force, and ACR-NPF PsA treatment recommendations working group
  - Scientific director, Corrona PsA-SpA registry

ACR=American College of Rheumatology; OMERACT=Outcome Measures in Rheumatology; NPF=National Psoriasis Foundation; SpA=Spondyloarthritis
Psoriatic Arthritis is a Distinct Disease Encompassing Numerous Clinical Manifestations

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
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| Peripheral Arthritis | - Arthritis affecting joints such as those in hands, feet and knees  
                    | - Progressive disability and joint destruction may occur                                                                                                                                                |
| Enthesitis         | - Enthesitis is inflammation where tendons and ligaments attach to bone. Enthesitis can occur virtually anywhere in the body. It often appears at the insertion of the Achilles tendon or plantar fascia in the heel, causing walking and standing disability |
| Dactylitis         | - Dactylitis is significant swelling in the fingers and toes, creating a sausage-like appearance. This is painful and causes stiffness and disability                                                                 |
| Spondylitis        | - Psoriatic arthritis in the spine and sacroiliac joints is called psoriatic spondylitis. This results in back pain, stiffness, inability to move and work impairment                                                                 |
| Skin Psoriasis     | - Psoriasis causes red, scaly, itchy, raised patches on the skin                                                                                                                                              |

PsA Impacts Patient’s Health Related Quality of Life, Physical and Mental Health

Comparison of Health-Related QoL in PsA and PsO using the SF-36

- Physical function
- Role physical
- Bodily pain
- General health
- Fatigue
- Social functioning
- Role emotional
- Mental health

Legend:
- Purple: Age and Gender Matched Norms
- Green: PsO
- Orange: PsA


QoL=Quality of Life; SF-36=Short-Form 36-question Health Survey
PsA Impacts Patient’s Health Related Quality of Life, Physical and Mental Health

Comparison of Health-Related QoL in PsA and PsO using the SF-36

- Physical function
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- Age and Gender Matched Norms
- PsO
- PsA

QoL=Quality of Life; SF-36=Short-Form 36-question Health Survey
PsA Impacts Patient’s Health Related Quality of Life, Physical and Mental Health

Comparison of Health-Related QoL in PsA and PsO using the SF-36

- Patients with PsA reported greater impact on physical function, pain, and fatigue compared to patients with PsO.
- Patients suffering from PsA or PsO also experience negative mental impact of the disease.

Health-Related QoL is severely affected in PsA, both for physical and mental health.

QoL=Quality of Life; SF-36=Short-Form 36-question Health Survey
Existing Therapeutic Options for PsA Have Limitations: A Need for Effective New Therapies Exists

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<th>NSAIDs and Glucocorticoids</th>
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csDMARD=conventional synthetic Disease-Modifying Anti-Rheumatic Drug; IL=Interleukin; MTX=Methotrexate; NSAID=Nonsteroidal Anti-Inflammatory Drug; PDE4=Phosphodiesterase type 4
### Existing Therapeutic Options for PsA Have Limitations: A Need for Effective New Therapies Exists

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#### Efficacy csDMARDs

- MTX is one of the most commonly used systemic medications in PsA, yet has demonstrated minimal clinical efficacy for PsA in studies. 
- MTX and sulfasalazine have little effect on enthesitis, dactylitis, and spondylitis.

#### Efficacy of Targeted and Biologic DMARDs

- The goal of achieving low disease activity or remission is now achievable, however:
  - 36%-63% of patients do not achieve an ACR20 response at 6 months.
  - 45%-69% may lose response over time or may experience adverse events.
- This leads to the need for additional medications to switch.

---

Median Drug Survival in PsA is 2 Years on TNFi

Clinical Response, Drug Survival, and Predictors of Response Among 548 Patients with Psoriatic Arthritis who Switched Tumor Necrosis Factor α Inhibitor Therapy: Results from the Danish Nationwide DANBIO Registry


DANBIO=Danish Registry for Biologic Therapies in Rheumatology
Several key reasons why treatment was viewed as burdensome were\textsuperscript{1,2}

- Lack/loss of effectiveness
- Adverse events
- Fear and anxiety of injections
- Pain and discomfort of injections
- Inconvenience

\textsuperscript{1} More than 50% of respondents found oral or biologic therapies to be burdensome. Traditional oral medications were burdensome primarily due to adverse events (30%), inconvenience (14%), and lack/loss of effectiveness (2%).

\textsuperscript{2} Biologics were burdensome primarily due to fear and anxiety of injections and physical preparation for self-injection such as icing and premedication (26%), inconvenience (15%), adverse events (15%), pain/discomfort (7%), and lack/loss of effectiveness (2%).

More Info:
Results from the Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey (N=3426) showed that.

Storage

- Shorthalf life,

appeals to patients concerned re. infections and ability to wash out from drug importance to patients

All together a new MOA that would address many of these issues regarding lack of response, intolerability and patient dissatisfaction would be very welcome in the rheumatology community.

Arthritis
Pathogenic Pathways

Arthritis

Enthesitis
Pathogenic Pathways

### Arthritis

**Enthesitis**

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<thead>
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<th>Pathogenic Cytokines are Mediated or Modified by Tofacitinib</th>
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<tbody>
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<td>----------------</td>
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<tr>
<td>CD4+ and CD8+ cells</td>
</tr>
<tr>
<td>Dendritic cells</td>
</tr>
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</tr>
<tr>
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Pathogenic Pathways

### Cytokines in red are JAK dependent

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<tr>
<th>Cell Type</th>
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<td>CD4+ and CD8+ cells</td>
<td>Enthesitis skin inflammation synovitis</td>
<td>IL-6, IL-7, IL-15, IL-12, IL-23</td>
<td>IL-17, IL-22</td>
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<tr>
<td>Dendritic cells</td>
<td>T cell activation</td>
<td>IL-15, IFN-α</td>
<td>IFN-γ, IL-12, IL-23</td>
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<tr>
<td>Innate lymphoid cells</td>
<td>Enthesitis</td>
<td>IL-7</td>
<td>IL-17, IL-22, TNF-5</td>
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<td>Hyperkeratosis systemic inflammation</td>
<td>IL-17, IL-22, IL-20 family</td>
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<td>Lymphocyte synoviocyte interaction</td>
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<td>Osteoclast</td>
<td>Bone resorption</td>
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<td>IL-22</td>
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CD=Cluster of Differentiation; IFN=Interferon; RANKL=Receptor Activator of Nuclear factor Kappa-B Ligand

# Pathogenic Pathways

**Arthritis**

![Image of arthritis](image)

**Enthesitis**

![Image of enthesis](image)

## Pathogenic Cytokines are Mediated or Modified by Tofacitinib

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Cytokines in **red** are JAK dependent
Tofacitinib reduces the production or downstream effects of cytokines in **blue**

---

**CD**=Cluster of Differentiation; **IFN**=Interferon; **RANKL**=Receptor Activator of Nuclear factor Kappa-B Ligand

Psoriatic arthritis has numerous clinical manifestations
- Resulting in physical disability and psychosocial impact

Each patient with PsA is clinically unique
- The disease burden is typically high

Despite the availability of several therapeutic options
- Drugs to treat patients with active PsA all have limitations

A need exists for medications that work across the spectrum of cytokines involved in the pathogenesis of PsA with a convenient mode of delivery, i.e. oral
- Tofacitinib has a well-characterized efficacy and safety profile well known to rheumatologists who have used it in RA
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| **Risk Management**                        | Thomas Jones, MD  
Senior Director, Safety Risk Management  
Pfizer Inc                                |
| **Benefit:Risk and Conclusions**           | Michael Corbo, PhD  
Senior VP, Chief Development Officer  
Inflammation and Immunology  
Pfizer Inc                                |
Tofacitinib PsA Development Program and Efficacy

Keith Kanik, MD, FACR
Senior Director, Global Clinical Lead PsA
Inflammation and Immunology
Pfizer Inc
Psoriatic Arthritis is a Complex Disease

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<td><strong>Dactylitis</strong></td>
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<td>- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)</td>
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SPARCC=Spondyloarthritis Research Consortium of Canada

Author: Keith Kanik
Source: Reviewed
In QC 27 July 2017
QC Complete 29 July 2017
Psoriatic Arthritis is a Complex Disease

### Study Endpoints Associated with PsA Disease Manifestations

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CASPAR Criteria to Classify PsA

To meet the CASPAR (Classification Criteria for Psoriatic Arthritis) criteria, a patient must have inflammatory articular disease (joint, spine, or enthesal) with 3 points from the following 5 categories:

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis
2. Typical psoriatic nail dystrophy including oncholysis, pitting, and hyperkeratosis observed on current physical examination
3. A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range
4. Either current dactylitis or a history of dactylitis recorded by a rheumatologist
5. Radiographic evidence of juxta-articular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot
Tofacitinib PsA Phase 3 Program Design

**TNFi-Naïve (Study 1091)**
- Randomization:
  - Placebo
  - Placebo
  - Tofacitinib 5 mg BID
  - Tofacitinib 10 mg BID
  - Adalimumab 40 mg SC Q2W

**TNFi-IR (Study 1125)**
- Randomization:
  - Placebo
  - Placebo
  - Tofacitinib 5 mg BID
  - Tofacitinib 10 mg BID
  - Tofacitinib 5 mg BID
  - Tofacitinib 10 mg BID

**LTE (Study 1092)**
- Randomization:
  - Tofa 5 mg
  - Tofa 5 or 10 mg BID dosing option

Abbreviations: ADA=adalimumab; BID=twice daily; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; IR= inadequate response; LTE=long-term extension; Pbo=placebo; SC=subcutaneous; SCE=summary of clinical efficacy; TNF= inadequate response to TNFi; Tofa=tofacitinib; 1091=Study A3921091; 1092=Study A3921092; 1125=Study A3921125. Tofacitinib 5 mg and 10 mg were BID and adalimumab 40 mg dosing was SC q2wk (every 2 weeks) in Study A3921091.

*Study A3921091 was a double-dummy design (placebo tablets and/or placebo injections included in each treatment group, as applicable).

†Subjects with inadequate PsA response permitted to increase to tofacitinib 10 mg BID; investigators permitted to reduce dose to 5 mg BID at any time in response to safety findings.

No 0.5 months for LTE.
TNFi-Naïve Patient Study Design (Study 1091)

Primary Efficacy Endpoints (Month 3)
- ACR20
- ΔHAQ-DI

Secondary Efficacy Endpoints (Month 3)
- PASI75
- ΔLEI
- ΔDSS
- ΔSF-36v2 PF
- ΔFACIT-F
- ACR50, ACR70: Month 3
- ACR20: pre-Month 3

Abbreviations: ADA=adalimumab; BID=twice daily; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; IR= inadequate response; LTE=long-term extension; Pbo=placebo; SC=subcutaneous; SCE=summary of clinical efficacy; TNF-IR= inadequate response to TNFi; Tofa=tofacitinib; 1091=Study A3921091; 1092=Study A3921092; 1125=Study A3921125.

* Study A3921091 was a double-dummy design (placebo tablets and/or placebo injections included in each treatment group, as applicable).

δ Study A3921091 & A3921125: All subjects randomized to placebo were advanced to tofacitinib 5 mg or 10 mg BID in a blinded manner at Month 3.

† Subjects with inadequate PsA response permitted to increase to tofacitinib 10 mg BID; investigators permitted to reduce dose to 5 mg BID at any time in response to safety findings.

No 0.5 months for LTE.
Patient Disposition in TNFi-Naïve Study (Study 1091)

Randomized N=422

Placebo → Tofacitinib 5 mg BID N=52
- Discontinued 15.4%
  - Completed 84.6%

Placebo → Tofacitinib 10 mg BID N=53
- Discontinued 18.9%
  - Completed 81.1%

Tofacitinib 5 mg BID N=107
- Discontinued 10.3%
  - Completed 89.7%

Tofacitinib 10 mg BID N=104
- Discontinued 7.7%
  - Completed 92.3%

Adalimumab 40 mg SC Q2W N=106
- Discontinued 11.3%
  - Completed 88.7%

Data shown through Month 12 for Study 1091 and Month 6 for Study 1125.

Percentages for the "Treated" row are calculated using the number of Assigned to Study Treatment (i.e., randomized) as the denominator. Other percentages are calculated using the number of treated subjects in the denominator.

Discontinued
- Placebo, Tofacitinib 5 mg BID: n=8 (15.4%)
  - Died: n=1
  - Insufficient response: n=2
  - No longer willing: n=2
  - Adverse event: n=2
  - Other: n=1

- Placebo, Tofacitinib 10 mg BID: n=10 (18.9%)
  - No longer willing: n=2
  - Adverse event: n=2
  - Protocol violation: n=3
  - Other: n=3

- Tofacitinib 5 mg BID: n=8 (7.7%)
  - Insufficient response: n=1
  - Lost to follow-up: n=2
  - Adverse event: n=3
  - Protocol violation: n=1
  - Other: n=1

- Tofacitinib 10 mg BID: n=11 (10.3%)
  - Does not meet criteria: n=1
  - No longer willing: n=2
  - Adverse event: n=6
  - Protocol violation: n=1
  - Other: n=1

- Adalimumab: n=12 (11.3%)
  - Does not meet criteria: n=1
  - Insufficient response: n=2
  - Lost to follow-up: n=1
  - No longer willing: n=3
  - Adverse event: n=4
  - Other: n=1

Reviewed
Ready for QC
In QC
27 July 2017
QC Complete
29 July 2017
TNFi-Inadequate Responder (TNFi-IR) Study Design (Study 1125)

**Primary Efficacy Endpoints (Month 3)**
- ACR20
- ∆HAQ-DI

**Secondary Efficacy Endpoints (Month 3)**
- PASI75
- ∆LEI
- ∆DSS
- ∆SF-36v2 PF
- ∆FACIT-F
- ACR50, ACR70: Month 3
- ACR20: pre-Month 3

**Abbreviations:**
- ADA = adalimumab
- BID = twice daily
- csDMARD = conventional synthetic disease-modifying anti-rheumatic drug
- IR = inadequate response
- LTE = long-term extension
- Pbo = placebo
- SC = subcutaneous
- SCE = summary of clinical efficacy
- TNF-IR = inadequate response to TNFi
- Tofa = tofacitinib
- 1091 = Study A3921091
- 1092 = Study A3921092
- 1125 = Study A3921125

Tofacitinib 5 mg and 10 mg were BID and adalimumab 40 mg dosing was SC q2wk (every 2 weeks) in Study A3921091.

*Study A3921091 was a double-dummy design (placebo tablets and/or placebo injections included in each treatment group, as applicable).*

δ Study A3921091 & A3921125: All subjects randomized to placebo were advanced to tofacitinib 5 mg or 10 mg BID in a blinded manner at Month 3.

† Subjects with inadequate PsA response permitted to increase to tofacitinib 10 mg BID; investigators permitted to reduce dose to 5 mg BID at any time in response to safety findings.

N=395

Randomization:
- Placebo n=66
- Placebo n=65
- Tofa 5 mg BID n=131
- Tofa 10 mg BID n=132

Months: 0 0.5 1 2 3 4 6
Patient Disposition in TNFi-IR Study (Study 1125)

- Placebo → Tofacitinib 5 mg BID N=66
  - Discontinued: 15.2%
  - Completed: 84.8%

- Placebo → Tofacitinib 10 mg BID N=65
  - Discontinued: 13.8%
  - Completed: 86.2%

- Tofacitinib 5 mg BID N=131
  - Discontinued: 6.9%
  - Completed: 93.1%

- Tofacitinib 10 mg BID N=132
  - Discontinued: 15.9%
  - Completed: 84.1%

Not treated N=1
No longer willing to participate
## Similar Baseline Demographics and Disease Characteristics Between PsA Studies

<table>
<thead>
<tr>
<th></th>
<th>TNFi-Naïve (Study 1091) N=422</th>
<th>TNFi-IR (Study 1125) N=394</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>197 (46.7)</td>
<td>176 (44.7)</td>
</tr>
<tr>
<td>Age, mean, years (SD)</td>
<td>47.9 (12.1)</td>
<td>50.0 (12.0)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>409 (96.9)</td>
<td>363 (92.1)</td>
</tr>
<tr>
<td>Mean PsA duration, years</td>
<td>6.1</td>
<td>9.4</td>
</tr>
<tr>
<td>Patients with BSA≥3% psoriasis, %</td>
<td>73.9</td>
<td>62.7</td>
</tr>
<tr>
<td>Patients with enthesitis, LEI &gt;0, %</td>
<td>66.4</td>
<td>69.8</td>
</tr>
<tr>
<td>Patients with dactylitis, DSS &gt;0, %</td>
<td>56.2</td>
<td>49.2</td>
</tr>
<tr>
<td>Mean swollen joint count</td>
<td>11.5</td>
<td>11.8</td>
</tr>
<tr>
<td>Mean tender joint count</td>
<td>19.6</td>
<td>22.0</td>
</tr>
<tr>
<td>Median CRP, mg/L (ULN 2.87 mg/L)</td>
<td>4.89</td>
<td>4.73</td>
</tr>
<tr>
<td>Mean HAQ-DI</td>
<td>1.11</td>
<td>1.30</td>
</tr>
<tr>
<td>Patients with concomitant csDMARD use, %</td>
<td>100.0</td>
<td>99.0</td>
</tr>
<tr>
<td>MTX use, %</td>
<td>83.9</td>
<td>71.6</td>
</tr>
<tr>
<td>Patients with oral corticosteroid use, %</td>
<td>19.2</td>
<td>24.1</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- BSA=Body Surface Area
- CRP=C-Reactive Protein
- csDMARD=conventional synthetic Disease Modifying Anti-Rheumatic Drugs
- SD=Standard Deviation
- ULN=Upper Limit of Normal

---

**Teasers:**
- Oral corticosteroid use is on Day 1
- TNFi-IR use was up to Month 3

---

**Reviewed:**
- 27 July 2017 Ready for QC
- 29 July 2017 QC Complete

---

**Source:**
- A3921091 CSR Table 14.1.2.2.1, Table 14.4.2.4.1.3, Table 14.4.2.4.6.1; Table 14.4.2.1.3.1; A3921125 CSR Table 14.1.2.1, Table 14.4.2.4.1.3, Table 14.4.2.1.5.1; SCE Table 13; SCS Table C1.3.3.1; Ad hoc Table 00013.2, Table 00013.3.; SCE table 1

---

**Translation:**
- MTX use was up to Month 3
- Oral corticosteroid use is on Day 1
- ROW= Brazil, Mexico, Taiwan
Significant Improvement in Peripheral Arthritis (Month 3)

*Achieved statistical significance under Type I error control
†95% CI for difference between active treatment and placebo excluded zero
FAS, MR=NR
CI=Confidence Interval; SE=Standard Error
Significant Improvement in Peripheral Arthritis (Month 3)

**TNFi-Naïve (Study 1091)**

- **ACR20**: Placebo 33.3%, Tofa 5 mg BID 50.5%, Tofa 10 mg BID 60.6%, Ada 40 mg SC Q2W 51.9%
- **ACR50**: Placebo 9.5%, Tofa 5 mg BID 28.0%, Tofa 10 mg BID 40.4%, Ada 40 mg SC Q2W 33.0%
- **ACR70**: Placebo 4.8%, Tofa 5 mg BID 16.8%, Tofa 10 mg BID 14.4%, Ada 40 mg SC Q2W 18.9%

**TNFi-IR (Study 1125)**

- **ACR20**: Placebo 23.7%, Tofa 5 mg BID 49.6%, Tofa 10 mg BID 47.0%
- **ACR50**: Placebo 14.5%, Tofa 5 mg BID 29.8%, Tofa 10 mg BID 28.0%
- **ACR70**: Placebo 9.9%, Tofa 5 mg BID 16.8%, Tofa 10 mg BID 14.4%

*Achieved statistical significance under Type I error control
†95% CI for difference between active treatment and placebo excluded zero
FAS, MR=NR
CI=Confidence Interval; SE=Standard Error

At all time points:
- Placebo (N=105)
- Tofa 5 mg BID (N=107)
- Tofa 10 mg BID (N=104)
- Ada 40 mg SC Q2W (N=106)

At all time points:
- Placebo (N=131)
- Tofa 5 mg BID (N=131)
- Tofa 10 mg BID (N=132)
Significant Improvement in Peripheral Arthritis (Month 3)

**TNFi-Naïve (Study 1091)**

- **ACR20**
  - Placebo: 33.3
  - Tofa 5 mg BID: 50.5*
  - Tofa 10 mg BID: 60.6*
  - Ada 40 mg SC Q2W: 51.9†

- **ACR50**
  - Placebo: 9.5
  - Tofa 5 mg BID: 28.0*
  - Tofa 10 mg BID: 40.4*
  - Ada 40 mg SC Q2W: 33.0†

- **ACR70**
  - Placebo: 4.8
  - Tofa 5 mg BID: 16.8*
  - Tofa 10 mg BID: 14.4*
  - Ada 40 mg SC Q2W: 18.9†

**TNFi-IR (Study 1125)**

- **ACR20**
  - Placebo: 23.7
  - Tofa 5 mg BID: 49.6*
  - Tofa 10 mg BID: 47.0*

- **ACR50**
  - Placebo: 14.5
  - Tofa 5 mg BID: 29.8*
  - Tofa 10 mg BID: 28.0*

- **ACR70**
  - Placebo: 9.9
  - Tofa 5 mg BID: 16.8
  - Tofa 10 mg BID: 14.4

*Achieved statistical significance under Type I error control
†95% CI for difference between active treatment and placebo excluded zero
FAS, MR=NR
CI=Confidence Interval; SE=Standard Error
Onset of Efficacy at 2 Weeks

**TNFi-Naïve (Study 1091)**

**TNFi-IR (Study 1125)**

* Achieved statistical significance under Type I error control
† 95% CI for difference between active treatment and placebo excluded zero
FAS, MR=NR
FAS=Full Analysis Set; MR=NR=Missing Response=Non-Response; N=Number of patients in FAS

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo N</th>
<th>Tofa 5 mg BID</th>
<th>Tofa 10 mg BID</th>
<th>Ada 40 mg SC Q2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>1091</td>
<td>105</td>
<td>107</td>
<td>104</td>
<td>106</td>
</tr>
<tr>
<td>1125</td>
<td>131</td>
<td>131</td>
<td>132</td>
<td>-</td>
</tr>
</tbody>
</table>

MA-41
Efficacy First Observed at 2 Weeks Continued to Improve to Month 3

**TNFi-Naïve (Study 1091)**

**TNFi-IR (Study 1125)**

*Achieved statistical significance under Type I error control
†95% CI for difference between active treatment and placebo excluded zero

FAS, MR=NR

FAS=Full Analysis Set; MR=NR=Missing Response=Non-Response; N=Number of patients in FAS
Efficacy Improved or Maintained Beyond Month 3

**ACR20 Response Rate, % (SE)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>Tofa 5 mg BID</th>
<th>Tofa 10 mg BID</th>
<th>Ada 40 mg SC Q2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>1091</td>
<td>105</td>
<td>107</td>
<td>104</td>
<td>106</td>
</tr>
<tr>
<td>1125</td>
<td>131</td>
<td>131</td>
<td>132</td>
<td>-</td>
</tr>
</tbody>
</table>

*Achieved statistical significance under Type I error control
†95% CI for difference between active treatment and placebo excluded zero
FAS, MR=NR
FAS=Full Analysis Set; MR=NR=Missing Response=Non-Response; N=Number of patients in FAS
Significant Improvements in ΔHAQ-DI (Month 3): Second Primary Endpoint

**TNFi-Naïve (Study 1091)**

- Placebo: N=104, LS Mean (SE) = -0.18
- Tofa 5 mg BID: N=107, LS Mean (SE) = -0.35*
- Tofa 10 mg BID: N=104, LS Mean (SE) = -0.40*
- Ada 40 mg SC Q2W: N=106, LS Mean (SE) = -0.38†

**TNFi-IR (Study 1125)**

- Placebo: N=131, LS Mean (SE) = -0.14
- Tofa 5 mg BID: N=129, LS Mean (SE) = -0.39*
- Tofa 10 mg BID: N=132, LS Mean (SE) = -0.35*

*Achieved statistical significance under Type I error control
†95% CI for difference between active treatment and placebo excluded zero
MMRM, FAS
LS=Least Square; MMRM=Mixed Model for Repeated Measures
Evaluation of Radiographic Progression

- Radiographs of hands and feet taken at baseline and Month 12 (or early termination) in TNFi-naïve patients (Study 1091)

- This pre-specified analysis was performed to assess lack of structural progression over 12 months of tofacitinib treatment

- Adalimumab 40 mg SC Q2W used as active comparator

- Study designed with consideration of regulatory agency advice
Change from Baseline in mTSS at Month 12 in TNFi-Naïve Patients (Study 1091)

FAS, Linear Extrapolation
mTSS=modified Total Sharp Score; N=number of subjects evaluable at Month 12 after linear extrapolation. n=number of progressors

Tofa 5 mg BID
Tofa 10 mg BID
Ada 40 mg SC Q2W
\(\Delta mTSS\) and Progressor Rates at Month 12 in TNFi-Naïve Patients (Study 1091)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>(\Delta mTSS&gt;0) n (%)</th>
<th>Difference from Ada 40 mg SC Q2W % (95% CI)</th>
<th>(\Delta mTSS&gt;0.5) n (%)</th>
<th>Difference from Ada 40 mg SC Q2W % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofa 5 mg BID</td>
<td>98</td>
<td>9 (9.2)</td>
<td>5.0 (-2.0, 12.0)</td>
<td>4 (4.1)</td>
<td>2.0 (-2.9, 6.8)</td>
</tr>
<tr>
<td>Tofa 10 mg BID</td>
<td>99</td>
<td>7 (7.1)</td>
<td>2.9 (-3.6, 9.3)</td>
<td>5 (5.1)</td>
<td>3.0 (-2.3, 8.1)</td>
</tr>
<tr>
<td>Ada 40 mg SC Q2W</td>
<td>95</td>
<td>4 (4.2)</td>
<td>-</td>
<td>2 (2.1)</td>
<td>-</td>
</tr>
</tbody>
</table>

FAS, Linear Extrapolation

\(mTSS=\)modified Total Sharp Score; N=number of subjects evaluable at Month 12 after linear extrapolation. n=number of progressors.
Improvements in Psoriasis (PASI75 Response Rate)

**TNFi-Naïve (Study 1091)**

<table>
<thead>
<tr>
<th>Month</th>
<th>Placebo</th>
<th>Tofa 5 mg BID</th>
<th>Tofa 10 mg BID</th>
<th>Ada 40 mg SC Q2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>21.3</td>
<td>42.3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>23.7</td>
<td>44.3</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

**TNFi-IR (Study 1125)**

<table>
<thead>
<tr>
<th>Month</th>
<th>Placebo</th>
<th>Tofa 5 mg BID</th>
<th>Tofa 10 mg BID</th>
<th>Ada 40 mg SC Q2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>14.0</td>
<td>42.3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>14.6</td>
<td>44.3</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Achieved statistical significance under Type I error control
†95% CI for difference between active treatment and placebo excluded zero
For patients with Baseline BSA≥3% and PASI>0 in FAS, MR=NR
## Improvements in Enthesitis (ΔLeeds Enthesitis Index)

<table>
<thead>
<tr>
<th></th>
<th>Study 1091</th>
<th>Study 1125</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Tofa 5 mg BID</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Tofa 10 mg BID</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Ada 40 mg SC Q2W</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

### Study Results

- **Study PBO**
  - **Tofa 5 mg**
  - **Tofa 10 mg**
  - **ADA**

<table>
<thead>
<tr>
<th></th>
<th>Study 1091</th>
<th>Study 1125</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS Mean Change from Baseline (SE)</td>
<td>-1.0</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

*Achieved statistical significance under Type I error control
†95% CI for difference between active treatment and placebo excluded zero
For patients with Baseline LEI>0 in FAS, MMRM
Improvements in Dactylitis (ΔDactylitis Severity Score)

### LS Mean Change from Baseline (SE)

**TNFi-Naïve (Study 1091)**

- Placebo: N = 57
- Tofa 5 mg BID: N = 60
- Tofa 10 mg BID: N = 60
- Ada 40 mg SC Q2W: N = 58

**TNFi-IR (Study 1125)**

- Placebo: N = 62
- Tofa 5 mg BID: N = 65
- Tofa 10 mg BID: N = 64
- Ada 40 mg SC Q2W: N = -

†95% CI for difference between active treatment and placebo excluded zero

For patients with Baseline DSS>0, in FAS, MMRM
Improvements in SF-36v2 Physical Functioning Domain and FACIT-F Total Score at Month 3

<table>
<thead>
<tr>
<th>Active Treatment</th>
<th>Placebo</th>
<th>Difference Between Active Treatment and Placebo LS Mean (95% CI)</th>
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</thead>
<tbody>
<tr>
<td><strong>ΔSF-36v2 Physical Functioning</strong> Domain</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TNFi-Naïve (Study 1091)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>106</td>
<td>104</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>106</td>
<td>104</td>
<td></td>
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<tr>
<td><strong>TNFi-IR (Study 1125)</strong></td>
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</tr>
<tr>
<td>128</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td>130</td>
<td>129</td>
<td></td>
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<tr>
<td><strong>ΔFACIT-F Total Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TNFi-Naïve (Study 1091)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>106</td>
<td>104</td>
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<tr>
<td>104</td>
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<tr>
<td>106</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td><strong>TNFi-IR (Study 1125)</strong></td>
<td></td>
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<tr>
<td>128</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td>130</td>
<td>129</td>
<td></td>
</tr>
</tbody>
</table>

MMRM, FAS
Tofacitinib 5 mg BID Demonstrated Efficacy Across PsA Disease Manifestations in Both TNFi-Naïve and TNFi-IR Patient Populations

**Peripheral Arthritis**
- ACR 20/50/70 response rates
- ΔHAQ-DI
- Maintenance of structural integrity

**Psoriasis**
- Psoriasis Area and Severity Index (PASI)75 response rate

**Enthesitis**
- ΔLeeds Enthesitis Index score (LEI)

**Dactylitis**
- ΔDactylitis Severity Score

Efficacy in improving patient reported outcomes including physical functioning and fatigue
# Overview of Presentation

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
</table>
| Introduction                               | Nancy McKay  
Director, Regulatory Affairs  
Pfizer Inc                                      |
| **Psoriatic Arthritis:**                   | **Philip Mease, MD, MACR**  
Director, Rheumatology Research, Swedish-Providence-St. Joseph’s Health Systems  
Clinical Professor, University of Washington School of Medicine, Seattle, WA |
| A Rheumatologist’s Perspective/Unmet Medical Need |                                                                         |
| Tofacitinib PsA Development Program and Efficacy | Keith Kanik, MD, FACR  
Senior Director, Global Clinical Lead PsA  
Inflammation and Immunology  
Pfizer Inc                                      |
| Tofacitinib PsA Safety                      | Daniela Graham, MD  
Clinician, PsA Development Program  
Inflammation and Immunology  
Pfizer Inc                                      |
| Risk Management                            | Thomas Jones, MD  
Senior Director, Safety Risk Management  
Pfizer Inc                                      |
| Benefit:Risk and Conclusions               | Michael Corbo, PhD  
Senior VP, Chief Development Officer  
Inflammation and Immunology  
Pfizer Inc                                      |
Tofacitinib PsA Safety

Daniela Graham, MD
Clinician, PsA Development Program
Inflammation and Immunology
Pfizer Inc
PsA
N=783
PY=775

Robust Database of Patients Studied in PsA
Tofacitinib Clinical Trial Patient-Years of Exposure

More than 80,000 PY exposure accrued in the post-marketing setting

PsA
N=783
PY=775

PsO
N=3662
PY=8537

RA
N=6300
PY=21,886

Total
N=10,745
PY=31,199

Reviewed
Ready for QC
In QC
Date
28JUL17
QC Complete
01 Aug 2017
PsA Program Structure

a. The investigator had the option to increase the dose to tofacitinib 10 mg BID in those subjects who were receiving tofacitinib 5 mg BID and, in the investigator’s opinion, had PsA symptoms that are not adequately controlled. Changes in the dose were only permitted at scheduled study visits, unless a reduction to tofacitinib 5 mg BID was required due to safety abnormalities.
PsA Program Structure

3 Month Placebo-Controlled

TNFi-Naïve (Study 1091)
- Placebo
- Placebo
- Tofa 5 mg BID
- Tofa 10 mg BID
- Ada 40 mg SC Q2W

TNFi-IR (Study 1125)
- Tofa 5 mg BID
- Tofa 10 mg BID
- Placebo
- Placebo

Months 0-3
- Placebo
- Tofa 5 mg BID
- Tofa 10 mg BID
- Placebo
- Tofa 5 mg BID
- Tofa 10 mg BID

Months 3-6
- Tofa 5 mg BID
- Tofa 10 mg BID
- Tofa 5 mg BID
- Tofa 10 mg BID

LTE (Study 1092)
- Tofa 5 mg BID
- Tofa 10 mg BID
- Tofa 5 mg BID
- Tofa 5 mg BID
- Tofa 10 mg BID
- Tofa 5 mg BID
- Tofa 10 mg BID
- Tofa 5 mg BID

a. The investigator had the option to increase the dose to tofacitinib 10 mg BID in those subjects who were receiving tofacitinib 5 mg BID and, in the investigator's opinion, had PsA symptoms that are not adequately controlled. Changes in the dose were only permitted at scheduled study visits, unless a reduction to tofacitinib 5 mg BID was required due to safety abnormalities.
PsA Program Structure

Up to 12 Month Dose Comparison

TNFi-Naïve (Study 1091)
- Placebo
- Placebo
- Tofa 5 mg BID
- Tofa 10 mg BID
- Ada 40 mg SC Q2W

TNFi-IR (Study 1125)
- Tofa 5 mg BID
- Tofa 10 mg BID
- Placebo
- Placebo

LTE (Study 1092)
- Tofa 5 mg BID
- Tofa 10 mg BID
- Placebo

a. The investigator had the option to increase the dose to tofacitinib 10 mg BID in those subjects who were receiving tofacitinib 5 mg BID and, in the investigator’s opinion, had PsA symptoms that are not adequately controlled. Changes in the dose were only permitted at scheduled study visits, unless a reduction to tofacitinib 5 mg BID was required due to safety abnormalities.
PsA Program Structure

TNFi-Naïve (Study 1091)
- Placebo
- Placebo
- Tofa 5 mg BID
- Tofa 10 mg BID
- Ada 40 mg SC Q2W

TNFi-IR (Study 1125)
- Tofa 5 mg BID
- Tofa 10 mg BID
- Placebo
- Placebo

All PsA
- Months 0-3
- Months 3-12
- Months 3-6
- 0-3 Years

LTE (Study 1092)
- Placebo
- Tofa 5 mg BID
- Tofa 10 mg BID
- Tofa 5 mg BID
- Tofa 10 mg BID
- Ada 40 mg SC Q2W
- Tofa 5 mg BID
- Tofa 10 mg BID
- Tofa 5 mg BID
- Tofa 10 mg BID

a. The investigator had the option to increase the dose to tofacitinib 10 mg BID in those subjects who were receiving tofacitinib 5 mg BID and, in the investigator’s opinion, had PsA symptoms that are not adequately controlled. Changes in the dose were only permitted at scheduled study visits, unless a reduction to tofacitinib 5 mg BID was required due to safety abnormalities.
PsA Program Structure

TNFi-Naïve (Study 1091)
- Placebo
- Placebo
- Tofa 5 mg BID
- Tofa 10 mg BID
- Ada 40 mg SC Q2W

TNFi-IR (Study 1125)
- Tofa 5 mg BID
- Tofa 10 mg BID
- Placebo
- Placebo

LTE (Study 1092)
- Tofa 5 mg BID
- Tofa 10 mg BID
- Ada 40 mg SC Q2W

+ Tofa 5 mg BID
+ Tofa 10 mg BID
+ Placebo

a. The investigator had the option to increase the dose to tofacitinib 10 mg BID in those subjects who were receiving tofacitinib 5 mg BID and, in the investigator's opinion, had PsA symptoms that are not adequately controlled. Changes in the dose were only permitted at scheduled study visits, unless a reduction to tofacitinib 5 mg BID was required due to safety abnormalities.
## Discontinuations During the 3 Month Placebo-Controlled Period (Pooled Data)

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=236 n (%)</th>
<th>Tofa 5 mg BID N=238 n (%)</th>
<th>Tofa 10 mg BID N=236 n (%)</th>
<th>Ada 40 mg SC Q2W (Study 1091 Only) N=106 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuations (any reason)</td>
<td>20 (8.5)</td>
<td>11 (4.6)</td>
<td>11 (4.7)</td>
<td>4 (3.8)</td>
</tr>
<tr>
<td>Subjects died</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adverse event</td>
<td>6 (2.5)</td>
<td>5 (2.1)</td>
<td>4 (1.7)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Insufficient clinical response</td>
<td>4 (1.7)</td>
<td>1 (0.4)</td>
<td>2 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Subject no longer willing to participate in study</td>
<td>6 (2.5)</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (1.7)</td>
<td>3 (1.3)</td>
<td>3 (1.3)</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

**Author:** Daniela Graham

**Source:** Table 11

**Reviewed:**

**Ready for QC:**

**Date:** 28 Jul 17

**QC Complete:** 01 Aug 2017
### Discontinuations During the 3 Month Placebo-Controlled Period (Pooled Data)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Placebo N=236 n (%)</th>
<th>Tofa 5 mg BID N=238 n (%)</th>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adverse event</td>
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<td>1 (0.9)</td>
</tr>
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<td>3 (1.3)</td>
<td>3 (1.3)</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

Author: Daniela Graham
Source: Table 11

Not All PsA, only Pooled Data

Reviewed
Ready for QC
In QC
Date: 28JUL17
QC Complete: 01 Aug 2017
### Discontinuations During the 3 Month Placebo-Controlled Period (Pooled Data)

<table>
<thead>
<tr>
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<td>0</td>
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<tr>
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<td>3 (1.3)</td>
<td>3 (1.3)</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>
Summary of Adverse Events in the 3 Month Placebo-Controlled Period (Pooled Data)

Most frequent AEs
- Nasopharyngitis
- Upper respiratory tract infections
- Headache

Most frequent SAEs were infections

AE=Adverse Event; SAE=Serious Adverse Event
Incidence Rate of SAEs Similar Between Tofacitinib Doses and Adalimumab

Up to 12 Month Dose Comparison (Pooled Data)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>N</th>
<th>n</th>
<th>PY of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Tofa 5 mg BID</td>
<td>347</td>
<td>15</td>
<td>198.1</td>
</tr>
<tr>
<td>All Tofa 10 mg BID</td>
<td>344</td>
<td>15</td>
<td>193.4</td>
</tr>
</tbody>
</table>

TNFi-Naïve (Study 1091) (12 Month Data)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>N</th>
<th>n</th>
<th>PY of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Tofa 5 mg BID</td>
<td>159</td>
<td>11</td>
<td>124.8</td>
</tr>
<tr>
<td>All Tofa 10 mg BID</td>
<td>154</td>
<td>7</td>
<td>122.2</td>
</tr>
<tr>
<td>Ada 40 mg SC Q2W</td>
<td>106</td>
<td>9</td>
<td>89.5</td>
</tr>
</tbody>
</table>
# Deaths in Patients Participating in the PsA Studies (All PsA, Pooled Data)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Dose at Time of Death</th>
<th>Randomized Sequence</th>
<th>Gender/Race/Age</th>
<th>Country</th>
<th>Days on Tofa^a</th>
<th>Medical History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden Cardiac Death</td>
<td>Tofa 5 mg BID</td>
<td>Placebo-Tofa 5 mg BID</td>
<td>Female/White/73</td>
<td>Poland</td>
<td>56</td>
<td>• Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Overweight</td>
</tr>
<tr>
<td>Acute Cardiac Failure</td>
<td>Tofa 10 mg BID</td>
<td>Placebo-Tofa 5 mg BID</td>
<td>Female/White/57</td>
<td>UK</td>
<td>273</td>
<td>• Hypertension</td>
</tr>
<tr>
<td>(secondary to hypertensive heart disease)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Hypercholesterolemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Recent elective surgery</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>Tofa 5 mg BID</td>
<td>Tofa 5 mg BID</td>
<td>Female/White/46</td>
<td>UK</td>
<td>346</td>
<td>• Obesity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Normal platelets and INR</td>
</tr>
<tr>
<td>Pancreatic Carcinoma Metastatic</td>
<td>Tofa 5 mg BID</td>
<td>Ada 40 mg SC Q2W</td>
<td>Male/White/54</td>
<td>Poland</td>
<td>84</td>
<td>• Smoker</td>
</tr>
</tbody>
</table>

- No deaths were related to study drug, per the investigators’ assessment

INR=International Normalized Ratio
Adverse Events of Special Interest

- Serious Infections
- Herpes Zoster
- Opportunistic Infections
- Major Adverse Cardiovascular Events
- Malignancies
- Gastrointestinal (GI) Perforations
- Hepatic Events
- Interstitial Lung Disease
External Comparison Cohort For Risk Contextualization: Truven MarketScan Claims Database

- Observational database comprised of US medical claims

- Cohort of PsA patients in a real-world clinical setting
  - Defined as ≥1 inpatient or ≥2 outpatient diagnosis codes of PsA
  - Moderate-severe disease
  - Exclusion criteria from the tofacitinib global Phase 3 PsA studies applied
  - Included 5799 patients

- Comparison with Phase 3 trial data should be made with consideration of the differences between the two distinct data sources
Serious Infections and Incidence Rate Similar to Adalimumab

- Serious infections were pneumonia, oral candidiasis, influenza, pyelonephritis, parotitis, herpes simplex/pyoderma streptococcal
- All resolved after treatment
Serious Infections Incidence Rate in PsA Similar to Other Tofacitinib RCT Programs

Incidence Rate/100 PY (95% CI)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Tofacitinib 5 mg BID</th>
<th>Tofacitinib 10 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis (Up to 12 Months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid Arthritis (Up to 24 Months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psoriatic Arthritis (Up to 12 Months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PsA Truvena Any bDMARDs</td>
<td>2.24</td>
<td>1.30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>1217</th>
<th>1589</th>
<th>238</th>
<th>5075</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>11</td>
<td>48</td>
<td>2</td>
<td>58</td>
</tr>
<tr>
<td>PY of Exposure</td>
<td>800.8</td>
<td>1733.8</td>
<td>154.1</td>
<td>2589.5</td>
</tr>
</tbody>
</table>

a. Hospitalizations only

RCT=Randomized Controlled Trial
Herpes Zoster Incidence Rate Similar Between Tofacitinib Doses

One case was a multidermatomal HZ and was considered an opportunistic infection

HZ=Herpes Zoster

N

347

344

159

154

106

n

3

4

2

2

0

PY of Exposure

199.6

196.4

126.0

124.5

92.6

Incidence Rate/100 PY (95% CI)
Herpes Zoster Incidence Rate in PsA Similar to Those in Other Tofacitinib RCT Programs

<table>
<thead>
<tr>
<th></th>
<th>Psoriasis (Up to 12 Months)</th>
<th>Rheumatoid Arthritis (Up to 24 Months)</th>
<th>Psoriatic Arthritis (Up to 12 Months)</th>
<th>PsA Truven Any bDMARDs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>1217</td>
<td>1589</td>
<td>238</td>
<td>5075</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>8</td>
<td>57</td>
<td>3</td>
<td>42</td>
</tr>
<tr>
<td><strong>PY of Exposure</strong></td>
<td>800.8</td>
<td>1702.7</td>
<td>152.7</td>
<td>3343.0</td>
</tr>
</tbody>
</table>

Incidence Rate/100 PY (95% CI)

- Psoriasis (Up to 12 Months) Tofa 5 mg BID: 1.00
- Rheumatoid Arthritis (Up to 24 Months) Tofa 5 mg BID: 3.35
- Psoriatic Arthritis (Up to 12 Months) Tofa 5 mg BID: 1.96
- PsA Truven Any bDMARDs: 1.26
Incidence of Major Adverse Cardiovascular Events (All PsA, Pooled Data)

- Major Adverse Cardiovascular Events (MACE)
  - MACE is a composite CV endpoint comprised of cardiovascular deaths and non-fatal CV events of myocardial infarction and cerebrovascular events

- 3 cases of MACE
  - Sudden cardiac death
  - Non-fatal MI
  - Non-fatal ischemic stroke

CV=Cardiovascular; MI=Myocardial Infarction
MACE Incidence Rate in PsA is Similar to Other Tofacitinib Long Term Study Data

- **Psoriasis (All PsO)**
  - All Tofa Doses
  - Incidence Rate/100 PY (95% CI): 0.24

- **Rheumatoid Arthritis (All RA)**
  - All Tofa Doses
  - Incidence Rate/100 PY (95% CI): 0.38

- **Psoriatic Arthritis (All PsA)**
  - All Tofa Doses
  - Incidence Rate/100 PY (95% CI): 0.38

- **Truven Any bDMARDs (PsA)**
  - Incidence Rate/100 PY (95% CI): 0.38

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
<th>n</th>
<th>PY of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis (All PsO)</td>
<td>3662</td>
<td>21</td>
<td>8759.3</td>
</tr>
<tr>
<td>Rheumatoid Arthritis (All RA)</td>
<td>5856</td>
<td>80</td>
<td>21,285.9</td>
</tr>
<tr>
<td>Psoriatic Arthritis (All PsA)</td>
<td>783</td>
<td>3</td>
<td>790.5</td>
</tr>
<tr>
<td>Truven Any bDMARDs (PsA)</td>
<td>5057</td>
<td>17</td>
<td>4467.8</td>
</tr>
</tbody>
</table>
Incidence Rates for MACE Risk Over Time (All PsA and PsO Pooled, and RA)

Confidence intervals for PsA data are not shown.
# Malignancies Excluding NMSC
(All PsA, Pooled Data)

<table>
<thead>
<tr>
<th>Malignancy Type</th>
<th>Randomization Sequence</th>
<th>LTE</th>
<th>Dose at Time of Onset</th>
<th>Gender/Race/Age&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Country</th>
<th>Days on Tofacitinib</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urothelial carcinoma</td>
<td>Tofa 5 mg BID</td>
<td>No</td>
<td>Tofa 5 mg BID</td>
<td>Male/White/58</td>
<td>Poland</td>
<td>48</td>
<td>Hematuria at baseline</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>Ada 40 mg SC Q2W</td>
<td>Yes</td>
<td>Tofa 5 mg BID</td>
<td>Male/Other/44</td>
<td>Mexico</td>
<td>32</td>
<td>Smoker</td>
</tr>
<tr>
<td>Pancreatic duct adenocarcinoma</td>
<td>Ada 40 mg SC Q2W</td>
<td>Yes</td>
<td>Tofa 5 mg BID</td>
<td>Male/White/52</td>
<td>Poland</td>
<td>84</td>
<td>Smoker</td>
</tr>
<tr>
<td>Squamous cell carcinoma of the vulva</td>
<td>Tofa 5 mg BID</td>
<td>No</td>
<td>Tofa 5 mg BID</td>
<td>Female/White/65</td>
<td>Mexico</td>
<td>65</td>
<td>Abnormal urinalysis since Study Day 11</td>
</tr>
<tr>
<td>Breast ductal carcinoma</td>
<td>Tofa 5 mg BID</td>
<td>No</td>
<td>Tofa 5 mg BID</td>
<td>Female/White/67</td>
<td>USA</td>
<td>244</td>
<td>Postmenopausal, Biopsy: ER (+), PgR (+), HER2 (-), Stage II</td>
</tr>
</tbody>
</table>

<sup>a</sup> Age at screening

ER=Estrogen Receptors; HER2=Human Epidermal growth factor Receptor 2; NMSC=Non-Melanoma Skin Cancer; PgR=Progesterone Receptor
Malignancies (Excl. NMSC) Incidence Rate in PsA within Range of Those Reported in Other Tofacitinib Long Term Study Data

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence Rate/100 PY (95% CI)</th>
<th>N</th>
<th>n</th>
<th>PY of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis (All PsO)</td>
<td>1.00</td>
<td>3623</td>
<td>52</td>
<td>5203.6</td>
</tr>
<tr>
<td>Rheumatoid Arthritis (All RA)</td>
<td>0.75</td>
<td>6300</td>
<td>168</td>
<td>22,353.7</td>
</tr>
<tr>
<td>Psoriatic Arthritis (All PsA)</td>
<td>0.63</td>
<td>783</td>
<td>5</td>
<td>790.5</td>
</tr>
<tr>
<td>Truven Any bDMARDs (PsA)</td>
<td>0.51</td>
<td>5075</td>
<td>28</td>
<td>5499.1</td>
</tr>
</tbody>
</table>

Excl.=Excluding

MA-78
Incidence Rate (95% CI) Rate of Malignancies (Excl. NMSC) Over Time (All PsA and PsO Pooled, and RA)

Confidence intervals for PsA data are not shown
Incidence of Non-Melanoma Skin Cancer (All PsA, Pooled Data)

- Basal cell carcinoma (n=2)
- Squamous cell carcinoma (n=2)
- All cases occurred in sun exposed areas of fair skinned individuals
NMSC Incidence Rate in PsA are within Range of Those Reported in Other Programs (All PsA, Pooled Data)

<table>
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<th>N</th>
<th>n</th>
<th>PY of Exposure</th>
</tr>
</thead>
<tbody>
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<td>51</td>
<td>8689.7</td>
</tr>
<tr>
<td>Rheumatoid Arthritis (All RA)</td>
<td>6300</td>
<td>121</td>
<td>22,131.5</td>
</tr>
<tr>
<td>Psoriatic Arthritis (All PsA)</td>
<td>783</td>
<td>4</td>
<td>789.2</td>
</tr>
<tr>
<td>Truven Any bDMARDs (PsA)</td>
<td>5075</td>
<td>76</td>
<td>5447.8</td>
</tr>
</tbody>
</table>
Laboratory Parameters Showed Similar Trends to Those Observed in Other Programs

- Modest dose dependent decreases in neutrophils and hemoglobin
  - Absolute neutrophil counts were not associated with an increased incidence of infections
- Modest decreases in the absolute lymphocyte counts in the long term extension study
- Modest dose dependent increases in high density lipoprotein (HDL) and low density lipoprotein (LDL)
- Transaminase changes
  - Liver transaminase elevations $>3X$ ULN were infrequent and not dose-dependent
  - One patient had $\geq 5X$ ULN elevation of ALT
  - No patients with $\geq 10X$ ULN
- Modest dose dependent increases in serum creatinine

ALT=Alanine Aminotransferase

Reviewed Ready for QC

Date 28JUL17

QC Complete 2 Aug 2017
Other AEs of Special Interest (All PsA, Pooled Data)

- Gastrointestinal perforations
  - 1 event of appendicitis with perforation
- Interstitial lung disease
  - No events
- Tuberculosis
  - No events
- Hepatic events
  - No events of hepatic failure, fibrosis or cirrhosis
  - No subjects met Hy’s Law criteria
Overarching Safety Conclusions

- Safety profile of tofacitinib is well characterized, stable and manageable
Overarching Safety Conclusions

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- No new signals have been identified in the PsA program
Overarching Safety Conclusions

- Safety profile of tofacitinib is well characterized, stable and manageable
- No new signals have been identified in the PsA program
- Rates of adverse events of special interest in the PsA program are similar to those observed in biologic DMARDs (except herpes zoster)
Overarching Safety Conclusions

- Safety profile of tofacitinib is well characterized, stable and manageable.
- No new signals have been identified in the PsA program.
- Rates of adverse events of special interest in the PsA program are similar to those observed in biologic DMARDs (except herpes zoster).
- Safety profile in the PsA program is consistent with those observed in the RA and PsO safety databases.
## Overview of Presentation

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
</table>
| **Introduction**                                | Nancy McKay  
Director, Regulatory Affairs  
Pfizer Inc                                         |
| **Psoriatic Arthritis: A Physician’s Perspective/Unmet Medical Need** | Philip Mease, MD, MACR  
Director, Rheumatology Research, Swedish-Providence-St.  
Joseph Health Systems  
Clinical Professor, University of Washington School of Medicine, Seattle, WA |
| **Tofacitinib PsA Development Program and Efficacy** | Keith Kanik, MD, FACR  
Senior Director, Global Clinical Lead PsA  
Inflammation and Immunology  
Pfizer Inc |
| **Tofacitinib PsA Safety**                       | Daniela Graham, MD  
Clinician, PsA Development Program  
Inflammation and Immunology  
Pfizer Inc |
| **Risk Management**                             | Thomas Jones, MD  
Senior Director, Safety Risk Management  
Pfizer Inc |
| **Benefit:Risk and Conclusions**                | Michael Corbo, PhD  
Senior VP, Chief Development Officer  
Inflammation and Immunology  
Pfizer Inc |
Risk Management

Thomas Jones, MD
Senior Director, Safety Risk Management
Pfizer Inc
Effective Approach to Risk Management for Tofacitinib

- Risk Management
  - Risk Mitigation
  - Pharmacovigilance
    - Risk Assessment
    - Reporting
<table>
<thead>
<tr>
<th>Risks and Other Safety Information</th>
<th>Mitigation</th>
</tr>
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<tbody>
<tr>
<td>Serious infections including TB, viral reactivation</td>
<td>Risk mitigation through product labeling proposed for PsA same as for RA</td>
</tr>
<tr>
<td>Malignancy including LPD</td>
<td>Asian</td>
</tr>
<tr>
<td>NMSC</td>
<td>Asian</td>
</tr>
<tr>
<td>GI Perforations</td>
<td>Asian</td>
</tr>
<tr>
<td>Abnormal labs (lymphocytes, neutropenia, anemia, liver enzyme and lipid elevations)</td>
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</tr>
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</tr>
<tr>
<td>Drug-drug interactions (DDI), concomitant immunosuppressants</td>
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</tr>
<tr>
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</tr>
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LPD=Lympho-Proliferative Disorders; TB=Tuberculosis
### Risk Management for Tofacitinib in PsA: Building on Effective Approach in RA and Consistent Safety Profile

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<th>Pharmacovigilance: Assessment and Reporting</th>
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<tr>
<td>Serious infections including TB, viral reactivation</td>
<td></td>
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LPD=Lympho-Proliferative Disorders; TB=Tuberculosis
# Risk Management for Tofacitinib in PsA: Building on Effective Approach in RA and Consistent Safety Profile

## Risks and Other Safety Information

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Mitigation</th>
<th>Routine Monitoring/Reporting</th>
<th>Study 1092 PsA LTE Study</th>
<th>Indirectly via RA Studies</th>
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</thead>
<tbody>
<tr>
<td>Serious infections including TB, viral reactivation</td>
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<td>✓</td>
<td>✓</td>
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<td>✓</td>
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</tr>
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<td></td>
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<td>✓</td>
<td>✓</td>
<td>Pregnancy registry</td>
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</table>

**Mitigation:** Risk mitigation through product labeling proposed for PsA same as for RA

**Pharmacovigilance:**

- **Routine Monitoring/Reporting**: ✓
- **Study 1092 PsA LTE Study**: ✓
- **Indirectly via RA Studies**: ✓

---

LPD = Lympho-Proliferative Disorders; TB = Tuberculosis
Study 1133 Study Design

- Prospective, Randomized, Open-label, Blinded Endpoint Study (PROBE)
- Phase 3b/4 Event-driven trial (FDA PMR study)
- Co-primary endpoints: MACE and malignancies
- Population: Adults with rheumatoid arthritis
- 4372 subjects randomized

Randomization 1:1:1
- Tofacitinib 5 mg BID
- Tofacitinib 10 mg BID
- Adalimumab 40 mg SC Q2W or Etanercept 50 mg Weekly

MTX-IR – Moderate- Severe RA with CV Risk Factors
Screening

Endpoint Adjudication Committees
- CV, malignancy, hepatic, opportunistic infections, GI perforation, ILD
Effective Approach to Risk Management for Tofacitinib

Risk Management

Risk Mitigation

Pharmacovigilance

Risk Assessment

Reporting
# Overview of Presentation

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| Introduction                                               | Nancy McKay  
Director, Regulatory Affairs  
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A Physician’s Perspective/  
Unmet Medical Need                                            | Philip Mease, MD, MACR  
Director, Rheumatology Research, Swedish-Providence-St. Joseph Health Systems  
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| Benefit:Risk and Conclusions                              | Michael Corbo, PhD  
Senior VP, Chief Development Officer  
Inflammation and Immunology  
Pfizer Inc                                                   |
Benefit:Risk and Conclusions

Michael Corbo, PhD
Senior VP, Chief Development Officer
Inflammation and Immunology
Pfizer Inc
XELJANZ® (tofacitinib) for PsA
Proposed USPI: Indication and Dosage

Proposed Indication in sNDA
(1. INDICATIONS AND USAGE)

XELJANZ is indicated for the treatment of adult patients with active psoriatic arthritis

Proposed Dosage in sNDA
(2. DOSAGE AND ADMINISTRATION)

The recommended dose of XELJANZ is 5 mg twice daily used in combination with conventional synthetic DMARDs
Efficacy of Tofacitinib 5 mg BID at Month 3 Across Multiple PsA Manifestations

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Difference Tofacitinib 5 mg BID – Placebo % Responders (95% CI)</th>
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<tbody>
<tr>
<td>ACR20</td>
<td>● TNFi-IR (Study 1125) ▲ TNFi Naïve (Study 1091) Pooled</td>
</tr>
<tr>
<td>ACR50</td>
<td></td>
</tr>
<tr>
<td>ACR70</td>
<td></td>
</tr>
<tr>
<td>( \Delta HAQ-DI \geq 0.35 ) (MCID)(^a)</td>
<td></td>
</tr>
<tr>
<td>PASI75(^b)</td>
<td></td>
</tr>
<tr>
<td>Resolution of Enthesitis (LEI=0)(^c)</td>
<td></td>
</tr>
<tr>
<td>Resolution of Dactylitis (DSS=0)(^c)</td>
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- For patients with baseline HAQ-DI\(\geq 0.35\)
- For patients with baseline BSA\(\geq 3\)% and baseline PASI\(>0\)
- For patients with baseline value\(>0\)

\(\text{MCID}=\text{Minimal Clinically Important Difference}\)
Efficacy of Tofacitinib 5 mg BID at Month 3 Across Multiple PsA Manifestations

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a. For patients with baseline HAQ-DI≥0.35
b. For patients with baseline BSA≥3% and baseline PASI>0
c. For patients with baseline value>0

MCID=Minimal Clinically Important Difference
Efficacy of Tofacitinib 5 mg BID at Month 3 Across Multiple PsA Manifestations

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\(^{a}\) For patients with baseline HAQ-DI≥0.35  
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- For patients with baseline HAQ-DI≥0.35
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MCID=Minimal Clinically Important Difference

MA-102

Hernan is asking to add the individual study level data to pooled data to the forest plot portion of the graph (ie., 3 bars in the order of 1125, 1091 and pooled from the top to bottom for each endpoint) and add pooled response rates to the table on the left portion of the graph. Please remove the data columns on the right. In the revised plot, each endpoint will have 3 bars in the order of 1125, 1091, and pooled from the top to bottom. We should keep the study column with 3 values (1125, 1091, pooled).

TNFi Naïve (Study 1091)
TNFi IR (Study 1125)
Pooled

Author: Hernan Valdez
Source: 1125 and 1091: Table 14.2.1.1.2.1, 14.2.2.4.2, 14.2.2.6.2, 14.2.2.2.1 etc. See tables at right

Reviewed
- 28 July 2017
- 31 July 2017
- 01 Aug 2017
- 01 Aug 2017

Favors Placebo  Favors Tofacitinib
Efficacy of Tofacitinib 5 mg BID at Month 3 Across Multiple PsA Manifestations

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\(^a\) For patients with baseline HAQ-DI ≥0.35
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MCID = Minimal Clinically Important Difference

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Author: Hernan Valdez
Source: 1125 and 1091: Table 14.2.1.1.2.1, 14.2.2.4.2, 14.2.2.6.2, 14.2.2.2.1 etc. See tables at right.

Reviewed

Favors Placebo Favors Tofacitinib

QC Complete

01 Aug 2017

QC Complete

01 Aug 2017

28 July 2017

In QC

31 July 2017

In RE–QC

01 Aug 2017

In QC

01 Aug 2017

Ready for QC

01 Aug 2017

QC Complete

01 Aug 2017
Improvement in Health Related Quality of Life with Tofacitinib at Month 3

<table>
<thead>
<tr>
<th>SF-36v2 Physical Functioning Domain (MCID=3.5)</th>
<th>Difference Between Active Treatment and Placebo Response Rate (95% CI)</th>
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<tbody>
<tr>
<td>Active Treatment N</td>
<td>Placebo N</td>
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<tr>
<td>TNFi-IR (Study 1125)</td>
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<tr>
<td>120</td>
<td>117</td>
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<tr>
<td>TNFi Naïve (Study 1091)</td>
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<tr>
<td>103</td>
<td>102</td>
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<th>HAQ-DI (MCID=0.35)</th>
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</table>

<table>
<thead>
<tr>
<th>FACIT-F Total Score (MCID=4)</th>
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<tr>
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</table>

Data shown are patients achieving MCID
Comparison Between Tofacitinib 5 mg BID and Adalimumab in TNFi-Naïve Patients (Study 1091) Across Multiple PsA Disease Manifestations (Month 12)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Difference (95% CI)</th>
<th>Favors</th>
<th>Non-Progressors, ΔmTSS≤0.5</th>
<th>Favors</th>
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<tr>
<td>ACR20 Response Rate</td>
<td>-0.4</td>
<td>Ada 40 mg SC Q2W</td>
<td>Favors ADA 40 mg SC Q2W</td>
<td>Favors Tofa 5 mg BID</td>
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<tr>
<td>ACR50 Response Rate</td>
<td>-0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR70 Response Rate</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASI75 Response Rate</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For the responder (left) column, please use -30 to 30 as the range with tick marks by an increment of 10. For the right column, use tick marks by an increment of 1.
Risk Assessment
Foundation of Safety Database for Tofacitinib

Extent of Exposure in Tofacitinib Development Programs

- PsO 3662 patients and 8537 PY exposure
- RA 6300 patients and 21,886 PY exposure
  Up to 9 years of exposure

PsO and RA Clinical Trials

Reviewed
Ready for QC
In QC
28 July 2017
QC Complete
31 July 2017
Foundation of Safety Database for Tofacitinib

Extent of Exposure in Tofacitinib Development Programs and Marketed Drug

PsO and RA Clinical Trials

Corrona Registry: 1261 patients with 1478 PY of exposure
Up to 9 years of exposure

PsO 3662 patients and 8537 PY exposure
RA 6300 patients and 21,886 PY exposure

Real World Since 2012

Experience with >80,000 PY of exposure with marketed tofacitinib

MA-108
Overall Tofacitinib Safety Database

Exposure to Tofacitinib Supporting Safety in PsA

PsA Clinical Trials

PsO and RA Clinical Trials

Real World Since 2012

Corrona Registry: 1261 patients with 1478 PY of exposure

Experience with >80,000 PY of exposure with marketed tofacitinib

PsO 3662 patients and 8537 PY exposure

RA 6300 patients and 21,886 PY exposure
Up to 9 years of exposure

PsA Clinical Trials

783 patients 775 PY of exposure
Safety of Tofacitinib 5 mg BID in PsA

- **Infections**
  - All
  - Serious
  - Herpes zoster

- **Lab Changes**
  - Lipids (LDL and HDL)
  - Lymphocytes
  - Transaminase changes

- **Non-Melanoma Skin Cancer**

- **Potential Risks**
  - Malignancies excluding NMSC
  - MACE
Risks with Tofacitinib Treatment are Consistent Across Diseases

Serious Infections
Tofa 5 mg BID

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence Rate/100 PY (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PsO ≤12 Months</td>
<td>1.37 (1.00, 1.85)</td>
</tr>
<tr>
<td>RA ≤24 Months</td>
<td>2.77 (2.30, 3.35)</td>
</tr>
<tr>
<td>PsA ≤12 Months</td>
<td>1.30 (0.86, 1.90)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>N</th>
<th>n</th>
<th>PY of Exposure</th>
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<tbody>
<tr>
<td>PsO</td>
<td>1217</td>
<td>11</td>
<td>800.8</td>
</tr>
<tr>
<td>RA</td>
<td>1589</td>
<td>48</td>
<td>1733.8</td>
</tr>
<tr>
<td>PsA</td>
<td>238</td>
<td>2</td>
<td>154.1</td>
</tr>
</tbody>
</table>
Risks with Tofacitinib Treatment are Consistent Across Diseases

### Incidence Rate/100 PY (95% CI)

#### Serious Infections
- **Tofa 5 mg BID**
  - PsO ≤12 Months: 1.37
  - RA ≤24 Months: 2.77
  - PsA ≤12 Months: 1.30

#### Malignancies (Excl. NMSC)
- **All Tofa Doses**
  - PsO: 1.00
  - RA: 0.75
  - PsA: 0.63

#### MACE
- **All Tofa Doses**
  - PsO: 0.24
  - RA: 0.38
  - PsA: 0.38

### Summary

<table>
<thead>
<tr>
<th>Disease</th>
<th>PsO ≤12 Months</th>
<th>RA ≤24 Months</th>
<th>PsA ≤12 Months</th>
<th>PsO All PsO</th>
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<td>1217</td>
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<td>238</td>
<td>3623</td>
<td>6300</td>
<td>783</td>
<td>3662</td>
<td>5856</td>
<td>783</td>
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<tr>
<td><strong>n</strong></td>
<td>11</td>
<td>48</td>
<td>2</td>
<td>52</td>
<td>168</td>
<td>5</td>
<td>21</td>
<td>80</td>
<td>3</td>
</tr>
<tr>
<td><strong>PY of Exposure</strong></td>
<td>800.8</td>
<td>1733.8</td>
<td>154.1</td>
<td>5203.6</td>
<td>22,353.7</td>
<td>790.5</td>
<td>8759.3</td>
<td>21,285.9</td>
<td>790.5</td>
</tr>
</tbody>
</table>

*MA-112*
Scope and Effectiveness of Risk Management of Tofacitinib

- Overlapping risks with RA

- Proven signal detection/assessment/reporting

- Addition of PsA-specific measures including
  - Labeling
  - Long term safety assessment in clinical trial setting up to 4 years
    - More detailed understanding of long-term events in PsA
NNT/NNH for Tofacitinib 5 and 10 mg BID vs. Placebo at Month 3

**Number Needed to Treat (NNT)**

- ACR50: 6 (Tofa 5 mg vs Placebo), 7 (Tofa 10 mg vs Placebo)
- Enthesitis Absence (LEI=0): 6 (Tofa 5 mg vs Placebo), 7 (Tofa 10 mg vs Placebo)
- Dactylitis Absence (DSS=0): 8 (Tofa 5 mg vs Placebo), 4 (Tofa 10 mg vs Placebo)
- PASI75: 6 (Tofa 5 mg vs Placebo), 3 (Tofa 10 mg vs Placebo)
- FACIT-F Total Score (MCID=4.0): 8 (Tofa 5 mg vs Placebo), 10 (Tofa 10 mg vs Placebo)

**Number Needed to Harm (NNH)**

- Serious Infections: 511 (Tofa 5 mg vs Placebo), 320 (Tofa 10 mg vs Placebo)
- Herpes Zoster: 110 (Tofa 5 mg vs Placebo), 256 (Tofa 10 mg vs Placebo)

NNT (efficacy)/NNH (safety) is defined as the inverse of the proportion difference between active treatment group and placebo adjusting for study effect in PsA trials (NNT) or adjusting for RA, PsO and PsA indications (NNH) using Cochran-Mantel-Haenszel weighted approach.
Tofacitinib: Favorable Benefit:Risk in the Treatment of PsA Patients

Benefits

Clinical effect across key manifestations
Tofacitinib: Favorable Benefit:Risk in the Treatment of PsA Patients

<table>
<thead>
<tr>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical effect across key manifestations</td>
</tr>
<tr>
<td>Efficacy in csDMARD IR and anti-TNF IR</td>
</tr>
</tbody>
</table>
## Tofacitinib: Favorable Benefit:Risk in the Treatment of PsA Patients

### Benefits

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</tr>
</tbody>
</table>

**PRO=Patient Reported Outcome**

**MA-117**

**Reviewed:**

- Ready for QC: 28 July 2017
- QC Complete: 31 July 2017
# Tofacitinib: Favorable Benefit:Risk in the Treatment of PsA Patients

## Benefits

- Clinical effect across key manifestations
- Efficacy in csDMARD IR and anti-TNF IR
- Effects demonstrated as early as 2 weeks
- Intracellular mechanism of action
- Oral, small molecule without anti-drug antibody formation

PRO=Patient Reported Outcome
# Tofacitinib: Favorable Benefit:Risk in the Treatment of PsA Patients

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PRO—Patient Reported Outcome
Tofacitinib: Favorable Benefit:Risk in the Treatment of PsA Patients

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Risks

- Consistent with RA safety profile
- Addressed through established Risk Management
- Further informed by long-term studies

Examples of events include infections, herpes zoster, NMSC and malignancies (excluding NMSC)

PRO=Patient Reported Outcome
Backup Slides Shown
Baseline Methotrexate Dose in TNFi-Naïve Patient Population (Study 1091)

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=92</th>
<th>Tofa 5 mg BID N=92</th>
<th>Tofa 10 mg BID N=92</th>
<th>Ada 40 mg SC Q2W N=79</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>15.5 (4.12)</td>
<td>16.4 (3.79)</td>
<td>16.8 (11.7)</td>
<td>15.8 (4.44)</td>
</tr>
<tr>
<td>Median (Range)</td>
<td>15.0 (5-20)</td>
<td>15.0 (10-25)</td>
<td>15.0 (5-105)</td>
<td>15.0 (5-25)</td>
</tr>
<tr>
<td>Baseline MTX dose, mg/week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dose of MTX 105 mg/week is data error
Immune Response to LZV in Zoster Vaccine Study 1237 in RA Patients

- RA patients starting Tofacitinib 5 mg BID had similar VZV-specific humoral and cell-mediated immune responses to LZV as compared to placebo-treated patients

<table>
<thead>
<tr>
<th>Immunogenicity assessment</th>
<th>Study 1237</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change in VZV IgG at week 6</strong> (IgG fold-rise)</td>
<td>Tofa 5 mg BID</td>
</tr>
<tr>
<td></td>
<td>2.11 fold rise</td>
</tr>
<tr>
<td></td>
<td>80% CI=(1.87, 2.37)</td>
</tr>
<tr>
<td><strong>Absolute Value of VZV IgG titer at week 6</strong> (ELISA Units/mL)</td>
<td>Baseline: 201</td>
</tr>
<tr>
<td></td>
<td>Week 6: 403</td>
</tr>
<tr>
<td><strong>Change in VZV ELISPOT at week 6</strong> (SFC fold-rise) (SFCs/10^6 PBMCs)</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>80% CI=(1.31, 1.70)</td>
</tr>
<tr>
<td><strong>Absolute Value of VZV SFCs/10^6 PBMCs</strong></td>
<td>Baseline: 48</td>
</tr>
<tr>
<td></td>
<td>Week 6: 70</td>
</tr>
</tbody>
</table>

ELISA=Enzyme-Linked Immunosorbent Assay; ELISPOT=Enzyme-Linked ImmunoSpot; LZV=Live Zoster Vaccine; PBMC=Peripheral Blood Mononuclear Cell; SFC=Spot Forming Cells; VZV=Varicella Zoster Virus