XELJANZ® (TOFACITINIB CITRATE) FOR THE TREATMENT OF PSORIATIC ARTHRITIS

Food and Drug Administration Advisory Committee Meeting

BRIEFING DOCUMENT

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations	Definitions
ACR	American College of Rheumatology
ACR20	American College of Rheumatology criteria ≥20% improvement
ACR50	American College of Rheumatology criteria ≥50% improvement
ACR70	American College of Rheumatology criteria ≥70% improvement
ADA	Adalimumab
AE	Adverse event
AEDC	Adverse event leading to discontinuation
ALC	Absolute lymphocyte count
ANC	Absolute neutrophil count
AR	autoregressive
AS	Ankylosing Spondylitis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BCC	Basal cell carcinoma
bDMARD	Biologic disease-modifying anti-rheumatic drug
BE	Bioequivalence
BID	Twice daily
BMI	Body mass index
BSA	Body surface area
CASPAR	ClASsification criteria for Psoriatic ARthritis
CI	Confidence interval
CK	Creatine kinase
CMH	Cochran–Mantel–Haenszel
Corrona	Consortium of Rheumatology Researchers of North America
CP-690,550	Tofacitinib
CRP	C-reactive protein
CS	Corticosteroids
CSA	Cyclosporin A
csDMARD	Conventional synthetic disease-modifying anti-rheumatic drug
CSF	Colony-stimulating factor
CSR	Clinical study report
CV	Cardiovascular
CYP	Cytochrome P450
Δ	Change from baseline
DDIs	Drug-drug interactions
DMARD	Disease-modifying anti-rheumatic drug
DSS	Dactylitis Severity Score
EPO	Erythropoietin
E-R	Exposure-response
F	Absolute bioavailability
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDA DDDP	Food and Drug Administration Division of Dermatology and Dental Products
GI	Gastrointestinal
GM-CSF	Granulocyte macrophage colony-stimulating factor
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	Health Assessment Questionnaire – Disability Index
Hgb	hemoglobin
HIV	Human Immunodeficiency Virus
HZ	Herpes zoster
IA	Intra-articular
IFN	Interferon

Abbreviations	Definitions
Ig	Immunoglobulin
IL	Interleukin
IR	Inadequate response
JAK	Janus kinase
JSN	Joint space narrowing
JTR	jump to reference
LEF	Leflunomide
LEI	Leeds Enthesitis Index
LS	least squares
LSLV	last subject/last visit
LTE	Long-term extension
MACE	Major Adverse Cardiovascular Events
MCID	Minimal Clinically Important Difference
MCS	Mental component summary score
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed model for repeated measures
MOA	Mechanism of action
MR = NR	Missing Response = Non-Response
MRI	Magnetic resonance imaging
mTSS	van der Heijde modified Total Sharp Score
MTX	Methotrexate
NA	Not available
NDA	New Drug Application
N1	Number of subjects evaluable at a visit of interest
NMSC	Non-melanoma skin cancer
OI	Opportunistic infection
PASDAS	Psoriasis Area and Severity Disease Activity Score
PASI	Psoriasis Area and Severity Index
PASI75	PASI 75% improvement from baseline
PASS	Post-authorization safety study
PBO	Placebo
PCS	Physical component summary
PDE4	Phosphodiesterase 4
PF	Physical Functioning domain
phototx	Phototherapy
PGA	Physician’s Global Assessment
PK	Pharmacokinetic
PsA	Psoriatic arthritis
PGA-PsO	Physician's Global Assessment of Psoriasis
PsO	Psoriasis
PT	Preferred Term
PYs	Patient years
q2w	Every 2 weeks
QD	Once daily
RA	Rheumatoid arthritis
RCT	Randomized clinical trial
ROA	Route of administration
SAE	Serious adverse event
SC	Subcutaneous
SCC	Squamous cell carcinoma
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SE	Standard error
SF-36v2	Short-Form-36 Health Survey version 2

Abbreviations	Definitions
SI(s)	Serious infection(s)
sNDA	Supplemental New Drug Application
SOC	System Organ Class
SpA	Spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SSZ	Sulfasalazine
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
Th17	T-helper phenotype
THIN	The Health Improvement Network
TNF	Tumor necrosis factor
TNFi	Tumor necrosis factor inhibitor
TNF-IR	Inadequate response to TNF
TNFi-IR	Inadequate response to TNFi
Tofa	Tofacitinib
TPO	Thrombopoietin
tsDMARD	Targeted synthetic disease-modifying antirheumatic drug
TyK2	Tyrosine kinase 2
UC	Ulcerative colitis
ULN	Upper limit of normal
US	United States
USPI	United States Package Insert
XR	Extended-release

1. EXECUTIVE SUMMARY

This Briefing Document is provided to the Agency in advance of the Advisory Committee meeting and supports the Xeljanz® (tofacitinib citrate, used interchangeably throughout) supplemental New Drug Application (sNDA) for the treatment of Psoriatic Arthritis (PsA) submitted on 22 February 2017. Tofacitinib was approved on 06 November 2012 in the United States (US New Drug Application [NDA] 203214) at a dose of 5 mg twice daily (BID) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate (MTX).

PsA is a distinct, chronic, progressive, inflammatory, musculoskeletal disease that manifests as a combination of peripheral joint inflammation and damage, enthesitis, dactylitis, spondylitis, and psoriatic skin and nail disease, leading to progressive disability and adverse effects on quality of life.[1]

For this sNDA, the tofacitinib PsA development program is based on 3 global studies, including 2 completed Phase 3 double-blind, placebo-controlled efficacy and safety randomized clinical trials (RCTs) investigating tofacitinib 5 mg BID and 10 mg BID (Study A3921125 and Study A3921091) and one ongoing Phase 3 open-label, long-term extension (LTE) study (Study A3921092). Study A3921091 had an active comparator arm. Populations studied separately include tumor necrosis factor inhibitor (TNFi)-naïve patients with an inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs; from here on TNFi-naive) (Study A3921091) and patients with a documented inadequate response to TNFi (TNFi-IR) (Study A3921125). In addition to tofacitinib, all patients in both studies needed to take a single csDMARD (e.g., MTX, leflunomide or sulfasalazine [SSZ]) as background therapy.

Overall observations of the efficacy and safety results from the tofacitinib PsA clinical development program include the following:

- Tofacitinib 5 mg BID met the primary endpoints (American College of Rheumatology criteria ≥20% [ACR20] response rates and change [Δ] from baseline in Health Assessment Questionnaire-Disability Index [HAQ-DI] at Month 3) in both RCTs, Study A3921091 and Study A3921125. Tofacitinib 5 mg BID was demonstrated to be an effective dose for the treatment of active PsA in both TNFi-naïve and TNFi-IR populations and across multiple PsA disease domains (peripheral arthritis, enthesitis, dactylitis, and psoriatic skin disease).
    - The efficacy of tofacitinib 5 mg BID was generally similar to adalimumab across multiple domains in a TNFi-naïve population (Study A3921091).
    - A comparison with published literature for ACR20/50/70 response rates also suggested that the magnitude of response seen with tofacitinib 5 mg BID was similar to that reported for TNFi treatment, in TNFi-naïve PsA patients (Study A3921091).

    - The efficacy of tofacitinib across multiple PsA domains was similar in the TNFi-naïve and TNFi-IR populations (Study A3921091 and Study A3921125).

- Overall safety observations from the tofacitinib PsA clinical development program include the following:

    - Most treatment-emergent adverse events (TEAEs) and TEAE by System Organ Class (SOC) and Preferred Term (PT) occurred in similar frequencies in both tofacitinib 5 mg BID and 10 mg BID treated subjects (Study A3921091 and Study A3921125), and in comparable frequency to those seen in adalimumab-treated subjects (Study A3921091). During the 3-month placebo-controlled cohort, discontinuations from all causes were more common in placebo compared to those in tofacitinib 5 and 10 mg BID. Discontinuations due to AEs were more common in the tofacitinib 10 mg BID compared to placebo. Temporary discontinuations due to adverse event (AE) were higher in the tofacitinib 10 mg BID compared to the 5 mg BID dose and placebo. Similar trends were identified in the 12-month dose comparison cohort.

    - There were 4 subjects who reported serious AEs (SAEs) in each of the tofacitinib 5 mg BID, 10 mg BID and placebo treatment groups, and 1 subject with an event reported for adalimumab during the 3 month placebo controlled period. The incidence rate for SAEs in subjects treated with tofacitinib 5 mg BID or 10 mg BID doses was similar both during the 3-month placebo-controlled and the 12-month dose comparison cohorts. Comparisons to adalimumab within the A3921091 study show a numerically higher rate for adalimumab compared to both the tofacitinib 5 mg BID and tofacitinib 10 mg BID. SAEs occurred in similar numbers in both tofacitinib doses, most commonly in the Infections and infestations SOC, followed by events in the Neoplasms benign, malignant and unspecified and General Disorders and Administration Site Conditions. SAE incidence rate for tofacitinib All PsA treated subjects with extended exposure for Tofacitinib All PsA Doses were within the range for both doses combined in 3 month and 12 month dose comparison groups. The SAE incidence rate for tofacitinib (Tofacitinib All PsA Doses) was 8.49 per 100 PY (95% confidence interval [CI]: 6.55, 10.82).

    - The safety risks are similar to those observed with TNFi with the exception of an increased risk of herpes zoster (HZ).

Evaluations of the supportive data from the integrated datasets for RA and psoriasis (PsO) are presented in this document as additional background and support the similarity across the program for the safe and effective use of tofacitinib 5 mg BID in the treatment of PsA. The longer exposures to tofacitinib in the RA and PsO programs provide context for the safety profile observed in PsA. This is especially useful for the assessment of certain safety events with long latency periods (such as malignancies).

- No new safety findings were identified in the PsA population compared to the tofacitinib RA, the PsO population, or additional exposure in the PsA population:

  - The RA program included 6,330 tofacitinib-treated subjects, with approximately 21,886 patient years (PYs) of exposure and up to 8 years of continuous exposure to tofacitinib.

  - The PsO program included 3,662 tofacitinib-treated subjects with approximately 8,537 PYs of exposure to tofacitinib and up to 6 years of continuous exposure to tofacitinib.

  - The Day 120 safety update for the PsA program includes the integrated safety data from the 2 completed Phase 3 studies (A3921091 and A3921125) and the incremental and cumulative safety data reported in the ongoing LTE study (A3921092) with an additional 474.94 PYs of exposure (as of 08 February 2017) bringing the total exposure to 1250.66 PY in the PsA program. No additional subjects were included in the updated dataset since the enrollment into the LTE was completed prior to the data snapshot date of 10 May 2016 for the initial submission. No new safety findings were identified since the initial tofacitinib PsA submission.

- The risks associated with tofacitinib treatment for PsA are the same as those seen in the RA program.

- These risks can be mitigated or managed via the existing measures that are already included in the US Package Insert (USPI).

The totality of the data supports the following conclusions:

- PsA is a complex, chronic, progressive, debilitating musculoskeletal disease with significant remaining medical need.

- Tofacitinib 5 mg BID in PsA is an oral targeted synthetic (ts)DMARD that has demonstrated efficacy consistent with bDMARDs for multiple domains in TNFi-naïve patients, and has also demonstrated similar efficacy in TNFi-IR PsA patients that addresses the unmet medical need in this patient population.

- The safety profile of tofacitinib is well characterized in PsA, consistent with the safety profile for RA, and clinically manageable. It is informed by a large and growing safety database, with consistency between 32,000 PY of clinical trial experience and 83,017 PY of post marketing surveillance.

- Based on the above, the benefit/risk of tofacitinib, when used as directed, is favorable in the treatment of PsA.

This Briefing Document supports the Xeljanz (tofacitinib citrate) sNDA for the treatment of PsA.

2. INTRODUCTION

This Briefing Document is provided to the Agency in advance of the Advisory Committee meeting and supports the Xeljanz (tofacitinib citrate) sNDA for the treatment of PsA submitted on 22 February 2017. The Advisory Committee meeting seeks to provide the Agency with an external assessment of the benefit/risk of using Xeljanz to treat adult patients with active PsA.

This document describes background information on the development history and rationale in support of the use of Xeljanz at a dose of 5 mg BID for the treatment of adult patients with active PsA, provides an overview of the special disease characteristics of PsA, and serves as a summary of the efficacy and safety data from the Xeljanz PsA program. The overview presented supports the use and overall benefit/risk of Xeljanz for adult patients with active PsA.

3. PREVALENCE AND CHARACTERISTICS OF PSORIATIC ARTHRITIS

PsA is a chronic progressive inflammatory musculoskeletal disease that may result in permanent joint damage and disability.[2,3] The disease manifestations can include a combination of peripheral joint inflammation and damage, enthesitis, dactylitis, spondylitis, and psoriatic skin and nail disease leading to progressive disability and adverse effects on quality of life.[1,2]

Epidemiology

PsA affects men and women equally with peak onset in adults between 30 to 50 years of age.[2] Prevalence estimates in the US range from 0.06% to 0.25%[3] and worldwide estimates can vary considerably from these estimates. The incidence of PsA ranges from 3.6 to 7.2 per 100,000 person-years.[3]

Psoriatic skin lesions precede the development of signs and symptoms of arthritis in 70% of patients. In 15% of PsA patients, skin and joint manifestations present simultaneously, and in the remaining 15% of patients, arthritis signs and symptoms occur first.

Pathogenesis

The pathogenesis of PsA is complex with multiple disease domains both overlapping and distinct from PsO or RA. In addition to progressive erosive arthritis which is also seen in RA, patients may also have pathologic bone formation, enthesitis, dactylitis, and psoriatic skin and nail disease.

The inflammatory environment differs across PsA domains: angiogenesis-related gene expression and interleukin (IL)-6 expression are upregulated in the synovium to a greater extent than in RA but are not increased in skin. Also, T-cell-derived inflammatory cytokines such as IL-1β, IL-2, interferon (IFN)-γ, and TNF-α are more dominant in the psoriatic synovium, while IL-17 genes are more upregulated in skin. IL-22 is implicated in keratinocyte activation and pathologic bone formation whereas IL-17 and IL-23 may be most prominent in skin and joints. IL-23 has been implicated as a key driver of enthesitis with inflammatory effects mediated through IL-17 and TNFi.[4,5]

Interventions which inhibit the effect of 1 or 2 cytokines, such as TNFi, anti-IL-23, anti-IL-17, and anti-IL-12/23 inhibitors, have shown efficacy in PsA using both ACR and PsO Area and Severity Index (PASI) measures of response[6]. Contrasting effect of these therapies across RA, PsO, and PsA further demonstrate that the pathogenic drivers of these diseases are distinct. For example anti-TNFi are efficacious in the treatment of RA, effective in treating PsA peripheral arthritis, and in slowing radiographic progression in both, but anti-TNFi are less effective on psoriatic skin lesions than other bDMARDs approved for treatment of PsO. In contrast anti- IL-17 therapies are not approved for RA, yet have efficacy on PsA peripheral arthritis and have superior efficacy to TNFi for the treatment of psoriatic skin lesions.[7] These observations further suggest differences in the pathogenesis of these diseases.

Clinical Evaluation and Diagnosis of PsA

For the purpose of clinical trials in PsA, the Classification criteria for PsA (CASPAR) Study Group developed, validated, and endorsed criteria for the classification of PsA.[8] These criteria provide a sensitivity and specificity of 0.914 and 0.987, respectively, to discriminate PsA from other rheumatic diseases. Table 1 presents an outline of the CASPAR criteria.[8]

Table 1. The CASPAR Criteria

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

1. Evidence of current psoriasis[a], a personal history of psoriasis[b], or a family history of psoriasis[c]
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 juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot

a. Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist. Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.
b. A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider.
c. A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report.
d. Dactylitis is defined as swelling of an entire digit.
Source: Clinical Overview, Table 1

Impact of PsA on Patients

The impact of PsA is significant and affected patients can experience functional impairment, reduced quality of life and long-term work disability.[9,10] Disease activity is an important factor in determining functional status and quality of life for patients. Clinical development programs, including this one, typically limit this heterogeneity by enrolling subjects with a minimal number of actively-involved peripheral joints required at baseline/screening.

Using the Physical Functioning domain (PF) and the Physical Component Summary (PCS) score of the Medical Outcomes Short-Form-36 Health Survey version 2 (SF-36v2), it was reported that subjects with PsA have considerably worse physical functioning and functional health status than the general population.[11,12,13] Individuals with PsA have similar or worse overall physical health than healthy men older than 75 years of age in the general population, and comparable to that reported by patients with other common chronic diseases[11] such as diabetes, heart disease, hypertension, kidney disease, liver disease, lung disease, osteoarthritis, and RA. Untreated or inadequately treated PsA is a significant health and socioeconomic burden for the individual patient and society.

Mortality and Morbidity Risks

PsA patients have an overall increased morbidity and decreased survival compared to the general public, mainly because of cardiovascular (CV) disease.[14,15] Epidemiologic studies report that in PsA patients associated comorbidities may occur more frequently than expected. Identifying these comorbidities may affect the management and treatment decisions to ensure an optimal clinical outcome for these patients.[16] Common comorbidities include an increased prevalence of obesity, insulin resistance, type 2 diabetes mellitus, osteoporosis, depression, anxiety, fatigue, kidney disease, hypertension, inflammatory bowel disease, and most importantly CV disease.[16] More than 50% of PsA patients have at least one comorbid condition[15] and approximately 40% of patients with PsA have 3 or more comorbid conditions, although the additional and independent effect of comorbidities on PsA patient reported health is more related to the type of comorbidity than the number of comorbidities.[17] These common comorbidities were included in and adequately represented in the patient population of the tofacitinib PsA development program.

Disease measures and available treatments

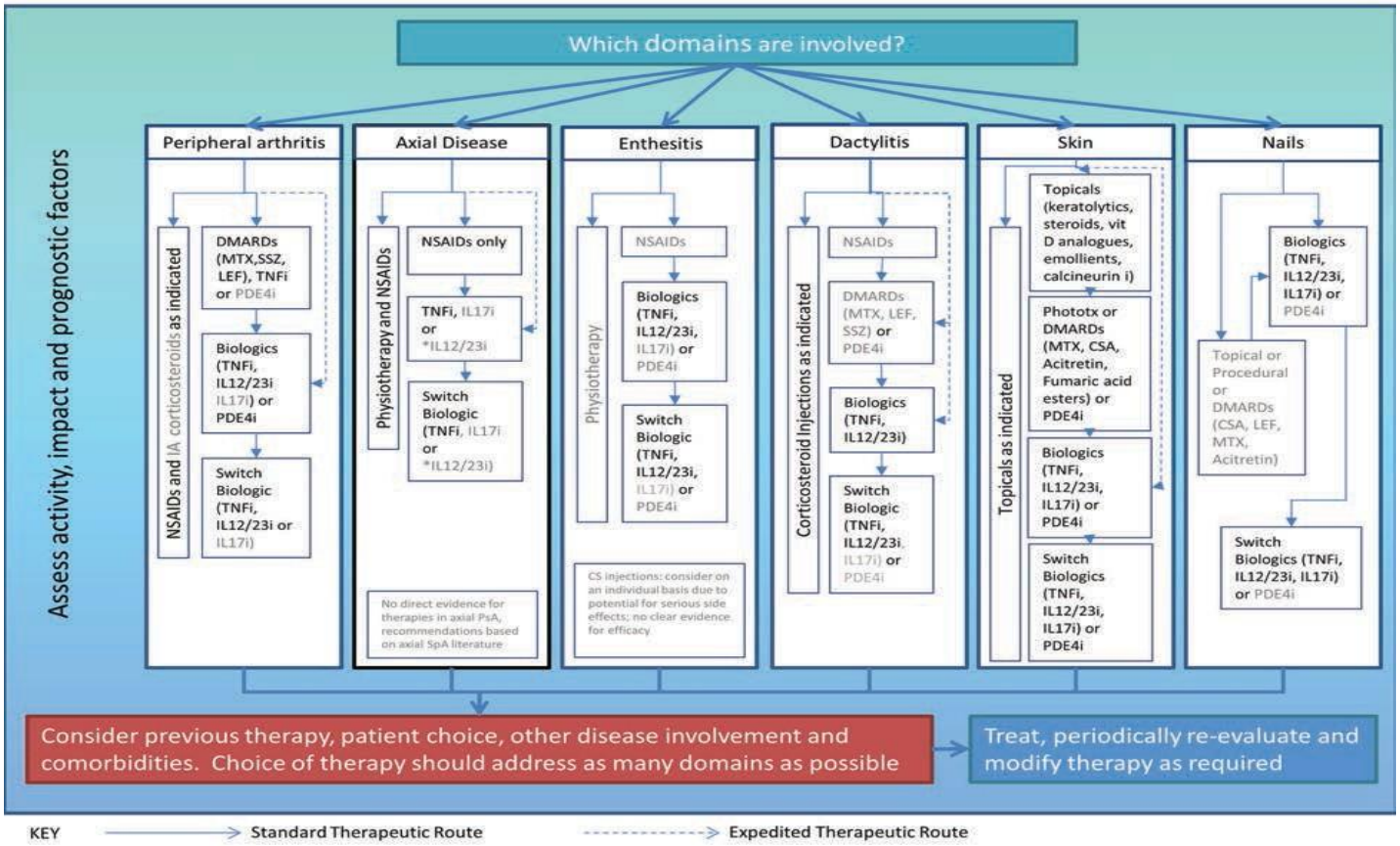
Despite the relative paucity of randomized controlled data in PsA trials supporting their efficacy and safety, and the lack of an approved indication for PsA treatment in the US, csDMARDs such as MTX are used for treatment of PsA. Their use can be limited by AEs including liver toxicity (MTX, leflunomide), hypersensitivity (leflunomide) and blood dyscrasias (SSZ and MTX),[18] and hypertension and nephrotoxicity (cyclosporine).[19,20,21]

The tsDMARD apremilast is a selective inhibitor of the enzyme phosphodiesterase 4 (PDE4) that was recently approved for the treatment of PsA. It has demonstrated modest efficacy on PsA signs and symptoms, evidenced by lack of statistical significance versus placebo for higher thresholds of efficacy for peripheral arthritis (eg, ACR50 and ACR70). Apremilast also has no PsA structural assessment data and its use can be limited by tolerability issues.

Currently 5 TNFis are approved by the US Food and Drug Administration (FDA) for use in PsA: infliximab, etanercept, adalimumab, golimumab, and certolizumab.[22] Within the last few years, additional bDMARDs have been approved for PsA including ustekinumab (a human mAb IL-12 and IL-23 antagonist) and secukinumab (a human mAb IL-17A antagonist). These biologic disease-modifying anti-rheumatic drug (bDMARD) therapies have demonstrated statistical significance versus placebo on ACR 20/50/70 responses as well as efficacy in other PsA domains.

Regarding the use of these various agents, therapeutic decision making should be based on the affected domain as per the 2016 Group for Research and Assessment of PsO and PsA (GRAPPA) guidance, although for patients suffering disease in multiple domains, treatment should be initiated with an intervention that has demonstrated efficacy in those domains that are involved.

Figure 1. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) Treatment Schema for Active PsA



Abbreviations: NSAIDs=nonsteroidal anti-inflammatory drugs; IA=intra-articular; DMARDs=disease-modifying anti-rheumatic drugs; MTX=methotrexate; SSZ=sulfasalazine; LEF=leflunomide; TNFi=tumor necrosis factor inhibitor; PDE-4i=phosphodiesterase 4 inhibitor (apremilast); IL-12/23i=interleukin-12/23 inhibitor; IL-17i= interleukin-17; SpA=spondyloarthritis; CS=corticosteroids; vit=vitamin; phototx=phototherapy; CSA=cyclosporin A.
Light text identifies conditional recommendations for drugs that do not currently have regulatory approvals or for which recommendations are based on abstract data only. Adapted: Coates et al, 2016.[47]

4. PRODUCT DEVELOPMENT HISTORY AND RATIONALE

4.1. Regulatory History

Xeljanz (tofacitinib citrate, ATC code: L04AA29), a selective inhibitor of the Janus kinase (JAK) family of kinases, is approved in the US at a dose of 5 mg BID (immediate-release tablets, approved on 06 November 2012), and at a dose of 11 mg once daily (QD) (extended-release [XR] tablets, approved on 23 February 2016) for the treatment of adult patients with active moderate to severe RA who have had an inadequate response or intolerance to MTX. It may be used as monotherapy or in combination with MTX or other non-biologic DMARDs. In addition to the approvals in the US, as of 28 March 2017, tofacitinib 5 mg immediate release tablets are approved in more than 52 countries, including US, Canada, European countries and Japan for the treatment of RA.

Pfizer has ongoing tofacitinib clinical studies in the RA population including Study A3921133, a post-marketing requirement at the time of the initial US approval of the immediate release formulation for RA. This study was designed to further inform the safety profile of tofacitinib, in collaboration with the Agency. The study is a prospective, randomized, open-label, blinded endpoint (PROBE) study of tofacitinib 5 mg BID versus tofacitinib 10 mg BID versus a TNFi in adult patients with active RA. The co-primary endpoints are major adverse cardiovascular events (MACE) and malignancies (excluding non-melanoma skin cancers [NMSC]).

The first subject was randomized in March 2014 and randomization was closed in January 2017 with 4,363 subjects randomized. The study is being conducted in approximately 30 countries. The exact timeline for study completion is based on the achievement of the pre-specified number of MACE, and the pre-specified number of malignancies (excluding NMSC) and 1500 subjects completing 3 years in the study. Based on statistical modeling, the expected last subject/last visit (LSLV) will be in 3Q2019 with a clinical summary report submitted to the Agency approximately 6 months after LSLV.

Due to the nature of the study, interim analysis of the data in this study has not been conducted and no data from this study is included in the RA RCT population, presented above.

Applications for tofacitinib were submitted in the US and in other countries for the treatment of moderate-to-severe chronic plaque PsO. In October 2015, the FDA Division of Dermatology and Dental Products (DDDP) provided Pfizer a Complete Response Letter noting that the submitted data “did not support marketing of tofacitinib for moderate to severe chronic plaque PsO at this time.” Pfizer subsequently submitted a request to withdraw the PsO sNDA in July 2016, without prejudice for future filing.

Several interactions occurred between Pfizer and the FDA that informed the design of the current PsA Phase 3 program.

End of Phase 2 PsA discussions focused on Phase 3 study designs as well as primary and secondary endpoints. A redesign of the program altered the geographic footprint for the study. The FDA agreed that, provided there are no unique safety signals in the PsA

population that require further characterization, 6-month efficacy and safety data in PsA, along with updated safety data from the RA population, would likely be adequate for the sNDA submission. For further information regarding regulatory interactions related to the tofacitinib PsA development program, please see Section 4.4.3.

4.2. Unmet Medical Need

As noted above, PsA is a complex, chronic, progressive, debilitating musculoskeletal disease with significant remaining medical need. There is a need for an oral medication which has a similar efficacy profile and a well-characterized safety profile relative to currently available TNFi, for PsA patients with active disease. Tofacitinib, if approved, would meet this unmet medical need.

A population-based multinational survey was conducted on 712 PsA patients to assess the impact of PsA on patients' activities of daily living and unmet medical needs. Only 41% of the PsA patients reported receiving any treatment. Of these, 31% received topical therapy only (which would not be effective for their musculoskeletal manifestations), 19% received conventional oral therapy, 14% received biologic therapy, and 8% the combination of oral and biologic therapy. Over 90% of patients with PsA felt there was a need for better therapies.[23]

Evidence of medical need for improvement of PsA treatment has been published in a cross-sectional study of 141 PsA outpatients in Norway fulfilling the CASPAR criteria and examined between January 2013 and May 2014. Musculoskeletal inflammatory involvement was more prominent than psoriatic skin involvement in these patients. The study showed that although the treatment options in PsA have been revolutionized in the last decade with the introduction of TNFis, still a substantial proportion of patients do not receive satisfactory results. Therefore, there is a continuing need for improvement of treatment in PsA patients who are not responding to currently available treatment options of PsA.[24]

4.2.1. Need for Additional Oral Medications in TNFi-naïve Patients

In contrast to RA, for which MTX, leflunomide, and other csDMARD agents are approved, there are no oral DMARDs approved for the treatment of PsA in the US other than apremilast. Recent GRAPPA guidelines concluded that PsA patients who have adverse prognostic risks factors (eg, multiple swollen or tender joints or elevated C-reactive protein [CRP]) are at high risk for structural progression. These patients should be treated promptly with interventions that are proven to be effective based upon available evidence.[25]

Choice of therapy should address as many active domains as possible: for example csDMARDs are not recommended for enthesitis or axial spondylitis. Per the 2016 guidelines, TNFi (which have proven efficacy in multiple PsA domains) are recommended as first line treatment for such patients. However, despite this proposed paradigm shift, TNFi-naïve patients may not be comfortable with the use of a parenterally administered treatment choice, and patient acceptability is also an important criterion for treatment selection per the same guidelines. Several studies in RA have assessed patients' preferences for oral versus parenteral modes of administration, which PsA patients may share. For instance, in a recent review of patient preference studies in rheumatology, the route of administration (ROA) of a

drug was found to be one of the most important factors in treatment decisions for people with moderate to severe RA.[26] Accumulating evidence suggests that when given a choice, many patients with RA prefer an oral therapy (tablet) over an injectable therapy.[27] Similarly, a recent Canadian study revealed significant preference for an oral therapy over a parenteral therapy in patients who had no previous experience with injected treatments.[28] These findings were confirmed in a large study spanning 8 European countries, which found that 83% of current RA patients prefer an oral therapy over an IV or injectable biologic.[29] In the same study, 79% of RA patients currently taking an IV or injectable biologic said they would prefer an oral therapy if one was available that had similar efficacy and safety to their current therapy.[29] The only approved oral option for PsA in the US is apremilast, which does not have efficacy comparable to a TNFi (eg, ACR50/70 not superior to placebo and no radiographic data by which to assess joint damage progression in PsA). There is therefore a need for an oral medication with similar efficacy (both in magnitude and domain coverage) to a TNFi for treatment naïve patients with adverse prognostic risk factors for joint damage, as well as to provide an oral option to those patients who have already had an inadequate response to csDMARD treatment.

4.2.2. Need for Treatment of Patients with an Inadequate Response to TNFi

Many patients with a chronic lifelong disease such as PsA will need additional effective treatment options when TNFi treatment is no longer adequate. PsA patients who have had an inadequate response to the TNFi class of drugs (either because of primary insufficient efficacy, a loss of efficacy after time, or due to a related AE) have limited treatment alternatives. There are PsA registry and observational data suggesting that efficacy, safety, and drug survival rates of a second TNFi agent are inferior to that reported from first time treatment with a TNFi.[30,31] An observational trial of PsA subjects in Sweden supports these conclusions. In this study, the Month 3 ACR20 response was achieved by 47% of first-time and 22% of second-time TNFi switchers; ACR50 rates were 21% and 14%, and ACR70 rates were 12% and 2%. Median drug survival time for patients in this study switching TNFi for the first time was 64 months (95% CI 31–97) compared with 14 months (95% CI 5–23) for second-time switchers.[32]

Additionally, the development of immunoglobulin (Ig) G/IgE anti-drug neutralizing antibodies against TNFi agents may decrease drug survival, increase the need for higher drug dosage, and increase the likelihood of AEs (eg, injection site reactions).[33] While concomitant administration of csDMARDs such as MTX or leflunomide may delay the development of neutralizing antibodies against TNFi, the addition of csDMARDs may also increase the risk of adverse effects.[33]

Currently approved non-TNFi bDMARD treatments (such as ustekinumab and secukinumab) demonstrate similar efficacy to TNFi on PsA musculoskeletal domains, along with superior efficacy on plaque PsO.[34] However, the majority of their study populations were TNFi-naïve, not TNFi-IR. The subset data on these agents suggest lower efficacy in TNFi-IR patients as compared to the rest of the study population. In addition, all of these bDMARDs require parenteral administration and their use may also be limited by the development of anti-drug neutralizing antibodies. The only other approved small molecule, apremilast, has

very limited data in TNFi-IR population, with ≤10% of its population having a history of TNFi therapeutic failures.[35]

4.2.3. Summary

No treatment currently approved in the US for the treatment of PsA will achieve successful, sustained, minimal disease activity in every patient. A substantial proportion of patients will either not respond initially or over time lose response to available treatments. Many patients may prefer oral medications over injectables. There is a need for an oral treatment with a novel mechanism of action (MOA) that has TNFi-like efficacy for multiple PsA domains that can be used to effectively treat TNFi-IR patients, and has an acceptable overall safety profile.

Tofacitinib addresses many of these unmet medical needs: it is an oral medication with a MOA that addresses many of the pathogenic mechanisms in PsA, and has robust and sustained efficacy in active PsA. It also has a well-established safety profile similar to the more than 32,000 PY experience in the tofacitinib RA and PsO development programs. Postmarketing exposure and other studies contribute to the overall experience with tofacitinib.

4.3. Rationale for the Mechanism of Tofacitinib as an Oral Treatment for Psoriatic Arthritis

Tofacitinib is a selective, reversible inhibitor of the JAK family. Tofacitinib inhibits JAK1, JAK2, JAK3 and to a lesser extent Tyrosine kinase 2 (TyK2). In a cellular setting where JAKs signal in combinations, tofacitinib preferentially inhibits cytokines which use JAK1 and/or JAK3 to signal.[36] The cytokines inhibited at clinical doses are known to have a role in multiple inflammatory diseases such as RA, PsA, ulcerative colitis (UC), ankylosing spondylitis (AS), and PsO. Cytokines implicated in PsA and their associated cell types are shown in Figure 2.

Figure 2. Cell Types in the Pathogenesis of Psoriatic Arthritis, Associated Effector Cytokines and JAKs Where Applicable

Cell type	Function / clinical signs and symptoms	Cytokines implicated in signaling	JAK pathways involved
CD4+ and CD8+ cells	Enthesitis Skin inflammation Synovitis	IFNγ, TNFα, IL-6, IL-7, IL-9, IL-17, IL-22, IL-26, IL-29	
Dendritic cells	T-cell activation	IFNγ, IL-12, IL-23	
Innate lymphoid cells	IL-17 expression	IFNγ, IL-7, IL-17	
Macrophages	Pruritus Swelling Joint damage	IFNγ, TNFα, IL-1, IL-2, IL-7, IL-18	
Neutrophils	New bone formation Hyperkeratosis Pustular psoriasis	TNFα, IL-17	Indirect effect[a]
Keratinocytes	Hyperkeratosis Systemic inflammation	IFNγ, TNFα, IL-12, IL-17, IL-19, IL-20, IL-22, IL-23, IL-24, IL-26, IL-29	
Synoviocytes	Synovial inflammation	IL-17	Indirect effect[a]
Osteoclasts	Bone resorption	IL-17	Indirect effect[a]
Osteoblasts	New bone formation	IL-17	Indirect effect[a]

Abbreviations: IL=interleukin; IFN=interferon; JAK= Janus-Kinase; TNF=tumor necrosis factor.
a: IL-17 production is indirectly inhibited through upstream inhibition of IL-23 signaling by JAK2/TYK2 blockade.
Adapted: O'Sullivan, L. A.; Liongue, C.; Lewis, R. S.; Stephenson, S. E.; Ward, A. C., Cytokine receptor signaling through the JAK-Stat-Socs pathway in disease. Mol Immunol 2007, 44 (10), 2497-506

Many of the cytokines that are associated specifically with the pathogenesis of PsA (eg, IL-7, IL-15, IFNα, IFN-γ, IL-20, IL-22 and to a lesser extent IL-23) are modulated directly or indirectly by JAK inhibition with tofacitinib. Furthermore, tofacitinib has been shown to directly suppress activation of keratinocytes by the IL-22/20 family of cytokines in PsO lesions, and at later time points IL-17 production in PsO lesions.[36,37,38,] Tofacitinib suppresses the production of IL-17 by T cells isolated from synovium and peripheral blood of RA patients and from PsA PBMCs.[39,40] Treatment with tofacitinib dosed at 5 mg BID for 52 weeks in RA patients significantly decreased the level of both IL-17 and IFN-γ produced by circulating T cells.[41] Tofacitinib does not inhibit RANKL signaling but does inhibit production from T-cells in preclinical models resulting in a decrease in osteoclastogenesis.[42]

As a result of its ability to block cytokine signaling by JAK inhibition, tofacitinib was predicted to have robust efficacy in the treatment of PsA. The results of the clinical studies presented in this summary document provide confirmation of the efficacy and safety of tofacitinib in PsA patients. Tofacitinib efficacy has also been demonstrated in RA as well as in comorbid diseases frequently seen in PsA such as plaque PsO, and UC. Additionally, a

single Phase 2 study suggested its efficacy in AS, a disease which is closely related to the spondylitis observed in PsA.[43,44,45]

4.3.1. Nonclinical Toxicology and Nonclinical/Clinical Mechanistic Studies Related to Tofacitinib

Collectively, nonclinical studies that evaluated the MOA in both RA and PsO models supported a rationale for the use of tofacitinib in the treatment of PsA. Further, the nonclinical pharmacokinetic (PK) and toxicology studies provide a thorough assessment of exposure and safety that supports the use of tofacitinib for the treatment of PsA.

4.3.2. Biopharmaceutics and Clinical Pharmacology

The tofacitinib biopharmaceutic clinical development program was comprised of 5 Phase 1 studies to characterize the absolute bioavailability (F) of tofacitinib, relative bioavailability/ bioequivalence (BE) of tablet formulations used in the clinical development program, and food effect. The results indicate that tofacitinib is well absorbed, has an F of 74%, the extent of absorption is similar to that of an oral solution and can be administered with or without food. More information on the metabolism of tofacitinib is presented in Section 7.6.

Exposure-response (E-R) analyses were conducted using pooled data from the 2 Phase 3 studies in PsA patients. The relationships between tofacitinib exposure and ACR response rates as well as between exposure and changes in hemoglobin (Hgb; a mechanistic marker of JAK2 inhibition by tofacitinib, which was previously identified as a useful biomarker to discriminate among doses, and which supported Phase 3 dose-selection in both RA and PsO programs) were evaluated in the PsA program. The results confirmed that the E-R relationships in PsA are consistent with those observed in RA.

4.4. Tofacitinib PsA Development Program

4.4.1. Phase 2 program

There was no Phase 2 program for tofacitinib in PsA. Appropriate doses for the Phase 3 studies were identified based on knowledge of the PK and pharmacodynamic properties of tofacitinib as characterized in RA and PsO patients.

4.4.2. Phase 3 Dose Selection Rationale

Pfizer proceeded directly to Phase 3 on the basis of robust dose-ranging studies conducted in both the RA and PsO Phase 2 programs, as well as the concept that tofacitinib would demonstrate efficacy via inhibition (directly or indirectly) of 1 or more key cytokines that are involved in PsA, RA and PsO. The PsA Phase 3 program evaluated the efficacy and safety of tofacitinib 5 mg BID and 10 mg BID doses, which were also studied in the RA and in the PsO Phase 3 development programs.

Dose selection in RA and PsO were based on modeling of extensive Phase 2 dose response data of those efficacy and safety outcomes that were thought to be most important. Efficacy responses such as ACR responses (RA) and PASI 75% improvement from baseline (PASI75) and Physician's Global Assessment (PGA) responses (PsO), as well as decrease in Hgb (a JAK2 mechanistic marker) and associated risk of anemia that was found to be useful to

discriminate between tofacitinib doses for safety (RA and PsO) were identified and selected for dose/E-R modeling. The probability of achieving a clinically meaningful target effect (PTE), where the target effect was defined in terms of a placebo-adjusted difference at a specific time point considered to be clinically meaningful, was utilized. Doses that were considered for Phase 3 were those that achieved a PTE of approximately 50% or higher on each endpoint. The 5 mg BID and 10 mg BID doses met the criteria (PTE of approximately 50% or higher on nearly all endpoints) for progression into Phase 3 for both RA and PsO. The internal consistency of these E-R relationships in both indications supported the selection of the same tofacitinib doses (5 and 10 mg BID) for the PsA program.

Following the completion of the PsA Phase 3 studies (Section 4.4.3), E-R analyses were conducted on the primary domain of peripheral arthritis for efficacy (ACR responses) and for changes in Hgb for safety. The results confirmed that E-R relationships in PsA are consistent with those observed in RA (E-R with ACR responses; E-R using changes in Hgb) and in PsO (E-R using changes in Hgb).

4.4.3. Phase 3 Studies in PsA

The design of the tofacitinib Phase 3 clinical trials generally aligns with current GRAPPA (see Figure 1) treatment recommendations summarized under Unmet Medical Need (Section 4.2 and Table 1), and the data generated from the Phase 3 studies in subjects with active PsA characterize the efficacy that can be expected when tofacitinib is administered at various points along the treatment continuum (ie, pre-TNFi to post-TNFi).

The studies compared the efficacy of tofacitinib 5 mg BID and 10 mg BID to that of placebo over 3 months for improvements in multiple PsA domains, examined the onset of efficacy, and assessed the persistence of efficacy of tofacitinib in csDMARD-IR/TNFi-naïve and TNFi-IR populations.

The Phase 3 study designs incorporated regulatory feedback received between 2010 to 2012; key elements of the most recent feedback from FDA (2012) included modification of Study A3921091 and Study A3921125 designs to require background csDMARD treatment in all patients and inclusion of radiographic assessments in Study A3921091. Reflecting prior regulatory advice, the placebo duration in Studies A3921091 and A3921125 was limited to 3 months to minimize pain and suffering and the possibility of progressive structural damage due to untreated inflammation while receiving placebo.

Study A3921091 included an active control, adalimumab 40 mg subcutaneous (SC) q2w, which at the time was, and remains, a standard of care treatment option. Adalimumab demonstrates efficacy in multiple PsA domains including inhibition of progression of structural damage, and was chosen to provide a direct comparison of treatment effects. A study duration of 12 months was considered sufficient, particularly in regard to assessing the inhibition of structural damage.

Study A3921125 was designed to specifically evaluate efficacy in the TNFi-IR population. There were no DMARDs with proven efficacy in a TNFi-IR population available at the time of study initiation to provide an active control. A study duration of 6 months was considered of sufficient duration to evaluate safety and efficacy in this more difficult-to-treat population.

Study A3921092 is an ongoing Phase 3, long term, open label extension study designed to evaluate the long-term (3 years) safety, tolerability and efficacy of tofacitinib in subjects with PsA who have previously participated in Studies A3921091 or A3921125.

Each of the RCTs was designed to establish the superiority of 2 doses (5 mg BID and 10 mg BID) of tofacitinib to placebo for the primary endpoints. All hypotheses were tested at the nominal alpha level of 5% (2-sided) using the step-down approach described below. The studies were sized to have sufficient power for comparisons between tofacitinib and placebo for the primary endpoints only.

In addition, the studies (Study A3921091 and A3921125) were designed to estimate the treatment difference for secondary comparisons including those between tofacitinib doses and between tofacitinib and adalimumab (Study A3921091) with reasonable precision. Study A3921091 was not designed for superiority or non-inferiority comparisons between tofacitinib and adalimumab.

4.4.4. Common Protocol and Analysis Criteria

4.4.4.1. Enrollment Criteria

The inclusion/exclusion criteria were similar for the 2 pivotal Studies A3921091 and A3921125. Multiple criteria were employed to facilitate inclusion of patients with active PsA and relevant comorbidities while excluding other related inflammatory arthritic diseases, such as RA with co-morbid PsO, as well as primary fibromyalgia. Patients were required to have a diagnosis of PsA and to meet CASPAR classification criteria,[8] as recommended by GRAPPA for PsA clinical trials.[25] Both protocols required subjects with at least 3 swollen and at least 3 tender/painful joints at screening and baseline, as well as active plaque PsO at screening (not required at baseline). Signs and symptoms consistent with the diagnosis of PsA were required to have been present for at least 6 months. Subjects were required to be on ongoing treatment with a stable dose of one csDMARD (ie, MTX, SSZ, leflunomide, or other as approved by the study clinician). The pivotal studies included mandatory minimum treatment durations of csDMARDs (Studies A3921091 and A3921125) or TNFi (Study A3921125). Both studies defined an inadequate response as either a lack of efficacy, or intolerability or AEs leading to discontinuation (AEDC). This was done in order to ensure objective assessment and appropriate documentation for both the TNFi-naïve and the TNFi-IR populations.

4.4.4.2. Efficacy Endpoints

PsA development programs evaluate the peripheral arthritis domain, the most common manifestation of PsA, with a population selected primarily on baseline number of involved joints (≥3 swollen and ≥3 tender/painful joints). The tofacitinib PsA pivotal studies were designed with sufficient power for the 2 primary endpoints (ACR20 response and ΔHAQ-DI at Month 3). Entry requirements at baseline did not require patients to have any PsO, enthesitis, dactylitis, or axial disease. Since these domains were not always present at baseline in patients with active peripheral arthritis, a lack of entry requirement may have resulted in insufficient power for assessments in these domains due to reduced sample size. Given that some patients did not have disease activity in these other domains, a lack of

statistical significance alone should not be interpreted as evidence of lack of efficacy due to the possibility of insufficient power. Considering this, and given the similar study designs of the 2 pivotal trials, the studies were pooled in order to obtain increased precision in incidence rate estimates for safety events and a more robust assessment of the events by subpopulations.

In addition to the primary endpoints, a specific group of secondary endpoints at Month 3 were Type I error controlled (see Section 4.4.4.5). These secondary endpoints were PASI75 response, Δ Leeds Enthesitis Index (LEI), Δ dactylitis severity score (DSS), ΔPF of SF-36v2, and change in Functional Assessment of Chronic Illness Therapy-Fatigue (ΔFACIT-F) (Total score, Experience domain score and Impact domain score). These represent efficacy in different domains that have a large impact on PsA patients. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was not selected because rigorous axial spondylitis diagnostic criteria were not specified in the protocols. Additional secondary, as well as other endpoints were used as supportive analyses.

4.4.4.3. Blinded Assessors

All rheumatologic and dermatologic assessments including the physician's global efficacy assessments were performed by qualified assessors who were blinded to treatment assignment, laboratory (including CRP), subject safety and prior efficacy data. The same qualified assessor was requested to score all evaluations for a particular assessment for a given subject throughout the study. Laboratory samples were analyzed by a central laboratory. Radiographic images from patients in A3921091 were evaluated by 2 independent central, blinded assessors.

4.4.4.4. Selection of the Efficacy Endpoints by Disease Domain

The primary endpoints of ACR20 and ΔHAQ-DI are validated measures previously utilized in registrational trials for PsA and consistent with FDA advice for the tofacitinib PsA development program. The secondary endpoints also are validated assessments previously utilized in registration trials for PsA which are consistent with FDA advice for the tofacitinib PsA development program. Specific selected secondary endpoints were also controlled for Type I error (see Section 4.4.4.5).

These assessment tools are described below:

Peripheral Arthritis Measures: The ACR criteria assess the level of improvement in 66 swollen and 68 tender/painful joints as well as improvement in at least 3 of 5 other ACR core set measures (Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Arthritis, PGA of Arthritis, CRP and HAQ-DI). The ACR response criteria are used in clinical trials at the 20%, 50%, and 70% improvement levels. ΔHAQ-DI is usually included not only as a component of the ACR response, but as a separate assessment of physical function. ACR20 response and ΔHAQ-DI at Month 3 were chosen as the primary endpoints in the PsA program based upon precedence in other PsA studies and regulatory agency concurrence. They were also primary endpoints in the tofacitinib RA program.

In order to measure joint radiographic damage in PsA, the van der Heijde-modified Total Sharp Score (mTSS) modified for PsA was utilized. This score has been validated specifically for PsA and measures both joint space narrowing (JSN) and erosion.[46] Radiographs of hands and feet were included in the A3921091 study at baseline and at 12 months for purposes of evaluation of disease progression and to provide a comparison with the active control adalimumab. No radiographs were obtained at Month 3.

Enthesitis Measures: There are multiple scales used to measure enthesitis that all measure tenderness at an involved site but differ in the location and number of body sites evaluated. The LEI was specifically designed and validated for PsA. However, measures designed for AS such as the Spondyloarthritis Research Consortium of Canada (SPARCC) are used in PsA as well.[47] Both were included in the tofacitinib PsA program.

Dactylitis Measures: Dactylitis represents a combination of synovitis, tenosynovitis plus enthesitis and can be assessed by a simple count of dactylitic digits, or by use of a DSS from 0-3 which includes a grading of dactylitis by assessor-rated tenderness and severity.[48] Both the presence of dactylitis and an evaluation of dactylitis severity were included in the tofacitinib PsA program.

Plaque PsO Measures: Plaque PsO is a skin disease that occurs in the majority of PsA patients. Methods to assess PsO clinically include evaluation of the extent of the body surface area (BSA) affected by PsO, the PASI,[49] and the PGA for PsO (PGA-PsO).[50] Seventy-five percent (75%) improvement from baseline in PASI (PASI75) is generally considered a clinically meaningful improvement.[50,51] PASI is influenced by the extent of BSA involvement. The PGA-PsO measures the severity of individual plaques but does not take the BSA involved into account. Subjects were required to have active plaque PsO at Screening in the 2 pivotal Phase 3 tofacitinib PsA studies, but PASI scores were only assessed if a subject had ≥3% BSA affected at baseline.

Axial Spondylitis: Although PsA commonly manifests as a disease of peripheral joints, it may include the signs and symptoms of axial disease such as inflammatory back pain and reduced range of motion, accompanied by signs of inflammation on magnetic resonance imaging (MRI) and structural damage on radiographs. The tofacitinib PsA development program did not specify methods to diagnose spondylitis and relied upon investigator identification. The BASDAI was included to evaluate symptoms of spondylitis in the tofacitinib PsA program.

Patient Reported Outcome Measures: Health status is measured by the SF-36v2 (acute). It measures 8 health domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. These domains are summarized as PCS and mental component summary scores (MCS). The FACIT-F assesses the experience and impact of fatigue on daily activities and functioning. Both patient assessed measures were included in the Tofacitinib PsA program

4.4.4.5. Statistical Analyses and Decision Rules

Statistical Decision Rules Used in the Individual RCTs

Each of the RCTs was designed to establish the superiority of 2 doses (5 mg BID and 10 mg BID) of tofacitinib to placebo for treatment of physical function and signs and symptoms of active PsA as measured by the 2 primary endpoints (ACR20 response and ΔHAQ-DI at Month 3).

A summary of the decision rules in the pivotal studies is provided below.

In order to protect the study-wise Type I error rate at the 0.05 (2-sided) level with respect to the primary and select secondary endpoints, a step-down testing procedure, as specified in the statistical analysis plans, was used; each endpoint/dose could only be declared significant if the prior endpoint's p-value was ≤0.05.

Primary endpoints: the order or fixed sequence for testing versus placebo was as follows:

a. Tofacitinib 10 mg BID ACR20 response rate at Month 3
b. Tofacitinib 5 mg BID ACR20 response rate at Month 3
c. Tofacitinib 10 mg BID ΔHAQ-DI at Month 3
d. Tofacitinib 5 mg BID ΔHAQ-DI at Month 3.

Selected Secondary endpoints: Upon achieving significance for the primary endpoints (4 tests), a step-down approach was also applied to a set of secondary efficacy endpoints, in the order presented here: PASI75, ΔLEI, ΔDSS, ΔPF of SF-36v2 and ΔFACIT-F (3 endpoints in order of testing priority: ΔFACIT-F Total score, ΔFACIT-F Experience domain score and ΔFACIT-F Impact domain score) at Month 3. For each endpoint, tofacitinib 10 mg was tested versus placebo first, followed by tofacitinib 5 mg versus placebo. Testing stopped at the first instance in which statistical significance was not achieved (p-value was >0.05).

ACR family of endpoints: A step-down approach to testing the ACR20, ACR50 and ACR70 response rates at Month 3 (order of testing: ACR20, ACR50 and ACR70) was also used for each endpoint and dose within each endpoint, ie, the high dose (tofacitinib 10 mg BID) at a given endpoint could achieve significance only if the high dose at the prior endpoint was significant; the low dose (tofacitinib 5 mg BID) at a given endpoint could achieve significance only if both the high dose at the same endpoint and the low dose at the prior endpoint was significant. Though this testing scheme did not protect the Type I error for the family of all possible comparisons, it provided Type I error protection for testing the family of ACR endpoints within each dose and doses within each ACR endpoint.

ACR20 at earlier time points: Similarly, in order to assess the onset of efficacy as measured by ACR20 response rate, a step-down approach with the ACR20 response from Month 3 to earlier time points (order of testing: Months 3, 2 and 1, and Week 2) was also used for each time point and doses within each time point. Though this testing scheme did not protect the Type I error for the family of all possible comparisons, it provided Type I error protection for testing the family of ACR20 response time points within each dose and doses within each time point.

For endpoints/doses that were not tested in the hierarchical procedure due to failure of a prior endpoint/dose, and for those that were not included in the procedure, nominal p values are

provided and used to guide interpretation of results without the intention to declare statistical significance.

Statistical Methods Used for the Individual RCTs

A high level summary of the statistical analyses in the RCTs is provided below:

The primary analysis population was the full analysis set (FAS), which included all patients who were randomized to the study and received at least 1 dose of the study drug. Continuous endpoints, such as ΔHAQ-DI, for which change or percent change from baseline was the measure to be analyzed, would require that a subject had a baseline value and at least 1 post-baseline value to be included in the FAS for that endpoint. The placebo treatment sequences were combined as a single placebo group for any visits prior to or at Month 3 in the analyses.

The normal approximation for the difference in binomial proportions was used to test the superiority of each dose of tofacitinib to placebo for ACR20 response at Month 3 on the FAS with missing values considered as non-response (Missing Response = Non-Response, or MR = NR) (primary analysis). 95% CI and p value are provided for treatment comparisons. As a supportive analysis, a generalized marginal linear model for repeated measures was used to analyze the ACR20 response data through Month 3 on the FAS without imputation for missing data. This model included fixed effects for visit (discrete, up to Month 3), treatment, and visit by treatment interaction; the dependent variable was the logit of the probability of "response". A common first order autoregressive [AR(1)] variance-covariance matrix for all treatment groups was used to model the variability among observations within a subject.

A mixed model for repeated measures (MMRM) was used to analyze the ΔHAQ-DI data through Month 3 (ie, Week 2, Months 1, 2 and 3) on the FAS without imputation for missing data (primary analysis). The model included the fixed effects of treatment, visit (discrete, up to Month 3), treatment by visit interaction, geographic location and baseline value. The model fitted a common unstructured variance-covariance matrix for all treatment groups. 95% CI and p value are provided for treatment comparisons. As a supportive analysis for ΔHAQ-DI through Month 3, a multiple imputation (MI) "jump to reference" (JTR) approach (MI-JTR) to the active dose groups (ie, tofacitinib jumps to placebo) but missing at random (MAR) imputation approach to the placebo group. Another supportive analysis was a responder analysis at Month 3 where patients with a change (ie, decrease) from baseline of $\geq$0.35 [minimal clinically important difference (MCID)[52]] were considered responders.

Analyses of the secondary binary endpoints were performed similarly as for the primary analysis of ACR20 response. Analyses of the secondary continuous endpoints were performed similarly as for the primary analysis of ΔHAQ-DI.

Statistical Methods for Pooled Analyses

All analyses using pooled data from A3921091 and A3921125 were supportive in nature and no hypothesis testing and no decision rules were used. Both Studies A3921091 and

A3921125 were designed to have the same efficacy assessments at the same time points through Month 6 thereby facilitating the pooling of data. The pooled data are used to provide a more robust assessment of consistency of effects of the primary endpoints in subgroups of subjects based on various demographic and disease characteristics. In addition, neither enthesitis nor dactylitis were mandatory inclusion criteria for subject entry into Studies A3921091 or A3921125 and approximately 70% and 50% of subjects had baseline presence of these, respectively. Pooling the ΔLEI or ΔDSS data for those subjects with baseline enthesitis or dactylitis, respectively, increases the sample size to provide a more robust assessment of tofacitinib effect on enthesitis and dactylitis. Likewise PASI was only assessed for those subjects (approximately 70%) with baseline BSA ≥3%; pooling PASI75 response increases the sample size to provide a more robust assessment of tofacitinib effect on psoriatic skin lesions.

Primarily, the data from Studies A3921091 and A3921125 through Month 6 are pooled for the primary endpoints and a subset of selected secondary endpoints based on the important disease domains of PsA. Analyses using data through Month 3 include patients randomized to the tofacitinib and placebo treatment groups only (for comparing tofacitinib 5 mg BID vs placebo, tofacitinib 10 mg BID vs placebo, and tofacitinib 5 mg BID vs tofacitinib 10 mg BID). Analyses using data through Month 6 include patients randomized to the tofacitinib treatment groups only (for comparing tofacitinib 5 mg BID vs tofacitinib 10 mg BID).

For binary endpoints (eg, ACR20 response at Month 3), difference in response proportion across studies is estimated using the Cochran–Mantel–Haenszel (CMH) approach adjusted for study. Large sample approximation to the difference in binomial proportions is used for treatment comparisons on the FAS with MR = NR.

For continuous endpoints (eg, ΔHAQ-DI) collected at 2 or more post-baseline visits, the data are analyzed with MMRM that included the fixed effects of treatment, visit (visit as discrete), treatment by visit interaction, geographic location, study and baseline value. The model fits a common unstructured variance-covariance matrix. Analyses are conducted on the FAS.

For each of the defined subgroups, subgroup analyses are conducted for the 2 primary endpoints (ACR20 response and ΔHAQ-DI) at Month 3. The CMH approach is used for ACR20 response, while the MMRM is used for ΔHAQ-DI, with the subgroup and its 2-way and 3-way interactions with treatment and visit as additional covariates in the MMRM model.

4.5. Comparison of PsA Study Feature and Characteristics of the Study Population

4.5.1. Tabular Presentation of PsA Clinical Studies

The PsA program enrolled patients from the US, Canada, Australia, Western Europe (Belgium, France, Germany, Spain, and United Kingdom), Eastern Europe (Bulgaria, Czech Republic, Hungary, Poland, Russia, and Slovakia), Asia (Taiwan), and Latin America (Mexico and Brazil) (Table 3).

The 2 pivotal RCTs have similar designs but different populations as previously discussed. An overview of the tofacitinib PsA program is provided in Table 2.

Table 2. Overview of Tofacitinib Psoriatic Arthritis Phase 3 Clinical Studies

Study Number / Study Population	Study Design/Primary Objective/Primary Endpoint/Duration	Treatment Groups	N[a]
Phase 3 Global Studies (Completed)			
A3921125 Patients with active PsA who had an inadequate response to at least one TNFi Tofacitinib added to previous stable background csDMARD in all patients. No monotherapy treatment was allowed.	Randomized, multicenter, global, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of 2 doses of tofacitinib in adult patients with active PsA. Primary Objectives: To compare the safety and tolerability of tofacitinib versus placebo at doses of 5 mg BID and 10 mg BID versus placebo for treatment of rheumatologic signs and symptoms, and function ability Primary Endpoints: • ACR20 response rates at Month 3; • ΔHAQ-DI at Month 3. Duration: 6 months	Total Randomized in a 2:2:1:1 ratio for: Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo to Month 3, then Tofacitinib 5 mg BID Placebo to Month 3, then Tofacitinib 10 mg BID	Total=394[b] 131 132 66 65
A3921091 Patients with active PsA who had an inadequate response to at least one csDMARD and were TNFi-naïve Tofacitinib added to previous stable background csDMARD in all patients. No monotherapy treatment was allowed.	Randomized, multicenter, global, double-blind, double-dummy, placebo-controlled, active-controlled parallel-group study to evaluate the efficacy and safety of two doses of tofacitinib in adult patients with active PsA. Primary Objectives: To compare the efficacy of tofacitinib at doses of 5 mg BID and 10 mg BID versus placebo for the treatment of rheumatologic signs and symptoms, and function ability Primary Endpoints: • ACR20 response rates at Month 3; • ΔHAQ-DI at Month 3. Duration: 12 months	Total Randomization 2:2:2:1:1 for: Tofacitinib 5 mg BID Tofacitinib 10 mg BID Adalimumab 40 mg SC q2w Placebo to Month 3, then Tofacitinib 5 mg BID Placebo to Month 3, then Tofacitinib 10 mg BID	Total=422 107 104 106 52 53

Table 2. Overview of Tofacitinib Psoriatic Arthritis Phase 3 Clinical Studies

Study Number / Study Population	Study Design/Primary Objective/Primary Endpoint/Duration	Treatment Groups	N[a]
Phase 3 Long-Term Extension Study (Ongoing)			
A3921092 Patients with active PsA who have previously participated in randomized PsA qualifying clinical studies (A3921091 or A3921125) with tofacitinib	Long-term, open-label extension study Primary Objective: To evaluate the long-term safety and tolerability of tofacitinib in adult patients with active PsA. Primary Endpoints: Safety and tolerability of tofacitinib (5 mg BID and 10 mg BID) as measured by a) Incidence and severity of AEs; b) Incidence of clinical abnormalities and change from baseline (in this and/or prior study) in clinical laboratory values during treatment. Duration: 3 years per subject	Tofacitinib 5 mg BID All LTE study patients began the study on 5 mg BID of tofacitinib. The tofacitinib dose could be increased to 10 mg BID at later study visits if, based upon investigator's discretion, patients receiving tofacitinib 5 mg BID would benefit from a higher dose and are not experiencing any tofacitinib-related AEs, including abnormalities in laboratory parameters that are judged to be related to tofacitinib. Tofacitinib dose could be decreased from 10 mg BID to 5 mg BID for safety reasons at any time during the study.	Total=680[c]

Abbreviations: ACR20 = American College of Rheumatology criteria ≥20% improvement; AEs = adverse events; BID twice daily; csDMARD = conventional synthetic disease-modifying anti-rheumatic drug; Δ = change from baseline; HAQ-DI = Health Assessment Questionnaire-Disability Index; LTE = long-term extension; N = number of patients; SC = subcutaneous; TNFi = tumor necrosis factor inhibitor
a. Number of patients who randomized and received at least one dose of study medication.
b. This is the number of patients randomized and treated. One patient was randomized to tofacitinib 5 mg BID but was not treated.
c. 685 patients enrolled; 5 not treated (no dosing record in database at data snapshot).
Sources: Clinical Overview, Table 3

4.5.2. Comparison of Key Features of PsA Clinical Studies

Table 3 summarizes key features of the completed RCTs and the ongoing LTE studies.

Table 3. Key Features in the Phase 3 Studies in Psoriatic Arthritis

	A3921091	A3921125	A3921092
Study population	csDMARD-IR[a] and TNFi-naïve	TNFi-IR[b]	csDMARD-IR[a], TNFi-naïve, TNFi-IR[c],
No. of patients randomized/treated (% treated)	422/422 (100.0)	395/394 (99.7)	685/680 (99.3)
Required background treatment	MTX or other csDMARD	MTX or other csDMARD	None
Key feature	TNFi-naïve	TNFi-IR	Open-label
Placebo controlled	yes	yes	no
Active Comparator	Adalimumab	None	None

Table 3. Key Features in the Phase 3 Studies in Psoriatic Arthritis

	A3921091	A3921125	A3921092
Study population	csDMARD-IR[a] and TNFi-naïve	TNFi-IR[b]	csDMARD-IR[a], TNFi-naïve, TNFi-IR[c],
Total study duration	12 months	6 months	3 years per patient
Geographic region (%)	Eastern Europe/Russia (68.2%) Western Europe/Australia (14.5%) US/Canada (12.3%) Rest of World (5.0%)	Eastern Europe/Russia (22.6%) Western Europe/Australia (31%) US/Canada (29.9%) Rest of World (16.5%)	Eastern Europe/Russia (49.3%) Western Europe/Australia (20.1%) US/Canada (19.4%) Rest of World (11.2%)

Abbreviations: DMARD=disease-modifying anti-rheumatic drug, IR=inadequate responder, MTX=methotrexate, csDMARD=conventional synthetic DMARD, TNFi=tumour necrosis factor inhibitor, No=number; US=United States.
a. Patients were to be receiving ongoing treatment with a stable dose of 1 csDMARDs (eg, MTX, sulfasalazine, leflunomide, or other as approved by the Sponsor study clinician).
b. Patients must have received at least one approved tumor necrosis factor (TNF) inhibiting biologic agent that was administered in accordance with its labeling recommendations and was inadequately effective and/or not tolerated.
c. All patients with active PsA who have previously participated in PsA clinical Studies A3921091 or A3921125 could have received tofacitinib in this study.
Source: Clinical Overview, Table 5

4.5.3. Demographic and Baseline Disease Characteristics of the PsA Study Population

Baseline demographic characteristics, such as age, gender, race, body mass index (BMI) and smoking status, were similar between the 2 Phase 3 RCTs.[2] Table 4 presents the demographic characteristics across Studies A3921091 and A3921125. In general, demographic and baseline characteristics were well balanced among all treatment groups, and are representative of the PsA population for which the treatment indication is being sought, including extent of baseline joint involvement, age and gender distribution.

Table 4. Demographics and Baseline Characteristics: Studies A3921091 and A3921125

Treatment Group	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo	Adalimumab (A3921091)
Number of Subjects (N)	238	236	236	106
Number (%) of Subjects				
Gender (%)				
Male	117 (49)	100 (42)	100 (42)	56 (53)
Female	121 (51)	136 (58)	136 (58)	50 (47)
Age years (%)				
18-44	82 (34.5)	78 (33.1)	94 (39.8)	42 (39.6)
45-64	132 (55.5)	137 (58.1)	117 (49.6)	57 (53.8)
≥65	24 (10.1)	21 (8.9)	25 (10.6)	7 (6.6)
Age (years)				
Mean (SD)	49.5 (12.4)	49.4 (11.7)	48.4 (12.5)	47.4 (11.3)
Range	20 -76	18 -74	18 -78	23 -81
Race (%)				
White	226 (95.0)	221 (93.6)	222 (94.1)	103 (97.2)
Black	1 (0.4)	1 (0.4)	1 (0.4)	0
Asian	2 (0.8)	10 (4.2)	9 (3.8)	2 (1.9)
Other	9 (3.8)	4 (1.7)	4 (1.7)	1 (0.9)
Geographic Region[a] (%)				
US/Canada	58 (24.4)	56 (23.7)	45 (19.1)	11 (10.4)
Eastern Europe/Russia	93 (39.1)	100 (42.4)	112 (47.5)	72 (67.9)
Western Europe/Australia	58 (24.4)	59 (25.0)	49 (20.8)	17 (16.0)
Asia	1 (<1.0)	7 (3.0)	6 (2.5)	1 (0.9)
Latin America	28 (11.8)	14 (5.9)	24 (10.2)	5 (4.7)
BMI (kg/m^2)				
Mean (SD)	29.8 (6.3)	30.2 (6.3)	29.2 (5.6)	28.8 (5.3)
Range	17.8 - 53.2	18.6 - 54.6	17.0 - 47.5	18.5 - 41.5
Diabetes (%)	29 (12.2)	37 (15.7)	34 (14.4)	13 (12.3)
Hypertension (%)	99 (41.6)	81 (34.3)	87 (36.9)	34 (32.1)
Dyslipidemia (%)	60 (25.2)	67 (28.4)	55 (23.3)	18 (17.0)
Metabolic Syndrome (%)	99 (41.6)	101 (42.8)	94 (39.8)	42 (39.6)

Table 4. Demographics and Baseline Characteristics: Studies A3921091 and A3921125

Treatment Group	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo	Adalimumab (A3921091)
Number of Subjects (N)	238	236	236	106
Number (%) of Subjects				
Smoking History (%)				
Never smoked	139 (58.4)	140 (59.3)	158 (66.9)	66 (62.3)
Smoker	37 (15.5)	45 (19.1)	39 (16.5)	23 (21.7)
Ex-smoker	62 (26.1)	51 (21.6)	39 (16.5)	17 (16.0)
Corticosteroid Use[b]	67 (28.2)	37 (15.7)	49 (20.8)	23 (21.7)
PsA Duration (year)				
Mean (SD)	8.6(7.9)	7.5(6.6)	8.1(7.5)	5.3(5.3)
Range	0.4-39.0	0.3-31.8	0.5-43.4	0.5-29.0
Baseline PsA Subtype				
<5 Joints	2 (0.8)	5 (2.1)	7 (3.0)	1 (0.9)
≥5 Joints	236 (99.2)	231 (97.9)	229 (97.0)	105 (99.1)
Baseline PASDAS				
Mean (SD)	6.1(1.2)	6.2(1.2)	6.0(1.2)	5.9(1.2)
Range	3.1-9.7	2.5-9.8	2.5-9.5	2.8-8.9
Baseline HAQ-DI				
Mean (SD)	1.2(0.7)	1.2(0.6)	1.2(0.7)	1.1(0.6)
Range	0.0-2.9	0.0-2.9	0.0-3.0	0.0-2.9
Baseline CPDAI for Subjects with Baseline BSA ≥3%				
Mean (SD)	10.0(2.5)	10.4(2.7)	9.8(2.8)	9.7(2.8)
Range	4.0-15.0	4.0-15.0	4.0-15.0	3.0-15.0
Baseline Swollen Joint Count				
Mean (SD)	12.5(10.3)	12.3(9.8)	10.9(8.9)	9.8(7.9)
Range	0.0-60.0	3.0-60.0	0.0-57.0	3.0-66.0
Baseline Tender/Painful Joint Count				
Mean (SD)	20.5(12.8)	23.2(15.8)	20.2(14.6)	17.1(11.2)
Range	3.0-68.0	3.0-68.0	3.0-66.0	4.0-64.0
Presence of Arthritis Mutilans				
Yes	16 (6.7)	18 (7.6)	23 (9.7)	9 (8.5)

Table 4. Demographics and Baseline Characteristics: Studies A3921091 and A3921125

Treatment Group	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo	Adalimumab (A3921091)
Number of Subjects (N)	238	236	236	106
Number (%) of Subjects				
Prior DMARD Therapy Category				
Concomitant Methotrexate Use				
Yes	190 (79.8)	184 (78.0)	193 (81.8)	80 (75.5)
TNFi experienced	131(55.0)	132 (55.9)	132 (55.9)	0 (0)
1 TNFi bDMARD[c]	76 (58.0)	80 (60.6)	79 (60.3)	NA
2 TNFi bDMARDs[c]	23 (17.6)	21 (15.9)	27 (20.6)	NA
≥3 TNFi bDMARDs[c]	21 (16.0)	17 (12.9)	14 (10.7)	NA
≥1 non-TNFi bDMARDs*	11 (8.4)	14 (10.6)	11 (8.4)	NA
TNFi-Naive	107 (45.0)	104 (44.1)	104 (44.1)	106 (100)

Abbreviations: SD = standard deviation; BMI = body mass index; PsA = psoriatic arthritis; bDMARD = biologic disease modifying anti-rheumatic drug; FAS = full analysis set; PASDAS = Psoriasis Area and Severity Disease Activity Score; CPDAI = Composite Psoriasis Disease Activity Index in Psoriatic Arthritis; DMARD = disease-modifying anti-rheumatic drug; TNFi = tumor necrosis factor inhibitor; US = United States; HAQ-DI = Health Assessment Questionnaire Disability Index; CSR = clinical study report; BSA = body surface area; UK = United Kingdom; BID = twice daily; NA = not available

a. Eastern Europe includes Bulgaria, Czech Republic, Hungary, Poland and Slovakia. Western Europe includes Belgium, France, Germany, Spain and UK. Asia includes Taiwan. Latin America includes Mexico and Brazil.

b. Oral systemic corticosteroid use at baseline (maximum allowed dose of 10 mg/day of prednisone equivalent)

c. Data from CSR A3921125 Table 14.4.2.1.5.1 The denominators used for the percentage calculation were the numbers of patients in FAS in Study A3921125: 131 in tofacitinib 5 mg BID, 132 in tofacitinib 10 mg BID; 131 in adalimumab.

*Subjects who were treated with any non-TNFi bDMARD or both TNFi bDMARD and non-TNFi bDMARDs were counted in the =1 non-TNFi bDMARDs category

Source: Clinical Overview, Table 6

The baseline disease characteristics were consistent with the diagnosis of active PsA at study entry. Domains other than peripheral arthritis were involved in substantial subsets of patients in each study at baseline; enthesitis (as measured by LEI): 66.4% and 69.8% in Studies A3921091 and A3921125, respectively; dactylitis (measured by DSS): 56.2% and 49.2% in Studies A3921091 and A3921125, respectively; and PsO with BSA ≥3%: 73.9% and 62.7% in Studies A3921091 and A3921125, respectively.

4.6. Description of the RA and PsO Study Population

The studies included in the integrated RA and PsO datasets are shown in Table 5 below. These datasets afford the opportunity to evaluate the similarity of events, rates of events, risk factor analysis, and whether the rates of certain safety events, especially those with long latency periods (such as malignancies), increase after exposure to tofacitinib for longer periods than those studied in PsA thus far.

Table 5. Studies (PsA and Non-PsA) Contributing to Safety Assessment for the PsA Program

Indication Phase/Status	Studies
Psoriatic Arthritis (PsA)	**783 patients**
Phase 3 completed	A3921125; A3921091
Long-term extension ongoing	A3921092
Safety Information From Other Indications	
Psoriasis (PsO)	**3,662 patients**
Phase 3 completed	A3921078; A3921079; A3921080; A3921111
Phase 2 completed	A3921047
Long-term extension ongoing	A3921061
Rheumatoid arthritis (RA)	**6,330 patients**
Phase 3 completed	A3921045; A3921046; A3921064; A3921032 A3921044; A3921069
Phase 2 completed	A3921019; A3921025; A3921035;A3921039 A3921040; A3921109; A3921073; A3921129; A3921068
Phase 1 completed	A3921130 A3921152
Japan specific Long-term extension study	A3921041
Long-term extension ongoing	A3921024

Abbreviations: PsA = psoriatic arthritis; RA = rheumatoid arthritis; PsO = psoriasis
Source: Summary of Clinical Safety, Table 4

5. OVERVIEW OF CLINICAL EFFICACY

In PsA, tofacitinib 5 mg BID has demonstrated efficacy consistent with bDMARDs in TNFi-naïve patients, as well as in TNFi-IR patients.

The PsA sNDA is based on evidence from the tofacitinib PsA development program which evaluated two doses of tofacitinib (5 mg BID and 10 mg BID). Although the Sponsor is not seeking approval of the 10 mg BID dose at this time, summarization of data will include results from tofacitinib 10 mg BID as well as 5 mg BID. The data provide substantial evidence to confirm a favorable benefit/risk in adult patients with active PsA when

tofacitinib is dosed at 5 mg BID. In this briefing document, results of the efficacy endpoints will concentrate on Studies A3921125 or A3921091. Specific results for the ongoing long-term safety extension Study A3921092 are not discussed.

The efficacy data presented for Studies A3921125 and A3921091 are based on a data cutoff date of 04 April 2016 (snapshot date 10 May 2016).

5.1. Summary of Efficacy Results by Randomized Clinical Trial

Tofacitinib 5 mg BID was shown to be effective in Study A3921125 (TNFi-IR) and Study A3921091 (TNFi-naïve). Efficacy results (the primary endpoints and selected secondary endpoints) for tofacitinib 5 mg BID and tofacitinib 10 mg BID in these 2 RCTs are presented in Table 6 and Table 7.

5.1.1. Study A3921125 (TNFi-IR)

Overall, the findings of this study demonstrated that tofacitinib 5 mg BID was an effective dose in TNFi-IR patients with active PsA.

Primary Efficacy Endpoints:

- Significantly greater improvements ($p \leq 0.05$) in ACR20 response rates and ΔHAQ-DI at Month 3 were observed for both tofacitinib doses versus placebo.
- All sensitivity and supportive analyses for both ACR20 response rates (including a generalized marginal linear model for repeated measures) and ΔHAQ-DI (including a ≥0.35 MCID responder analysis and a MI-JTR analysis) were consistent with the primary analyses.

Secondary Efficacy Endpoints:

- ACR50 (but not ACR70) response rates demonstrated superiority ($p \leq 0.05$) of both tofacitinib doses to placebo at Month 3.
- Tofacitinib 5 mg and 10 mg BID demonstrated superiority ($p \leq 0.05$) to placebo at Week 2, Month 1, and Month 2 for ACR20 response rates.
- Tofacitinib 10 mg BID (but not tofacitinib 5 mg BID) demonstrated superiority ($p \leq 0.05$) to placebo at Month 3 for PASI75 response.
- Greater mean improvements (nominal $p \leq 0.05$) for both tofacitinib 5 mg and 10 mg BID were seen versus placebo at Month 3 for ΔLEI, ΔDSS, ΔSF-36v2 PF, ΔSF-36v2 PCS, and ΔFACIT-F Scores.
- A larger percentage of patients who had enthesitis at baseline achieved a LEI of 0 (absence of enthesitis) at month 3 with tofacitinib 5 mg BID (39.76%; nominal $p<0.05$ versus placebo) and tofacitinib 10 mg BID (32.32%; nominal $p=0.0882$) relative to placebo (21.51%; post-hoc analysis).

- A larger percentage of patients who had dactylitis at baseline achieved a DSS of 0 (absence of dactylitis) at month 3 with tofacitinib 5 mg BID (51.52%) and tofacitinib 10 mg BID (50.77%) relative to placebo (28.57%; nominal $p<0.05$; post-hoc analysis).

- At Month 3, all ACR response rate components showed greater mean reductions (nominal $p \leq 0.05$) from baseline for both tofacitinib doses vs placebo.

- Improvements seen by Month 3 in the primary and secondary efficacy assessments were either sustained or continued to improve through Month 6.

Table 6. Primary and Selected Secondary Efficacy Endpoints at Month 3 and Month 6 (FAS)[a] – Study A3921125

	Month 3 (active treatment vs placebo)			Month 6			
	Tofacitinib 5 mg BID (N = 131)	**Tofacitinib 10 mg BID (N = 132)**	**Placebo (N = 131)**	**Tofacitinib 5 mg BID (N = 131)**	**Tofacitinib 10 mg BID (N = 132)**	**Placebo→ tofacitinib 5 mg BID (N = 66)**	**Placebo→ tofacitinib 10 mg BID (N = 65)**
Primary efficacy endpoints (subject to hierarchical testing procedure for global Type I error control)							
ACR20,[b] n (%)	65 (49.6)***[e]	62 (47.0)***[e]	31 (23.7)	78 (59.5)	65 (49.2)	33 (50.0)	35 (53.9)
ΔHAQ-DI,[b] LS mean (SE) [N1]	-0.39 (0.05)***[e] [124]	-0.35 (0.05)**[e] [120]	-0.14 (0.05) [117]	-0.44 (0.05) [122]	-0.34 (0.05) [112]	-0.48 (0.07) [56]	-0.42 (0.07) [56]
Key secondary efficacy endpoints (subject to hierarchical testing procedure for global Type I error control)							
PASI75,[c] n/N1 (%)	17/80 (21.3)	35/81 (43.2) ***[e]	12/86 (14.0)	27/80 (33.8)	37/81 (45.7)	11/42 (26.2)	14/44 (31.8)
ΔLEI,[d] LS mean (SE) [N1]	-1.3 (0.2)* [79]	-1.3 (0.2)* [86]	-0.5 (0.2) [82]	-1.5 (0.2) [77]	-1.6 (0.2) [84]	-1.4 (0.3) [38]	-1.3 (0.3) [41]
ΔDSS,[d] LS mean (SE) [N1]	-5.2 (0.7)* [64]	-5.4 (0.8)* [58]	-1.9 (0.8) [55]	-6.0 (0.8) [61]	-6.0 (0.9) [55]	-5.4 (1.3) [25]	-5.2 (1.3) [26]
ΔSF-36v2 PF Domain LS mean (SE) [N1]	5.0 (0.72)* [124]	4.1 (0.73)* [120]	1.7 (0.73) [117]	5.4 (0.80) [121]	3.9 (0.82) [112]	5.9 (1.15) [56]	5.6 (1.15) [56]
ΔFACIT-F Total Score LS mean (SE) [N1]	7.0 (0.81)** [124]	5.8 (0.82)* [120]	3.0 (0.82) [117]	7.1 (0.87) [122]	6.2 (0.90) [113]	7.6 (1.28) [56]	8.5 (1.28) [56]
ΔFACIT-F Experience Domain Score LS mean (SE) [N1]	3.1 (0.38)* [124]	2.6 (0.39)* [120]	1.5 (0.39) [117]	2.9 (0.40) [122]	2.8 (0.41) [113]	3.2 (0.58) [56]	4.1 (0.58) [56]
ΔFACIT-F Impact Domain Score LS mean (SE) [N1]	3.9 (0.48)** [124]	3.2 (0.49)* [120]	1.6 (0.49) [117]	4.2 (0.52) [122]	3.5 (0.54) [113]	4.3 (0.76) [56]	4.5 (0.76) [56]

Table 6. Primary and Selected Secondary Efficacy Endpoints at Month 3 and Month 6 (FAS)[a] – Study A3921125

	Month 3 (active treatment vs placebo)			Month 6			
	Tofacitinib 5 mg BID (N = 131)	**Tofacitinib 10 mg BID (N = 132)**	**Placebo (N = 131)**	**Tofacitinib 5 mg BID (N = 131)**	**Tofacitinib 10 mg BID (N = 132)**	**Placebo→ tofacitinib 5 mg BID (N = 66)**	**Placebo→ tofacitinib 10 mg BID (N = 65)**
Secondary efficacy endpoints (subject to hierarchical testing procedure for Type I error control within the family of ACR responses)							
ACR50, n (%)	39 (29.8)*[f]	37 (28.0)*[f]	19 (14.5)	50 (38.2)	39 (29.6)	21 (31.8)	23 (35.4)
ACR70, n (%)	22 (16.8)	19 (14.4)	13 (9.9)	28 (21.4)	19 (14.4)	10 (15.2)	12 (18.5)
Secondary efficacy endpoints (not controlled for Type I error)							
ΔSF-36v2 PCS Domain LS mean (SE) [N1]	5.18 (0.684) 121	5.34 (0.687) 120	--	5.71 (0.751) 118	5.00 (0.768) 110	6.45 (1.076) 56	6.98 (1.074) 56

Nominal *p≤0.05; **p<0.001; ***p<0.0001 vs placebo at Month 3

Δ = change from baseline; ACR = American College of Rheumatology; ACR20/50/70 = ACR criteria ≥20%/50%/70% response; BID = twice daily; BSA = body surface area; DSS = Dactylitis Severity Score; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; FAS = Full Analysis Set; HAQ-DI = Health Assessment Questionnaire – Disability Index; LEI = Leeds Enthesitis Index; LS = least squares; N = number of patients in FAS; N1 = number of patients evaluable at a visit of interest; n = number of patients meeting the criteria; PASI = Psoriasis Area and Severity Index; PASI75 = ≥75% reduction from baseline in PASI; PF = physical functioning; SE = Standard Error; SF-36v2 = Short-Form - 36 Health Survey Version 2; vs = versus

[a] All randomised patients who received ≥1 dose of study medication (N = 394); [b] Primary study endpoints at Month 3; [c] In patients with baseline BSA ≥3% and baseline PASI >0; [d] In patients with baseline score >0; [e] Achieved statistical significance globally at p≤0.05 per the pre-specified step-down testing procedure; [f] Achieved statistical significance within the ACR family at p≤0.05 per the pre-specified step-down testing procedure.

Continuous endpoints were analyzed with a mixed model for repeated measures; p values for binary endpoints were based on the normal approximation for the difference in binomial proportions.

Missing values for ACR20, ACR50, ACR70, and PASI75 were considered as non-response. Missing values for continuous endpoints were not imputed.

Source: Summary of Clinical Efficacy, Tables 8 and 34

5.1.2. Study A3921091 (TNFi-naïve)

Overall, the findings of this study demonstrated that tofacitinib 5 mg BID was an effective dose in TNFi-naïve patients with active PsA.

Primary Efficacy Endpoints:

- The ACR20 response rates and improvement in HAQ-DI at Month 3 were significant ($p \leq 0.05$) for tofacitinib 5 mg BID and 10 mg BID doses versus placebo.
    - All sensitivity and supportive analyses for both ACR20 response rates (including a generalized marginal linear model for repeated measures) and ΔHAQ-DI (including a ≥0.35 MCID responder analysis and a MI-JTR analysis) were consistent with the primary analyses.
- Greater improvements (nominal $p \leq 0.05$) in these endpoints were also observed for adalimumab versus placebo.

Secondary Efficacy Endpoints:

- Tofacitinib 5 mg BID and 10 mg BID demonstrated superiority to placebo at Month 3 for ACR50 ($p \leq 0.05$), ACR70 ($p \leq 0.05$) and PASI75 ($p \leq 0.05$) response rates; tofacitinib 10 mg BID (but not tofacitinib 5 mg BID) demonstrated superiority ($p \leq 0.05$) to placebo at Month 3 in ΔLEI. Enthesitis improved at a slower rate with tofacitinib 5 mg BID; however, the 12-month improvement measures were similar for 5 mg BID and 10 mg BID. Results for tofacitinib 10 mg BID (but not tofacitinib 5 mg BID) had greater mean improvement (nominal $p \leq 0.05$) compared to placebo at Month 3 in ΔDSS at Month 3 as well. Overall there were similar improvements in DSS in the tofacitinib 5 mg BID and 10 mg BID groups.
- Tofacitinib 5 mg and 10 mg BID demonstrated superiority ($p \leq 0.05$) to placebo at Week 2, Month 1, and Month 2 for ACR20 response rate.
- Greater mean improvement (nominal $p \leq 0.05$) for tofacitinib 5 mg and 10 mg BID versus placebo at Month 3 was observed for ΔSF-36v2 PF, ΔSF-36v2 PCS and ΔFACIT-F Scores.
- At Month 3, most individual ACR components showed greater mean reductions (nominal $p \leq 0.05$) from baseline for both tofacitinib doses over placebo (exceptions were the tender/painful joint count and PGA of Arthritis for tofacitinib 5 mg BID).
- Improvements observed by Month 3 in the primary and secondary efficacy assessments were either sustained or continued to improve through Month 12 (Table 7).
- Despite baseline characteristics which placed them at risk for progressive joint damage, few patients randomized to any of the active treatment arms (including adalimumab) had radiographic evidence of joint damage progression (i.e., mTSS score >0.5; Table 7). As

noted above, patients randomized to placebo were advanced to tofacitinib 5 or 10 mg BID at Month 3 in order to minimize their risk of such progression and few of them had radiographic evidence of joint damage progression. Radiographic assessments in Study A3921091 were not Type 1 error controlled.

- A larger percentage of patients who had enthesitis at baseline achieved a LEI of 0 (absence of enthesitis) at month 3 with tofacitinib 5 mg BID (33.33%; nominal p=0.1138 versus placebo) and tofacitinib 10 mg BID (40.63%; nominal $p \leq 0.05$) relative to placebo (21.54%; post-hoc analysis).

- A larger percentage of patients who had dactylitis at baseline achieved a DSS of 0 (absence of dactylitis) at month 3 with tofacitinib 10 mg BID (60.00%) relative to placebo (32.76%, nominal $p \leq 0.05$). The dactylitis absence rates at Month 3 were 34.4% and 46.6% with tofacitinib 5 mg BID and adalimumab, respectively (post hoc analysis).

- The efficacy of tofacitinib 5 mg BID and 10 mg BID was generally similar to adalimumab on multiple domains including maintenance of baseline joint structure assessed by radiograph.

Table 7. Primary and Selected Secondary Efficacy Endpoints at Month 3 and Month 12 (FAS)[a] – Study A3921091

	Month 3[f]				Month 12				
	Tofacitinib 5 mg BID (N = 107)	**Tofacitinib 10 mg BID (N = 104)**	**Adalimumab 40 mg SC q2w (N = 106)**	**Placebo (N = 105)**	**Tofacitinib 5 mg BID (N = 107)**	**Tofacitinib 10 mg BID (N = 104)**	**Adalimumab 40 mg SC q2w (N = 106)**	**Placebo→ tofacitinib 5 mg BID (N = 52)**	**Placebo→ tofacitinib 10 mg BID (N = 53)**
Primary efficacy endpoints (subject to hierarchical testing procedure for global Type I error control)									
ACR20,[b] n (%)	54 (50.5)*[g]	63 (60.6)***[g]	55 (51.9)*	35 (33.3)	73 (68.2)	73 (70.2)	64 (60.4)	35 (67.3)	31 (58.5)
ΔHAQ-DI,b LS mean (SE) [N1]	-0.35 (0.05)*[g] [103]	-0.40 (0.05)**[g] [103]	-0.38 (0.05)* [101]	-0.18 (0.05) [102]	-0.54 (0.05) [96]	-0.51 (0.05) [96]	-0.45 (0.05) [94]	-0.41 (0.08) [44]	-0.46 (0.08) [44]
Key secondary efficacy endpoints (subject to hierarchical testing procedure for global Type I error control)									
PASI75,[c] n/N1 (%)	35/82 (42.7)***[g]	31/70 (44.3)***[g]	30/77 (39.0)**	12/82 (14.6)	46/82 (56.1)	47/70 (67.1)	43/77 (55.8)	15/42 (35.7)	21/40 (52.5)
ΔLEI,[d] LS mean (SE) [N1]	-0.82 (0.22) [70]	-1.46 (0.24)**g [63]	-1.10 (0.23)* [73]	-0.43 (0.25) [63]	-1.7 (0.19) [67]	-1.6 (0.21) [56]	-1.6 (0.20) [67]	-1.4 (0.30) [24]	-1.9 (0.28) [29]
ΔDSS,[d] LS mean (SE) [N1]	-3.5 (0.95) [58]	-5.5 (0.91)* [60]	-4.0 (0.97) [56]	-2.0 (1.06) [55]	-7.4 (0.65) [54]	-7.5 (0.62) [58]	-6.1 (0.67) [52]	-6.7 (0.93) [26]	-7.7 (0.96) [24]
ΔSF-36v2 PF Domain LS mean (SE) [N1]	5.17 (0.85)* [102]	5.23 (0.85)* [103]	5.22 (0.86)* [101]	2.06 (0.91) [102]	7.67 (0.90) [96]	7.11 (0.90) [96]	6.81 (0.92) [94]	6.49 (1.29) [44]	4.77 (1.31) [44]
ΔFACIT-F Total Score LS mean (SE) [N1]	7.0 (0.85)* [102]	6.0 (0.85)* [102]	6.0 (0.87)* [101]	3.3 (0.91) [102]	8.5 (0.95) [96]	8.4 (0.95) [96]	6.9 (0.97) [94]	5.7 (1.36) [44]	7.6 (1.38) [44]
ΔFACIT-F Experience Domain Score LS mean (SE) [N1]	3.3 (0.38)** [102]	2.8 (0.38)* [102]	2.9 (0.39)* [101]	1.6 (0.41) [102]	3.9 (0.44) [96]	3.7 (0.44) [96]	3.2 (0.45) [94]	2.7 (0.63) [44]	3.4 (0.63) [44]
ΔFACIT-F Impact Domain Score LS mean (SE) [N1]	3.8 (0.52)* [102]	3.2 (0.52)* [102]	3.2 (0.53)* [101]	1.8 (0.56) [102]	4.6 (0.57) [96]	4.7 (0.57) [96)	3.7 (0.58) [94]	2.9 (0.82) [44]	4.3 (0.82) [44]
Secondary efficacy endpoints (subject to hierarchical testing procedure for Type I error control within the family of ACR responses)									
ACR50, n (%)	30 (28.0)**[h]	42 (40.4)***[h]	35 (33.0)***	10 (9.5)	48 (44.9)	50 (48.1)	43 (40.6)	21 (40.4)	19 (35.9)
ACR70, n (%)	18 (16.8)*[h]	15 (14.4)*[h]	20 (18.9)*	5 (4.8)	25 (23.4)	32 (30.8)	31 (29.2)	12 (23.1)	12 (22.6)
Secondary efficacy endpoints (not controlled for Type I error)									
ΔmTSS,[e] LS mean (SE) [N1]	-	-	-	-	0.01 (0.07) [98]	-0.01 (0.07) [99]	-0.07 (0.07) [95]	0.00 (0.09) [48]	0.09 (0.10) [45]
mTSS	-	-	-	-	4/98 (4.1)	5/99 (5.1)	2/95 (2.1)	2/48 (4.2)	4/45 (8.9)

Table 7. Primary and Selected Secondary Efficacy Endpoints at Month 3 and Month 12 (FAS)[a] – Study A3921091

	Month 3[f]				Month 12				
	Tofacitinib 5 mg BID (N = 107)	**Tofacitinib 10 mg BID (N = 104)**	**Adalimumab 40 mg SC q2w (N = 106)**	**Placebo (N = 105)**	**Tofacitinib 5 mg BID (N = 107)**	**Tofacitinib 10 mg BID (N = 104)**	**Adalimumab 40 mg SC q2w (N = 106)**	**Placebo→ tofacitinib 5 mg BID (N = 52)**	**Placebo→ tofacitinib 10 mg BID (N = 53)**
progression >0.5,[e] n/N1 (%)									
ΔSF-36v2 PCS Domain LS mean (SE) [N1]	5.51 (0.73)* [102]	5.69 (0.74)* [103]	6.23 (0.75)** [100]	2.68 (0.79) [102]	7.61 (0.81) [96]	7.67 (0.81) [96]	6.74 (0.82) [94]	5.82 (1.16) [44]	5.72 (1.18) [43]

Nominal *p≤0.05; **p<0.001; ***p<0.0001 vs placebo at Month 3

Δ = change from baseline; ACR20/50/70 = ACR criteria ≥20%/50%/70% response; BID = twice daily; BSA = body surface area; DSS = Dactylitis Severity Score; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; FAS = Full Analysis Set; HAQ-DI = Health Assessment Questionnaire – Disability Index; LEI = Leeds Enthesitis Index; LS = least squares; mTSS = modified Total Sharp Score; N = number of patients in FAS; N1 = number of patients evaluable at a visit of interest; n = number of patients meeting the criteria; PASI = Psoriasis Area and Severity Index; PASI75 = ≥75% reduction from baseline in PASI; PF = physical functioning; q2w = once every 2 weeks; SC = subcutaneous; SE = Standard Error; SF-36v2 = Short-Form - 36 Health Survey Version 2; vs = versus

[a] All randomized patients who received ≥1 dose of study medication; [b] Primary study endpoints at Month 3; [c] Among patients with baseline BSA ≥3% and baseline PASI>0; [d] In patients with baseline score >0; [e] mTSS was assessed post-baseline at Month 12 only; [f] The study was not designed as a superiority or a non-inferiority clinical trial for comparison of tofacitinib with adalimumab; [g] Achieved statistical significance globally at p≤0.05 per the pre-specified step-down testing procedure; [h] Achieved statistical significance within the ACR family at p≤0.05 per the pre-specified step-down testing procedure.

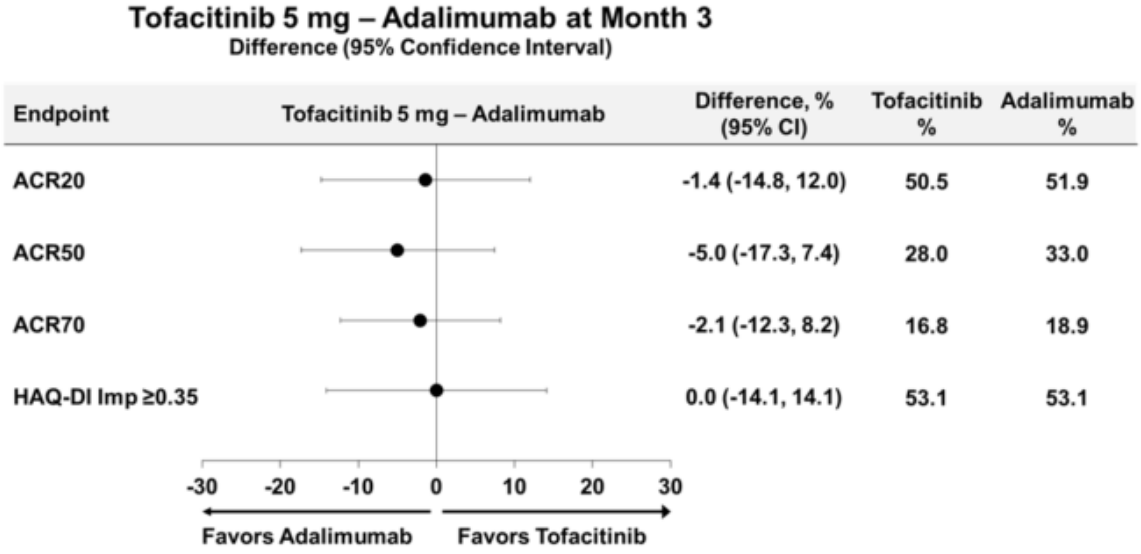
Continuous endpoints were analyzed with a mixed model for repeated measures; p values for binary endpoints were based on the normal approximation for the difference in binomial proportions.

Missing values for ACR20, ACR50, ACR70, and PASI75 were considered as non-response to treatment. Missing values for mTSS and mTSS progression at Month 12 were imputed by linear extrapolation. Missing values for continuous endpoints except mTSS were not imputed.

Source: Summary of Clinical Efficacy, Tables 6 and 34

- The Month 3 results for selected efficacy response endpoints presented as the difference in the proportion of subjects achieving a response (ie, tofacitinib 5 mg BID difference from adalimumab) are presented in Figure 3. Point estimates to the left of the vertical line favor adalimumab whereas those to the right favor tofacitinib 5 mg BID. At Month 3, tofacitinib 5 mg BID had ACR20/50/70, and HAQ-DI response (defined as a decrease from Baseline of ≥0.35 [a MCID]; excludes subjects with Baseline HAQ-DI <0.35) rates similar to those for adalimumab (2-sided 95% CIs for the differences included 0).

Figure 3. Direct Comparison of Tofacitinib 5 mg BID Versus Adalimumab 40 mg SC q2w for Selected Efficacy Endpoints at Month 3 in Phase 3 Study A3921091 (FAS, Missing Response = Non-Response)



Source: Summary of Clinical Efficacy, Figure 10

5.1.2.1. Evaluation of Structural Damage Progression

Risk factors for progression of structural damage include elevated CRP and baseline joint damage.[53] At baseline, a majority of patients were at high risk for progression of structural damage: 61.8 % with hsCRP > than the upper limit of normal (ULN) (>2.87 mg/L) and 91.5% of patients with baseline mTSS> 0. Patients randomized to placebo were advanced to tofacitinib 5 or 10 mg BID at Month 3 in order to minimize time on placebo. Mean ΔmTSS at 12 months was minimal and comparable between tofacitinib 5 mg BID and 10 mg BID and adalimumab 40 mg SC q2w at Month 12; few had radiographic evidence of joint damage progression at Month 12 (Table 7).

The majority of patients in all active treatment groups in Study A3921091 showed no radiographic evidence of joint damage progression at Month 12, despite risk factors for progression of structural damage at baseline. mTSS progressor rates (defined as an increase from baseline in mTSS >0.5) were low and similar between tofacitinib 5 mg BID and

tofacitinib 10 mg BID and there was no clinically meaningful difference between the 2 doses. The rates of progression were comparable to adalimumab at Month 12 (Table 7).

Although, in general, joint erosions and JSN progresses less rapidly in PsA patients than in RA patients, radiographic data at 12 months post-baseline (but not at Month 3) is sufficient to observe progression. [54,55,56] In the A3921091 study, in all treatment groups, including adalimumab, minimal structural progression was noted and joint integrity was maintained through Month 12. As previously shown in RA and given that adalimumab has been shown to inhibit the progression of structural damage, these data suggest that tofacitinib inhibits progression of structural damage similarly in active PsA.[57,58]

5.1.3. Supportive Ad Hoc Analyses for PsA RCTs (Studies A3921125 and A3921091)

Although conducted in different patient populations, the clinical trials, A3921125 and A3921091, were similarly designed (Figure 6), which allowed data from each study to be pooled for greater precision of endpoint analyses. Likewise, ad hoc analyses were conducted to provide supportive efficacy data. Overall, these analyses supported the primary analyses that tofacitinib 5 mg BID was an effective dose for the treatment of PsA peripheral arthritis as measured by ACR20, ACR50 and ACR70 response rates, ΔHAQ-DI, enthesitis, and dactylitis in TNFi-naïve and TNFi-IR PsA patients.

5.1.3.1. ACR 20 Response Rate and ΔHAQ-DI

Multiple subgroup analyses were performed on the ACR20 response rate and ΔHAQ-DI primary endpoints at Month 3. Pooled efficacy results were generally consistent across a range of baseline demographic (including age, gender, and race) and disease characteristics, as well as geographic regions (US/Canada, Western Europe/Australia, Eastern European/Russia, and Rest of World). The only subgroup that appeared different was Current Smokers, whose efficacy results were lower compared to the FAS population as well as the "Never Smoked" or "Ex-Smoker groups". An association between tobacco smoking and lower efficacy with the use of TNFi in PsA patient has been reported;[59] in this cited reference, differences in baseline disease activity and poorer treatment adherence potentially contributed to this association.

In general for the individual study and the pooled data subgroup analyses, no appreciable differences were observed in ACR20 response rates and ΔHAQ-DI at Month 3 among categories within each subgroup or between tofacitinib 5 mg BID and 10 mg BID. For both tofacitinib doses compared to placebo, efficacy observed in the FAS was also observed in the subgroups, and the overall ACR20 response rates and ΔHAQ-DI results did not appear to be driven by any dominant subgroup. Examination of age, sex, race, Baseline disease activity and PsA subtype did not identify differences in response to tofacitinib. The number of subjects with the PsA subtype of arthritis mutilans was too small to allow meaningful assessment.

5.1.3.2. Enthesitis

In a supportive analysis of pooled data from both studies, the mean decreases in ΔLEI at Month 3 for both tofacitinib 5 mg BID and 10 mg BID were higher than placebo (nominal $p \leq 0.05$).

In addition, an ad-hoc supportive analysis in the enthesitis disease domain was conducted to assess resolution (absence) of enthesitis as measured by the LEI. In Study A3921125, the LEI resolution rate at Month 3 for tofacitinib 5 mg BID was greater than placebo (nominal $p \leq 0.05$), but it was not for tofacitinib 10 mg BID. In Study A3921091, the LEI resolution rates at Month 3 were greater than placebo for tofacitinib 10 mg BID (nominal $p \leq 0.05$), but not for tofacitinib 5 mg BID. In Study A3921091, adalimumab was numerically higher than either tofacitinib dose at Month 3, but by Month 6 and after, responses were generally similar (Table 8).

Table 8. Enthesitis Resolution: Enthesitis Absence Rates at Month 3, Month 6, and Month 12 – Studies A3921125 and A3921091 (for Subjects With Baseline LEI >0 in FAS, Missing Response = Non-Response)

Treatment Group	N	n	Absence Rate %	Difference From Placebo[a]	
				Difference (95% CI)	P-value[b]
Study A3921125 – Ad hoc Supportive Analysis[c]					
Month 3					
Tofa 5	83	33	39.76	18.25 (4.82, 31.69)	0.0078
Tofa 10	99	32	32.32	10.82 (-1.62, 23.25)	0.0882
PBO	93	20	21.51		
Month 6					
Tofa 5	83	37	44.58	-	-
Tofa 10	99	43	43.43	-	-
Study A3921091 – Ad hoc Supportive Analysis					
Month 3					
Tofa 5	75	25	33.33	11.79 (-2.82, 26.41)	0.1138
Tofa 10	64	26	40.63	19.09 (3.45, 34.73)	0.0168
ADA	76	36	47.37	25.83 (10.80, 40.86)	0.0008
PBO	65	14	21.54		
Month 6					
Tofa 5	75	38	50.67	-	-
Tofa 10	64	28	43.75	-	-
ADA	76	38	50.00	-	-
Month 12					
Tofa 5	75	42	56.00	-	-
Tofa 10	64	33	51.56	-	-
ADA	76	42	55.26	-	-
Studied A3921091 and A3921125 Pooled– Ad hoc Supportive Analysis[d]					
Month 3					
Tofa 5	158	58	36.71	15.40 (5.50, 25.29)	0.0023
Tofa 10	163	58	35.58	14.14 (4.40, 23.88)	0.0044
PBO	158	34	21.52		

Table 8. Enthesitis Resolution: Enthesitis Absence Rates at Month 3, Month 6, and Month 12 – Studies A3921125 and A3921091 (for Subjects With Baseline LEI >0 in FAS, Missing Response = Non-Response)

Treatment Group	N	n	Absence Rate %	Difference From Placebo[a]	
				Difference (95% CI)	P-value[b]
Month 6					
Tofa 5	158	75	47.47	-	-
Tofa 10	163	71	43.56	-	-

Abbreviations: ADA = Adalimumab 40 mg SC q2w; FAS = Full Analysis Set; N = number of subjects in FAS with Baseline Leeds Enthesitis Index>0; n = number of subjects with Leeds Enthesitis Absent; PBO = Placebo; Tofa 5 = Tofacitinib 5 mg BID; Tofa 10 = Tofacitinib 10 mg BID
[a] Comparisons versus placebo were conducted at Month 3 only.
[b] P-values are nominal.
[c] Study A3921125 was 6 months in duration; therefore there are no values at Month 12 for Study A3921125 or Pooled Data.
[d] Pooled data consists of Tofa 5, Tofa 10, and PBO treatment group data pooled across Studies A3921091 and A3921125 by treatment group.
Subjects with Baseline Leeds Enthesitis Index=0 were excluded from the Leeds Enthesitis Index analysis. Enthesitis absence is defined as having a resolution of enthesitis, ie, absence of enthesitis in all of the 6 assessed sites. Two-sided 95% CI and p-value are based on the normal approximation for the difference in binomial proportions.
Source: Summary of Clinical Efficacy, Table 29

5.1.3.3. Dactylitis

In Study A3921091, the dactylitis absence rates at Month 3 for tofacitinib 10 mg BID (60.0%) was higher than placebo (32.8%) (2-sided 95% CI for the difference excluded 0); tofacitinib 5 mg BID (34.4%) did not have a higher rate compared to placebo at Month 3 (2-sided 95% CI for the difference included 0) (Table 9). In Study A3921125, the dactylitis absence rate at Month 3 for tofacitinib 5 mg BID (51.5%) and 10 mg BID (50.8%) were higher than placebo (28.6%) (2-sided 95% CI for the difference excluded 0; Table 9). In the pooled analysis, the dactylitis absence rates at Month 3 for both tofacitinib 5 mg BID and 10 mg BID were higher than placebo (2-sided 95% CI for the differences excluded 0).

In Study A3921091, the dactylitis absence rate was numerically higher for adalimumab 40 mg SC q2w (46.6%) than placebo (32.8%) at Month 3, although the 2-sided 95% CI for the difference included 0 (Table 9). The dactylitis absence rate for adalimumab (46.6%) was numerically higher than tofacitinib 5 mg BID (34.4%) and numerically lower than tofacitinib 10 mg BID (60.0%) at Month 3, although the 2-sided 95% CI for the difference from each tofacitinib dose included 0. At Month 12, the dactylitis absence rate was similar for tofacitinib 5 mg BID and adalimumab 40 mg SC q2w whereas tofacitinib 10 mg BID had a higher absence rate.

Table 9. Dactylitis Resolution - Dactylitis Absence Rates at Month 3, Month 6, and Month 12 in Studies A3921091 and A3921125 (for Subjects With Baseline Dactylitis Severity Score >0 in FAS, Missing Response = Non-response)

Treatment Group	N	n	Absence Rate %	SE %	Difference From Placebo[a]			
					Difference (SE) %	95% CI (%)		P-value[b]
						Lower	Upper	
Study A3921091 – Ad hoc Analysis								
Month 3								
Tofa 5	61	21	34.43	6.08	1.67 (8.66)	-15.30	18.64	0.8473
Tofa 10	60	36	60.00	6.32	27.24 (8.83)	9.93	44.55	0.0020
ADA	58	27	46.55	6.55	13.79 (8.99)	-3.83	31.42	0.1251
PBO	58	19	32.76	6.16				
Month 6								
Tofa 5	61	33	54.10	6.38	-	-	-	-
Tofa 10	60	40	66.67	6.09	-	-	-	-
ADA	58	39	67.24	6.16	-	-	-	-
Month 12								
Tofa 5	61	39	63.93	6.15	-	-	-	-
Tofa 10	60	47	78.33	5.32	-	-	-	-
ADA	58	40	68.97	6.07	-	-	-	-
Study A3921125 – Ad hoc Analysis[c]								
Month 3								
Tofa 5	66	34	51.52	6.15	22.94 (8.38)	6.52	39.37	0.0062
Tofa 10	65	33	50.77	6.20	22.20 (8.42)	5.70	38.69	0.0084
PBO	63	18	28.57	5.69				
Month 6								
Tofa 5	66	38	57.58	6.08	-	-	-	-
Tofa 10	65	36	55.38	6.17	-	-	-	-
Studies A3921091 and A3921125 Pooled – Ad hoc Analysis[d]								
Month 3								
Tofa 5	127	55	43.31	4.40	12.74 (6.02)	0.93	24.54	0.0345
Tofa 10	125	69	55.20	4.45	24.62 (6.09)	12.68	36.56	<0.0001
PBO	121	37	30.58	4.19				
Month 6								
Tofa 5	127	71	55.91	4.41	-	-	-	-
Tofa 10	125	76	60.80	4.37	-	-	-	-

Abbreviations: ADA = Adalimumab 40 mg SC q2w; FAS = Full Analysis Set; N = number of subjects in FAS with Baseline Dactylitis Severity Score >0; n = number of subjects with Dactylitis Absent; PBO = Placebo; SE = Standard Error; Tofa 5 = Tofacitinib 5 mg BID; Tofa 10 = Tofacitinib 10 mg BID

[a] Comparisons versus placebo were conducted at Month 3 only.

[b] P-values are nominal.

[c] Study A3921125 was 6 months in duration; therefore there are no values at Month 12 for Study A3921125 or Pooled Data.

[d] Pooled data consists of Tofa 5, Tofa 10, and PBO treatment group data pooled across Studies A3921091 and A3921125 by treatment group.

Absence is defined as "no presence" for any digit. Subjects with Baseline dactylitis score = 0 were excluded from analysis. Two-sided 95% CI and p-value are based on the normal approximation for the difference in binomial.

Source: Summary of Clinical Efficacy, Table 32

5.1.4. Study A3921092 (Long-term Extension [LTE] Trial, TNFi-IR and TNFi-naïve)

Study A3921092 is an ongoing open label extension study designed to evaluate the long-term safety (3 years), tolerability and efficacy of tofacitinib in subjects with PsA who have previously participated in Studies A3921091 or A3921125. Long term efficacy of treatment with tofacitinib (5 mg BID and 10 mg BID) is a secondary objective for this study.

As of the 10 May 2016 data snapshot, 685 subjects were enrolled (363 from Study A3921091 and 322 from Study A3921125), 680 (99.3%) subjects were treated, and 72 (10.6%) subjects discontinued; 608 (89.4%) subjects were ongoing and no subjects had completed the study. For any efficacy endpoints using baseline data for the calculation (eg, change from baseline), the baseline of the qualifying study (A3921091, A3921125) was used.

For this interim analysis, numbers of subjects included in the analyses at each visit decrease over time as a result of staggered entry in the study and subject discontinuation from the study. Only observed data without imputation for missing values are summarized. The main efficacy results are summarized below.

- ACR20 response rate overall and by qualifying studies A3921125 and A3921091 was stable over time in Study A3921092.
- ACR50 and ACR70 response rates were stable over time in Study A3921092.
- ΔHAQ-DI was stable over time in Study A3921092.
- For subjects with baseline BSA ≥3% and baseline PASI >0, the PASI75 response rate was stable over time in Study A3921092.
- For subjects with baseline DSS >0, the mean decrease from baseline in DSS was stable over time in Study A3921092.
- For subjects with baseline LEI >0, the mean decrease from baseline in LEI was stable over time in Study A3921092.

In conclusion, the interim analysis showed the stability in improvements in efficacy outcomes over time in ongoing Study A3921092.

5.2. Comparative Efficacy Analyses of Tofacitinib and Other DMARDs

5.2.1. Direct and Indirect Comparison of Tofacitinib and Other DMARDs

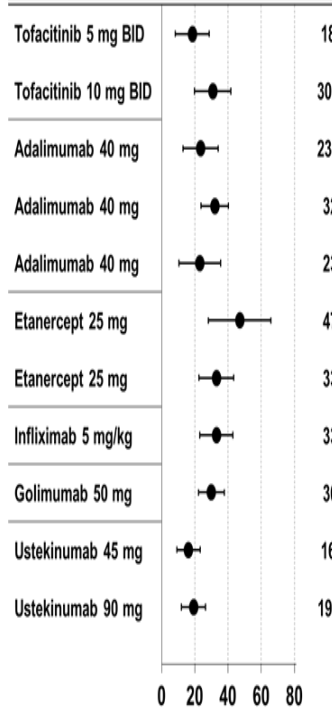
In a direct comparison in Study A3921091 (TNFi-naïve) at Month 3, tofacitinib 5 mg BID and 10 mg BID had ACR20 response rates (Peripheral Arthritis Signs and Symptoms) and mean improvements in ΔHAQ-DI (Physical Function) that were similar to those for the active control, adalimumab. Similar improvements were also seen on secondary endpoints, including the ACR50 and ACR70 response rates, as well as the PASI75 response rate, ΔLEI, ΔDSS, ΔSF-36v2 and ΔFACIT-F (Table 7). Modest differences on some endpoints were noted between tofacitinib dosed at 5 mg BID and adalimumab in Study A3921091 initially although responses were generally similar by the end of the study (Table 7).

As a means of providing indirect comparisons of tofacitinib versus other DMARDs for two commonly reported endpoints, ACR50, and ACR70 response rates, a systematic review of literature identified 7 RCTs in TNFi-naïve patients that were relatively similar in population and study design to Study A3921091.

For ACR50 and ACR70, response rates for tofacitinib 5 mg BID were generally similar to those of the bDMARDs adalimumab, etanercept, golimumab, infliximab, and ustekinumab. The results of the 7 RCTs in TNFi-naïve patients that included the endpoints of ACR50 and ACR70 and the differences in response rates (of active drug from placebo) are presented in Figure 4. The time point of ACR response criteria assessment in the RCTs was similar to that employed in the tofacitinib PsA studies, with the exception of ustekinumab, which was assessed at 24 weeks in contrast to Month 3 for tofacitinib.

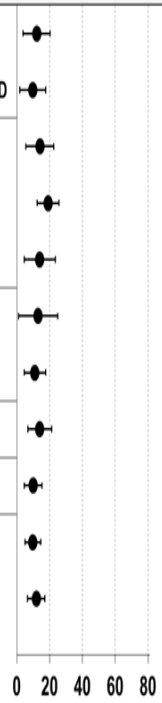
Figure 4. ACR50/70 Response Rates Difference From Placebo at the Time Point of the Primary Endpoint: Tofacitinib Versus Other DMARDs in TNFi-Naïve Patients

ACR50



Drug	Drug – Placebo ACR50 Difference, % (95% CI)	Drug %	Placebo %	Drug N	Placebo N	Time Point	Trial
Tofacitinib 5 mg BID	18.5 (8.3, 28.7)	28.0	9.5	107	105	3m	A3921091
Tofacitinib 10 mg BID	30.9 (19.9, 41.8)	40.4	9.5	104	105	3m	A3921091
Adalimumab 40 mg	23.5 (12.9, 34.1)	33.0	9.5	106	105	3m	A3921091
Adalimumab 40 mg	32 (23.8, 40.2)	36	4	151	162	12w	Mease 2005
Adalimumab 40 mg	23 (10.5, 35.5)	25	2	51	49	12w	Genovese 2007
Etanercept 25 mg	47 (28.1, 65.9)	50	3	30	30	12w	Mease 2000
Etanercept 25 mg	33 (22.6, 43.4)	38	5	101	104	12w	Mease 2004
Infliximab 5 mg/kg	33 (23.0, 43.0)	36	3	100	100	14w	Antoni 2005
Golimumab 50 mg	30 (22.3, 37.7)	31	1	146	113	14w	Kavanaugh 2009
Ustekinumab 45 mg	16.2 (9.1, 23.3)	24.9	8.7	205	206	24w	McInnes 2013
Ustekinumab 90 mg	19.2 (11.9, 26.5)	27.9	8.7	204	206	24w	McInnes 2013

ACR70



Drug	Drug – Placebo ACR70 Difference, % (95% CI)	Drug %	Placebo %	Drug N	Placebo N	Time Point	Trial
Tofacitinib 5 mg BID	12.1 (3.9, 20.2)	16.8	4.8	107	105	3m	A3921091
Tofacitinib 10 mg BID	9.7 (1.8, 17.6)	14.4	4.8	104	105	3m	A3921091
Adalimumab 40 mg	14.1 (5.6, 22.6)	18.9	4.8	106	105	3m	A3921091
Adalimumab 40 mg	19 (12.4, 25.6)	20	1	151	162	12w	Mease 2005
Adalimumab 40 mg	14 (4.5, 23.5)	14	0	51	49	12w	Genovese 2007
Etanercept 25 mg	13 (1.0, 25.0)	13	0	30	30	12w	Mease 2000
Etanercept 25 mg	11 (4.4, 17.6)	12	1	101	104	12w	Mease 2004
Infliximab 5 mg/kg	14 (6.7, 21.3)	15	1	100	100	14w	Antoni 2005
Golimumab 50 mg	10 (4.6, 15.4)	11	1	146	113	14w	Kavanaugh 2009
Ustekinumab 45 mg	9.8 (4.9, 14.7)	12.2	2.4	205	206	24w	McInnes 2013
Ustekinumab 90 mg	11.8 (6.6, 17.0)	14.2	2.4	204	206	24w	McInnes 2013

Abbreviations: ACR50/70= ACR criteria ≥50% improvement/ACR criteria ≥70% improvement; BID = twice daily; CI = confidence interval; DMARDs=disease modifying anti-rheumatic drugs; csDMARDs= conventional synthetic DMARDs; Pbo = Placebo.
Literature Sources: Mease, et al. 2000[60], Mease et al. 2005[54], Mease et al. 2004[55], Genovese et al. 2007[61], Antoni et al. 2005[62], Kavanaugh et al. 2009[63], McInnes et al. 2013.[64]
Source: Clinical Overview, Figure 7

5.3. Overall Efficacy Conclusions

- In adult patients with active PsA, tofacitinib 5 mg BID demonstrates:
    - Efficacy for peripheral arthritis
        - Clinically meaningful efficacy for peripheral arthritis (ACR20 and ACR50 response rates) and improvement in physical function (ΔHAQ-DI)
            - Rapid onset of efficacy for peripheral arthritis
            - Sustained or improved efficacy for peripheral arthritis after Month 3
            - Lack of joint damage progression (Month 12, A3921091) in the majority of patients (>95%) in a population with risk factors for progression.
- In support of the primary endpoints, tofacitinib 5 mg BID provides clinically meaningful improvements in:
            - Other PsA disease domains (enthesitis, dactylitis, skin), which are sustained/improved after Month 3
            - Patient-Reported Outcomes (PROs) of pain (as a component of ACR), fatigue, physical health status
- Effects of tofacitinib 5 mg BID on ACR20 response rates and ΔHAQ-DI (primary endpoints) were:
            - Generally consistent across all subpopulations evaluated
            - Apparent in both csDMARD-IR/TNFi-naïve and TNFi-IR populations

In PsA, tofacitinib 5 mg BID has demonstrated efficacy consistent with bDMARDs in TNFi-naïve patients, as well as in TNFi-IR patients.

6. OVERVIEW OF CLINICAL SAFETY

The safety profile of tofacitinib is well characterized, stable over time and clinically manageable. It is informed by a large and growing safety database, with consistency between clinical trial data, postmarketing experience, and the Truven database. Multiple data sources, including relevant non-PsA studies (RA and PsO), were used to inform characterization of the tofacitinib safety profile in PsA patients, as described below.

RA and PsO Clinical Databases: The RA clinical development program includes approximately 30,000 PYs of exposure to tofacitinib with 6330 tofacitinib-treated patients, who have accumulated a total of approximately 21,886 PYs of exposure accumulated over a period of more than 8 years of continuous exposure to tofacitinib, and the PsO clinical trial program with 3662 patients and approximately 8537 PYs of exposure to tofacitinib.

The incidence rates per 100 PY with 95% CIs for the AEs of Special Interest for the RA and PsO indications for patients treated with tofacitinib 5 mg BID and 10 mg BID are presented in Table 10 and Table 11, respectively. Important differences in the study population, study design, and exposure by dose should be considered when interpreting these rates. However, the safety risks are typical of those observed with bDMARD products approved for the treatment of PsA,[65] with the exception of a higher rate of HZ with tofacitinib. AEs of special interest are discussed in Section 6.3.6.

Table 10. Cumulative Incidence Rates (Events/100 Subject Years) for Selected Safety Events of Interest in Patients Treated with Tofacitinib 5 mg in the Psoriatic Arthritis (Randomized Phase 3 Studies), Psoriasis (Phase 3), and Rheumatoid Arthritis (Randomized Phase 3) Programs

Safety Event	Psoriatic Arthritis (12-month dose comparison cohort) *5 mg BID*[a] *N = 238* *PY = 150.7*			Rheumatoid Arthritis (All tofacitinib) *5 mg BID*[a,b] *N = 1589* *PY = 1743.93*			Psoriasis (First Year Experience) *5 mg BID*[c] *N = 1217* *PY = 800.8*		
	n	**%**	**Incidence Rate (95% CI)**	**n**	**%**	**Incidence Rate (95% CI)**	**n**	**%**	**Incidence Rate (95% CI)**
Serious infections	2	0.8	1.30 (0.16, 4.69)	48	3.0	2.77 (2.09, 3.67)	11	0.9	1.37 (0.69, 2.46)
Opportunistic infection*	1	0.4	0.65 (0.02, 3.62)	3	0.2	0.17 (0.04, 0.50)	2	0.2	0.25 (0.03, 0.90)
Tuberculosis*	0	0.0	0.00 (0.00, 2.39)	0	0.0	0.00 (0.00, 0.21)	0	0.0	0.00 (0.00, 0.46)
Herpes zoster	3	1.3	1.96 (0.41, 5.74)	57	3.6	3.35 (2.58, 4.34)	8	0.7	1.00 (0.43, 1.98)
Malignancies excl NMSC**	3	1.3	1.95 (0.40, 5.70)	11	0.7	0.63 (0.35, 1.14)	9	0.7	1.12 (0.51, 2.13)
NMSC**	0	0.0	0.00 (0.00, 2.39)	10	0.6	0.58 (0.31, 1.07)	5	0.4	0.63 (0.20, 1.46)
MACE*	0	0.0	0.00 (0.00, 2.39)	11	0.7	0.63 (0.35, 1.14)	4	0.3	0.50 (0.14, 1.28)
CV death*	0	0.0	0.00 (0.00, 2.39)	5	0.3	0.29 (0.12, 0.69)	3	0.2	0.37 (0.08, 1.09)

Abbreviations: N = number of patients; n = number of patients with event; PY = patient years; BID = twice daily; CI = confidence interval; excl = excluding; NMSC = non-melanoma skin cancer; CV = cardiovascular; MACE = major adverse cardiovascular event.
a. The patients that are randomized to tofacitinib 5 mg BID
b. Includes patients in tofacitinib monotherapy and in combination with conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs)
c. The patients that are advanced from placebo to tofacitinib are counted in placebo until advancement and only in the tofacitinib group post advancement.
*Adjudicated events in all studies
** Adjudicated events in PsA studies only
Opportunistic infections exclude Tuberculosis.
For PsA, events are counted up to 28 days beyond the last dose or to the end of the cohort; for RA and PsO, events are counted up to the end of the cohort.
Incidence rate was a naïve estimate without adjusting for study.
Source: Summary of Clinical Safety, Table 62

Table 11. Cumulative Incidence Rates (Events/100 Patients Years) for Selected Safety Events of Interest in Patients Treated with Tofacitinib 10 mg in in the Psoriatic Arthritis (Randomized Phase 3 Studies), Psoriasis (Phase 3), and Rheumatoid Arthritis (Randomized Phase 3) Programs

Safety Event	Psoriatic Arthritis (12-month dose comparison cohort) 10 mg BID[a] N = 236 PY = 147.3			Rheumatoid Arthritis (All tofacitinib) 10 mg BID[a,b] N=1611 PY=1799.53			Psoriasis (First Year Experience) 10 mg BID[c] N=1219 PY=868.85		
	n	%	Incidence Rate (95% CI)	n	%	Incidence Rate (95% CI)	n	%	Incidence Rate (95% CI)
Serious infections	3	1.3	2.00 (0.41, 5.83)	47	2.9	2.62 (1.97, 3.48)	21	1.7	2.42 (1.50, 3.70)
Opportunistic infection*	0	0.0	0.00 (0.00, 2.44)	6	0.4	0.33 (0.12, 0.73)	0	0.0	0.00 (0.00, 0.42)
Tuberculosis*	0	0.0	0.00 (0.00, 2.44)	9	0.6	0.50 (0.23, 0.95)	0	0.0	0.00 (0.00, 0.42)
Herpes zoster	4	1.7	2.66 (0.73, 6.81)	72	4.5	4.11 (3.26, 5.18)	20	1.6	2.32 (1.42, 3.58)
Malignancies excl NMSC**	0	0.0	0.00 (0.00, 2.44)	13	0.8	0.72 (0.42, 1.25)	7	0.6	0.81 (0.32, 1.66)
NMSC**	1	0.4	0.66 (0.02, 3.69)	9	0.6	0.50 (0.26, 0.96)	11	0.9	1.27 (0.64, 2.28)
MACE*	1	0.4	0.66 (0.02, 3.69)	10	0. 6	0.56 (0.30, 1.03)	2	0.2	0.23 (0.03, 0.83)
CV death*	0	0.0	0.00 (0.00, 2.44)	2	0.1	0.11 (0.03, 0.44)	1	0.1	0.12 (0.00, 0.64)

Abbreviations: N = number of patients; n = number of patients with event; PY = patient years; BID = twice daily; CI = confidence interval; excl = excluding; NMSC = non-melanoma skin cancer; CV = cardiovascular; MACE = major adverse cardiovascular event
a. The patients that are randomized to tofacitinib 10 mg BID
b. Includes patients in tofacitinib monotherapy and in combination with csDMARDs
c. The patients that are advanced from placebo to tofacitinib are counted in placebo until advancement and only in the tofacitinib group post advancement.
*Adjudicated events in all studies
** Adjudicated events in PsA studies only
Opportunistic infections excluding Tuberculosis.
Incidence Rate was a naïve estimate without adjusting for study.
For PsA, events are counted up to 28 days beyond the last dose or to the end of the cohort; for RA and PsO, events are counted up to the end of the cohort.
Source: Summary of Clinical Safety, Table 63

PsA data presented in the submission was based on a clinical development program that consisted of 783 PsA patients who had been exposed to tofacitinib, with a total of 776 PYs of tofacitinib exposure and a median duration of exposure of 343 days.

For safety events that can occur within a short period of starting therapy, such as serious infections (SIs), opportunistic infection (OI), and HZ, 12-month data are presented in this briefing document for tofacitinib and adalimumab comparison.

In order to assess the relationship between treatment and event, other events of special interest are evaluated in the 12-month data comparisons and the larger RA and PsO clinical databases.

The discussion of safety results from the PsA program in this section focuses on integrated data from the 2 completed Phase 3 pivotal studies and the ongoing LTE study with a data cutoff of 04 April 2016 (data snapshot of 10 May 2016; Table 2). Given the similar study designs of the 2 pivotal trials, the studies were pooled in order to obtain increased precision in incidence rate estimates for safety events and a more robust assessment of the events by subpopulations. Since Study A3921125 did not have an adalimumab treatment group, the treatment comparisons with adalimumab were performed within Study A3921091 only.

The data sources of the 3 main PsA safety populations are described in Table 12.

Further information is detailed in the respective sub-sections describing each safety population, method of data pooling and definition of dose groups.

Table 12. Overview of PsA Safety Populations for the Integrated Analysis

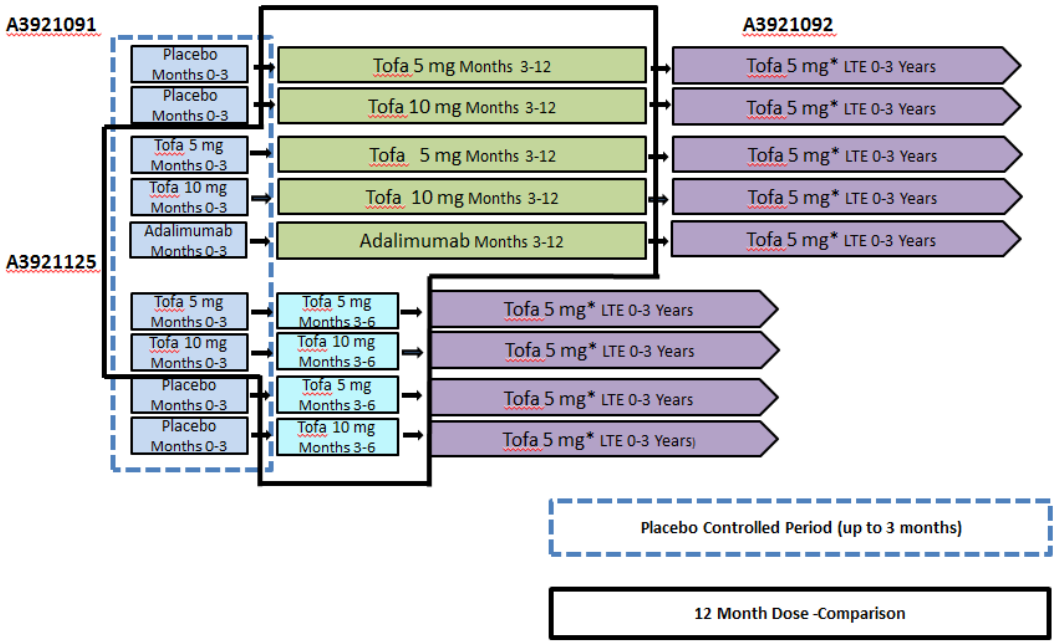
3-Month Placebo-Controlled Period	12-Month Dose-Comparison	All tofacitinib
Description		
Consists of the placebo controlled portions of the 2 Phase 3 clinical trials from all treatment groups (0-3 months)	Includes all the patients and their data from the 2 qualifying studies except the placebo portion of the data from the patients who were randomized to the placebo→tofacitinib treatment sequences (0 through 12 months)	Consists of data from all the tofacitinib treated patients from the Phase 3 randomized controlled clinical trials and LTE study
Objective		
Primary dataset comparing the first 3 months of Tofa treatment (5 mg BID and 10 mg BID) with placebo and ADA (1091 data only)	Dataset comparing safety profile between Tofa 5 mg BID, Tofa 10 mg BID and ADA (1091 data only) in the entirety of the double-blind period for both studies (12 months from A3921091 and 6 months from A3921125)	Primary dataset assessing safety of tofacitinib in PsA patients for durations of up to 36 months of therapy. No conclusion on dose comparisons can be made given the ability of patients to switch doses in the LTE study.
Study Protocols in Each Population		
A3921091, A3921125	A3921091, A3921125	A3921091, A3921125, A3921092
Number of Patients and Exposure to Tofacitinib in Each Population		
N = 816 107.5 PY exposure to tofacitinib	N = 797 388.4 PY exposure to tofacitinib	N = 783 775.72 PY exposure to tofacitinib Median duration of exposure: 343 days (All tofacitinib doses)
Treatment/Dose Groups in Each Population		
Tofa 5 Tofa 10 Tofa 5 and Tofa 10 Placebo Tofa 5 from the A3921091 study Tofa 10 from the A3921091 study ADA from the A3921091 study	Tofa 5 Tofa 10 All Tofa 5 All Tofa 10 Tofa 5 from the A3921091 study Tofa 10 from the A3921091 study All Tofa 5 from the A3921091 study All Tofa 10 from the A3921091 study ADA from the A3921091 study	Average Tofa 5 Average Tofa 10 Constant Tofa 5 All Tofa
Tofacitinib Treatment Duration		
0-3 months	0-12 months	~up to 36 months
Placebo- Controlled Period	**Active-controlled Period**	**Active-controlled + Open Label Periods**
3 months	Up to 12 months	Not applicable

Abbreviations: ADA = adalimumab; BID = twice daily; PsA = psoriatic arthritis; PY = patient-years; LTE = long-term extension; N = number of patients evaluable; Tofa = tofacitinib; Tofa 5 = all patients randomized to tofacitinib 5 mg BID; Tofa 10 = all patients randomized to tofacitinib 10 mg BID; Average Tofa 5 = average tofacitinib 5 mg BID (as defined above under All PsA in Section 6); Average Tofa 10 = average tofacitinib 10 mg BID (as defined above in Section 6 under All PsA); Constant Tofa 5 = constant tofacitinib 5 mg BID (as defined above in Section 6 under All PsA); All Tofa 5 = all patients randomized to tofacitinib 5 mg BID and the tofacitinib exposed periods for all patients switching to tofacitinib 5 mg BID from placebo; All Tofa 10 = all patients randomized to tofacitinib 10 mg BID and the tofacitinib exposed periods for all patients switching to tofacitinib 10 mg BID from placebo; All Tofa = all tofacitinib dose groups
Source: Summary of Clinical Safety, Table 2

6.1. Pooling Approach of PsA Studies for Safety Analyses

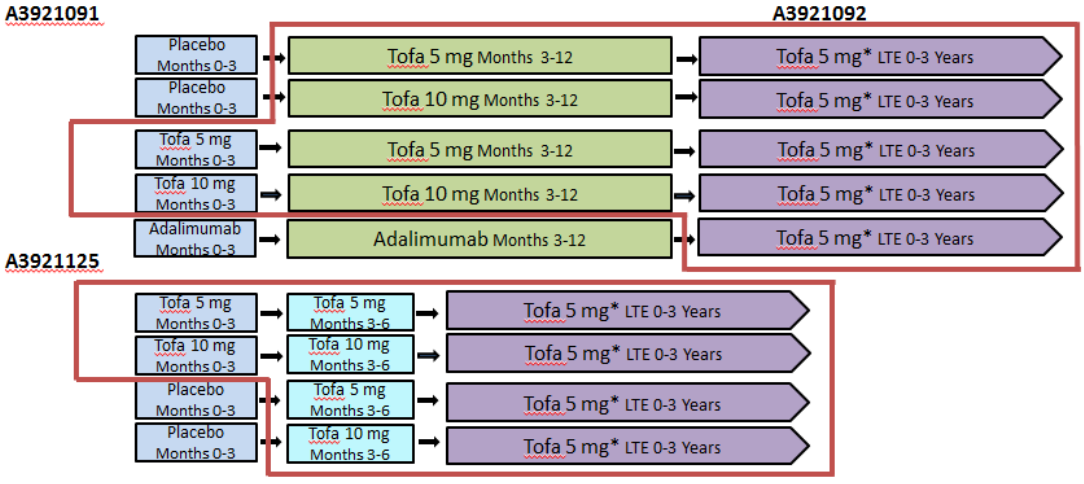
A schematic of the pooling approach is shown below in Figure 5 and Figure 6.

Figure 5. Schematic of 3-Month Placebo-Controlled and 12-Month Dose Comparison Cohorts



Abbreviations: Tofa = tofacitinib; LTE = long-term extension; BID = twice daily
* All patients were to start on tofacitinib 5 mg BID upon entry into the LTE.
Source: Summary of Clinical Safety, Figure 1

Figure 6. Schematic of All Tofacitinib PsA Cohort



Abbreviations: Tofa = tofacitinib; LTE = long-term extension; BID = twice daily; PsA = psoriatic arthritis
* All patients were to start on tofacitinib 5 mg BID upon entry into the LTE.
Source: Summary of Clinical Safety, Figure 2

6.2. Safety Endpoints for Adverse Events of Special Interest

Based on theoretical risks, risks observed with other products used to treat PsA and RA, and the emerging safety profile from previous tofacitinib development programs, safety endpoints of special interest (ie, infections including SIs, OIs, HZ, malignancy excluding NMSC, NMSC, MACE, gastrointestinal [GI] perforation, and hepatic events) were evaluated.

6.2.1. Safety Data from External Sources

To aid the contextualization of incidence rates for AEs of special interest in the tofacitinib PsA program and to complement the adalimumab active comparator from the A3921091 study, incidence rates from both external published PsA RCTs and observational studies were identified. Additionally, data from an additional external population is presented. The Sponsor conducted a retrospective descriptive cohort study embedded within the Truven MarketScan claims database to estimate incidence rates of safety events of special interest among a cohort of patients with PsA. Data from this cohort of patients is herein referred to as the "comparison cohort".

6.2.1.1. Truven MarketScan Comparison Cohort

The comparison cohort of patients with PsA is derived from the Truven MarketScan claims database in the US, a nationally representative sample of Americans with employer-provided health insurance and Medicaid. This database was selected to maximize sample size, given the low prevalence of the indication and frequency of the safety events of interest. Comparisons between the 'comparison cohort' and the PsA tofacitinib clinical development program should be made with consideration of varying population characteristics, including the exclusively US-based Truven cohort, the capture and definition of events (events from the 'comparison cohort' are captured using administrative codes and have not been adjudicated), and the limited number of events of interest in the PsA tofacitinib development program.

The comparison cohort consisted of a general population of patients with moderate to severe PsA, defined as having ≥ 1 inpatient or ≥ 2 outpatient diagnosis codes of 696.0 (psoriatic arthropathy) on two unique calendar days, at least one from a rheumatologist, on 01 October 2010 through 30 September 2015, with treatment with an approved systemic anti- psoriatic arthritic agent, serving as a proxy for moderate-severe disease. To increase comparability between data sources, exclusion criteria from the tofacitinib global Phase 3 PsA studies which could be operationalized in Truven Marketscan data were then applied to more closely reflect the trial populations. Given the possible time-varying hazard between tofacitinib and SI, incidence rates for SI included a follow-up time truncation at 1 year, to reflect the average follow-up time of the tofacitinib PsA 12-month comparison group.

Truven incidence rates for the short latency events of interest are compared to the 12-month comparison group (tofacitinib 5 mg BID and tofacitinib 10 mg BID) data from the clinical development program. Truven incidence rates for the long latency term events of interest are compared to tofacitinib All PsA data from the clinical development program.

The Truven comparison population characteristics as compared to the 12-month comparison group and the all tofacitinib group of the PsA tofacitinib clinical development program (Pfizer, Data on File), are presented in Table 13. Baseline characteristics assessed were generally similar to those in the PsA program population with the exception of csDMARD use, which may be due to the mandatory nature of the concomitant csDMARD in the phase 3 studies of the tofacitinib program.

Table 13. Baseline Characteristics: PsA Tofacitinib Cohorts and Truven Marketscan Comparison Cohorts

	12-month dose comparison		All tofacitinib	Truven Comparison Cohorts*
	5 mg BID (N=238)	10 mg BID (N=236)	(N=783)	(N=5799)
Age n (%)				
Mean	49.5	49.4	48.7	48.9
18-<45	82 (34.5)	78 (33.1)	287 (36.7)	1952 (33.7)
45-<65	132 (55.5)	137 (58.1)	424 (54.2)	3523 (60.8)
≥65	24 (10.1)	21 (8.9)	72 (9.2)	324 (5.6)
Gender n (%)				
Male	117 (49.2)	100 (42.4)	355 (45.3)	2672 (46.1)
Female	121 (50.8)	136 (57.6)	428 (54.7)	3127 (53.9)
Diabetes n (%)	29 (12.2)	37 (15.7)	107 (13.7)	706 (12.2)
Corticosteroid use n (%)	67 (28.2)	37 (15.7)	170 (21.7)	856 (11.9)[¥]
TNF inadequate responders n (%)	131 (55.0)	132 (55.9)	377 (48.1)	2125 (36.6)
csDMARD experience				
Any csDMARD n (%)	238 (100.0)	236 (100.0)	783 (100.0)	2703 (46.6)
MTX n (%)	220 (92.4)	212 (89.8)	609 (77.8)	2202 (38.0)
Leflunomide n (%)	NA	NA	NA	274 (4.7)
Sulfasalazine n (%)	NA	NA	NA	471 (8.1)
Hypertension n (%)	99 (41.6)	81 (34.3)	299 (38.2)	1776 (30.6)
Coronary Heart Disease n (%)	NA	NA	39 (5)	190 (3.3)

Abbreviations: BID = twice daily; TNF = tumor necrosis factor; csDMARD = conventional synthetic disease modifying anti-rheumatic drug; MTX = methotrexate; n = number of patients with an event; PsA = psoriatic arthritis; N = number of patients evaluable; NA = not available
* estimates based moderate-severe PsA on index date and 365 days prior, unless otherwise specified
[¥] use on index date
Source: Summary of Clinical Safety, Table 6; Pfizer 2016, Data on File

All comparisons between the PsA tofacitinib development program and the Truven comparison cohort should be made with consideration of the distinct data sources, including varying background csDMARD use, capture and definition of events, and few events of interest in the PsA tofacitinib development program.

6.3. Summary of Safety Results of PsA Clinical Development Program

6.3.1. General Tolerability and Safety Measures

As noted above, given the similar study designs of the 2 pivotal trials, the studies were pooled in order to obtain increased precision in incidence rate estimates for safety events and a more robust assessment of the events by subpopulations. The treatment comparisons with

adalimumab were performed within Study A3921091 only, because Study A3921125 did not have an adalimumab group. Subpopulation analyses of intrinsic and extrinsic factors did not identify any new or unexpected AE trends. There were no conclusive relationships identified between any of these factors with any AEs of special interest in PsA.

6.3.2. Common Adverse Events

6.3.2.1. Common Adverse Events for the Three-Month Placebo Controlled Period

The percentages of patients with AEs, SAEs, and severe AEs were similar between tofacitinib 5 mg BID, tofacitinib 10 mg BID and placebo. Discontinuations from all causes were more common in placebo group compared to those in tofacitinib 5 and 10 mg BID groups. Discontinuations due to AEs were more common in the tofacitinib 10 mg BID group compared to placebo. Temporary discontinuations due to AE were higher in the tofacitinib 10 mg BID group compared to the 5 mg BID dose group and placebo group. In Study A3921091, adalimumab treated patients had similar percentages of AEs and severe AEs compared to tofacitinib 5 mg BID patients as well as AEDC, but SAEs occurred less frequently in the adalimumab treated patients compared to placebo and both tofacitinib doses (Table 14).

Table 14. Treatment-emergent Adverse Events (All Causalities): Placebo-Controlled Period (3-month Placebo Controlled Cohort)

Treatment Group	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo	Adalimumab (A3921091)
Number (%) of Subjects				
Subjects Evaluable for Adverse Events	238	236	236	106
Subjects with Adverse Events n (%)	114 (47.9)	117 (49.6)	95 (40.3)	49 (46.2)
Subjects with Serious Adverse Events n (%)	4 (1.7)	4 (1.7)	4 (1.7)	1 (0.9)
Subjects with Severe Adverse Events n (%)	4 (1.7)	6 (2.5)	6 (2.5)	2 (1.9)
Subjects Discontinued due to Adverse Events n (%)	5 (2.1)	10 (4.2)	6 (2.5)	2 (1.9)
Subjects with dose reduced or temporary discontinuation due to Adverse Event n (%)	19 (8.0)	33 (14.0)	18 (7.6)	3 (2.8)
Incidence Rate (95% CI) Discontinuations from Study per 100 PY	14.77 (6.38, 29.10)	14.85 (6.41, 29.25)	28.35 (15.87, 46.76)	16.59 (4.52, 42.48)

Abbreviation: BID = twice daily; PY = patient-years; CI = confidence interval; NC = not calculated; Inf = infinity; ; n = number of subjects
Incidence Rate was a naïve estimate without adjusting for study.
Except for the Number of Adverse Events, subjects are counted only once per treatment in each row.
Medical Dictionary for Regulatory Activities ([MedDRA] v19.0 coding dictionary applied.
Treatment-Emergent: initial event onset or worsened in severity during treatment relative to pre-treatment
Source: Summary of Clinical Safety, Table 16

Table 15 summarizes events occurring in ≥2% of subjects by PT in any treatment group during the placebo-controlled period. The most frequently reported AEs were in the following SOCs: Infections and infestations, GI disorders, and Nervous System disorders. Overall, the most frequently reported PTs were nasopharyngitis, headache, and upper respiratory tract infections.

None of these differences between treatment groups were considered clinically significant.

Table 15. Treatment-emergent Adverse Events with Preferred Term ≥2% Occurrence in Any Treatment Group, by System Organ Class and Preferred Term (All Causalities): 3-month Placebo-Controlled Period

System Organ Class Preferred Term	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo	Adalimumab (A3921091)
Subjects Evaluable For Adverse Events	238	236	236	106
Number (%) of Subjects with Adverse Events				
Gastrointestinal disorders				
Diarrhoea	8 (3.4)	9 (3.8)	1 (0.4)	1 (0.9)
Dyspepsia	5 (2.1)	2 (0.8)	2 (0.8)	1 (0.9)
Nausea	6 (2.5)	5 (2.1)	7 (3.0)	4 (3.8)
General disorders and administration site conditions				
Injection site erythema	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.7)
Injection site swelling	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.8)
Fatigue	0 (0.0)	7 (3.0)	1 (0.4)	1 (0.9)
Infections and infestations				
Bronchitis	6 (2.5)	4 (1.7)	0 (0.0)	0 (0.0)
Nasopharyngitis	14 (5.9)	13 (5.5)	6 (2.5)	5 (4.7)
Pharyngitis	1 (0.4)	7 (3.0)	3 (1.3)	1 (0.9)
Upper respiratory tract infection	12 (5.0)	11 (4.7)	11 (4.7)	3 (2.8)
Urinary tract infection	3 (1.3)	6 (2.5)	5 (2.1)	1 (0.9)
Investigations				
Alanine aminotransferase increased	1 (0.4)	2 (0.8)	1 (0.4)	4 (3.8)
Aspartate aminotransferase increased	0 (0.0)	1 (0.4)	0 (0.0)	3 (2.8)
Nervous system disorders				
Headache	9 (3.8)	20 (8.5)	11 (4.7)	5 (4.7)
Dizziness	6 (2.5)	1 (0.4)	3 (1.3)	0 (0.0)
Skin and subcutaneous tissue disorders				
Acne	3 (1.3)	5 (2.1)	0 (0.0)	0 (0.0)
Vascular disorders				
Hypertension	4 (1.7)	5 (2.1)	3 (1.3)	1 (0.9)

Abbreviations: BID = twice daily
MedDRA (v19.0) coding dictionary applied.
Subjects are counted only once per treatment in each row
Source: Summary of Clinical Safety, Table 20

6.3.2.2. Dose Comparisons of Adverse Events at 12 Months

The safety profile of tofacitinib 5 mg and 10 mg BID at 12 Months were similar to the 3-month placebo controlled period. The 12 Month safety profile of tofacitinib was also similar to that observed for adalimumab.

For the 12-Month Comparison, weight increase and creatine kinase (CK) increases were also more frequently reported for tofacitinib 10 mg BID than for tofacitinib 5 mg BID and adalimumab. Dyspepsia, as observed in the 3-month placebo period, occurred more

frequently in patients receiving tofacitinib 5 mg BID versus tofacitinib 10 mg BID and adalimumab.

The evaluation of the "All tofacitinib" cohort followed similar trends as those reported for the 3-Month Placebo-Controlled and the 12-month Dose Comparison cohorts. In the all PsA cohort, the most frequently reported AEs by PT were: nasopharyngitis (n=88 [11.2%]) and upper respiratory tract infection (n=88 [11. 2%]) followed by headache (n=50 [6.4%]), bronchitis (n=44 [5.6%]), urinary tract infection (n=38 [4.9%]), blood creatine phosphokinase increase (n=38 [4.9%]), and hypertension (n=38 [4.9%]).

6.3.3. Serious Adverse Events

6.3.3.1. Serious Adverse Events for the Three-Month Placebo Controlled Period

During the placebo controlled period there were 4 SAEs in each of the tofacitinib 5 mg BID, 10 mg BID and placebo groups and 1 event in the adalimumab group. The incidence rate for SAEs in patients treated with tofacitinib 5 mg BID or 10 mg BID were similar to placebo (7.39 per 100 PY [95% CI: 2.01, 18.93], 7.40 per 100 PY [95% CI: 2.02, 18.96], and 7.53 per 100 PY [95% CI: 2.05, 19.27] for tofacitinib 5 mg BID, 10 mg BID, and placebo respectively). The incidence rate for adalimumab was 4.14 per 100 PY (95% CI: 0.10, 23.08). The rates do not differ significantly. The most common SAEs in this cohort occurred in the Infections and infestations SOC and were SIs. SIs were defined, per protocol, as infections that required parenteral antimicrobial therapy or hospitalization for treatment or management, or met other criteria that required that the event be classified as serious. SIs were identified programmatically by selecting all patients who had an AE in the SOC of Infections and infestations that was reported as serious (described in Section 6.3.6.1).

6.3.3.2. Dose Comparisons of Serious Adverse Events at 12 Months

The incidence rates of SAEs for the 2 tofacitinib doses were similar in the 12-month dose comparison cohort, 7.57 per 100 PY (95% CI: 4.24, 12.49) and 7.76 per 100 PY (95% CI: 4.34, 12.80) for the All tofacitinib 5 mg BID and All tofacitinib 10 mg BID doses respectively. Comparisons to adalimumab within the A3921091 study show a numerically higher rate for adalimumab compared to both the All tofacitinib 5 mg BID and All tofacitinib 10 mg BID, with incidence rates of 8.81 per 100 PY (95% CI: 4.40, 15.77), 5.73 per 100 PY (95% CI: 2.30, 11.80), and 10.06 per 100 PY (95% CI: 4.60, 19.09) for the tofacitinib 5 mg BID, 10 mg BID, and adalimumab doses (Table 16).

Table 16. Incidence Rates for Serious Adverse Events: 12 Month Dose-Comparison

	Pooled Data				Study A3921091				
	Tofacitinib 5 mg BID	**Tofacitinib 10 mg BID**	**All Tofacitinib 5 mg BID***	**All Tofacitinib 10 mg***	**Tofacitinib 5 mg BID**	**Tofacitinib 10 mg BID**	**All Tofacitinib 5 mg BID**	**All Tofacitinib 10 mg BID**	**Adalimumab**
Number of Patients with Exposure	238	236	347	344	107	104	159	154	106
Number of Patients with Event n (%)	12 (5.0)	12 (5.1)	15 (4.3)	15 (4.4)	8 (7.5)	4 (3.8)	11 (6.9)	7 (4.5)	9 (8.5)
Total Drug Exposure (PY)	151.44	147.98	198.14	193.35	91.72	90.56	124.84	122.24	89.48
Incidence Rates (95% CI)	7.92 (4.09, 13.84)	8.11 (4.19, 14.17)	7.57 (4.24, 12.49)	7.76 (4.34, 12.80)	8.72 (3.77, 17.19)	4.42 (1.20, 11.31)	8.81 (4.40, 15.77)	5.73 (2.30, 11.80)	10.06 (4.60, 19.09)

Abbreviations: BID = twice daily; CI = confidence interval; HR = hazard ratio; PY = patient-year; Tofa = Tofacitinib.
*Includes the tofacitinib-exposed period from patients that advanced from placebo treatment
Gaps in between the qualifying studies and long term extension studies are included up to 28 days or to the end of Cohort 2a.
Incidence Rate was a naïve estimate without adjusting for study.
Source: Summary of Clinical Safety, Table 25

The frequency of SAEs was similar in all tofacitinib 5 mg BID (All Tofacitinib 5 mg) and 10 mg BID (All Tofacitinib 1mg) doses; most frequently in the Infections and infestations SOC, followed by events in the Neoplasms benign, malignant and unspecified and General disorders and Administration site conditions.

6.3.3.3. Serious Adverse Events in All Tofacitinib Patients

The overall SAE incidence rate for tofacitinib in the All PsA cohort was 8.49/100 PY (95% CI: 6.55, 10.82), similar to the range of rates seen in the different tofacitinib doses in the 3-month Placebo, and the 12-month Dose Comparison groups. The frequency distribution of SAEs by SOC followed the same pattern as that for all TEAEs.

6.3.4. Deaths

There were 4 deaths reported in the tofacitinib PsA program. None were considered by the investigator to have been related to the study drug. Two (2) of the deaths occurred within 3 months of starting treatment with tofacitinib. No deaths occurred while patients were on placebo or adalimumab.

- One death occurred in Study A3921091 (Subject 10781015). The subject was a 72 year-old post-menopausal female who received tofacitinib 5 mg BID for 56 days prior to experiencing sudden cardiac death. The patient was a non-smoker and had a medical history of overweight, diabetes mellitus, hypertension, and hyperuricemia. The subject presented with general fatigue, pain in the joints of the feet and slow speech and was hospitalized. IV fluids containing glucose were administered. The next morning, the subject was found unresponsive; resuscitation efforts were unsuccessful. Autopsy results showed pathologic diagnosis including: hepatomegaly and splenomegaly; acquired mitral insufficiency; left and right ventricular hypertrophy; severe atherosclerosis; and passive congestion of internal organs.

The other 3 deaths occurred in Study A3921092:

- A 52 year old male subject received tofacitinib 5 mg BID (Subject 12031013) in Study A3921091 for 84 days after 12 months of adalimumab. The subject was discontinued from the study drug and subsequently died approximately 39 days thereafter as a consequence of metastatic pancreatic cell carcinoma.

- A 56-year old female subject who had received tofacitinib 10 mg BID (Subject 12421003) for 274 days died of acute cardiac failure 65 days after her last known study drug dose. The subject had a history of asthma, hypertension and hypercholesterolemia, and was a non-smoker. After having undergone elective surgery for Achilles tendinopathy on (b) (6), the patient felt unwell on (b) (6) and died at home that day.

- A 46 year old female subject received tofacitinib 5 mg BID (Subject 12701001) for 346 days and died from a bilateral pulmonary embolism. The subject had a relevant medical history of obesity, hypothyroidism, impaired glucose tolerance, and sleep apnea, developed a cold on 19 Dec 2015, that then developed into a chest infection on

22 Dec 2015 which was managed with antibiotics, steroids and nebulizer treatments. On (b) (6) the subject reported shortness of breath, needing to use her inhaler more. Her condition exacerbated and paramedics were dispatched. The subject was tachycardic with epigastric pain. En route to the hospital she went into cardiac arrest and cardiopulmonary resuscitation (CPR) was commenced. On admission to the emergency department the subject was in full arrest. Despite all efforts the subject could not be resuscitated and death was confirmed.

The mortality rate of 0.25 per 100 PY (95% CI 0.03, 0.91,) is similar to that reported in the literature for PsA observational studies; however, these observational studies were longer in follow up duration than the tofacitinib PsA program.[66] PsA is associated, in age and gender adjusted observational studies, with increased mortality compared with the general population. The cause of death most often reported in the PsA population in the literature is CV disease, followed by respiratory disease and cancer.

6.3.5. Adverse Events Resulting in Discontinuations from the Study

6.3.5.1. Adverse Events Resulting in Discontinuations for the Three-Month Placebo Controlled Period

During the placebo-controlled period, numerical differences in AEDC were noted by dosing group. Discontinuations from all causes were more common in placebo compared to those in tofacitinib 5 and 10 mg BID. Discontinuations due to AEs were more common in the tofacitinib 10 mg BID compared to placebo. Temporary discontinuations due to AE were higher in the tofacitinib 10 mg BID compared to the 5 mg BID dose and placebo.

6.3.5.2. Dose Comparisons of Adverse Events Resulting in Discontinuations from the Study in the 3-Month Placebo Controlled Period

The incidence rate for AEDC was lower in the tofacitinib 5 mg BID (5.51 per 100 PY [95% CI: 1.14, 16.11]) than on placebo (7.49 per 100 PY [95% CI: 2.04, 19.17]), while the incidence rate for tofacitinib 10 mg BID was higher (12.96 per 100 PY [95% CI: 5.21, 26.70]) than on placebo. In Study A3921091, the incidence rate for AEDC was lower in the tofacitinib 5 mg BID (4.11 per 100 PY [95% CI: 0.10, 22.91]) than on adalimumab (8.25 per 100 PY [95% CI: 1.00, 29.80]); no subjects reported AEDC in the tofacitinib 10 mg BID.

Table 17. Exposure Estimates and Incidence Rates for Adverse Events Leading to Discontinuation: 3-Month Placebo-Controlled Period

Treatment Group	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo	Tofacitinib 5 mg BID (A3921091)	Tofacitinib 10 mg BID (A3921091)	Adalimumab (A3921091)
Number of Patients with Exposure	238	236	236	107	104	106
Number of Patients with Event n (%)	3(1.3)	7(3.0)	4(1.7)	1(0.9)	0(0.0)	2(1.9)
Total PY Exposure for Event	54.41	54.01	53.43	24.31	24.06	24.24
Incidence Rate/100 PY (95% CI)	5.51 (1.14, 16.11)	12.96 (5.21, 26.70)	7.49 (2.04, 19.17)	4.11 (0.10, 22.91)	0.00 (0.00, 15.33)	8.25 (1.00, 29.80)

Abbreviations: BID = twice daily; CI = confidence interval; PY = patient-years; NC = not calculated; n = number of patients
Incidence Rate was a naïve estimate without adjusting for study.
Source: Summary of Clinical Safety, Table 29

6.3.5.3. Adverse Events Resulting in Discontinuations in 12-Month Comparison Group

Contrary to the results seen in the 3-month placebo controlled cohort, AEDC occurred in a similar proportion for both tofacitinib doses (Table 18). These results are consistent when evaluating the "All tofacitinib 5 mg BID and 10 mg BID" treatment arms which include subjects randomized to placebo that transitioned to active treatment in the qualifying studies.

Compared to adalimumab, within the A3921091 study, there was a higher rate of AEDC in tofacitinib 5 mg BID but lower for tofacitinib 10 mg BID.

Table 18. Incidence Rates for Adverse Events Leading to Discontinuation: 12 Month Dose-Comparison

	Pooled Data				Study A3921091				
	Tofacitinib 5 mg BID	**Tofacitinib 10 mg BID**	**All Tofacitinib 5 mg BID***	**All Tofacitinib 10 mg***	**Tofacitinib 5 mg BID**	**Tofacitinib 10 mg BID**	**All Tofacitinib 5 mg BID**	**All Tofacitinib 10 mg BID**	**Adalimumab**
Number of Patients with Exposure	238	236	347	344	107	104	159	154	106
Number (%) of Patients	11 (4.6)	11 (4.7)	13 (3.7)	12 (3.5)	6 (5.6)	2 (1.9)	8 (5.0)	3 (1.9)	3 (2.8)
Total Drug Exposure (PY)	153.58	150.52	200.39	196.61	93.66	92.30	126.90	124.69	92.44
Incidence Rates	7.16 (3.58, 12.82)	7.31 (3.65, 13.08)	6.49 (3.45, 11.09)	6.10 (3.15, 10.66)	6.41 (2.35, 13.94)	2.17 (0.26, 7.83)	6.30 (2.72, 12.42)	2.41 (0.50,7.03)	3.25 (0.67, 9.48)

Abbreviations: BID = twice daily; CI = confidence interval; HR = hazard ratio; PY = patient-year; Tofa = Tofacitinib
*Includes the tofacitinib-exposed period from patients that advanced from placebo treatment
**HR and its associated CI for adalimumab comparisons with tofacitinib (5 and 10 mg BID) were estimated from Study A3921091 only
HR and its associated CI were estimated from a Cox regression model including fixed effects of treatment and study for comparisons that did not involve Adalimumab.
Incidence Rate was a naïve estimate without adjusting for study.
Gaps in between the qualifying studies and long term extension studies are included up to 28 days or to the end of 12-month dose comparison.
Source: Summary of Clinical Safety, Table 31

6.3.5.4. Adverse Events Resulting in Discontinuations in All PsA Cohort

The most frequent AEDC from the study were events in the Infections and infestations SOC with 18 (2.3%) events followed by events in the Neoplasms benign, malignant and unspecified class, with 7 (0.9%) events.

6.3.6. Safety Events of Special Interest

There were no new safety signals identified in the safety database for the PsA studies. The events identified as safety events of interest in the tofacitinib program are: SIs, HZ, OI (excluding TB), malignancies (excluding NMSC), NMSC, MACE, TB, GI perforations, hepatic safety, and interstitial lung disease.

Analysis of incidence rate estimates for safety events of special interest are provided for 3-month placebo-controlled period cohort, the 12-month dose comparison cohort, and the all tofacitinib PsA cohort as described in Table 12. Given the relatively small number of events in the tofacitinib PsA safety database, and the limited time of subject follow-up, the evaluation of AEs of special interest also utilizes data from the tofacitinib RA and PsO integrated datasets; specifically the RA RCT experience (up to 2 year RCT data) and PsO RCT first year experience (including 3 studies with up to 54 weeks RCT data) which are most comparable to the PsA 12-month data. The accumulated safety data of tofacitinib in RA and PsO is similar to what is seen in the PsA development program over the period studied. Based on the consistency of safety data in other long-term extension programs, and what has been learned for other drugs used to treat RA, PsA and PsO,[69] it is unlikely that long-term data will differ for PsA. Cumulative incidence rates for selected AEs of special interest are discussed individually below and also presented by dose in Table 10 and Table 11 for tofacitinib 5 mg BID and 10 mg BID respectively.

The cumulative incidence rates for selected safety events of interest in subjects treated with tofacitinib in PsA (randomized tofacitinib), RA (randomized Phase 2, Phase 3, and LTE studies), and PsO (all tofacitinib) is presented in Table 19.

Evaluations of the supportive data from the integrated datasets for RA and PsO are presented within this document as additional background for the safe and effective use of tofacitinib 5 mg BID in the treatment of PsA. These data provide context to compare the similarity of rates, risk factor analysis, and the assessment of certain safety events, especially those with long latency periods (such as malignancies) after exposures to tofacitinib for longer periods than have been studied in PsA to date.

Table 19. Cumulative Incidence Rates (Events/100 Subjects Years) for Selected Safety Events of Interest in Subjects Treated with Tofacitinib All Doses in the PsA, Psoriasis (Total Exposure) and Rheumatoid Arthritis (Phase 2, Phase 3, and LTE Studies) Programs

Safety Event	Psoriatic Arthritis *All Tofacitinib* *N= 783* *PY = 775.72*			Rheumatoid Arthritis (P123LTE)[a] *All Tofacitinib* *N = 6330* *PY = 21886.05*			Psoriasis (total exposure) *All Tofacitinib* *N =3662* *PY = 8537.14*		
	n	**%**	**Incidence Rate/100 PY (95% CI)**	**n**	**%**	**Incidence Rate/100 PY (95% CI)**	**n**	**%**	**Incidence Rate/100 PY (95% CI)**
Serious Infections	11	1.4	1.40 (0.70, 2.50)	546	8.7	2.47 (2.26, 2.68)	111	3.0	1.27 (1.05,1.53)
Opportunistic infection *	3	0.4	0.38 (0.08, 1.11)	70	1.1	0.31 (0.24, 0.40)	26	0.7	0.30 (0.19,0.44)
Tuberculosis*	0	0.0	0.00 (0.00, 0.47)	35	0.6	0.16 (0.11, 0.22)	1	0.0	0.01 (0.00,0.06)
Herpes zoster	16	2.0	2.05 (1.17, 3.33)	747	11.9	3.64 (3.38, 3.91)	201	5.5	2.38 (2.06,2.74)
Malignancies excl NMSC	5	0.6	0.63 (0.21, 1.48)	168	2.7	0.75 (0.64, 0.87)	56	1.5	0.64 (0.48, 0.83)
NMSC	4	0.5	0.51 (0.14, 1.30)	121	1.9	0.55 (0.45, 0.65)	51	1.4	0.59 (0.44, 0.77)
MACE*	3	0.4	0.38 (0.08, 1.11)	80	1.4	0.38 (0.30, 0.47)	21	0.6	0.24 (0.15,0.37)
GI Perforation	1	0.1	0.13 (0.00, 0.70)	27	0.4	0.12 (0.08, 0.18)	6	0.2	0.07 (0.03,0.15)
ILD	0	0.0	0.00 (0.00, 0.47)	39	0.6	0.17 (0.12, 0.24)	2	0.1	0.02 (0.00, 0.08)

Abbreviations: N = number of subjects; n = number of subjects with an event; PY = patient-years; CI = confidence interval; excl = excluding; NMSC = non-melanoma skin cancer; MACE = major adverse cardiovascular event; GI = gastrointestinal; ILD = interstitial lung disease; LTE = long-term extension; PsA = psoriatic arthritis

Events are counted up to 28 days beyond the last dose or to the data cutoff date. PY is defined as the total follow up time calculated up to the day of the first event, subject to a risk period of 28 days beyond the last dose or to the data cutoff date. Gaps in dosing between Index and LTE studies are included up to 28 days or to the data cutoff date.

N in the RA program is 5856 and 5199 for MACE and breast cancer , respectively

a. Includes subjects in tofacitinib monotherapy and in combination with conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs)

* Adjudicated events

Incidence Rate was a naïve estimate without adjusting for study.

Source: Summary of Clinical Safety, Table 64

6.3.6.1. Infections of Special Interest (Serious infections, Herpes Zoster, Opportunistic Infections)

6.3.6.1.1. Serious Infections

The PsA population is at an increased risk of developing infections that require hospitalization when compared to an age and gender matched population without PsA. Subjects treated with bDMARDs have an increased risk of SIs and OIs.[17,67]

3-month placebo-controlled period cohort: During this period, no events of SI occurred in the tofacitinib 5 mg treatment group.

12-month dose comparison cohort: Incidence Rates for SIs in pooled tofacitinib data and comparison of tofacitinib Study A3921091 to adalimumab are presented in Table 20. Overall, there were very few SIs.

In Study A3921091, 2 subjects experienced SIs in all tofacitinib 5 mg and 1 subject who experienced SI and received adalimumab.

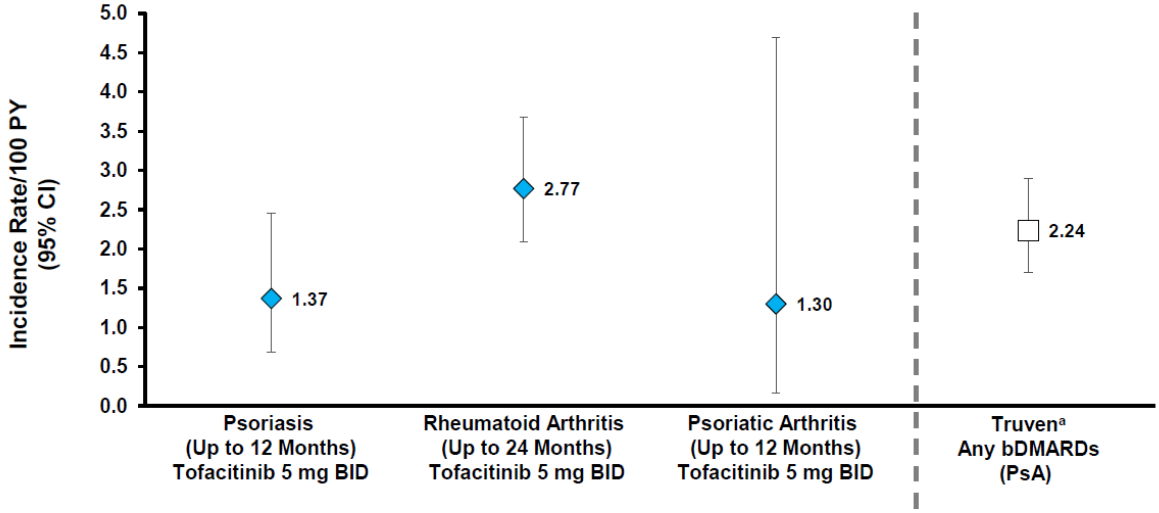
Table 20. Incidence Rates for Serious Infections: 12 Month Dose Comparison

	Pooled Data				Study A3921091				
	Tofacitinib 5 mg BID	**Tofacitinib 10 mg BID**	**All Tofacitinib 5 mg BID***	**All Tofacitinib 10 mg***	**Tofacitinib 5 mg BID**	**Tofacitinib 10 mg BID**	**All Tofacitinib 5 mg BID**	**All Tofacitinib 10 mg BID**	**Adalimumab**
Number of Subjects with Exposure	238	236	347	344	107	104	159	154	106
Number (%) of Subjects	2 (0.8)	3 (1.3)	4 (1.2)	3 (0.9)	0 (0.0)	1 (1.0)	2 (1.3)	1 (0.6)	1 (0.9)
Total Drug Exposure (PY)	154.05	150.37	200.74	196.47	93.97	91.89	127.09	124.29	92.55
Incidence Rates	1.30 (0.16, 4.69)	2.00 (0.41, 5.83)	1.99 (0.54, 5.10)	1.53 (0.31, 4.46)	0.00 (0.00, 3.93)	1.09 (0.03, 6.06)	1.57 (0.19, 5.68)	0.80 (0.02, 4.48)	1.08 (0.03, 6.02)

Abbreviations: BID = twice daily; PY = patient-year;
*Includes the tofacitinib-exposed period from subjects that advanced from placebo treatment
Incidence Rate was a naïve estimate without adjusting for study.
Gaps in between the qualifying studies and long term extension studies are included up to 28 days or to the end of 12-month dose comparison.
Source: Summary of Clinical Safety, Table 34

Figure 7 presents the incidence rates for SIs in the PsA, RA and PsO tofacitinib development programs in comparable cohorts. Overall, the incidence rates in the PsA program are in the same range of those in the RA and PsO programs. Contextualization with the Truven comparison cohort is presented in Section 6.3.6.1.1.1.

Figure 7. Incidence Rates for Serious Infections in PsA, RA, and PsO (12 Month Dose Comparison and Truven Marketscan Comparison Cohort)



N	1217	1589	238	5075
n	11	48	2	58
PY of Exposure	800.8	1733.8	154.1	2589.5

Abbreviations: CI = confidence interval; PY = Patient Years; N = number of subjects evaluable; n = number of subjects with an event; PsA = psoriatic arthritis; RA = rheumatoid arthritis; PsO = psoriasis; BID = twice daily.
[a]Hospitalizations only; follow-up time was truncated at 1 year for comparability to the tofacitinib PsA 12-month comparison group
Vertical bars represent 95% CI of the incidence rate.
Source: Summary of Clinical Safety, Table 2.1.1.1.2 (PsO), Table 777.s18.1 (RA), Table C2a.2.1.1 (PsA) and Table 4, V3 (Truven).

All PsA Cohort: Incidence rates for SIs in the all PsA cohort are presented in Table 21. Cumulatively, the incidence rate of SIs for the All PsA cohort for long term tofacitinib treatment is similar to that seen in the 12-month dose comparison cohort for both treatment doses combined, suggesting no increase over time.

Table 21. Exposure Estimates and Incidence Rates for Serious Infections: All PsA

Treatment Groups	Tofacitinib All Doses	Average Tofacitinib 5 mg BIDa	Average Tofacitinib 10 mg BIDb	Constant Tofacitinib 5 mg BIDc
Total Subjects with Exposure	783	463	320	348
Number of Subjects with event n (%)	11(1.4)	7(1.5)	4(1.3)	6(1.7)
Total PY Exposure for Event	788.24	462.29	325.95	317.46
Incidence Rate/100 PY (95% CI)	1.40 (0.70, 2.50)	1.51 (0.61, 3.12)	1.23 (0.33, 3.14)	1.89 (0.69, 4.11)

Abbreviations: BID = twice daily; CI = confidence interval; PY = patient-years; n = number of subjects; PsA = psoriatic arthritis

a. Patients with an average total daily dose of <15 mg over the course of observation.
b. Patients with an average total daily dose of ≥15 mg over the course of observation.
c. Subjects assigned to 5 mg BID, or advanced from placebo to 5 mg BID in the qualifying studies.

Tofacitinib exposure begins at 5 mg BID dosing through subject discontinuation or switch to 10 mg BID during A3921092

Incidence Rate was a naïve estimate without adjusting for study.

Source: Summary of Clinical Safety, Table 35

All tofacitinib PsA Cohort: The incidence rate of SIs for long term tofacitinib treatment (All PsA) was similar to that seen in the 12-Month Cohort for the all tofacitinib 5 mg BID and 10 mg BID groups (Table 20). In addition, the cumulative SIs observed for in PsA is similar to the incidence rates observed in the RA and PsO development program (Table 19). The most frequently reported SIs (by PT) are presented in Table 22. None of these events resulted in death.

Table 22. Listing of Subjects with Serious Infections: All PsA Cohort

Subject ID	Gender/Race/Age	Tofacitinib Dose At Time of Event	Preferred Term	Outcome	Event Exposure (Days)	Out of Risk Period (Days)
1091-10171022	M/W/45	5 mg BID	Appendicitis	Resolved	18	No
1091-10801022 1092-12091017	M/W/66	5 mg BID	Herpes zoster	Resolved	419	No
1091-11111006	F/W/36	5 mg BID	Pneumonia	Resolved	248	No
1091-11521012 1092-12121012	M/W/45	5 mg BID	Serratia sepsis	Resolved	87	No
1091-11801007 1092-13201006	F/W/68	NA	Post procedural infection	Resolved	424	Yes (28)
1125-11031005 1092-11811004	F/W/60	NA	Upper respiratory tract infection	Resolved	252	Yes (23)
1125-11581002	F/W/27	5 mg BID	Pneumonia	Resolved	166	No
1125-11811003 1092-13141002	F/W/56	5 mg BID	Pneumonia	Resolved	431	No
1125-12111001	F/W/33	5 mg BID	Oral candidiasis	Resolved	135	No
1091-10311001 1092-12591003	F/W/50	10 mg BID	Influenza	Resolved	132	No
1125-10421002	M/W/46	10 mg BID	Pyelonephritis	Resolved	10	No
1125-10901001 1092-12331001	M/A/39	10 mg BID	Gastroenteritis	Resolved	232	No

Source: Summary of Clinical Safety, Table 36

6.3.6.1.1.1. Contextualization Data for Serious Infections

Randomized Clinical Trial Literature for Serious Infections

Tofacitinib incidence rates during the end-of-study period comparison (12 month dose comparison cohort) were 1.30 per 100 PY (95% CI: 0.160, 4.69) and 2.00 per 100 PY (95% CI: 0.410, 5.83), for 5 and 10 mg BID doses, respectively, which were comparable to those reported with other PsA treatments (ranging from 0.00 per 100 PY to 3.00 per 100 PY). Adalimumab incidence rate for SI in A3921091 was comparable [1.08 (95% CI: 0.030, 6.02) events/100 PY] to the tofacitinib incidence rate reported in the ADEPT trial [0.994 (95% CI: 0.12, 3.59) events/100 PY]).

Observational Literature for Serious Infections

A comprehensive literature search using Medline and EMBASE [search terms (PsA) and (serious infection)] was conducted to identify observational studies evaluating the incidence of SI among PsA patients.

Among SAEs reported for PsA patients prescribed TNFi alone (n= 100) and TNFi + MTX users (n=161) in a Swedish arthritis registry, the incidence rate of SI was 0.96 (95% CI: 0.11, 3.46) per 100 PY (2 events/ 209 PY), and 1.56 (95% CI: 0.50, 3.65) per 100 PY (5 events /319.5 PY), respectively.[68]

Incidence rate comparisons between the tofacitinib development program and this single observational study must be made with consideration of differing population characteristics, capture and definition of events, length of available follow-up time, and few events of interest within the tofacitinib development program and observational study.

Rates of Serious Infection in Subjects with Psoriatic Arthritis from the Truven Marketscan Comparison Cohort

The definition of SI in the comparison cohort was restricted to only those which required hospitalization. Using this more restricted definition of SI, the incidence rate in the PsA tofacitinib remained unchanged, and the incidence rate in the Truven comparison cohort (Figure 7) was 2.24 (95% CI: 1.70, 2.90) among bDMARD users.

6.3.6.1.1.2. Overall Summary for Serious Infections

Few events of SI were observed. Incidence rates of SI for tofacitinib 5 mg BID are similar to adalimumab. Consistent with what has been reported in the literature for adalimumab for patients with RA and PsA[69], point estimates for SI in PsA subjects were in the same range as than those seen in RA subjects. The incidence rates of SI for tofacitinib are also comparable to the available external contextualization sources. Infections were treatable and none resulted in death. The current USPI presents information for SIs within the black box warning, Section 2 Dosage and Administration, Section 5 Warnings and Precautions and Section 6 Adverse Reactions.

6.3.6.1.2. Herpes Zoster

HZ occurs at an increased frequency in subjects with PsA receiving immunomodulatory agents relative to the general population.[70,71] HZ is a risk for treatment with tofacitinib as documented in the labeling (Section 5.1 Warnings and Precautions and Section 6 Adverse Reactions) for the approved RA indication.

3-month placebo-controlled period cohort: During this period, 2 HZ events were reported (2 subjects treated with tofacitinib 5 mg BID). No events were reported in the placebo or adalimumab treatment groups.

12-month dose comparison cohort: Incidence rates for HZ (both pooled tofacitinib data and comparison of tofacitinib [Study A3921091] compared to adalimumab) are presented in Table 23. Seven events of HZ were reported; 3 for tofacitinib in the All 5 mg BID and 4 in the tofacitinib All 10 mg BID treatment groups. Four (4) of these events occurred in Study A3921091 in patients who received tofacitinib; no events were reported in adalimumab-treated subjects.

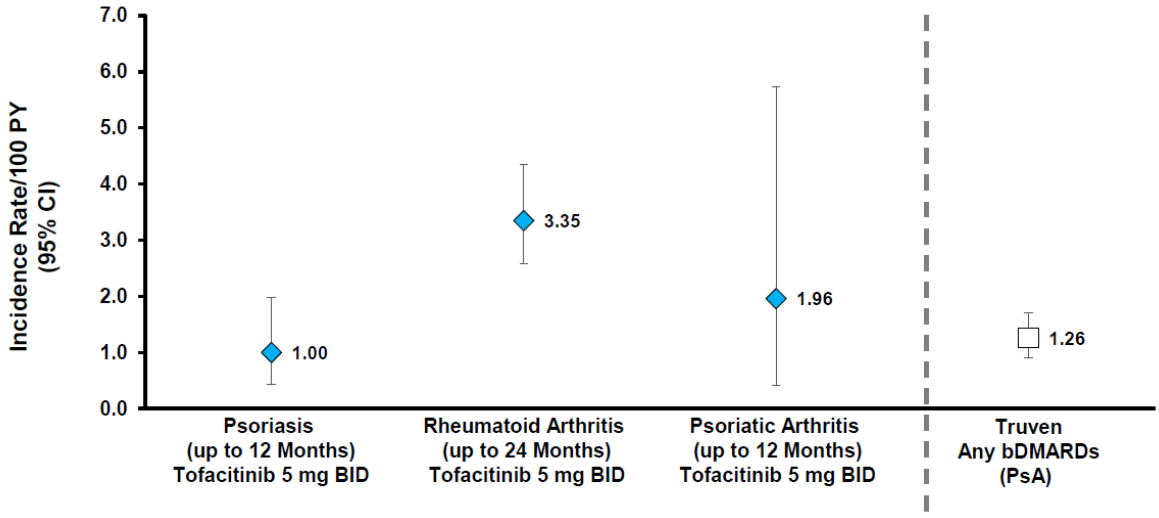
Table 23. Incidence Rates for Herpes Zoster: 12 Month Dose Comparison

	Pooled Data				Study A3921091				
	Tofacitinib 5 mg BID	**Tofacitinib 10 mg BID**	**All Tofacitinib 5 mg BID***	**All Tofacitinib 10 mg***	**Tofacitinib 5 mg BID**	**Tofacitinib 10 mg BID**	**All Tofacitinib 5 mg BID**	**All Tofacitinib 10 mg BID**	**Adalimumab**
Number of Subjects with Exposure	238	236	347	344	107	104	159	154	106
Number (%) of Subjects	3 (1.3)	4 (1.7)	3 (0.9)	4 (1.2)	2 (1.9)	2 (1.9)	2 (1.3)	2 (1.3)	0 (0.0)
Total Drug Exposure (PY)	152.70	150.28	199.58	196.38	92.71	92.07	126.01	124.46	92.62
Incidence Rates	1.96 (0.41, 5.74)	2.66 (0.73, 6.81)	1.50 (0.31, 4.39)	2.04 (0.55, 5.22)	2.16 (0.26, 7.79)	2.17 (0.26, 7.85)	1.59 (0.19, 5.73)	1.61 (0.19, 5.80)	0.00 (0.00, 3.98)

Abbreviations: BID = twice daily; PY = patient-year
*Includes the exposure period inclusive of Subjects that advanced from placebo treatment.
Incidence rate was a naïve estimate without adjusting for study.
Gaps in between the qualifying studies and long term extension studies are included up to 28 days or to the end of 12-month dose comparison.
Source: Summary of Clinical Safety, Table 39

Figure 8 displays the incidence rates and CIs for HZ in the PsO, RA and PsA program in comparable datasets. Similarly to SIs, the incidence rate for HZ in PsA is in the range of those described for RA and PsO. Contextualization with the Truven comparison cohort is presented in Section 6.3.6.1.2.1.

Figure 8. Incidence Rates for Herpes Zoster in PsA, RA, and PsO (12 Month Dose Comparison and Truven Marketscan Comparison Cohort)



N	1217	1589	238	5075
n	8	57	3	42
PY of Exposure	800.8	1702.7	152.7	3343.0

Abbreviations: PY = Patient Years; CI = confidence interval; N = number of subjects evaluable; n = number of subjects with an event; PsA = psoriatic arthritis; RA = rheumatoid arthritis; PsO = psoriasis; BID = twice daily
Vertical bars represent 95% CI of the incidence rate.
Source: Summary of Clinical Safety, Table 2.1.1.2 (PsO), Table 777.s18.17 (RA), Table C2a.2.1.1 (PsA), and Table 9 (Truven).

All PsA Cohort: A total of 16 subjects (9 tofacitinib 5 mg BID and 7 tofacitinib 10 mg BID) reported HZ in the All PsA population. The incidence rate of HZ for long term tofacitinib treatment (All PsA) was similar to that seen in the 12-Month Cohort (Table 24). In addition, the cumulative incidence rates observed for HZ in PsA is lower than the incidence rates observed in the RA and PsO development program (Table 19).

Table 24. Exposure Estimates and Incidence Rates for Herpes Zoster: All PsA Cohort

Treatment Group	Tofacitinib All Doses	Average Tofacitinib 5 mg BID[a]	Average Tofacitinib 10 mg BID[b]	Constant Tofacitinib 5 mg BID[c]
Total Subjects with Exposure (N)	783	463	320	348
Subjects with Event n (%)	16 (2.0)	9(1.9)	7(2.2)	5 (1.4)
Total PY Exposure for Event	781.43	457.77	323.67	315.39
Incidence Rate/100 PY (95% CI)	2.05 (1.17, 3.33)	1.97 (0.90, 3.73)	2.16 (0.87, 4.46)	1.59 (0.51, 3.70)

Abbreviations: BID = twice daily; CI = confidence interval; PY = patient-years; n = number of subjects; PsA = psoriatic arthritis

a. Subjects with an average total daily dose of <15 mg over the course of observation
b. Subjects with an average total daily dose of ≥15 mg over the course of observation
c. Subjects assigned to 5 mg BID, or advanced from placebo to 5 mg BID in the qualifying studies.

Tofacitinib exposure begins at 5 mg BID dosing through subject discontinuation or switch to 10 mg BID during A3921092
Incidence rate was a naïve estimate without adjusting for study.
Source: Summary of Clinical Safety, Table 40

Most events involved a single dermatome (Table 25). One HZ event involving a single facial dermatome HZ was reported as serious, and the subject was hospitalized. The majority of HZ events resolved. No events of visceral dissemination or cutaneous disseminated disease have been reported in the PsA study population.

Table 25. Extent of Involvement of Herpes Zoster in Tofacitinib All PsA Cohort

Extent of Involvement	N=17 n (%)
1 dermatome	13 (76.5)
2 adjacent dermatomes	1 (5.9)
Non-adjacent or >2 dermatomes	3 (17.6)
Disseminated	0

Abbreviation: N = number of subjects evaluable; n = number of subjects meeting the criteria; PsA = psoriatic arthritis
Source: Summary of Clinical Safety, Table 41

6.3.6.1.2.1. Contextualization Data for Herpes Zoster

Randomized Clinical Trial Literature for Herpes Zoster

There were few published literature reports of HZ in the PsA patient population. Overall, these results are inconclusive due to the paucity of studies reporting HZ events.

Published incidence of HZ in an analogous placebo-controlled period for the 2 external agents that reported HZ are both 0.00 events per 100 PY.

Observational Literature for Herpes Zoster

A comprehensive literature search using Medline and EMBASE [search terms (PsA) and ("herpes zoster")] was conducted to identify observational studies evaluating the incidence of HZ among PsA patients.

Only one published observational study resulted from this search. A retrospective cohort study[72] within the largest healthcare database in Israel (52% of Israel's population) reported the following rates of HZ (serious and non-serious) among treated PsA populations: TNFi (n=587): 0.86 per 100 PY (95% CI: 0.48, 1.43) (15 events/ 1735.5 PY); TNFi + csDMARDs (n=427): 1.79 per 100 PY (95% CI: 1.09, 2.76) (20 events/1119.7 PY).

Incidence rate comparisons between the tofacitinib development program and this single observational study must be made with consideration of differing population characteristics, capture and definition of events, and lengths of follow-up.

Rates of Herpes Zoster in Patients with Psoriatic Arthritis from the Truven Marketscan Comparison Cohort

The incidence rate for HZ within the tofacitinib PsA program is somewhat higher than that seen for in the Truven comparison cohort (bDMARD users: incidence rate 1.26 per 100 PY (95% CI: 0.91, 1.70). As described in Section 6.3.1, comparisons should be made with consideration of the distinct data sources, including varying background csDMARD use, capture and definition of events, and few events of interest in the PsA tofacitinib development program.

6.3.6.1.2.2. Overall Summary for Herpes Zoster

Rates of HZ for tofacitinib in PsA are within range of those reported with tofacitinib in RA and PsO subjects. No events occurred in adalimumab- or placebo-treated subjects. The incidence rates within the PsA program appear higher than those seen for other drugs in the Truven comparison cohort. Further discussion on the management and monitoring of SIs and other important infections is presented in Section 7.1. The current USPI presents information for HZ in Section 5 Warnings and Precautions and Section 6 Adverse Reactions.

6.3.6.1.3. Opportunistic Infections (OIs)

All OIs reported in the PsA program were events of multidermatomal HZ.

All PsA Cohort: A total of 3 OI events (2 tofacitinib 5 mg BID and 1 tofacitinib 10 mg BID) occurred in the All PsA cohort.

The cumulative incidence rate observed for OIs in PsA is overall consistent with the pattern observed in the RA and PsO development program (Table 19).

6.3.6.1.3.1. Contextualization Data of Opportunistic Infections

There was limited reporting of OIs in PsA clinical trials or observational studies in the published literature.

6.3.6.1.3.2. Overall Summary of Opportunistic Infections

OIs in tofacitinib treated PsA subjects occurred infrequently; all were events of multidermatomal HZ (nonadjacent or > 2 adjacent dermatomes).

Refer to Section 7.1 for details on the management and monitoring of serious and other important infections. The current USPI presents information for OIs within the black box warning, Section 5.1 Warnings and Precautions and Section 6 Adverse Reactions.

6.3.6.2. Malignancies

6.3.6.2.1. All Malignancies (Excluding NMSC)

Background

In addition to common risk factors of obesity, metabolic syndrome and smoking, chronic inflammation and autoimmune diseases are associated with the development of malignancies.[73,74] The relationship between malignancies and autoimmune disorders (eg, PsA, RA, and PsO) is complex as the immune response and some treatments for these diseases can also affect malignancy rates.[73,75] Complicating the assessment of malignancy in these patients is a malignancy risk associated with the treatments used for chronic inflammation and autoimmune diseases that involve modulation of the immune system.[73,75]

Patients with RA and other inflammatory diseases have been associated with increased risk of malignancy. [75,76,77] PsO patients have been associated with an increased risk of malignancies, especially NMSCs.[78,79,80,81]

This section summarizes "all malignancy" data (excluding NMSC) from the tofacitinib PsA program in context with RA and PsO clinical program data for "all malignancies" (excluding NMSC); NMSC is described separately.

3-month placebo-controlled period cohort: Two malignancies (a bladder transitional cell carcinoma and a squamous cell carcinoma (SCC) of the vulva) were reported during the first 3 months of therapy in the placebo controlled period of the 2 Phase 3 studies. Both events were reported in patients receiving tofacitinib 5 mg BID and started shortly after initiation of study treatment (Day 1 and Day 11 respectively). These events are described in detail for the All PSA Cohort experience below. No events were reported in the tofacitinib 10 mg BID, placebo or adalimumab groups.

12-month dose comparison cohort: IRs for malignancies in pooled tofacitinib data and comparison of tofacitinib (Study A3921091) to adalimumab are presented in Table 26. There were 3 reported malignancies in the all tofacitinib 5 mg BID treatment group. There were no reported events of malignancies (excluding NMSC) in patients treated with tofacitinib 10 mg BID or adalimumab.

Table 26. Incidence Rates for All Malignancy (Excluding NMSC): 12 Month Dose-Comparison

	Pooled Data				Study A3921091				
	Tofacitinib 5 mg BID	**Tofacitinib 10 mg BID**	**All Tofacitinib 5 mg BID***	**All Tofacitinib 10 mg***	**Tofacitinib 5 mg BID**	**Tofacitinib 10 mg BID**	**All Tofacitinib 5 mg BID**	**All Tofacitinib 10 mg BID**	**Adalimumab**
Number of Patients with Exposure	238	236	347	344	107	104	159	154	106
Number (%) of Patients	3 (1.3)	0 (0.0)	3 (0.9)	0 (0.0)	3 (2.8)	0 (0.0)	3 (1.9)	0 (0.0)	0 (0.0)
Total Drug Exposure (PY)	153.88	151.13	200.76	197.23	93.64	92.45	126.94	124.85	92.62
Incidence Rates	1.95 (0.40, 5.70)	0.00 (0.00, 2.44)	1.49 (0.31, 4.37)	0.00 (0.00, 1.87)	3.20 (0.66, 9.36)	0.00 (0.00, 3.99)	2.36 (0.49, 6.91)	0.00 (0.00, 2.95)	0.00 (0.00, 3.98)

Abbreviations: BID = twice daily;
NMSC = non-melanoma skin cancer; PY = patient-year
*Includes the tofacitinib-exposed period from patients that advanced from placebo treatment
Gaps in between the qualifying studies and long term extension studies are included up to 28 days or to the end of 12-month dose comparison.
Incidence rate was a naïve estimate without adjusting for study.
Source: Summary of Clinical Safety, Table 44

All PsA Cohort: Five (5) malignancies (excluding NMSC) in patients receiving tofacitinib 5 mg BID were reported in the PsA program (Table 27).

Table 27. Exposure Estimates and Incidence Rates for All Malignancies Excluding NMSC (All PsA)

Treatment Group	Tofacitinib All Doses	Tofacitinib 5 mg BID[a]	Tofacitinib 10 mg BID[b]
Total Patients with Exposure	783	463	320
Number of Patients with Event n (%)	5	5	0
Total PY Exposure for Event	790.51	462.57	327.94
Incidence Rate/100 PY (95% CI)	0.63 (0.21, 1.48)	1.08 (0.35, 2.52)	0.00 (0.00, 1.12)

Abbreviations: BID = twice daily; CI = confidence interval; PY = patient-years; NMSC = non-melanoma skin cancer; n = number of patients; PsA = psoriatic arthritis
a. Patients with an average total daily dose of <15 mg over the course of observation
b. Patients with an average total daily dose of ≥15 mg over the course of observation
Incidence rate was a naïve estimate without adjusting for study.
Source: Summary of Clinical Safety, Table 45

A listing of patients with Malignancies (excluding NMSC) is presented in Table 28.

Table 28. Listing of Patients with Malignancies (excluding NMSC)

Patient	Randomization Sequence	Dose at Event Onset	Gender/ Race/ Age	Days on Tofacitinib	Preferred Term
1091-10221017	Tofacitinib 5 mg BID	Tofacitinib 5 mg BID	M/W/58	48	Bladder transitional cell carcinoma
1091- 11471002	Tofacitinib 5 mg BID	Tofacitinib 5 mg BID	F/W/65	65	Squamous cell carcinoma of the vulva
1091-11821002	Tofacitinib 5 mg BID	Tofacitinib 5 mg BID	F/W/67	244	Breast cancer
1092-12001001 (1091-10361003)	Adalimumab	Tofacitinib 5 mg BID	M/O/44	32 (342 days on ADA)	Renal cell carcinoma
1092-12031013 (1091-10621004)	Adalimumab	Tofacitinib 5 mg BID	M/W/52	84 (353 days on ADA)	Pancreatic cell carcinoma metastatic

Source: Abbreviations: Tofa= tofacitinib; BID = twice daily; NMSC = non-melanoma skin cancer; M = Male; F = Female; W = White; O = Other; ADA = adalimumab.
a. Days of Exposure on Tofa is cumulative of index and LTE exposure at time of onset
b. Number in parentheses indicates the number of days outside of the risk period when the event occurred
* International Classification of Disease –Oncology Version 3
Risk period for calculation: Total follow up time calculated up to the day of the first event, patient to a risk period of 28 days beyond the last dose or to the data cutoff date. Gaps in dosing between treatment switches or between the qualifying and LTE studies are included up to 28 days or to the data cutoff date
Source: Summary of Clinical Safety, Table 46

Patient Narratives

Patient A3921091 10221017, a white 58 year old male from Poland, was recruited for participation in Study A3921091. The reported relevant medical history included type II diabetes mellitus since 1997, dyslipidemia since 2005 and autoimmune thyroiditis since 2006. He had never smoked. The patient was randomized to the tofacitinib 5 mg BID group

and received treatment from 30 Oct 2014 to 22 Jan 2015. At the randomization visit the central laboratory results reported hematuria which was not associated with other signs and symptoms. Upon investigation of the hematuria an ultrasound showed an exophytic tumor of the bladder (b) (6)). The patient was hospitalized and had a transurethral resection of the tumor. Pathology results were not immediately available. The patient was discharged from the hospital without complications. Pathology results reported a "low grade urothelial urinary bladder carcinoma". The patient was withdrawn from the study as a result of this event. The patient was reported to have recovered from the event.

Patient A3921091 11471002, a 65 year old white female patient from Mexico, was enrolled in Study A3921091 and randomized to the tofacitinib 5 mg BID treatment group. She received treatment from 22 Dec 2014 to 24 Feb 2015. After 60 days on treatment the central laboratory reported multiple abnormalities in the urine specimen. The patient had reported to the investigator some nonspecific urinary symptoms and ankle pain. Upon a targeted physical exam and further investigation an inguinal abscess was identified. The patient was hospitalized to treat the infection and surgical debridement of what was found to be a solid tumor of the external genital area. A computed tomography (CT) scan and ultrasound were also completed and revealed multiple enlarged lymph nodes and the tumor. Local pathology reported the tissue from the tumor to be an invasive squamous cell keratinizing carcinoma of the vulva. The MAC and central histopathology over read concurred with the local laboratory report. The patient was withdrawn from the study as a result of this event and was reported as not recovered at the time of the last observation.

The patient reported to have had breast cancer was a 67 year old white female from the US (PID A3921091- 11821002). The relevant medical history included cholecystectomy in 2001, hysterectomy in 2010, pleural effusion in 2008, and menopause in 2011 in addition to present history of Meniere's disease, depression, hypothyroidism, gastroesophageal reflux disease (GERD) and atrial flutter. The patient was randomized to the tofacitinib 5 mg BID arm and received treatment from 20 Aug 2014 to 22 Apr 2015. After 244 days of treatment the patient was diagnosed with Invasive Ductal breast carcinoma of the left breast. The diagnosis was made when her yearly mammogram was compared to the previous one and calcifications were observed. A biopsy of the left breast was completed on 14 April 2015 and diagnosis was confirmed with a stereotactic biopsy on 20 Apr 2015. The tumor was removed after a partial left mastectomy. No lymphovascular invasion was identified. The patient was discontinued from the study as a result of this event. The MAC concurred with the local pathology report. At the time of the snapshot, the patient was reported to be recovered from the event.

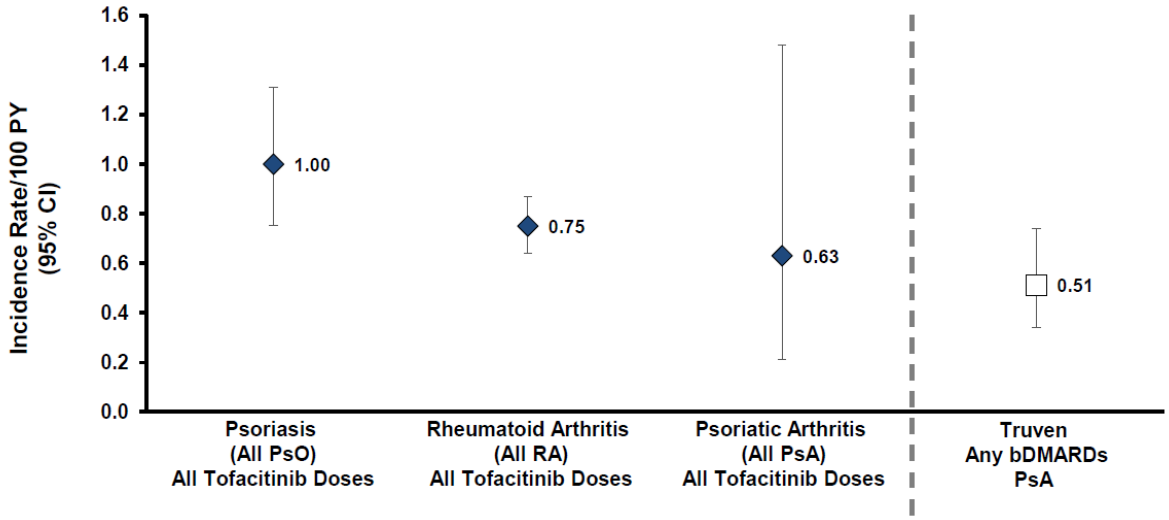
Patient A3921092 12001001 was a 45 year old Hispanic male from Mexico with relevant medical history of hypertension since 2008 and active smoking status (18 cigarettes/day since age 14). No family history of malignancy was reported or personal prior history of malignancy, hematuria, or exposure to chemicals or radioactive substances. The patient was enrolled in study A3921091 and randomized to the adalimumab treatment arm. He started study treatment with adalimumab 40 mg SC every 2 weeks (q2w) and placebo from 16 Dec 2014 to 22 Nov 2015. Upon completion the patient rolled over to the LTE study on and started tofacitinib 5 mg BID on 23 Nov 2015. After 32 days of treatment with tofacitinib the subjected experienced hematuria. He did not report abdominal pain, fever, or dysuria,

complaints during bowel movements or intestinal bleeding. On Day 33 an abdominal ultrasound was completed and a CT scan was done the next day. Both showed a solid tumor on the left kidney. The patient underwent a total left nephrectomy on (b) (6). The pathology laboratory results reported "renal cell carcinoma". The patient was withdrawn from the study as a result of this diagnosis and was reported as recovered on 9 March 2016. At the time of the last observation the patient was reported as recovered from the event.

Patient A3921092 12031013 was a 52 year old white male from Poland, with a relevant medical history of lumbar spondyloarthropathy since 2002, PsO since 1990, varicose veins in both legs since 2004. He was reported as an active smoker (pack-years unknown) at the time of enrollment. The patient enrolled in study A3921091 and was randomized to the adalimumab arm on (b) (6). The patient received treatment with adalimumab 40 mg SC q2w for the 12 months study duration. Upon completion he entered the long term extension (LTE) study A3921092 where he started treatment with tofacitinib 5 mg BID. After 84 days on tofacitinib the patient experienced back and abdominal pain ((b) (6)), for which he sought treatment at the emergency room in the local hospital. As part of initial investigations of the pain, an abdominal ultrasound was performed, which reported initially a mass of the liver and several other small masses. The largest mass was biopsied, by fine needle aspiration on (b) (6) and was read as metastatic pancreatic adenocarcinoma. A CT scan, performed on the same day reported: disseminated metastasis in the liver (the largest measuring 140mm x 98mm) and in several retroperitoneal lymph nodes. The gallbladder was described with the fundus involved in the infiltrate, and had no signs of cholestasis. Chest x-ray revealed signs suspicious of bone lytic metastasis. Colonoscopy and gastroscopy, both performed on (b) (6), did not show other signs of malignancy. As a result of the diagnosis the patient was discontinued from the study drug on (b) (6) and subsequently died as a consequence of the event on (b) (6).

Malignancies (excluding NMSC) incidence rate for patients in the tofacitinib 5 mg BID group and the incidence rates calculated for all patients receiving tofacitinib in the PsA program in PsA are within range of those reported in other tofacitinib long term study data. The incidence rate for patients receiving tofacitinib in the PsA program is within range of those observed in the RA and PsO programs (Figure 9 and Table 19). Contextualization with the Truven comparison cohort is presented in Section 6.3.6.2.1.1.

Figure 9. Incidence Rates for Malignancies (Excluding NMSC in PsA, RA, and PsO (All PsA Cohort Comparison and Truven Marketscan Comparison Cohort)



N	3623	6300	783	5075
n	52	168	5	28
PY of Exposure	5203.6	22,353.7	790.5	5499.1

Abbreviations: CI = confidence interval; PY = Patient Years; N = number of patients evaluable; n = number of patients with an event; NMSN = non-melanoma skin cancer; LTE = long-term extension; PsA = psoriatic arthritis; RA = rheumatoid arthritis; PsO = psoriasis; tofa = tofacitinib
Vertical bars represent 95% CI of the incidence rate
Source: Source: Summary of Clinical Safety, Table 2.1.2.1.3 (PsO), Table 1182.2.6 (RA), Table C3.2.2.1 (PsA), and Table 13 (Truven).

6.3.6.2.1.1. Contextualization Data for All Malignancies (Excluding NMSC)

Randomized Clinical Trial Literature

Although there were limited reports of malignancies (excluding NMSC) available in the published literature (including LTE trials), the incidence rates for malignancies (excluding NMSC) in tofacitinib treated PsA subjects were found to be within the range of those that were reported.

Observational Literature All Malignancies (Excluding NMSC)

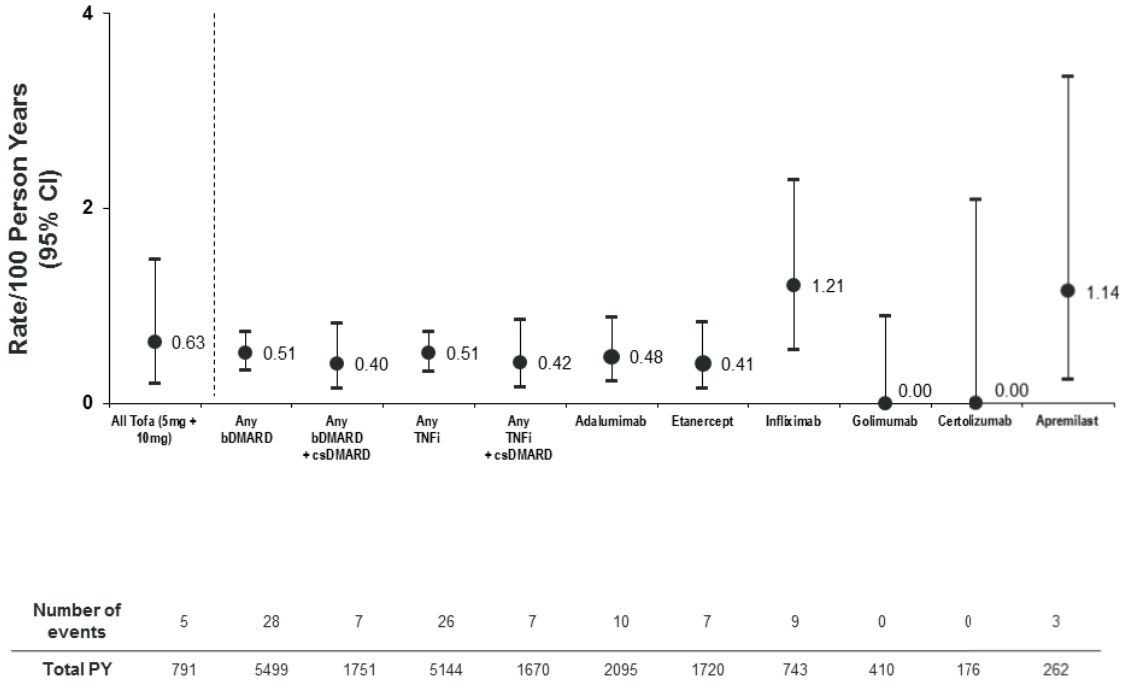
There was no observational literature for malignancies excluding NMSC.

Rates of Malignancies in Patients with Psoriatic Arthritis from the Truven Marketscan Comparison Cohort

Rates of malignancy (excluding NMSC) from tofacitinib All PsA cohort are presented alongside those obtained from the Truven comparison cohort. The CIs for the incidence rates overlap, and the rates appear similar. As described in Section 6.3.1, all comparisons between

the PsA tofacitinib development program and the Truven comparison cohort should be made with consideration of the distinct data sources, including varying background csDMARD use, capture and definition of events, and few events of interest in the PsA tofacitinib development program

Figure 10. Malignancy (excluding NMSC) Events among Tofacitinib All PsA and Truven PsA Comparison Cohorts



	All Tofa (5mg + 10mg)	Any bDMARD	Any bDMARD + csDMARD	Any TNFi	Any TNFi + csDMARD	Adalumimab	Etanercept	Infliximab	Golimumab	Certolizumab	Apremilast
Number of events	5	28	7	26	7	10	7	9	0	0	3
Total PY	791	5499	1751	5144	1670	2095	1720	743	410	176	262

Abbreviations: bDMARD = biologic disease modifying anti-rheumatic drug; CI = confidence interval; csDMARD = conventional synthetic disease modifying anti-rheumatic drug; NMSC = non-melanoma skin cancer; PsA = psoriatic arthritis; TNFi = tumor necrosis factor inhibitor; PY = patient-years; tofa = tofacitinib
Source: Summary of Clinical Safety, Figure 16

6.3.6.2.1.2. Overall Summary of Malignancy (Excluding NMSC) Events

All 5 events reported were single occurrences of different malignancy types and all occurred in patients receiving tofacitinib 5 mg BID. The incidence rate was comparable to those observed in the RA and PsO datasets and the comparison cohort. Only the event of breast cancer occurred >3 months after initiation of tofacitinib administration; based on the long latency of the other malignancy events, it is unlikely that these events had a causal relationship to tofacitinib administration.

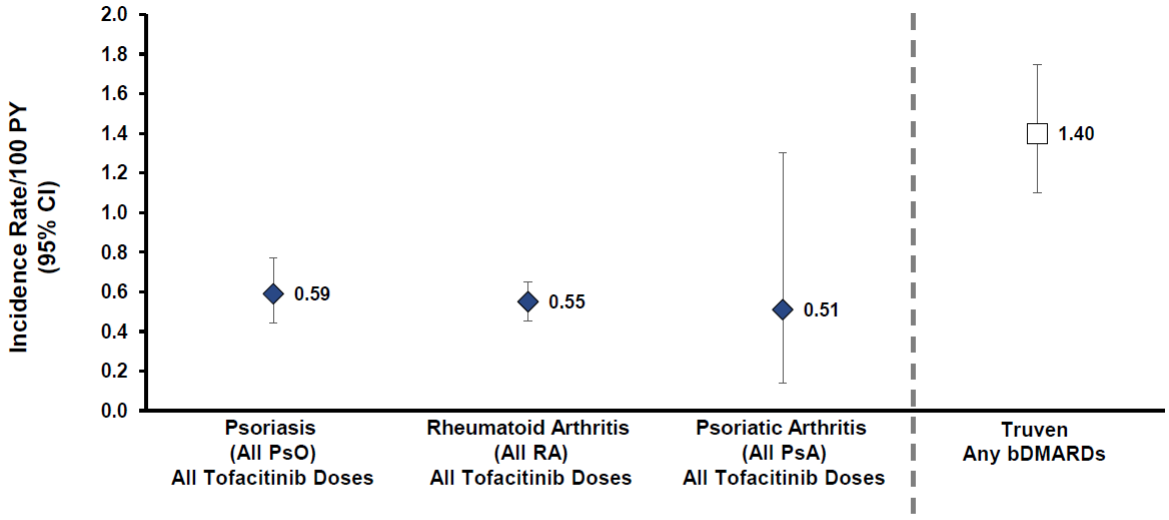
6.3.6.2.2. Non-melanoma Skin Cancer (NMSC)

Known risk factors for the development of NMSC include age, male sex, fair skin, sun exposure, history of actinic keratosis, and history of substantial exposures to ionizing radiation.[82] The rates of skin cancer are expected to vary with geographic location, due in

part to differences in the irradiation content of sun exposure. While other types of NMSC occur, basal cell carcinoma (BCC) and SCC are the most common. Immune suppression may play a key role in the development of both BCC and SCC although the incidence of SCC may be more affected by immunosuppression than BCC.[82]

All PsA Cohort: The incidence rates for NMSC in PsA, RA, and PsO and Truven comparison cohort are presented in Figure 11. Four patients (2 in tofacitinib 5 mg BID and 2 in tofacitinib 10 mg BID) experienced NMSC. The incidence rate for NMSC in the all tofacitinib dose group were in the same range as the incidence rates reported in the PsO and RA development programs (Table 19).

Figure 11. Incidence Rates for NMSC in PsA, RA, and PsO (All PsA Cohort & Truven Marketscan Comparison Cohort)



N	3662	6300	783	5075
n	51	121	4	76
PY of Exposure	8689.7	22,131.5	789.2	5447.8

Abbreviations: CI = confidence interval; PY = Patient Years; N = number of patients evaluable; n = number of patients with an event; NMSN = non-melanoma skin cancer; PsA = psoriatic arthritis; RA = rheumatoid arthritis; PsO = psoriasis; BID = twice daily
Vertical bars represent 95% CI of the incidence rate
Source: Source: Summary of Clinical Safety, Table 198.2.1.2 (PsO), Table 1182.5.13 (RA), Table C3.2.2.1 (PsA), and Table 19 V2 (Truven).

A listing of patients with NMSC is presented in Table 29. There were 2 patient with BCC and 2 patients with SCC.

Table 29. Listing of Patients with NMSC

Study Subject	Randomization Sequence	Dose at Event Onset	Gender/ Race/ Age	Days on Tofacitinib	Preferred Term
A3921091 10561002	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	F/W/67	443	Squamous cell carcinoma
A3921125 10531005	Placebo – Tofacitinib 10 mg BID	Tofacitinib 5 mg BID	F/W/45	212	Squamous cell carcinoma
A3921091 11141001	Tofacitinib 10 mg BID	Tofacitinib 10 mg BID	M/W/63	103	Basal cell carcinoma
A3921125 12041005	Tofacitinib 10 mg BID	Tofacitinib 10 mg BID	M/W/53	269	Basal cell carcinoma

Source: Abbreviations: Tofa= tofacitinib; BID = twice daily; NMSC = non-melanoma skin cancer; M = Male; F = Female; W = White
a. Days of Exposure on Tofa is cumulative of index and LTE exposure at time of onset
b. Number in parentheses indicates the number of days outside of the risk period when the event occurred
* International Classification of Disease –Oncology Version 3
Risk period for calculation: Total follow up time calculated up to the day of the first event, subject to a risk period of 28 days beyond the last dose or to the data cutoff date. Gaps in dosing between treatment switches or between the qualifying and LTE studies are included up to 28 days or
to the data cutoff date
Source: Summary of Clinical Safety, Table 49

6.3.6.2.2.1. Contextualization Data for NMSC

Randomized Clinical Trial Literature for NMSC

Although there were limited reports of NMSC available in the published literature (including LTE trials), the incidence rates for NMSC in tofacitinib treated PsA patients were found to be within the range of those that were reported. Tofacitinib incidence rate for NMSC from the Tofacitinib All group was 0.51 per 100 PY (95% CI: 0.14, 1.30) compared to published NMSC incidence rates that ranged from 0.00 per 100 PY to 0.52 per 100 PY.

Observational Literature

No observational literature reporting the incidence of NMSC in treated PsA populations was identified.

6.3.6.2.2.2. Overall Summary of NMSC

Four events of NMSC (2 SCC and 2 BCC) occurred in patients who received all tofacitinib (1 patient received tofacitinib 5 mg BID and 3 patients received tofacitinib 10 mg BID). The incidence rate was within range of that previously reported for patients with PsA and similar to that seen in patients with RA and PsO exposed to tofacitinib.

6.3.6.3. Cardiovascular Risk Factors and MACE

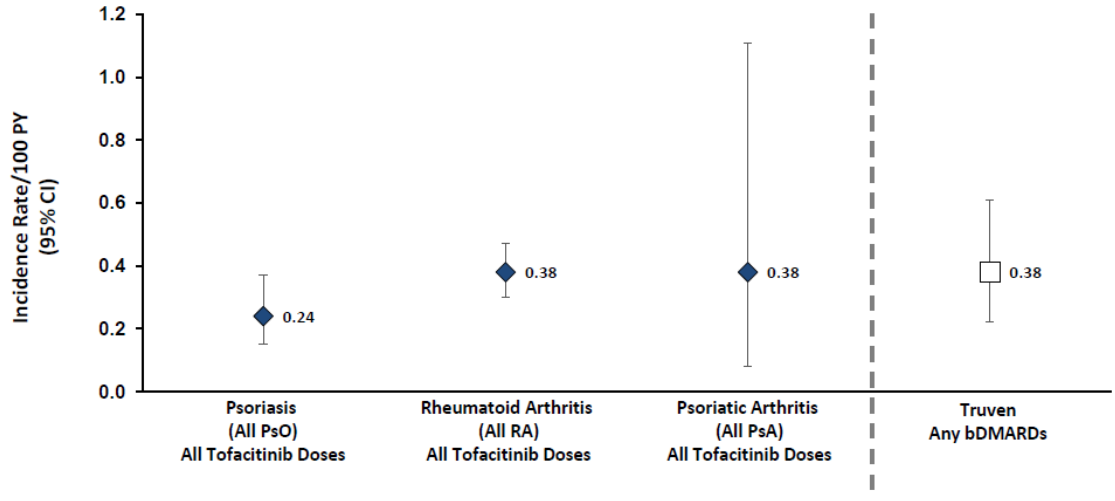
An association between PsA and increased CV risk has been described in the literature.[15] The effects of tofacitinib on key modifiable CV risk factors (such as lipid levels and blood pressure) were comprehensively investigated in the RA program, and included several mechanistic and functional studies.[83] The effects of tofacitinib on lipid profiles in RA patients compared to biological DMARDs were recently reported. No difference was found in the incidence of CV events with tofacitinib compared to other therapies, despite different lipid profile changes.[84] Potential CV events were carefully evaluated, monitored, and adjudicated during the PsA program.

All PsA Cohort: There were 3 MACE events reported in the tofacitinib All PsA (2 tofacitinib 5 mg BID and 1 tofacitinib 10 mg BID). Incidence rates for all tofacitinib doses were low. One MACE event in the tofacitinib 5 mg BID group was fatal (Subject 10781015; sudden cardiac death). The other nonfatal MACE events were myocardial infarction and ischemic stroke.

12-Month Dose Comparison Cohort: There was one MACE event (non-fatal ischemic stroke) was reported in the adalimumab treatment arm in Study A3921091.

The incidence rate for MACE in tofacitinib-treated patients in the PsA program is similar to those observed in the RA and PsO programs (Table 19 and Figure 12). Contextualization with the Truven comparison cohort is presented in Section 6.3.6.3.1

Figure 12. MACE Exposure Estimate and Incidence Rates in PsA, RA, and PsO



N	3662	5856	783	5057
n	21	80	3	17
PY of Exposure	8759.3	21,285.9	790.5	4467.8

Abbreviation: CI = confidence interval; PY = Patient Years; N = number of patients evaluable; n = number of events; LTE = long-term extension; MACE = major adverse cardiovascular event; PsA = psoriatic arthritis; RA = rheumatoid arthritis; PsO = psoriasis
Vertical bars represent 95% CI of the incidence rate
Source: Summary of Clinical Safety, Table 198.2.1.6 (PsO), Table 1182.2.19 (RA), Table C3.2.5.1 (PsA), and Table 21 (Truven).

6.3.6.3.1. Contextualization Data for MACE

Observational Literature

A single population-based cohort study conducted within the UK's The Health Improvement Network (THIN) database reported an incidence rate of MACE of 0.46 (95% CI: 0.38, 0.56) per 100 PY (101 events/21,829 patient-years)[15] among DMARD-exposed PsA patients (n=4532), consistent with the incidence rate observed for tofacitinib in this development program. However, incidence rate comparisons between the tofacitinib development program and the single published report must be made with consideration of differing population characteristics, capture and definition of events, and lengths of follow-up.

Rates of MACE in Patients with Psoriatic Arthritis from the Truven Marketscan Comparison Cohort

The Truven database only reported CV deaths that occurred in the hospital and was unable to identify MACE events occurring outside the hospital setting, limiting the utility of these event rates (Figure 12).

6.3.6.3.2. Overall Summary of Cardiovascular Safety

There were few MACE events in the PsA program. The incidence rates of MACE were within the range of rates reported for the PsO and RA datasets.

6.3.6.4. Other Events of Special Interest (Tuberculosis, Interstitial Lung Disease Hepatic Safety, and Gastrointestinal Perforations)

There were no events of TB or interstitial lung disease reported in the PsA program. There were no events of hepatic failure, fibrosis or cirrhosis reported for any patients on the PsA development program. No patients met Hy's Law criteria in the tofacitinib PsA development program.

There was a single event of GI perforation reported in a patient while on tofacitinib 5 mg BID (Subject A3921091- 10171022) for 18 days with treatment-emergent appendicitis and subsequent appendiceal perforation.

6.3.7. Evaluation of Laboratory Parameters

Patients in the PsA program were excluded for preexisting laboratory abnormalities, illnesses or safety concerns that could adversely affect subject health or confound study safety results. These exclusion criteria were based on previous tofacitinib studies and regulatory interactions in other indications. In addition, laboratory abnormalities were subject to strict monitoring and discontinuation guidelines.

Few patients in the tofacitinib PsA studies had abnormal laboratory findings requiring discontinuation due to laboratory abnormalities. Tofacitinib's effects on laboratory parameters were well characterized in previous tofacitinib development programs. The following describes the laboratory abnormalities in the PsA program which are consistent with those observed in the tofacitinib development program as described in the current USPI:

Lymphocyte Abnormalities

The effect of tofacitinib administration on absolute lymphocyte counts (ALCs) in PsA subjects was biphasic, with an initial, dose dependent and transient increase. A modest ALC decline was observed in the long term (eg, up to Month 18) with median change from baseline of -0.14 ($10^3/mm^3$) for All tofacitinib.

Neutropenia

After initiation of tofacitinib treatment, a rapid, dose-dependent decrease from baseline in mean absolute neutrophil count (ANC) was observed which remained relatively constant after 2 months. A similar pattern was observed in subjects treated with adalimumab. During the 6 month treatment period, the number (%) of subjects who experienced ANC <0.8 x lower limit of normal (LLN) was similar across treatment groups (tofacitinib 5 mg BID = 9 (3.8%); tofacitinib 10 mg BID =13 (5.5%) and adalimumab = 5 (4.7%).

Anemia

For all subjects receiving tofacitinib, the proportion (0.9%) and incidence rate per 100 PY (0.89 [95% CI: 0.36, 1.83]) for anemia as reported by the investigator were low. Of the anemia AEs reported, most were mild 7(0.9%), few moderate 1 (0.1%) and none severe. Most anemia events resolved (6 of 8).

Liver Enzymes

In tofacitinib-treated subjects, ALT increases ≥3 x ULN were uncommon (1 subject in the tofacitinib 5 mg BID and 1 in adalimumab) and did not follow a dose- dependent pattern. AST increases ≥3 x ULN did not occur. There were no bilirubin increases ≥2 x ULN in subjects receiving active treatment.

Lipid Elevations

In the PsA studies, there was a dose dependent increase of total cholesterol evident as early as Month 1, which stabilized at Month 3, with a median percent change from baseline of approximately 8.2% for subjects treated with tofacitinib 5 mg BID and 11.3% for 10 mg BID. Results for adalimumab are similar in magnitude and trend to those of tofacitinib 5 mg BID, which are consistent and numerically lower than findings reported in the RA and PsO development programs.

Serum Creatinine

In the tofacitinib program, small, reversible increases in serum creatinine have been reported in the clinical RA trials. Changes in measured glomerular filtration rate were not observed in a study of healthy volunteers.

Treatment with tofacitinib in the PsA program resulted in rapid, modest, dose-dependent mean increases from baseline in serum creatinine levels. At Month 3 visit, subjects treated with tofacitinib showed median (Q1, Q3) increases in serum creatinine that were 0.011 (-0.023, 0.10) mg/dL and 0.034 (-0.011, 0.1) mg/dL for tofacitinib 5 mg BID and 10 mg BID,

respectively. These changes were slightly greater than for adalimumab (median change=0) or placebo (median change=0) at Month 3.

6.4. Post-marketing Data for RA

Review of the types and frequencies of AE reports from post-marketing spontaneous/non-interventional studies/non-interventional solicited source supports the known safety profile of tofacitinib identified through the tofacitinib clinical development program and no new safety signals were identified. No new ADRs were identified in postmarketing compared to clinical trials. As the PsA safety profile is similar to that of RA, it is expected that the PsA post-marketing safety data will be similar.

As of 05 May 2016, there were approximately 45,410 PY of post-marketing exposure to tofacitinib. There were 13,574 case reports received by the Sponsor during the 3.5-year reporting period from 06 November 2012 through 05 May 2016. A total of 37,788 AEs were reported, and of these, 37,445 were from spontaneous sources. The other 343 AEs were reported from non-interventional studies and other non-interventional solicited sources. Of the 37,788 AEs, the majority (30,905; 81.8%) were non-serious and the remainder (6,883; 18.2%) were SAEs. The most common SAEs reported were RA (5.0%), condition aggravated (4.4%), and pneumonia (2.3%). These events are already described in the product labeling for tofacitinib.

Of the 13,574 AEs reported, the most common (≥2%) AEs were drug ineffective (13.8%), headache (8.8%), condition aggravated (6.9%), pain (6.3%), fatigue (5.9%), nausea (5.8%); diarrhoea (5.7%), arthralgia (5.4%), RA (5.0%), pain in extremity (4.4%), nasopharyngitis (4.0%), malaise (3.9%), product use issue (3.6%), peripheral swelling (3.4%), cough (3.0%), abdominal discomfort (2.9%), joint swelling (2.9%), abdominal pain upper (2.9%), HZ (2.6%); sinusitis (2.4%), rash (2.3%), pneumonia (2.3%), drug effect incomplete (2.3%), drug dose omission (2.3%), vomiting (2.2%), dyspnoea (2.2%), pyrexia (2.2%), urinary tract infection (2.2%), weight increased (2.1%), and influenza (2.0%). Of the 13574 AEs reported, the most common SAEs (≥ 1%) were RA, (5.0%), condition aggravated (4.4%), and pneumonia (2.3%).

A post-authorization safety study (PASS) in RA patients is being conducted within the US Consortium of Rheumatology Researchers of North America (Corrona) Registry evaluating rates of safety events among initiators of tofacitinib and 2 comparator cohorts (i.e., bDMARD initiators and csDMARD initiators). As of the last interim report (dated 31 May 2016), a total of 1073 patients with RA who initiated therapy with tofacitinib were enrolled. Of these patients, 874 patients had a least 1 follow-up visit reported within the registry, representing approximately 904 PYs of exposure. While the initial event counts are small, current estimated rates of safety events are in line with reported rates in the literature (e.g., Dixon WG, et al. 2006).[85] Furthermore, there are no substantial differences among the cohorts in event rates. The additional accumulation of initiators and person years of follow-up will allow a full comparative risk analysis as planned and the quarterly updates provide the opportunity to quickly detect any signal that might occur and provide a full analytic assessment of any risk. No new safety signals have been identified as of 31 May 2016.

6.5. 120-Day Safety Update Conclusions

Reference is made to the Tofacitinib 120-Day Safety update that was submitted to the FDA on 22 June 2017. This 120-Day safety update provides additional safety data from the tofacitinib ongoing PsA LTE Study A3921092 obtained between the date of the initial submission data snapshot (10 May 2016) through 08 February 2017. With the data update, there were an additional 474.94 PY of exposure to both doses of tofacitinib, representing a 61.2% increase in patient exposure from the initial submission, resulting in a total of 1250.66 PY of exposure in the PsA program. This increase occurred as a result of continued participation in the LTE study. While a full summary is not provided in this document, the safety profile presented in the 120-Day safety update is similar to that presented in the initial PsA sNDA. No new safety findings were identified since the initial tofacitinib PsA submission and the risks associated with tofacitinib 5 mg BID treatment in active PsA remain of the same magnitudes as before and have been manageable via the existing measures employed for the approved indication of RA described in the current prescribing information. Tofacitinib continues having a similar safety profile to the one reported in the initial submission. The rates, patterns over time and outcomes of AEs of special interest occurring since the initial submission remain consistent with that reported in this document as well as in the initial submission.

6.6. Safety Conclusions

The safety profile of tofacitinib, including that of PsA, is well characterized, stable and clinically manageable. It is informed by a growing safety database, with consistency between clinical trial data, postmarketing experience, and the Truven database.

The PsA safety findings were consistent with those observed in the RA and PsO development programs (which are substantially larger and have a longer follow-up period). In addition, the safety profile is similar compared with that of other drugs used to treat PsA.

No new safety findings were identified and the risks associated with tofacitinib treatment can be mitigated or are manageable via the existing measures employed for the approved indication of RA as described in the current prescribing information.

7. RISK MONITORING AND MITIGATION

The risk management and pharmacovigilance plan assures effective detection, assessment, mitigation and communication of safety risks.

There are no new risks identified in the PsA program based on the completed studies. The current product labeling information regarding the risks with tofacitinib can be viewed as appropriate for the PsA indication.

Current product labeling includes the following warnings and precautions: SIs and other important infections (OIs, TB, viral reactivation), malignancy and lymphoproliferative disorders (including NMSC), GI perforation, and laboratory abnormalities. The labeling also states to avoid use of live vaccines concurrently as well as recommendations for dose modifications include considerations for renal/hepatic impairment, and management of certain drug-drug interactions (DDIs).

General strategies for risk assessment and pharmacovigilance have already been successfully established for tofacitinib for the treatment of RA. A number of potential safety signals have been evaluated since the approval of tofacitinib in RA. As a result, some of these safety signals led to proposed labeling updates such as events related to infections and malignancies. The proposed risk management plan supports effective detection, assessment, mitigation and communication of risks.

Since the overall risks with tofacitinib for PsA are the same as that in RA, the same strategy for risk mitigation will be extended to the PsA program. The findings from ongoing RA clinical trials and pharmacovigilance activities will further inform the safety profile in PsA.

7.1. Management and Monitoring Risk of Serious and Other Important Infections

Management of the risk of serious and other important infections is addressed in the current tofacitinib USPI (Section 5.1) for RA. Considerations prior to treatment include the following:

- Avoid use in patients with an active, SI, including localized infections. The risks and benefits of treatment should be considered prior to initiating treatment in patients with chronic or recurrent infection, those who have been exposed to TB, those with a history of a SI or an OI, those who have resided or traveled in areas of endemic TB or endemic mycoses, and those with underlying conditions that may predispose them to infection.

- Patients should be evaluated and tested for latent or active TB prior to treatment. Patients with latent TB should start anti-TB therapy prior to treatment, and anti-TB therapy should also be considered prior to treatment in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but who have risk factors for TB. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting treatment.

- It is recommended that tofacitinib treatment not be initiated in patients with an ALC less than 500 cells/mm^3 or an ANC less than 1000 cells/mm^3. Update immunizations in agreement with current guidelines prior to initiating treatment.

Considerations during treatment include the following:

- Dose interruption is recommended for management of lymphopenia or neutropenia. Specifically, for ALC less than 500 cells/mm^3, discontinue tofacitinib. Additionally, for persistent decreases of ANC of 500-1000 cells/mm^3, interrupt dosing until ANC is greater than 1000 cells/mm^3. When ANC is greater than 1000 cells/mm^3, resume tofacitinib 5 mg BID. For ANC less than 500 cells/mm^3, discontinue tofacitinib.

- Patients should be closely monitored for the development of infection during and after treatment. Treatment should be interrupted if a patient develops a SI until the infection is controlled. A patient who develops a new infection during treatment should undergo prompt and complete diagnostic testing appropriate for an

immunocompromised patient; appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

Additionally, the proposed USPI in support of the PsA indication includes infections (nasopharyngitis and upper respiratory infections) that were observed in ≥2% of patients treated with tofacitinib (either 5 mg BID or 10 mg BID) and at least 1% greater than the proportion observed in placebo in the PsA pivotal clinical trials.

7.2. Management and Monitoring Risk of Malignancies

Management of the potential risk of malignancies (excluding NMSC) and the risk of NMSC is addressed in the current USPI (Section 5.2). Considerations prior to and during treatment include the following:

Consider the risks and benefits of treatment prior to initiating treatment in patients with a known malignancy other than a successfully treated NMSC or when considering continuing treatment in patients who develop a malignancy.

Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

7.3. Management and Monitoring Risk of MACE

Management of the potential risk of CV events and monitoring of lipid elevations are addressed in the current USPI (Section 5.4). Considerations during treatment include the following:

Assessment of lipid parameters should be performed approximately 4-8 weeks following initiation of treatment. Patients with hyperlipidemia should be managed according to clinical guidelines.

7.4. Use in Pregnancy and Lactation

There are no adequate and well-controlled studies in pregnant women. XELJANZ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Tofacitinib has been shown to be fetocidal and teratogenic in rats and rabbits when given at exposures 146 times and 13 times, respectively, the maximum recommended human dose (MRHD).

Tofacitinib was secreted in milk of lactating rats. It is not known whether tofacitinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from tofacitinib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug for the mother.

In the PsA clinical development program, as of 10 May 2016, there were 3 cases of maternal exposure and 2 cases of paternal exposure during pregnancy. Exposure to tofacitinib occurred in the first trimester in all cases. In 2 of the maternal exposure cases, the dose taken was 5 mg BID; the outcomes were 1 spontaneous abortion and 1 pending. In the other

maternal exposure case, the dose taken was 10 mg BID, and the outcome was elective abortion. The dose taken in the paternal exposure cases was 5 mg BID in one case and 10 mg BID in the other case. The outcome of one paternal exposure case was outcome pending, and in the other case, outcome is unknown. No cases of exposure during breast feeding were reported in the PsA development program.

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to tofacitinib during pregnancy. A PsA component will be added to the existing registry activities supporting tofacitinib's RA indication. Tofacitinib should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The current USPI presents information for Pregnancy in Section 8.1 Use in Specific Populations and information for Lactation in Section 8.3, Nursing Mothers.

7.5. Overdose

There were no intentional overdoses in the PsA program. Drug over-compliance was reported infrequently with no reports of associated AEs. This result was similar to those reported in the tofacitinib RA and PsO programs. The current USPI presents information for Overdose in Section 10, Overdosage.

7.6. Drug Interactions

The clearance mechanisms for tofacitinib are approximately 70% hepatic metabolism and 30% renal excretion of unchanged drug. The metabolism of tofacitinib is primarily mediated by cytochrome P450 (CYP)3A4 (accounting for ~53% of total clearance) and by CYP2C19 (accounting for ~17% of total clearance). Thus, drugs that are inhibitors or inducers of CYP3A4 are likely to influence the PK of tofacitinib; the recommended tofacitinib dose is 5 mg QD in:

- Patients receiving potent inhibitors of CYP3A4 (eg., itraconazole)
- Patients receiving one or more concomitant medications that result in moderate inhibition of CYP3A4 as well as potent inhibition of CYP2C19 (for example, fluconazole).

Coadministration of tofacitinib to PsA patients with potent inducers of CYP3A4, such as rifampin, may result in loss of or reduced clinical response to tofacitinib.

The potential for tofacitinib to affect the PK of other drugs, including those metabolized by CYP450 isoforms, is low. The drugs evaluated for interactions included midazolam, oral contraceptives, MTX and metformin.

There is a risk of added immunosuppression when tofacitinib is coadministered with potent immunosuppressive drugs (e.g., azathioprine, tacrolimus, cyclosporine). Combined use of multiple-dose tofacitinib with potent immunosuppressants has not been studied. Use of tofacitinib in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

The current USPI presents information for Drug Interactions in Section 2.3 Dosage Modifications due to Drug Interactions and Section 7, Drug Interactions.

7.7. Drug Abuse

There were no reports of drug abuse or dependence or other information relevant to the potential for drug abuse in the PsA or RA clinical development programs.

7.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

In the PsA program, there have been no reports of impairment of the senses, coordination, or other factors that would result in diminished ability to drive vehicles or operate machinery or that would impair mental ability. This was similar to what has been reported in the tofacitinib RA program.

7.9. Patient Populations Not Studied

A number of exclusion criteria were applied in the clinical development program. Subjects <18 years of age were excluded. Subjects were excluded from the studies if they had recent, chronic, active, or untreated latent infections, including evidence of infection with hepatitis B, hepatitis C or Human immunodeficiency virus (HIV). Subjects were excluded if they currently had non-plaque forms of PsO, e.g., erythrodermic, guttate or pustular, with the exception of nail PsO, which was allowed. Pregnant females, breastfeeding females, females of childbearing potential not using highly effective contraception or not agreeing to continue highly effective contraception were excluded from the studies. Subjects were excluded if they had current or recent history of a severe, progressive or uncontrolled renal, hepatic, hematological, GI, metabolic (including hypercholesterolemia), endocrine, pulmonary, CV, or neurologic disease. Subjects were specifically excluded if they were considered at increased risk for GI perforation (e.g., patients with diverticulitis).

Tofacitinib has not been studied in PsA patients with elevated baseline transaminases (≥1.5x ULN), or those with creatinine clearance, Hgb, ALC, neutrophil or platelet counts below specified cutoff values.

8. BENEFIT/RISK PROFILE FOR TOFACITINIB IN PsA

PsA is a progressive, distinct, complex, chronic, inflammatory, musculoskeletal disease with manifestations in multiple domains that results in disability and impaired quality of life. There is a substantial unmet medical need for an oral medication, such as tofacitinib, which has a similar efficacy profile and a well-characterized safety profile relative to a TNFi, for PsA patients with active disease. The overall benefit/risk for tofacitinib in PsA is supported by efficacy and safety data from large RA and PsO development programs with a clinical safety database of up to 8 years of clinical experience, as well as a large and expanding postmarketing experience. The results of the comprehensive risk/benefit framework analysis of tofacitinib efficacy and safety in patients with active PsA are presented in Appendix 1.

- The efficacy responses of patients with PsA to tofacitinib were consistently effective across a broad range of patients, from those naïve to TNFi to those who have failed TNFi therapy for a variety of reasons. In both studies (A3921091 and A3921125) tofacitinib 5 mg BID met the primary endpoints of ACR20 response rate and HAQ-

DI. Improvements in the primary endpoints were noted by Week 2, the first assessment visit. Collectively, the data from these studies demonstrated consistent and clinically meaningful improvement across the primary and secondary PsA disease domains of peripheral arthritis, enthesitis, dactylitis, and psoriatic skin lesions. Additionally, clinically meaningful improvements were observed in patient-reported measures encompassing physical function, overall quality of life, pain, and fatigue.

- The cumulative safety data in the tofacitinib program encompasses over 30,000 PY in clinical trials with exposure durations up to 9 years in patients with RA and approximately 75,000 PY in real world data. The majority of knowledge with identifying risk and implementing risk mitigation comes from this experience. The safety data in the PsA program is very consistent with which has been reported in the RA program.

- In the PsA program, the identified risks associated with tofacitinib in PsA patients include infections and NMSC. HZ infection was recognized as a risk in the RA program. The incidence rate of other infections was consistent with that observed in RA and similar to those reported in clinical trials of TNFi. Based on the cumulative safety data, infections including HZ respond to treatment and follow a typical clinical course. This is consistent for SIs as well as OIs. As with any immune-modulatory therapy, the potential risks include malignancies other than NMSC.

- The similarity and the consistency of the risk profile of tofacitinib observed in the PsA and RA clinical trial experience, the postmarketing data, and the real world safety data, representing more than 100,000 PY exposure to tofacitinib combined, provide a robust understanding of the safety risk profile of tofacitinib.

In summary, the benefit/risk profile of tofacitinib in the treatment of PsA, when used as directed, is favorable and optimized when dosed at 5 mg BID based on substantial clinical evidence.

- Tofacitinib 5 mg BID was demonstrated to be an efficacious dose for the treatment of active PsA across the 2 pivotal Phase 3 studies in TNFi-naïve and TNF-IR populations and across multiple PsA disease domains (peripheral arthritis, enthesitis, dactylitis and psoriatic skin lesions).

- In a TNFi-naïve population (A3921091), tofacitinib 5 mg BID achieved efficacy similar to adalimumab 40 mg SC q2w on multiple PsA domains and had a similar safety profile.

- Pooled efficacy results (primary endpoints) were generally consistent across a range of baseline demographic (including age, gender, and race) and disease characteristics, geographic regions (US/Canada, Western Europe/Australia, Eastern European/Russia, and Rest of World).

- The safety profile of tofacitinib in patients with PsA is consistent with data from the RA and PsO safety databases, which are much larger and have longer follow-up periods. No new safety findings were identified.

- The risks identified for tofacitinib after up to 9 years of follow-up in clinical trials are similar to what has been observed in the post-marketing experience supporting a stable risk profile.

- The safety risks are typical of those observed with bDMARD products approved for the treatment of PsA, with the exception of a higher rate of HZ.[65] The risks associated with treatment of tofacitinib can be mitigated as per the current USPI.

9. OVERALL CONCLUSIONS AND RECOMMENDATIONS

Based on the data generated in the PsA program and summarized in this document, the following conclusions and recommendations are supported:

PsA is a complex, chronic, progressive, debilitating disease with significant remaining medical need.

In PsA, tofacitinib 5 mg BID has demonstrated efficacy consistent with approved bDMARDs in TNFi-naïve patients, in addition to demonstrating clear efficacy in TNFi-IR patients.

The safety profile of tofacitinib, including that of PsA, is well characterized, is clinically manageable and has been stable over a substantial period of time. It is informed by a large and growing safety database, with consistency between clinical trial data, postmarketing experience, and the Truven database.

Based on the totality of the safety and efficacy data, Pfizer believes that the benefit-risk profile of tofacitinib 5 mg BID in the treatment of PsA, when used as directed, is favorable.

The recommended dosing regimen for tofacitinib for the treatment of adult patients with active PsA is 5 mg BID.

APPENDIX 1 - MEDICAL NEED AND BENEFIT:RISK SUMMARY FOR TOFACITINIB FOR TREATMENT OF ACTIVE PSA

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition • Prevalence • Clinical Manifestations • Quality of Life • Physical and Mental Health Functioning • Systemic Comorbidities	• 0.06% to 0.25% of US adults. • Peripheral arthritis, enthesitis, dactylitis, axial spondylitis, plaque PsO. • Significantly decreased. • Significantly decreased. Profound impact akin to other major medical diseases such as diabetes, heart disease, hypertension, kidney disease, liver disease, lung disease, osteoarthritis, and RA. • Cardiovascular disease, metabolic syndrome, obesity, insulin resistance, type 2 diabetes mellitus, hyperlipidemia, osteoporosis, depression, anxiety, fatigue, kidney disease, hypertension.	PsA is a chronic progressive inflammatory disease that may result in permanent tenosynovial damage and disability. The disease manifestations can include a combination of peripheral arthritis, enthesitis, dactylitis, spondylitis, and psoriatic skin disease leading to additional progressive disability and adverse effects on quality of life.[1,2] PsA is characterized by multiple comorbidities and is associated with worse health status than many other common chronic diseases including diabetes, osteoarthritis, and RA.[16]

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition (Continued) **Available DMARD therapy** • csDMARDs • tsDMARD (Apremilast) • bDMARDs (adalimumab, certolizumab, etanercept, golimumab, infliximab, secukinumab, ustekinumab)	• Few studies • Lower efficacy compared to bDMARDs, limited data in TNF-IR, no data on inhibition of structural progression and intolerance. • Incomplete clinical response in some patients, parenteral ROA, immunogenicity, specific safety concerns, lack of dedicated or robust data in TNF-IR population. (Figure 4)	**Unmet Medical need:** • None of the current available therapeutic choices are effective for all patients in achieving target disease activity in all domains. • The overall drug survival times of currently approved DMARDs are insufficient for a chronic (often lifelong) disease, and there remain tolerability issues with both oral and injectable DMARDs. • There is a need for early intervention in both treatment naïve and csDMARD-IR patients, especially those at high risk for structural progression. Oral medications may be more acceptable to many patients than injectables. • There is a need for treatment options for patients with an inadequate response to TNFi • There is a need for therapies with different MOAs.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Benefits **Study designs**	**Study Description** • Two (2) confirmatory placebo-controlled RCTs were conducted (Study A3921091 which included an active control arm adalimumab and Study A3921125) with the following: 1) similar enrollment criteria and design for both, 2) robust approach to blinding, 3) adequate duration to establish efficacy and durability of effects [A3921091] across multiple demographics, 4) baseline characteristics representative of target PsA population, and balanced across treatment groups. • The study population did not include DMARD-naïve subjects. The efficacy of tofacitinib in DMARD-naïve subjects was demonstrated for RA subjects based on ACR20/50/70 and structural assessments (A3921069). In the RA development programs, safety was established in a substantial number of subjects who were DMARD-naïve. • Due to the redesign of the program pursuant to FDA recommendations, the geographic footprint included fewer sites in Asia compared to what was previously proposed, leading to inclusion of fewer Asian subjects. In addition, fewer black subjects were enrolled than originally expected, due to the large Eastern European site contribution combined with the overall lower prevalence of PsA in black subjects.[86] Geographic distribution also varied between the 2 studies, likely due to differences in access to TNFi between different countries.	• The study program was well designed to provide substantive evidence of efficacy, enrolled a population generally representative of that seen in clinical practice and employed robust design and analytical approaches to ensure integrity of the data. • Well-designed studies followed Regulatory Advice and controlled for potential confounding factors of geographical regional differences in clinical practice; these factors were prospectively mitigated by rigorous entry criteria regarding active PsA. • Study Design required certification/experience and training of assessors and protocol-mandated criteria regarding definitions of inadequate response to prior therapies. • Furthermore, subgroup analyses conducted on integrated data did not identify regional differences for efficacy.

<table>
<tr><th>Decision Factor</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td>Benefits (Continued)
Peripheral Arthritis</td><td>
Peripheral arthritis was study inclusion criterion at study entry and the study was specifically powered for the ACR20 and HAQ-DI endpoints at Month 3.
Tofacitinib 5 mg BID and 10 mg BID demonstrated statistically significant and clinically meaningful efficacy compared to placebo for the primary endpoints of ACR20 response rate and ΔHAQ-DI at Month 3 in both A3921091 and A3921125.
ACR20 and HAQ-DI Response Rates at Month 3 - Individual Studies A3921091 and A3921125
<table>
<tr><th colspan="3">ACR20 (FAS, Missing Response = Non-Response)</th><th colspan="2">HAQ-DI (MMRM, FAS, No Imputation)</th></tr>
<tr><th>Treat-ment Group</th><th>n/N</th><th>Response Rate (SE) (%)</th><th>n/N</th><th>LS Mean (SE)</th></tr>
<tr><td colspan="5">Study A3921091 – Primary Analysis</td></tr>
<tr><td>Tofa 5</td><td>54/107</td><td>50.47 (4.83)</td><td>103/107</td><td>-0.3499 (0.04665)</td></tr>
<tr><td>Tofa 10</td><td>63/104</td><td>60.58 (4.79)</td><td>103/104</td><td>-0.3998 (0.04716)</td></tr>
<tr><td>ADA</td><td>55/106</td><td>51.89 (4.85)</td><td>101/106</td><td>-0.3808 (0.04767)</td></tr>
<tr><td>PBO</td><td>35/105</td><td>33.33 (4.60)</td><td>102/104</td><td>-0.1802 (0.05031)</td></tr>
<tr><td colspan="5">Study A3921125 – Primary Analysis</td></tr>
<tr><td>Tofa 5</td><td>65/131</td><td>49.62 (4.37)</td><td>124/129</td><td>-0.3920 (0.04544)</td></tr>
<tr><td>Tofa 10</td><td>62/132</td><td>46.97 (4.34)</td><td>120/132</td><td>-0.3540 (0.04579)</td></tr>
<tr><td>PBO</td><td>31/131</td><td>23.66 (3.71)</td><td>117/131</td><td>-0.1391 (0.04573)</td></tr>
<tr><td colspan="5">Abbreviations: Tofa 5 = tofacitinib 5 mg BID; Tofa 10 = tofacitinib 10 mg BID; ADA=adalimumab; PBO=placebo. Source: for ACR20: Module 5.3.5.1 A3921091 Report Body Table 14.2.1.1.2.1; A3921125 Report Body Table 14.2.1.1.2.1; for HAQ-DI: Module 5.3.5.1 A3921091 Report Body Table 14.2.1.3.3.1; Module 5.3.5.1 A3921125 Report Body Table 14.2.1.3.3.1.</td></tr>
</table>
These data are supported by multiple sensitivity analyses, supportive analyses, subgroup analyses, and comparisons to the adalimumab active control in Study A3921091. Superior efficacy in subjects receiving either dose of tofacitinib was observed versus placebo for ACR20 as early as 2 weeks. Superior ACR50 response rate of both tofacitinib doses relative to placebo was demonstrated at Month 3 in A3921091 and A3921125 and superior ACR70 response rate of both tofacitinib doses relative to placebo was demonstrated at Month 3 in A3921091.
</td><td>Tofacitinib doses of 5 mg BID and 10 mg BID are both effective for the treatment of the signs and symptoms of peripheral arthritis as well as improvement of physical function.

Although exposure response analyses predict additional modest benefit for 10 mg over 5 mg BID using the ACR response endpoints, the observed numerical differences in efficacy between the 2 tofacitinib doses were inconsistent in magnitude and in direction between the 2 studies in the peripheral arthritis domains. Dose differences generally decreased in magnitude over time.</td></tr>
</table>

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Benefits (Continued) **Inhibition of structural progression**	A3921091 included a radiographic endpoint at 12 months. TNFi have demonstrated inhibition of structural progression in TNFi-naïve patients. Tofacitinib 5 mg, 10 mg and adalimumab mTSS progression rates were all ≤ 5% at Month 12. ΔmTSS at Month 12 were small and also similar between tofacitinib 5 mg, tofacitinib 10 mg, and ADA for total score as well as JSN and erosions. The study was not powered or designed to detect structural differences between study arms and there was no placebo group of sufficient duration for comparison.[53] Study A3921125 did not include any radiographic assessments.	Subjects in Study A3921091 were at risk for structural progression based upon risk factors at baseline but did not show progression following 12 months of treatment. Tofacitinib given at doses of 5 mg BID is similarly effective to adalimumab at inhibiting structural progression in a TNFi-naïve population.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Benefits (Continued) **Psoriatic Skin Disease**	Active plaque PsO was required at study entry but a BSA ≥ 3% was not required. In Studies A3921091 and A3921125 73.9% and 62.7% of subjects, respectively, had BSA ≥ 3% at baseline. Psoriatic skin disease was assessed by both PGA – PsO and PASI response (PASI was determined only in those subjects with a BSA ≥3% at baseline). The analysis of PASI75 response was controlled for Type I error at Month 3. Subjects in both studies generally had mild to moderate psoriatic skin disease at baseline. Both tofacitinib doses were statistically significantly superior to placebo on the PASI75 at Month 3 in A3921091 and were generally numerically similar to adalimumab. In A3921125, tofacitinib 10 mg BID was statistically significantly superior to placebo for PASI75 at Month 3; the improvement for tofacitinib 5 mg BID relative to placebo did not achieve statistical significance. In both studies, responses were further improved or sustained after Month 3. For the supportive analysis of mean ΔPGA-PsO (not Type I error controlled), in both studies, the tofacitinib 5 mg and 10 mg BID treatment groups both had higher mean ΔPGA-PsO than that seen in the placebo group as early as Month 1 which was further improved at Month 3 and sustained through the rest of the study.	Tofacitinib 5 mg BID is an effective dose for the treatment of psoriatic skin disease in PsA.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Benefits (continued) **Enthesitis**	The presence of enthesitis was not required at study entry (66.4% and 69.8% of subjects in Studies A3921091 and A3921125 had enthesitis at baseline, respectively). Enthesitis was assessed for both presence and severity (LEI) and the ΔLEI was controlled for Type I error at Month 3. Testing was stopped at 10 mg BID for Study A3921091 and at a step prior to ΔLEI testing for Study A3921125. The tofacitinib 10 mg BID dose in the A3921091 study achieved superiority to placebo on the ΔLEI at 3 months. Although the tofacitinib 5 mg BID dose in study A3921091 was not superior to placebo on the ΔLEI during the first 3 months, it was generally numerically similar to both 10 mg BID and adalimumab by Month 6 and there were no clinically meaningful differences between doses through Month 12. In A3921125, a greater difference on the ΔLEI was seen compared to placebo for both doses as early as Month 1. This greater difference from placebo increased through Month 3 and the tofacitinib responses were sustained or increased further through Month 6. Results for the absence of enthesitis during the 2 studies were generally similar.	Tofacitinib 5 mg is an effective dose for the treatment of enthesitis in PsA.
Benefits (continued) **Dactylitis**	Dactylitis was not required for study entry (56.2% and 49.2% of subjects in Studies A3921091 and A3921125 had dactylitis at baseline, respectively). Dactylitis was assessed for both presence and severity (DSS). The ΔDSS was controlled for Type I error at Month 3 but testing stopped at an earlier step for both studies. In A3921091, the tofacitinib 5 mg BID dose was not greater than placebo during the first 3 months for either the ΔDSS or absence of dactylitis. Tofacitinib 5 mg BID was generally similar to adalimumab and tofacitinib 10 mg BID from Months 6-12 for both endpoints. In A3921125, there was a greater difference between both tofacitinib doses and placebo for absence of dactylitis as early as Month 1 and ΔDSS at Month 3.	Tofacitinib 5 mg BID is an effective dose for the treatment of dactylitis in PsA.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Benefits (continued) **Health Status** **SF-36v2**	For the SF-36v2 only the PF was Type I error controlled but testing stopped at an earlier step. In Studies A3921091 and A3921125, the mean improvement in SF-36v2 PF at Month 3 for both tofacitinib 5 mg BID and 10 mg BID was greater than placebo. Results were similar for the PCS. These improvements were maintained or improved for both tofacitinib 5 mg BID and 10 mg BID from Month 3 to the end of study. Smaller numerical improvements were noted on the MCS.	Tofacitinib 5 mg BID provided benefits on the SF-36v2 PF and the PCS.
Fatigue **FACIT-F**	The FACIT-F was Type I error controlled but testing stopped at an earlier step in both studies. In Studies A3921091 and A3921125, the mean improvements in FACIT-F Total score, FACIT-F Experience domain score and FACIT-F Impact domain score at Month 3 were greater than placebo for both tofacitinib 5 mg BID and 10 mg BID and were maintained for both tofacitinib 5 mg BID and 10 mg BID from Month 3 to the end of study.	Tofacitinib 5 mg BID provided benefits on the fatigue associated with PsA.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risks **General Safety**	The most common AEs were from the Infections and Infestations SOC. Common AEs (nausea and headache) occurred at similar rates as in placebo. Discontinuation rates due to AEs were similar to placebo regardless of tofacitinib dose. The overall rates of SAEs and AEDCs were generally similar between both tofacitinib doses and adalimumab. The overall incidence rate for tofacitinib (Cohort 3) for SAEs was 8.49/ 100 PY. Overall the AE profile is consistent with tofacitinib experience in the RA and PsO development programs.	The safety profile of tofacitinib 5 mg BID is acceptable and similar to the internal control adalimumab.
Deaths	Four (4) deaths were reported in the tofacitinib PsA program up to the snapshot date of 10 May 2016. Two (2) deaths were from CV causes, one from a pulmonary embolism and one from cancer. No deaths occurred while receiving placebo or adalimumab although the single cancer death (pancreatic cancer) occurred in a subject who was randomized to adalimumab in the 12 month A3921091 study prior to joining the LTE and was then treated with tofacitinib for 84 days. The mortality rate of 0.25 per 100 PY (95% CI 0.03, 0.91) in the tofacitinib PsA program was lower than that reported in the literature for observational studies.	The number of fatalities was low; the mortality rate and the reported causes of death were consistent with expected values for PsA with multiple co-morbidities.
Serious infections (SIs)	Overall, there were very few SIs. When assessing incidence rate in the 12-month dose comparison cohort (Cohort 2a), a single case influenced the difference between the 2 tofacitinib doses in subjects in the "as randomized" groups, where the incidence rate for tofacitinib 10 mg BID (2.00 per 100 PY [95% CI: 0.41, 5.83]) is numerically higher compared to 5 mg BID (1.30 per 100 PY [95% CI: 0.16, 4.69]). The number of SIs was increased in subjects ≥65 years of age. Overall, the rates of SIs in the PsA program are similar to those in the tofacitinib RA and PsO programs, and published incidence rate for other bDMARDs.	In PsA subjects treated with tofacitinib, SIs were few, and did not increase over long-term exposure. Incidence rates for SIs were consistent with those seen in RA, despite the relatively smaller PsA data set. Management of the risk of serious and other important infections is described in Section 7 and addressed in the current tofacitinib USPI.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risks (Continued) **Herpes Zoster**	There were 7 cases in total reported during the 12-month dose comparison cohort (Cohort 2a); 4 for tofacitinib 10 mg BID and 3 for tofacitinib 5 mg BID. The incidence rate for HZ was 1.96 per 100 PY (95% CI: 0.41, 5.74) and 2.66 per 100 PY (95% CI: 0.73, 6.81) for tofacitinib 5 and 10 mg BID, respectively. Analogous to the results described for SIs, in the 12-month dose comparison, a single case in the tofacitinib 10 mg BID influenced the difference observed relative to the tofacitinib 5 mg BID. No cases were reported in adalimumab treated subjects. There were insufficient subjects in some geographic regions (eg Asia) to determine any role of ethnicity as a risk factor for HZ in PsA patients.	HZ is considered a documented risk for tofacitinib in the current label for the approved RA indication. HZ may occur at increased frequency in subjects with active PsA receiving immunomodulatory agents relative to the general population.[87,88]
Opportunistic infections (OIs)	The only OI reported was multidermatomal HZ and there were 3 cases reported in the PsA program. Dose response cannot be determined. No cases of TB were observed.	The cumulative incidence rate seen for OIs to date in PsA is overall consistent with the pattern seen with the much larger RA development program.
Malignancies (excluding NMSC)	The number of malignancies excluding non-melanoma skin cancers were few, and all presented as single cases. A total of 5 malignancies other than NMSC were reported in the PsA program. All cases occurred in subjects receiving tofacitinib 5 mg BID at the time of the events, with an incidence rate of 0.63 per 100 PY (95% CI 0.21, 1.48) for "All Tofacitinib" doses. Two (2) malignancies (a bladder transitional cell carcinoma and a SCC of the vulva) were detected on Day 1 and Day 11 of pivotal Study A3921091 and hence a causal relationship to tofacitinib is not biologically plausible. A case of Invasive Ductal breast carcinoma of the left breast was reported on Day 232 of the same study as well. Two (2) malignancies (pancreatic cancer, renal cell cancer) were reported within 3 months of treatment in the LTE study but both cases followed 12 months of treatment with adalimumab in the Phase 3 pivotal Study A3921091, suggesting that a causal relationship to tofacitinib is biologically unlikely.	Chronic inflammation and autoimmune diseases are associated with the development of malignancies.[89,90,91] The incidence rates for malignancies excluding NMSC were similar to those seen in subjects with RA treated with tofacitinib. However, 4 of the 5 malignancies excluding NMSC occurred within 3 months of tofacitinib exposure making a biological relationship implausible. Management of the potential risk of malignancies (excluding NMSC) is described in Section 6.3.6.2 and addressed in the current USPI.

Risks (Continued) ○ **NMSC**	There was only one reported case of NMSC in Cohort 2a (tofacitinib 10 mg BID). The incident rate for NMSC from Cohort 3 in the All PsA group was 0.51 per 100 PY. Published NMSC incidence rates in PsA patients ranged from 0.00 per 100 PY to 0.90 per 100 PY.	The overall NMSC rates were consistent with those seen in external cohorts. Management of the risk of NMSC is described in Section 6.3.6.2 and addressed in the current USPI.
MACE	The incidence rate for MACE in Cohort 2a (incidence rate 0.50 per 100 PY) was similar to rates reported in the tofacitinib PsO and RA integrated datasets. The incidence rate for MACE in Cohort 3 (incidence rate 0.38 per 100 PY) was consistent with the incidence rate of MACE from a published population-based cohort study conducted within the UK's THIN database (0.46 per 100 PY among DMARD-exposed PsA patients) [92] and lower or similar to those obtained from the Truven "Trial-Criteria" Cohort (Cohort B cohort) using the same definition for MACE as the PsA development program.	The overall MACE rates were consistent with the rates for tofacitinib in the RA program as well as those seen in external cohorts. Management of the potential risk of CV events and monitoring of lipid elevations is described in Section 7 and is addressed in the current USPI.
Other safety events of special interest	DILI and GI perforation events have been observed in the RA and PsO programs. There was 1 case of possible DILI in a subject on tofacitinib 10 mg BID and MTX. There were no cases of confirmed DILI or Hy's law cases. There was one case of appendiceal perforation.	These single events are consistent with the low rates of events in the larger RA program.
Risks (Continued) **Laboratory Abnormalities**	• Modest dose dependent increases in serum creatinine. • Modest dose dependent decreases in neutrophils, Hgb. • Modest dose dependent increases in HDL, LDL and liver enzymes. • Modest decreases in the absolute lymphocyte counts in the long-term extension study. These changes are characteristic for tofacitinib and were found reversible in tofacitinib Phase 2 dose-ranging studies in RA, AS, and PsO.	Laboratory abnormalities were subject to strict monitoring and discontinuation guidelines. There were very few subjects in the PsA program requiring discontinuation for any laboratory abnormality. All laboratory changes in the tofacitinib PsA program were consistent with those subjects treated in the tofacitinib RA program. Laboratory changes were generally mild, and rarely required discontinuation. Recommendations for dose interruption for cytopenias are address in the current USPI.

Risk Management	• Current product labeling includes the following warnings and precautions: SIs and other important infections (OIs, TB, viral reactivation), malignancy and lymphoproliferative disorders (including NMSC), GI perforation, and laboratory abnormalities. The product labeling also includes a statement on avoiding concurrent use of live vaccines, as well as recommendations for dose modifications for renal/hepatic impairment and management of the potential for certain DDIs • Ongoing PsA LTE A3921092 study • Post-marketing pharmacovigilance as already established for RA o Ongoing RA studies (A3921024, A3921133) o CORRONA RA registry safety study o OTIS registry for following pregnancies.	No new risks have been identified for the PsA program based on the completed studies and the current product labelling information regarding the risks with tofacitinib can be viewed as appropriate for the PsA indication. General strategies for risk assessment and pharmacovigilance have already been successfully established for tofacitinib for the treatment of RA. Since the overall risks with tofacitinib for PsA are similar to RA, the same strategy for risk mitigation will be extended to PsA program. The findings from RA risk assessment studies will further inform the safety profile in PsA.

Abbreviations: PsA=psoriatic Arthritis; US=United States; BID=twice daily; RA=rheumatoid arthritis; PsO=psoriasis; AS=ankylosing spondylitis; bDMARD=biologic disease-modifying anti-rheumatic drug; DMARD= disease-modifying anti-rheumatic drug; TNFi= tumor necrosis factor inhibitor; MOA=mechanisms of action; LTE= long-term extension; ACR20=American College of Rheumatology criteria ≥20% improvement; PBO=placebo; HAQ-DI=Health Assessment Questionnaire–Disability Index; FDA= Food and Drug Administration; LS=least squares; csDMARD= conventional synthetic disease-modifying anti-rheumatic drug; IR=inadequate responders; LEI=Leeds Enthesitis Index; DSS= Dactylitis Severity Score; PGA–PsO=Physician's Global Assessment of Psoriasis; mTSS= van der Heijde modified Total Sharp Score; PASI=Psoriasis Area and Severity Index; BSA=body surface area; JSN=joint space narrowing; CI=confidence interval; SF-36v2=Short-Form-36 Health Survey; PCS=physical component summary; MCS= mental component summary score; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; AE=adverse event; ADA=adalimumab; SCC=squamous cell carcinoma; FAS= Full Analysis Set; RCT=randomized controlled trial; tsDMARD= targeted synthetic disease-modifying antirheumatic drug; USPI=United States Package Insert; PY=patient year; HZ= herpes zoster; TNF=tumor necrosis factor; AEDC= adverse event leading to discontinuation; SI=serious infection; MACE= Major Adverse Cardiovascular Events; SE= Standard Error; Hgb=hemoglobin; MMRM= mixed model for repeated measures; DDIs=drug-drug interactions; ROA= route of administration; SOC= System Organ Class; UK=United Kingdom; THIN=The Health Improvement Network; SAEs=serious adverse events; TB=tuberculosis; NMSC=non-melanoma skin cancer; CV=cardiovascular; DILI=drug-induced liver injury; LDL=low density lipoprotein; HDL=high density lipoprotein; OIs=opportunistic infections; GI=gastrointestinal; MTX=methotrexate; CORRONA=Consortium of Rheumatology Researchers of North America; OTIS=Organization of Teratology Specialists Pregnancy Registry.

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