

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

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**CLINICAL REVIEW(S)**



DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE

**Memorandum**

Food and Drug Administration  
Center for Drug Evaluation and Research  
CDER/ODE 2/DPARP

Date: December 3, 2019

From: Keith Hull, MD, PhD  
Medical Officer

Through: Rachel Glaser, MD  
Clinical Team Leader, DPARP

Product: upadacitinib (RINVOQ)

Subject: Amended Primary Clinical Review

Sponsor: AbbVie

Application: NDA 211675

The attached amended primary clinical review of RINVOQ contains minor grammatical edits as well as several amended tables that had contained transposed data in the original version of the document.

Clinical Review  
Keith M Hull, MD, PhD  
NDA 211675  
RINVOQ (upadacitinib)

## CLINICAL REVIEW

<b>Application Type</b>	NDA
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<b>Priority or Standard</b>	Priority
<b>Submit Date(s)</b>	18 Dec 2018
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<b>Division/Office</b>	Division of Pulmonary, Allergy and Rheumatology Products
<b>Reviewer Name(s)</b>	Keith M Hull, MD, PhD
<b>Review Completion Date</b>	17 May 2019
<b>Established/Proper Name</b>	Upadacitinib
<b>(Proposed) Trade Name</b>	RINVOQ
<b>Applicant</b>	AbbVie Inc
<b>Dosage Form(s)</b>	15 mg extended release tablets
<b>Applicant Proposed Dosing Regimen(s)</b>	15 mg orally administered QD
<b>Applicant Proposed Indication(s)/Population(s)</b>	(b) (4)
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	Treatment of adults with moderately to severely active rheumatoid arthritis who had an inadequate response or intolerance to methotrexate

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## Glossary

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ACR	American College of Rheumatology
ACR20/50/70	American College of Rheumatology 20, 50, 70 response
ADA	adalimumab
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-CCP	anti-cyclic citrullinated peptide
apoA1	apolipoprotein A-1
apoB	apolipoprotein B
AST	aspartate aminotransferase
AUC	area under the curve
bDMARD	biologic disease-modifying anti-rheumatic drug
BID	twice daily
BMI	body mass index
CAC	Cardiovascular Adjudication Committee
CDAI	clinical disease activity index
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
C <sub>max</sub>	maximum observed concentration
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPK	creatine phosphokinase
CRF	case report form
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying anti-rheumatic drug
CV	cardiovascular
DAS	disease activity score
DAS28	disease activity score 28
DMARD	disease-modifying anti-rheumatic drug
DMC	data monitoring committee
DVT	deep vein thrombosis

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EAER	exposure adjusted event rate
EAIR	exposure adjusted incident rate
ECG	electrocardiogram
EMA	European Medicines Agency
eow	every other week
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
GFR	glomerular filtration rate
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HDL-C	high-density lipoprotein cholesterol
hsCRP	high-sensitivity C-reactive protein
ICH	International Council for Harmonization
Ig	immunoglobulin
IL	interleukin
IND	Investigational New Drug Application
INH	isoniazid
IR	inadequate responder
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
JAK	Janus kinase
LDA	low disease activity
LDL-C	low-density lipoprotein cholesterol
LOCF	last observation carried forward
MCS	mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mTSS	modified total sharp score
MTX	methotrexate
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for AE
NDA	new drug application
NME	new molecular entity
NMSC	non-melanoma skin cancer
NRI	non-responder imputation
NSAID	nonsteroidal anti-inflammatory drug
OMERACT	Outcome Measures in Rheumatology

## Clinical Review

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OSI	Office of Scientific Investigation
PBO	placebo
PCS	physical component summary
PE	pulmonary embolism
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPD	purified protein derivative
PT	preferred term
PY	patient year
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's correction
RA	rheumatoid arthritis
RF	rheumatoid factor
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SC	subcutaneous
SEER	Surveillance, Epidemiology, and End Results
SF-36	Short Form-36
SIR	standardized incidence ratio
SJC	swollen joint count
SOC	system organ class
TB	tuberculosis
TC	total cholesterol
TEAE	treatment emergent adverse event
TIA	transient ischemic attack
TJC	tender joint count
TNF	tumor necrosis factor
tsDMARDs	target synthetic disease-modifying anti-rheumatic drug
ULN	upper limit of normal
UPA	upadacitinib
URI	upper respiratory infection
US	United States
UTI	urinary tract infection
VAS	visual analog scale
Vs	versus
VTE	venous thromboembolic events

## 1. Executive Summary

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### 1.1. Product Introduction

Upadacitinib (UPA; RINVOQ) is a new molecular entity that derives its mechanism of action by reversibly inhibiting Janus kinase-1 (JAK1). AbbVie Inc (Applicant) has submitted the current application to support approval of orally administered UPA 15 mg extended-release tablets once daily [REDACTED] (b) (4)

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has submitted substantial evidence meeting the evidentiary standard for the clinical effectiveness of UPA 15 mg based on the results from five well-controlled phase 3 studies that enrolled a broad population of subjects who were representative of the target US patient population. The studies all used validated and well-established primary and secondary endpoints that were designed to capture clinically meaningful changes in patients' disease activity. Based on the results of my analysis, the data included in this application supports the approval of UPA 15 mg QD for the treatment of adults with moderately to severely active RA who have had an inadequate (IR) response or intolerance to methotrexate.

### 1.3. Benefit-Risk Assessment

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Keith M Hull, MD, PhD  
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RINVOQ (upadacitinib)

### Benefit-Risk Integrated Assessment

Upadacitinib (UPA; RINVOQ) 15 mg QD is being proposed [REDACTED] (b) (4)

[REDACTED] The data demonstrate that treatment with UPA is able to produce clinically meaningful improvement in the signs, symptoms, physical function, inhibition of radiographic progression, and fatigue associated with RA. After review of the data, I recommend approval of UPA 15 mg QD for the intended indication.

Rheumatoid arthritis is a serious medical condition that affects over 1.3 million Americans and causes severe disease manifestations that limit patients' quality of life and is associated with a higher risk of mortality. Current treatment guidelines<sup>1</sup> recommend newly diagnosed patients be treated using csDMARD (e.g., methotrexate [MTX]) monotherapy as first-line therapy. Patients who have an inadequate response to csDMARD therapy can then be treated using biologic DMARDs (bDMARDs; e.g., adalimumab) or target selective DMARDs (tsDMARDs; e.g., tofacitinib) as monotherapy or in combination with csDMARDs. Two JAK inhibitors, tofacitinib and baricitinib, are currently approved for the treatment of RA, making UPA the third drug in its class.

The Applicant has submitted five well-controlled phase 3 studies that demonstrated the effectiveness of UPA 15 mg QD to produce a clinically meaningful benefit in the reduction of signs and symptoms of subjects with moderately to severely active disease. Upadacitinib was shown to be effective either as monotherapy or in combination with MTX or csDMARDs in subjects who were MTX-naïve, or who had an inadequate response to MTX, csDMARDs and/or bDMARDs. The primary endpoint assessed the proportion of subjects achieving an ACR20 at Week 12 or 14 (except for Study M13-545 which used the ACR50). Each of the studies achieved statistical significance for the primary endpoint with an average treatment effect size ranging between 24% and 36% for subjects treated with UPA 15 mg. Upadacitinib-treated subjects also experienced a clinical benefit compared to control subjects for the secondary endpoints which were chosen to assess other potential treatment benefits to patients with RA. These endpoints measured the change from baseline for the improvement of physical function, inhibition of radiographic progression, achievement of low disease activity, and improvement in fatigue. Additionally, analyses did show a clear additional clinically meaningful benefit with UPA 30 mg treatment compared to the lower dose in these studies and given the increase safety risk with the UPA 30 mg dose, the Applicant is only proposing the 15 mg dose for marketing.

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<sup>1</sup> Arthritis Rheumatol 2016 Jan;68(1):1-26

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Analyses of the safety database demonstrated that UPA 15 mg-treated subjects experienced a greater frequency of adverse events (AEs), serious AEs (SAEs) and AEs of special interest (AESI) including serious/opportunistic infections, reactivation of herpes zoster and hepatitis B virus, gastrointestinal perforations, anemia, neutropenia, elevated CPK, and elevated lipids. In contrast to what has been identified with other JAK inhibitors, the data from the UPA program did not identify an increased rate of malignancies (other than nonmelanoma skin cancers) or venous thromboembolic events (VTE); however, these results need to be interpreted cautiously since the majority of subjects had been exposed to UPA for one-year or less. Additionally, during the course of the review, the nonclinical review team identified a potential safety signal in animals that may relate to human embryo-fetal toxicity. Consequently, appropriate language describing the risk will be included in the product labeling. Given UPA's mechanism of action and the potential for AEs with longer durations of treatment, the overall safety database is limited to some extent by the small number of subjects treated with UPA for longer periods of time than one year; however, this limitation did not affect the ability to conclude an overall determination of the risk-benefit assessment of UPA for the treatment of RA.

Based on my review of the data submitted by the Applicant, the potential benefits of UPA 15 mg QD for the treatment of adults with moderately to severely active RA who have failed first-line therapy with a csDMARD, outweigh the overall risks as currently known. Each of the five clinical trials demonstrated statistically significant and clinically meaningful improvements in the signs, symptoms, improved physical function and fatigue associated with RA, and inhibition of radiographic progression was demonstrated in both studies in which it was assessed. While the safety analyses demonstrated increased frequencies of AEs, the types of events including infections were similar between treatment groups. However, given the increased risks associated with UPA therapy at this time, I recommend that UPA treatment be limited to RA patients who have failed first-line therapy with a csDMARD, which is consistent with 2015 the recommendations of the American College of Rheumatology<sup>1</sup>.

Key labeling recommendations should include language detailing UPA-related AEs as well as the potential for embryo-fetal toxicity. At present, the data contained in the UPA application for the treatment of RA does not require the Applicant to conduct a REMS or PMR/PMC.

**Benefit-Risk Dimensions**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><a href="#"><u>Analysis of Condition</u></a></p>	<ul style="list-style-type: none"> <li>• Rheumatoid arthritis is a chronic systemic inflammatory disease that primarily affects the joints but frequently involves other organs as well, such as lungs, heart, and blood vessels.</li> <li>• Approximately 1% of the general population is affected worldwide and although RA may occur at any age, the peak incidence of onset is usually between the 4th and 6th decades with females being 2-3 times more likely affected than males.</li> <li>• The majority of patients develop symmetrical polyarticular pain and/or stiffness of the hands, wrists, shoulders, knees, ankles, and feet that limits their activities of daily living and impacts the quality of their social and work activities.</li> <li>• As the disease progresses patients may develop joint deformities caused by bone erosions and tendon/ligament damage that limit physical function resulting in deformity, early disability, and even death.</li> <li>• The goal of treatment is early and aggressive use of medications to try to prevent functional impairment and irreversible joint damage.</li> </ul>	<p>Rheumatoid arthritis is a serious medical condition that affects over 1.3 million Americans. Most patients have a chronic progressive disease that is associated with morbidity and a higher risk of mortality.</p>
<p><a href="#"><u>Current Treatment Options</u></a></p>	<ul style="list-style-type: none"> <li>• Current treatment options for RA include NSAIDs, corticosteroids, csDMARDs, tsDMARDs, and bDMARDs.</li> <li>• NSAIDs reduce inflammation and relieve pain but are not effective in slowing disease progression. Corticosteroids also treat pain and inflammation and may slow disease progression, but long-term use is associated with significant toxicity.</li> <li>• Use of csDMARDs as monotherapy or combination therapy is the current standard of care in newly diagnosed patients. In general, csDMARDs are effective for patients with mild to moderately active disease and who are at low risk to develop erosions. The drugs are typically well-tolerated and have a favorable benefit-risk profile.</li> <li>• Based on current treatment guidelines, RA patients who are inadequate responders to csDMARDs are treated with bDMARDs or tsDMARDs as monotherapy or in combination with csDMARDs. These drugs are typically more effective than csDMARDs in treating the signs and</li> </ul>	<p>The drug armamentarium available to treat RA has grown tremendously over the last 20 years and has provided very effective therapies. However, despite this progress, a significant proportion of patients are still unable to achieve low disease activity. Further drug development could identify new drugs with novel mechanisms of action that will better address the needs of those patients who do not respond to current therapies.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>symptoms of RA as well as inhibiting the radiographic progression. They are generally well-tolerated; however, they pose a greater safety risk compared to csDMARDs alone.</p> <ul style="list-style-type: none"> <li>The main safety concerns of the bDMARDs and tsDMARDs are related to the drugs' potent immunosuppressive effects and include increased risks of serious infection, opportunistic infections, malignancy and hematologic changes. Additionally, clinical studies of the tsDMARDs, tofacitinib and baricitinib, have suggested potential drug class-related adverse effects, most notably increased rates of malignancy and venous thromboembolic events.</li> </ul>	
<p><b>Benefit</b></p>	<ul style="list-style-type: none"> <li>The Applicant has submitted five randomized and well-controlled phase 3 studies that enrolled 4381 subjects with moderately to severely active RA and whose baseline demographics and disease characteristics were representative of the target US patient population. Studies M13-542 and M13-549 compared two UPA doses, 15 mg QD and 30 mg QD, versus subjects treated with placebo (PBO). Studies M13-545 and M15-555 used active comparator control arms (MTX or csDMARDs, respectively) and assessed subjects treated with UPA 15 mg QD or UPA 30 mg QD. Study M14-465 studied subjects treated with UPA 15 mg QD compared to PBO or an active comparator, adalimumab (ADA). All of the studies used validated and well-established primary and secondary endpoints that were designed to capture clinically meaningful changes in patients' disease activity.</li> <li>The primary endpoint assessed the proportion of subjects achieving an ACR20 at Week 12 or 14, except for Study M13-545 which utilized the ACR50. This endpoint was appropriate and consistent with Agency's guidelines to assess the clinical effectiveness of UPA to improved signs and symptoms of subjects with RA.</li> <li>Secondary endpoints were chosen to support the primary endpoint and to assess other potential treatment benefits to patients with RA. These endpoints measured the change from baseline for the improvement of physical function (HAQ-DI), inhibition of radiographic progression (mTSS), achievement of low disease activity (ACR 50/70 and DAS28-CRP &lt;2.6), and improvement in fatigue (FACIT-F) and general health status (SF-36).</li> <li>All five studies demonstrated a statistically significantly greater proportion of UPA-treated subjects achieved the prespecified ACR response compared to subjects treated with PBO or an active comparator (see Table). Subjects treated with UPA 15 mg demonstrated a treatment effect size that ranged between 24% to 36% compared to the respective control arm. All major secondary endpoints demonstrated a statistically significant and clinically meaningful effect in UPA-treated subject compared to their respective controls.</li> </ul>	<p>The Applicant has submitted substantial evidence meeting the evidentiary standard for the clinical effectiveness of UPA 15 mg based on the results from five well-controlled phase 3 studies that enrolled a broad population of subjects who were representative of the target US patient population. Study M13-545 enrolled subjects who were naïve to MTX, while Studies M13-542, M13-549, M14-465 and M15-555 enrolled subjects who were inadequate responders to MTX and/or csDMARDs and refractory/intolerant to bDMARDs, thus, representing a more difficult to treat patient population as they had already failed generally accepted first-line and/or second line-therapy. The studies all used validated and well-established primary and secondary endpoints that were designed to capture clinically meaningful changes in patients' disease activity.</p> <p>The effectiveness of UPA 15 mg was clearly demonstrated to produce a clinically meaningful benefit in subjects with moderately to severely active RA either as monotherapy or in combination with MTX or csDMARDs in subjects who were MTX-naïve, or who had an inadequate response to MTX, csDMARDs and/or bDMARDs. There was not a clear additional benefit observed with the UPA 30 mg dose in these studies and</p>

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	<p><b>Table. All Five Phase 3 Studies: Summary of Primary Efficacy Endpoint</b></p> <table border="1"> <thead> <tr> <th>Treatment Arm</th> <th>N</th> <th>ACR20</th> <th>Diff (%) (95% CI)</th> </tr> </thead> <tbody> <tr> <td colspan="4" style="text-align: center;">M13-542</td> </tr> <tr> <td>PBO</td> <td>169</td> <td>48 (28%)</td> <td></td> </tr> <tr> <td>UPA 15 mg</td> <td>164</td> <td>106 (65%)</td> <td>36 (26-46)</td> </tr> <tr> <td>UPA 30 mg</td> <td>165</td> <td>93 (56%)</td> <td>28 (18-38)</td> </tr> <tr> <td colspan="4" style="text-align: center;">M13-549</td> </tr> <tr> <td>PBO</td> <td>221</td> <td>79 (36%)</td> <td></td> </tr> <tr> <td>UPA 15 mg</td> <td>221</td> <td>141 (64%)</td> <td>28 (19-37)</td> </tr> <tr> <td>UPA 30 mg</td> <td>219</td> <td>145 (66%)</td> <td>31 (22-39)</td> </tr> <tr> <td colspan="4" style="text-align: center;">M14-465</td> </tr> <tr> <td>PBO</td> <td>651</td> <td>237 (36%)</td> <td></td> </tr> <tr> <td>UPA 15 mg</td> <td>651</td> <td>456 (71%)</td> <td>34 (29-39)</td> </tr> <tr> <td>ADA 40 mg</td> <td>327</td> <td>206 (63%)</td> <td>27 (20-33)</td> </tr> <tr> <td colspan="4" style="text-align: center;">M15-555</td> </tr> <tr> <td>MTX</td> <td>216</td> <td>89 (41%)</td> <td></td> </tr> <tr> <td>UPA 15 mg</td> <td>217</td> <td>147 (68%)</td> <td>27 (18-36)</td> </tr> <tr> <td>UPA 30 mg</td> <td>215</td> <td>153 (71%)</td> <td>30 (21-39)</td> </tr> <tr> <td colspan="4" style="text-align: center;">M13-545 (ACR50)</td> </tr> <tr> <td>MTX</td> <td>314</td> <td>89 (28%)</td> <td></td> </tr> <tr> <td>UPA 15 mg</td> <td>317</td> <td>165 (52%)</td> <td>24 (16-31)</td> </tr> <tr> <td>UPA 30 mg</td> <td>314</td> <td>177 (56%)</td> <td>28 (21-35)</td> </tr> </tbody> </table> <p>Source: FDA Biostatistics Review for NDA 211675; Abbreviations: ACR=American College of Rheumatology; MTX=methotrexate; UPA=upadacitinib; QD=once daily; CI=confidence intervals; EOW=every other week; ADA=adalimumab</p>	Treatment Arm	N	ACR20	Diff (%) (95% CI)	M13-542				PBO	169	48 (28%)		UPA 15 mg	164	106 (65%)	36 (26-46)	UPA 30 mg	165	93 (56%)	28 (18-38)	M13-549				PBO	221	79 (36%)		UPA 15 mg	221	141 (64%)	28 (19-37)	UPA 30 mg	219	145 (66%)	31 (22-39)	M14-465				PBO	651	237 (36%)		UPA 15 mg	651	456 (71%)	34 (29-39)	ADA 40 mg	327	206 (63%)	27 (20-33)	M15-555				MTX	216	89 (41%)		UPA 15 mg	217	147 (68%)	27 (18-36)	UPA 30 mg	215	153 (71%)	30 (21-39)	M13-545 (ACR50)				MTX	314	89 (28%)		UPA 15 mg	317	165 (52%)	24 (16-31)	UPA 30 mg	314	177 (56%)	28 (21-35)	<p>given the increased safety risk with the higher UPA dose, the Applicant is only proposing the 15 mg dose for marketing.</p>
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<p><a href="#">Risk and Risk Management</a></p>	<ul style="list-style-type: none"> <li>A total of 4443 subjects were exposed to UPA in the combined periods of the phase 2 and phase 3 RA trials and formed the primary source of evidence for the safety review. Of these subjects, 2972 (67%) were exposed to UPA for at least 48 weeks which provides sufficient data to allow for the initial determination of the overall risk-benefit assessment of UPA for the treatment of adults with moderately to severely active RA; however, as UPA is a member of the JAK-inhibitor class, caution is required when interpreting the data as certain types of</li> </ul>	<p>The Applicant has submitted adequate data on which to conclude the initial safety of UPA 15 mg QD in subjects with moderately to severely active RA including subjects who were naïve to MTX, inadequate responders to MTX and/or csDMARDs and refractory/intolerant to bDMARDs. Overall, there was a greater frequency of AEs,</p>																																																																																				

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	<p>adverse events (AEs) may present more frequently with longer durations of exposure to UPA, e.g., malignancies, venous thromboembolic events (VTEs) .</p> <ul style="list-style-type: none"> <li>• There was a greater percentage of subjects experiencing an AE or serious adverse event (SAE) in subjects treated with UPA 15 mg compared to PBO-treated subjects. This greater percentage of AEs and SAEs was dose-dependent and observed during both the controlled and long-term periods of the phase 3 studies. The types of AEs and SAEs were similar between treatment arms and were consistent with events reported in other RA studies of immunosuppressants and JAK inhibitors. Review of the data did not identify a temporal relationship between the duration of UPA treatment and the onset of AEs or SAEs.</li> <li>• The age-gender adjusted standard incidence ratios for malignancies other than nonmelanoma skin cancer indicates that the malignancy risk with UPA 15 mg was within the expected range for the general population. The types of malignancies reported in the UPA studies are consistent with that anticipated in a RA study population.</li> <li>• A higher rate of serious infections was observed in a dose-dependent manner of UPA-treated subjects compared to control subjects across all analysis sets. Overall, there was a greater percentage of subjects experiencing a serious infection when treated with UPA 15 mg compared to PBO-treated subjects. The types of serious infections were similar between treatment arms and no clear temporal relationship between the duration of UPA treatment and onset of serious infection was identified.</li> <li>• In the UPA clinical development program, adjudicated VTEs were reported at comparable rates in UPA-treated subjects and subjects treated with PBO, MTX and ADA. No dose-dependent relationship in the rates of VTE, patterns in the time to onset of the events, or association with platelet count were observed. The long-term incidence rates for UPA 15 mg were within the range of VTE rates reported for the general RA population. As stated with the malignancy analysis, these data need to be interpreted with caution due to the majority of subjects having been exposed for one-year or less. It is unclear whether an increase of VTEs may occur with longer term (&gt;1 year) treatment with UPA in light of safety signals from other drugs in the JAK inhibitor class.</li> <li>• A total of six plausible UPA-related cases of gastrointestinal perforations were reported in the phase 3 studies compared to no cases in subjects treated with PBO, MTX or ADA. In light of the data from other JAK inhibitors, the data suggest that subjects treated with UPA are at an increased risk of developing gastrointestinal perforations.</li> </ul>	<p>SAEs and AEs of special interest for UPA 15 mg compared to PBO and MTX controls.</p> <p>In contrast to what has been identified with other JAK inhibitors, the data from the UPA program did not demonstrate an increased rate of malignancies (other than NMSC) or VTE. However, these results need to be interpreted cautiously since the majority of subjects had been exposed for one-year or less. Given UPA’s mechanism of action and the degree of immunosuppression, it is unclear whether an increased frequency of malignancies or VTEs may occur with longer duration of treatment. After internal discussions language for malignancies and VTEs for UPA 15 mg will be added to the label.</p> <p>Although UPA 15 mg QD has demonstrated a greater treatment effect compared to MTX and csDMARDs, there is also a greater risk to patient safety. Consequently, it is the Agency’s recommendation that UPA 15 mg QD be indicated for subjects with moderately to severely active RA who have had an inadequate response to MTX. Product labeling should include language detailing UPA-related AEs including serious/opportunistic infections, reactivation of herpes zoster and hepatitis B virus, gastrointestinal perforations, anemia, neutropenia, elevated CPK, elevated lipids and potential embryo-fetal toxicity.</p> <p>At present, the data contained in the UPA application for the treatment of RA does not warrant the Applicant to conduct a REMS or PMR/PMC at the time.</p>

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	<ul style="list-style-type: none"> <li>• Viral reactivation, e.g. herpes zoster, has been reported in patients treated with potent immunosuppressants including members of the JAK inhibitor family of drugs. The rates of herpes zoster infection were higher in subjects treated with UPA compared to subjects in the PBO, MTX and ADA groups. There was a dose-dependent effect observed with higher rates of herpes zoster infections in subjects treated with UPA 30 mg compared to UPA 15 mg subjects. There were two definitive cases of HBV reactivation reported in UPA-treated subjects during the phase 2 and phase 3 program.</li> <li>• As noted with other drugs of its class, UPA-treated subjects reported a greater frequency of Grade 2 and Grade 3 neutropenia compared to subjects treated with PBO. Adverse events of neutropenia were observed at similar rates in the UPA 15 mg group compared to the ADA and MTX treatment groups. No clear evidence of an association of serious infections, opportunistic infections or herpes zoster with a low neutrophil count was observed.</li> <li>• Similar to lipid elevations observed with other JAK inhibitors, UPA treatment was associated with a dose-dependent increase in all lipid parameters including TC, LDL-C and HDL-C; however, the increased lipid concentrations did not affect the overall atherogenic indices as evidenced by ratios of TC/HDL-C and LDL-C/HDL-C. The observed lipid elevations were responsive to statin therapy and there was no relationship identified between subjects with elevated lipids and MACE in the phase 3 studies.</li> <li>• Elevation of CPK levels were higher in the UPA treatment groups compared to PBO, MTX, or ADA comparator arms. While there was a dose-dependent increase in CPK elevations, the majority of elevations were asymptomatic. There were several cases of CPK elevation that led to study discontinuations but no cases of UPA-induced rhabdomyolysis. These findings are consistent with other JAK inhibitors, which have also been demonstrated to increase CPK levels.</li> <li>• Review of the data did not identify any clinically relevant food-drug interactions, but the Clinical Pharmacology reviewers did conclude that UPA should not be used in patients receiving treatment with strong CYP3A4 inducers and should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors.</li> <li>• The nonclinical review team and reviewers from the Division of Pediatric and Maternal Health identified a teratogenicity signal in rats and rabbits at clinically relevant exposures that represent a potential serious risk for human fetal toxicity.</li> </ul>	

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## 1.4. Patient Experience Data

The Applicant submitted patient experience data that was reviewed as part of this application (Table 1).

**Table 1. Patient Experience Data Relevant to this Application**

<input checked="" type="checkbox"/>	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	<input checked="" type="checkbox"/> Clinical outcome assessment (COA) data, such as	Sections 6.1-6.5
	<input checked="" type="checkbox"/> Patient reported outcome (PRO)	Sections 6.1-6.5
	<input type="checkbox"/> Observer reported outcome (ObsRO)	
	<input checked="" type="checkbox"/> Clinician reported outcome (ClinRO)	Sections 6.1-6.5
	<input type="checkbox"/> Performance outcome (PerfO)	
	<input type="checkbox"/> Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Natural history studies	
	<input type="checkbox"/> Patient preference studies (e.g., submitted studies or scientific publications)	
	<input type="checkbox"/> Other: (Please specify)	
<input type="checkbox"/>	Patient experience data that were not submitted in the application, but were considered in this review:	
	<input type="checkbox"/> Input informed from participation in meetings with patient stakeholders	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Other: (Please specify)	
<input type="checkbox"/>	Patient experience data was not submitted as part of this application.	

## 2. Therapeutic Context

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### 2.1. Analysis of Condition

Rheumatoid arthritis is a chronic systemic inflammatory disease that primarily affects diarthrodial joints but frequently involves other organs as well. Approximately 1% of the general population is affected worldwide and although RA may occur at any age, the peak incidence of onset is usually between the 4th and 6th decades with females being 2-3 times more likely affected than males. The etiology of RA is unknown but there clearly appears to be a combination of both genetic and environmental factors that allow for the onset and progression of the disease. Evidence suggests that a major portion of the pathogenesis of RA is mediated by antigen-driven T cells and macrophages which produce proinflammatory cytokines including IL-1 and tumor necrosis factor- $\alpha$ . This process contributes to osteoclast activation and proliferation of synoviocytes surrounding the joint that can ultimately expand and resorb cartilage and bone and present radiographically as erosions.

The initial clinical presentation of RA can be extremely variable, but the majority of patients develop symmetrical polyarticular pain and/or stiffness of the proximal interphalangeal, metacarpophalangeal, wrist, shoulder, knee, ankle, and metatarsophalangeal joints over the course of weeks to months which then develop into frank synovitis and joint swelling. Extra-articular manifestations occur in about 40% of patients with RA.<sup>3</sup> Extra-articular manifestations include rheumatoid nodules, pleurisy, interstitial lung disease, pericarditis, myocarditis, and rheumatoid vasculitis.<sup>4</sup> As the disease progresses most patients develop joint deformities caused by bone erosions and tendon/ligament damage that limit physical function resulting in deformity, early disability, and even death.

Diagnosis of RA, especially for inclusion in clinical trials, has most recently relied on the ACR/EULAR 2010 criteria<sup>2</sup>. Using these criteria, a patient who has had at least one joint with synovitis which is not better explained by another disease is said to have RA if the patient has satisfied a score  $\geq 6/10$  based on the following criteria:

A. Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (with/without involvement of large joints)	2
4-10 small joints (with/without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF and negative anti-CCP	0

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<sup>2</sup> Aletaha D et al. Arthritis Rheum 2010 Sep;62(9):2569-81.

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Low-positive RF or low-positive anti-CCP	2
High-positive RF or high-positive anti-CCP	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
<6 weeks	0
≥6 weeks	1

## 2.2. Analysis of Current Treatment Options

Many effective therapies are approved for the treatment of patients with RA including NSAIDs (e.g., naproxen), glucocorticosteroids (e.g., prednisone), conventional synthetic DMARDs (csDMARDs; e.g., MTX), biologic DMARDs (e.g. adalimumab) and targeted synthetic DMARDs (tsDMARDs, e.g., tofacitinib). Table 2 and

Table 3 lists the currently approved csDMARDs, bDMARDs and tsDMARDs marketed in the US.

Product Name (Trade Name) [Sponsor]	Year of First Approval for RA	Dosing/ Administration	Mechanism of Action in RA
Sulfasalazine (AZULFIDINE) [Pfizer]	1950	Oral	Anti-inflammatory and antimicrobial
Methotrexate sodium (METHOTREXATE SODIUM) [Multiple]	1988	Oral, SC (autoinjectors)	Anti-metabolite
Hydroxychloroquine (PLAQUENIL) [Sanofi-Aventis]	1955	Oral	Interference with antigen processing (?)
Azathioprine (IMURAN) [Prometheus Labs]	1968	Oral	Cytostatic
Penicillamine (CUPRIMINE) [Alton]	1970	Oral	Unknown
Auranofin (RIDAURA) [Prometheus Labs]	1985	Oral	Unknown
Cyclosporine (NEORAL) Cyclosporine (SANDIMMUNE) [Novartis]	1995 1990	Oral	T-cell activation inhibitor
Leflunomide (ARAVA) [Sanofi-Aventis]	1998	Oral	Anti-metabolite

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Steroids and NSAIDs are approved for the reduction of the signs and symptoms of RA.

**Table 2. Summary of Approved csDMARD Drugs Available for the Treatment of Rheumatoid Arthritis**

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**Table 3. Summary of Approved bDMARD and tsDMARD Drugs Available for the Treatment of Rheumatoid Arthritis**

Product Name (Trade Name)	Year approved for RA	BLA/NDA (sponsor)	ROA	Description	MOA
Etanercept (ENBREL)	1998	103795 Immunex/Amgen)	SC	Fusion protein TNFR:IgG1 Fc	TNF inhibitor
Infliximab (REMICADE)	1999	103772 (Centocor)	IV	Chimeric IgG1k mAb	TNF inhibitor
Anakinra (KINERET)	2001	103950 (Amgen)	SC	Recombinant polypeptide	IL-1r antagonist
Adalimumab (HUMIRA)	2002	125057 (Abbott/Abbvie)	SC	Human IgG1k mAb	TNF inhibitor
Abatacept (ORENCIA)	2005 2011	125118 (Bristol-Myers Squibb)	IV SC	Fusion protein consisting of CTLA-4 and human IgG1 Fc	T cell activation inhibitor
Rituximab (RITUXAN)	2006	103705 (Genentech & Biogen Idec)	IV	Chimeric murine/human IgG1k mAb	AntiCD20, B cell depletor
Golimumab (SIMPONI)	2009	125289 (Centocor & Janssen)	SC	Humanized IgG1k mAb	TNF inhibitor
Certolizumab Pegol (CIMZIA)	2009	125160 (UCB Inc)	SC	Humanized Fab fragment	TNF inhibitor
Tocilizumab (ACTEMRA)	2010 2013	125276 125472 (Genentech/Roche)	IV SC	Humanized IgG1k mAb	IL-6 receptor inhibitor
Tofacitinib (XELJANZ)	2012	203214 (Pfizer/PF Prism CV)	PO	Citrate salt	JAK inhibitor
Golimumab IV (SIMPONIA)	2013	125433 (Janssen)	IV	Humanized IgG1k mAb	TNF inhibitor
Tofacitinib (XELJANZ XR)	2016	208246 (Pfizer/PF Prism CV)	PO	Citrate salt	JAK inhibitor
Baricitinib (Olumiant)	2018	207924 (Eli Lilly and Co)	po	-	JAK inhibitor
Infliximab-DYYB (INFLECTRA)	2016	125544 (Celltrion Inc)	IV	Chimeric IgG1k mAb	TNF inhibitor
Etanercept-szsz (ERELZI)	2016	761042 (Sandoz)	SC	Fusion protein consisting of TNFR linked to human IgG1 Fc	TNF inhibitor
Adalimumab-atto (AMJEVITA)	2016	761024 (Amgen)	SC	Human IgG1k mAb	TNF inhibitor
Infliximab-abda (Renflexis)	2017	761054 (Samsung)	IV	Chimeric IgG1k mAb	TNF inhibitor
Adalimumab-adbm (Cyltezo)	2017	761058 (Boehringer-Ingelheim)	SC	Human IgG1k mAb	TNF inhibitor
Infliximab-qbtx (Ixifi)	2017	761072 (Pfizer)	IV	Chimeric IgG1k mAb	TNF inhibitor
Adalimumab-adaz (Hyrimoz)	2018	761071 (Sandoz)	SC	Human IgG1k mAb	TNF inhibitor
Etanercept-ykro (Eticovo)	2019	761066 (Samsung)	SC	Fusion protein TNFR:IgG1 Fc	TNF inhibitor

Abbreviations: ROA = Route of administration; MOA= Mechanism of action; TNF=tumor necrosis factor; TNFR=tumor necrosis factor receptor; IL=interleukin; JAK=janus kinase; mAb=monoclonal antibody; CTLA-4=cytotoxic T-lymphocyte-associated protein 4; SC=subcutaneous; IV=intravenous

Given the many different therapies available, the healthcare practitioners' choice of therapy is dependent on numerous factors including the severity of the patient's disease, the potential benefit-risk assessment of the drug, and an individual patient's comorbidities. The American College of Rheumatology (ACR) published treatment guidelines in 2016 to help practitioners

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choose appropriate therapies for their patients<sup>3</sup>. A key recommendation from the guidelines is starting DMARD-naïve patients with early RA ( $\leq 6$  months disease duration) on csDMARD monotherapy, preferably MTX, with or without glucocorticosteroids depending on the degree of the patient's symptoms. This recommendation was made based on review of the published literature, grading of clinician recommendations, and balancing the potential risks and benefits to patients. These specific treatment recommendations are of particular importance in this review as Study M13-545 demonstrated UPA to be more clinically effective than MTX in MTX-naïve subjects with RA; however, this is balanced by the greater potential for increased risk of adverse drug reactions (ADR) related to UPA therapy. Given the increased risk of ADRs and the relatively limited long-term safety data available for UPA, it is this reviewer's opinion that UPA should not be indicated for patients with early RA who are MTX-naïve, which is consistent with the current ACR guidelines.

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<sup>3</sup> Arthritis Rheumatol 2016 Jan;68(1):1-26

### 3. Regulatory Background

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#### 3.1. U.S. Regulatory Actions and Marketing History

Upadacitinib is a new molecular entity that is not currently marketed in the US or any other country. The current application is the initial NDA for UPA and has been submitted to the Division of Pulmonology, Allergy and Rheumatology Products for the proposed indication for the treatment of subjects with RA.

#### 3.2. Summary of Presubmission/Submission Regulatory Activity

Upadacitinib was studied under IND 114717 which was first opened in July 2012. An End-of-Phase 2 meeting was held with Applicant in October 2015 and agreement was reached regarding dose and dosing regimen, extent and duration of safety exposure and selection of active comparators, namely MTX in Study M13-545 and adalimumab in Study M14-465. In June 2016, the Agency communicated with the Applicant regarding an Agreed Initial Pediatric Study Plan for RA.

As per the Applicant, key changes made to the phase 3 studies after scientific advice from the Agency are summarized in Table 4.

**Table 4. Changes to Phase 3 Studies Designs Following Agency’s Scientific Advice**

FDA Scientific Advice	Applicant’s Subsequent Changes
Changes in dose between 15 mg and 30 mg would confound interpretation of the specific safety and efficacy data for each dose.	Switching between upadacitinib doses was not allowed in the Phase 3 studies.
The proposed (b) (4) in Study M15-555 was not acceptable.	(b) (4) Timing of primary endpoint analysis for Study M15-555 changed from Week 12 to Week 14 to minimize residual effect of MTX.
For Study M14-465, FDA indicated that patients with ongoing disease activity should receive rescue therapy starting no later than Week 16.	AbbVie allowed rescue therapy for non-responders as early as Week 14 for all study arms.
Assess primary and key ranked secondary endpoints before initial rescue therapy (recommendation did not apply to assessment of radiographic data).	In all studies rescue therapy was allowed only after primary and key ranked secondary endpoints were evaluated.
It is acceptable to utilize separate statistical analysis plans to address differing requirements from global regulatory agencies.	Applicant established separate primary endpoints and statistical plans for US, EU and Japan to address feedback from the FDA, EMA and PMDA.
Source: Applicant’s Clinical Overview, Table 3.	

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The current NDA was submitted to the Agency on December 18, 2018. The Applicant requested a Priority Review and deployed its Rare Pediatric Disease Priority Review Voucher No. PRV BLA 125516 to support their request. The Rare Pediatric Disease Priority Review Voucher No. PRV BLA 125516 was transferred to AbbVie Ireland Unlimited Company by United Therapeutics Corporation on October 09, 2015. Subsequently, AbbVie Ireland Unlimited Company transferred the PRV to AbbVie Inc. on October 31, 2018.

### **3.3. Foreign Regulatory Actions and Marketing History**

The UPA global development program incorporated scientific advice from the European Medicines Agency and the Japan Pharmaceuticals and Medical Devices Agency as well as the US Food and Drug Administration with the aim of a global marketing strategy. Advice from non-US agencies were incorporated in the overall phase 3 development plan and on the whole strengthened the scientific integrity of the phase 3 studies.

## 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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### 4.1. Office of Scientific Investigations (OSI)

The Division of Clinical Compliance Investigations from the Office of Scientific Investigations (OSI) was consulted to conduct clinical site inspections of three facilities:

- Christine Coddington. Oklahoma City, OK, US
- Roy Fleischmann. Dallas, TX, US
- Juan Vargas. Puerto Varas, NA. Chile

The three clinical sites were selected using risk ranking from the clinical site selection tool for the five phase 3 studies based on high enrollment, better efficacy, participating in multiple studies used to support this application, and financial disclosure. Upon completion of study site inspections, OSI Investigations concluded the following:

- *Three clinical sites (Drs. Coddington, Fleischmann, and Vargas) were selected for inspection for five Phase 3 study protocols (Protocols M13-545, M14-465, M15-555, M13-549, and M13-542). Each site enrolled subjects for three different studies. The study data derived from these clinical sites, based on the inspections, are considered reliable and the studies in support of this application appear to have been conducted adequately.*

*The final regulatory compliance classification of Drs. Coddington's and Fleischmann's sites is No Action Indicated (NAI). The preliminary compliance classification of Dr. Vargas's site is NAI.*

*Preliminary classification is based on communications with the ORA investigators. Inspection classification becomes final when the Establishment Inspection Report (EIR) is received from the field, has been reviewed, and a letter is issued to the inspected entity.*

Overall, inspection of the study data derived from these clinical sites were considered reliable and the studies in support of this application appeared to have been adequately conducted. The reader is directed to the review by OSI's Medical Officer, Min Lu, MD, MPH for detailed information regarding the clinical site inspections.

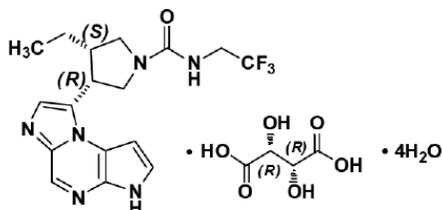
### 4.2. Product Quality

The active component of the drug substance, upadacitinib hemihydrate, is proposed by the Applicant to be a novel, oral, selective, reversible JAK-1 inhibitor. The Applicant developed the

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extended-release (ER) product in 7.5 mg, 15 mg and 30 mg strengths, to be administered orally once daily, but only intends on marketing the 15 mg strength for the treatment of patients with RA. The dosing and formulation of UPA used in the phase 3 clinical studies is the same as the to-be-marketed drug. The structure of UPA is shown in Figure 1.

**Figure 1. Upadacitinib Chemical Structure**



RINVOQ (upadacitinib) 15mg ER tablets for oral administration are purple or mottled purple, biconvex oblong, with dimensions of 14 x 8 mm and debossed with 'a15' on one side.

Each tablet contains the following inactive ingredients: microcrystalline cellulose, hypromellose, mannitol, tartaric acid, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, ferrousferrous oxide, and iron oxide red.

The reader is directed to the combined review by the Office of Product Quality for detailed information regarding the product quality of the UPA development program.

### **4.3. Nonclinical Pharmacology/Toxicology**

The pharmacology/toxicology review concludes that the results of the nonclinical toxicology studies submitted by the sponsor adequately support the approval of UPA for treatment of patients with RA. The effects observed in the non-clinical studies reflect the intended pharmacological effect of the product.

The target organs of toxicity for UPA in rats were identified as the kidneys, thymus, spleen, and lymph nodes, while in dogs, the skin, lymph nodes spleen and thymus were identified. The majority of the toxicity was monitorable and reversible. Given the safety signals identified in the nonclinical data, special attention was focused on these parameters during my review of the clinical safety database of UPA.

No mutagenic potential of UPA and no chromosomal aberrations were observed in a battery of in vitro genotoxicity studies. Carcinogenicity of UPA was evaluated in a six-month study in CByB6F1-Tg (HRAS)2Jic (TgRasH2) mice and a two-year study in Sprague Dawley rats. The CDER Executive Carcinogenicity Assessment Committee (ECAC) concurred that the studies were adequate and that there were no drug-related neoplasms in males or females in either study.

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The nonclinical review team identified a teratogenicity signal in rats and rabbits at clinically relevant exposures that represent a potential serious risk for human fetal toxicity. The nonclinical reviewer, Brett Jones, PhD, considered the embryo-fetal toxicity data with UPA as comparatively more concerning than that observed with previously approved JAK inhibitor products, namely tofacitinib and baricitinib, based on the observed lower exposure margins to proposed clinical dose levels.

Dr. Jones' concerns were discussed at the March 4, 2019 Safety Mid-Cycle Meeting and the review team agreed that safety signal potentially warranted inclusion in the Warnings and Precautions section of the label, particularly in light of the large number of women of childbearing potential in the RA patient population. A consult to the Division of Pediatric and Maternal Health (DPMH) was submitted on April 11, 2019.

The DPMH consult review concluded that a higher level of concern regarding the animal findings for UPA was reasonable based on the lower exposure margins to proposed clinical dose levels. The precedent regarding labeling for other approved products in the class of small molecule kinase inhibitors (e.g., for oncologic indications) was also considered. These products exhibit similar exposure ratios to that observed with UPA and carry Warnings and Precautions for embryo-fetal toxicity in their approved labels. Therefore, based on the guidance and precedent, DPMH stated that labeling for UPA should include a Warning and Precaution for embryo-fetal toxicity.

There were no unresolved toxicology issues and the application was deemed approvable from a nonclinical perspective. See the non-clinical pharmacology/toxicology review by Dr. Jones for a detailed discussion of the UPA nonclinical program.

#### **4.1. Clinical Pharmacology**

The Applicant states UPA's mechanism of action as a selective and reversible JAK-1 inhibitor. Important PK characteristics as per the Clinical Pharmacology review team are as follows:

**Absorption:** Following a single dose administration of upadacitinib, the median T<sub>max</sub> was 2-3 hours. High-fat and high-caloric meal increased UPA C<sub>max</sub> and AUC<sub>0-inf</sub> by 40% and 30%, respectively. Following QD dosing, steady state was achieved within 4 days with minimal accumulation. Upadacitinib C<sub>max</sub> and AUC were approximately dose-proportional over evaluated dose ranges.

**Distribution:** Upadacitinib is approximately 52% bound to human plasma proteins. The blood to plasma with body weight of 74 kg, upadacitinib volume of distribution at steady state is estimated to be 224 L following the administration of ER formulation.

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**Elimination:** Upadacitinib mean terminal elimination  $t_{1/2}$  ranged from 8 to 14 hours following the administration of ER formulation. The typical clearance of upadacitinib was 40.9 L/h in patients with RA as estimated by population PK analysis.

**Metabolism:** UPA is metabolized by CYP3A4 and to a minor extent, by CYP2D6. In the mass balance study, unchanged upadacitinib accounted for 79% of the total radioactivity in plasma. There are no known active metabolites.

**Excretion:** In the mass balance study, approximately 53% and 43% of the administered dose was excreted in feces and urine, respectively. Upadacitinib was eliminated predominantly in feces (38%) and urine (24%), and approximately 34% of upadacitinib dose was excreted as metabolites.

Christine Garnett, Pharm D of the CDER DCRP QT Interdisciplinary Review Team assessed the effect of UPA on the QTc interval prolongation and concluded a lack of clinically relevant effect on the QTc interval at the maximum exposure level observed in the QT assessment (314 ng/mL, approximately six-times the mean maximum exposure of the 15 mg once daily dose).

Review of the data did not identify any clinically relevant food-drug interactions, but the Clinical Pharmacology reviewers did conclude that UPA should not be co-administered with strong CYP3A4 inducers and should be used with caution in patients receiving chronic treatment strong CYP3A4 inhibitors or inducers.

Review of UPA dosing in patient subgroups was notable that no dose adjustment would be needed for subjects with mild, moderate or severe renal impairment and mild or moderate hepatic impairment.

The reader is directed to the Office of Clinical Pharmacology's review for detailed review of the pharmacokinetic and pharmacodynamic properties of UPA.

## 5. Sources of Clinical Data and Review Strategy

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### 5.1. Table of Clinical Studies

The clinical development program for UPA consisted of twenty-two phase 1 studies, three phase 2 studies and five phase 3 studies.

The phase 1 studies consisted of single- and multiple-ascending dose studies in healthy volunteers who received a maximum single dose of UPA 48 mg and multiple doses of 24 mg BID for 14 days.

The phase 2 studies were designed as proof-of-concept and dose-ranging trials in subjects with RA. Study M13-537 assessed the UPA immediate-release formulation at doses of 3 mg, 6 mg, 12 mg, 18 mg BID and 24 mg QD in MTX-IR subjects. Study M13-550 evaluated the UPA immediate-release formulation at doses of 3 mg, 6 mg, 12 mg and 18 mg in TNF-IR subjects. Study M13-538 was a bioavailability study that compared the immediate-release and extended-release formulations to support the selection of the extended-release formulations of UPA 15 mg and 30 mg QD dosing for the phase 3 studies. Given the extensive phase 3 program with the use of the to-be-marketed extended-release formulation, the phase 2 studies are primarily used in this application to support safety.

Study M14-663 was an additional phase 2 study conducted in Japan at the request of the Japan Pharmaceuticals and Medical Devices Agency. This study was used in this review for the analysis of safety only and is not further discussed regarding the assessment of efficacy.

As shown in Table 5, five phase 3 studies were designed to demonstrate the safety and efficacy of UPA 15 mg and 30 mg in subjects with RA as monotherapy (Study M13-545) or in subjects who had an inadequate response to either csDMARDs (Studies M13-549, M14-465, M15-555) or bDMARDs (Study M13-542). Details of the five phase 3 studies are reviewed in Section 6.

**Table 5. Phase 3 Clinical Studies Trials Relevant to NDA 211675**

	<b>M13-549</b>	<b>M13-542</b>	<b>M14-465</b>	<b>M13-545</b>	<b>M15-555</b>
<b>Study design Controlled Period</b>	DB, MC, PG 12-week PC study	DB, MC, MS, PG 24-week (12-week PC →12-week CO to UPA)	DB, MC, DD, PG 48-week PC (CO at Week 26)	DB, MC, PG 48-week AC (CO to UPA at Week 26)	DB, MC, MS, PG 14-week AC (CO to UPA at Week 12)
<b>Extension</b>	Long-term extension (260 weeks) with subjects who completed Period 1	Long-term extension (216 weeks) with subjects who completed Period 1	Long-term extension (260 weeks)	Long-term extension (226 weeks) with subjects who completed Period 1	Long-term extension (226 weeks) with subjects who completed Period 1
<b>Treatment Arms</b>	UPA 15 mg (n=221) UPA 30 mg (n=219) PBO (n=221)  <u>CO at week 12</u> PBO → UPA 15 mg PBO → UPA 30 mg	UPA 15 mg (n=164) UPA 30 mg (n=165) PBO (n=169)  <u>CO at week 12</u> PBO → UPA 15 mg PBO → UPA 30 mg	UPA 15 mg (n=651) PBO (n=651) ADA 40 mg Q2W (n=327)	UPA 15 mg (n=317) UPA 30 mg (n=314) MTX (n=314)	UPA 15 mg (n=217) UPA 30 mg (n=215) MTX (n=216)  <u>CO at week 14</u> MTX → UPA 15 mg MTX → UPA 30 mg
<b>Subjects</b>	csDMARDs-IR	bDMARDs-IR	MTX-IR	MTX Naïve	MTX-IR
<b>Rescue Criteria</b>	1. CDAI ≤10 2. TJC and SJC ≤20% improvement	1. CDAI ≤10 2. TJC and SJC ≤20% improvement	1. CDAI ≤10 2. TJC and SJC ≤20% improvement	1. CR (CDAI ≤2.8) 2. TJC and SJC ≤20% improvement	1. CDAI ≤10 2. TJC and SJC ≤20% improvement
<b>Primary Endpoint</b>	ACR20 at Week 12	ACR20 at Week 12	ACR20 at Week 12	ACR50 at Week 12	ACR20 at Week 14
DB: double-blind; MC: multicenter; PG: parallel group; PC: placebo-controlled; UPA: upadacitinib; PBO: placebo; DMARD: disease modifying anti-rheumatic drug; csDMARD: conventional synthesized DMARD; bDMARD: biologic DMARD; CDAI: clinical disease activity index; TJC: tender joint count; SJC: swollen joint count; CO: cross-over; CR: complete response as defined by CDAI ≤2.8; MTX: methotrexate; ADA: adalimumab; IR: inadequate responder					

## 5.2.Review Strategy

Efficacy analyses were conducted on the results from the individual five phase 3 studies and included review of the primary endpoints, secondary endpoints, sensitivity testing and subgroup analyses. Review of efficacy in the phase 2 studies was not performed for two reasons: 1) the phase 2 studies used the immediate-release formulation of UPA versus the to-be-marketed extended-release formulation used in the phase 3 studies; and 2) the large number of well-designed and well-conducted phase 3 studies provided better data in which to assess efficacy.

The review of efficacy was conducted in collaboration with the biostatistical reviewer, William Koh, PhD. Given Dr. Koh’s expertise and independent analysis of the data, my review of efficacy

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is largely based on the results of his analyses and for which I have provided comments regarding the clinical meaningfulness of the data as it relates to the treatment of patients with RA.

Safety analyses included all subjects enrolled in the UPA development program with emphasis on the pooled data from the phase 3 studies. To best identify potential safety signals, the Agency requested the Applicant to submit analyses based on UPA dose and comparator during the controlled periods and long-term extension periods of the phase 3 studies. These six analysis sets will be referred to extensively in Section 8 and include the following:

- Integrated controlled-period analysis sets:
  - The “PBO-Controlled UPA 15 mg” analysis set consists of data from Studies M13-542, M13-549 and M14-465. All three of these studies randomized subjects to a PBO and UPA 15 mg group during the 12-week controlled period of the studies. This analysis set allows for the direct comparison of AEs between the proposed marketed dose of UPA 15 mg and PBO treatment arms.
  - The “PBO-Controlled UPA 15 mg and 30 mg” analysis set consists of data from Studies M13-542 and M13-549. These two studies randomized subjects to one of three treatment arms PBO, UPA 15 mg or UPA 30 mg during the 12-week controlled period of the studies. This analysis set allows for the relative comparison of the two UPA doses to assess for a dose-dependent effect of UPA as well as the comparison to PBO-treated subjects.
  - The “MTX-Controlled” analysis set included data from Studies M13-545 and M15-555. These studies randomized subjects to receive either MTX, UPA 15 mg or UPA 30 mg during the 12- or 14-week controlled period, respectively. These studies again allowed for the relative comparison of the two UPA doses to assess for a dose-dependent effect as well as the comparison to MTX-treated subjects. Pooling of these two studies was deemed acceptable given the comparison to active MTX control despite Study M13-545 having enrolled MTX-naïve subjects while Study M15-555 enrolled MTX-IR subjects.
- Integrated long-term analysis sets:
  - The “Any Phase 3 UPA 15 mg” analysis set consists of data from all five phase 3 studies, M13-542, M13-549, M13-545, M15-555 and M14-465. These studies all followed subjects treated with UPA 15 mg either from the time of randomization or from the time of crossover following the end of the controlled periods up to one year.
  - The “Any Phase 3 UPA 15 mg and 30 mg” analysis set consists of Studies M13-542, M13-546, M13-545 and M15-555. These studies followed subjects treated with UPA 15 mg or UPA 30 mg either from the time of

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randomization or from the time of crossover following the end of the controlled periods up to one year.

- The “Any RA UPA” analysis set consists of all subjects enrolled in the phase 2 and phase 3 studies. For this analysis set, the Applicant pooled subjects treated with the immediate-release formulation used in the phase 2 studies and the respective extended-release formulations used in the phase 3 studies. Since the Applicant demonstrated the bioequivalence between the BID dosing of the immediate-release formulation and the daily extended-release formulation in Study M13-538, pooling of these subjects was deemed acceptable for the safety analyses.

Study M14-465, which included PBO, UPA 15 mg and ADA treatment arms, was analyzed separately to compare the relative safety of UPA 15 mg versus subjects treated with ADA and PBO in the controlled period and long-term periods of the study.

This reviewer largely relied on the Applicant’s analysis of the safety data as prespecified at our pre-NDA meeting with commentary related to the clinical meaningfulness of the data. Any potential safety signal was further analyzed by me as required.

## 6. Review of Relevant Individual Trials Used to Support Efficacy

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### 6.1. Study M13-542

#### 6.1.1. Study Design

##### Overview and Objective

*“A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo on Stable Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) in Subjects with Moderately to Severely Active Rheumatoid Arthritis with Inadequate Response or Intolerance to Biologic DMARDs (bDMARDs)”.*

The primary objective of Study M13-542 was to assess the safety and efficacy of UPA 15 mg and UPA 30 mg compared to PBO in subjects with moderately to severely active RA on stable concomitant csDMARDs and who have had an inadequate response to a bDMARD. For the purposes of this study csDMARDs were restricted to MTX, chloroquine, hydroxychloroquine, sulfasalazine or leflunomide.

##### Trial Design

Study M13-542 was a phase 3 multicenter study conducted in two periods:

- Period 1 was a 24-week, randomized, double-blind, parallel-group, PBO-controlled period designed to compare the safety and efficacy of orally administered UPA 15 mg QD and 30 mg QD versus PBO for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to or intolerance to at least one bDMARD.
- Period 2 was a blinded long-term extension period to evaluate the long-term safety, tolerability, and efficacy of UPA 30 mg QD and 15 mg QD in subjects with RA who had completed Period 1.

The study was designed to enroll approximately 450 subjects and actually enrolled 498 subjects at 152 study sites in 26 countries (Australia, Austria, Belgium, Canada, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Korea, Latvia, New Zealand, Poland, Portugal, Puerto Rico, Russian Federation, Slovakia, Spain, Sweden, Turkey, United Kingdom, United States). Subjects meeting eligibility criteria were randomized in a 2:2:1:1 ratio to one of four treatment groups:

- Group 1: UPA 30 mg PO QD (Day 1 to Week 12) → UPA 30 mg PO QD (remainder of study)

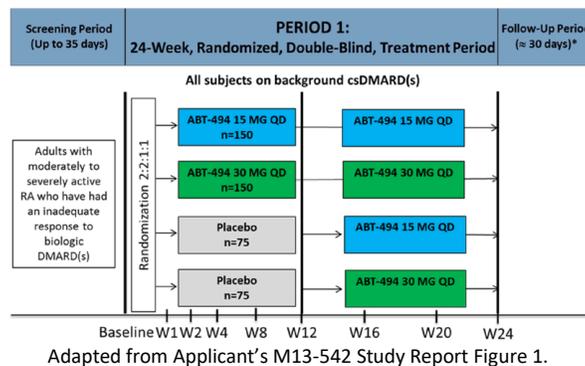
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- Group 2: UPA 15 mg PO QD (Day 1 to Week 12) → UPA 15 mg PO QD (remainder of study)
- Group 3: PBO PO (Day 1 to Week 12) → UPA 30 mg PO QD (remainder of study)
- Group 4: PBO PO (Day 1 to Week 12) → UPA 15 mg PO QD (remainder of study)

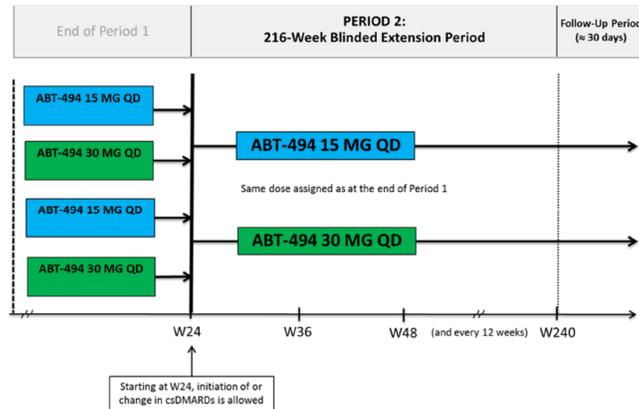
Subjects entered the study on a stable dose of csDMARD(s) for  $\geq 4$  weeks prior to the first dose of study drug and remained on a stable dose until Week 24. Starting at Week 24, subjects who did not meet low disease activity by the clinical disease activity index criterion ( $CDAI \leq 10$ ) were able to have concomitant medication adjusted including the initiation/change of corticosteroids, NSAIDs, acetaminophen, or adding or increasing doses in up to two csDMARD. Starting at Week 24, at least 20% improvement in both tender joint count and swollen joint count was required to remain on study drug. Anyone who did not fulfill this criterion at two consecutive visits (starting at Week 24) were discontinued from study drug.

Subjects who completed the Week 24 visit entered Period 2 of the study, the blinded long-term extension of 216 weeks. Subjects who were assigned to UPA treatment groups in Period 1 continued to receive UPA 15 mg QD or 30 mg QD per the original randomization assignment in a blinded manner. Subjects who were assigned to PBO for the first 12 weeks of Period 1 and subsequently switched to UPA 15 mg QD or 30 mg QD per their prespecified randomization assignments at Week 12, continued to receive the same dose of UPA per their original randomization assignment in a blinded manner. Figure 2 and Figure 3 illustrate the general schema of Study M13-542.

**Figure 2. Study M13-542: Period 1 Overview**



**Figure 3. Study M13-542: Period 2 Overview**



Adapted from Applicant's M13-542 Study Report Figure 2.

Major inclusion criteria:

- Male and female subjects  $\geq 18$  years-of-age
- Diagnosis of RA based on the 2010 ACR/EULAR criteria for a duration for  $\geq 3$  months
- $\geq 6$  swollen joints (based on 66 joint counts)
- $\geq 6$  tender joints (based on 68 joint counts)
- hsCRP  $\geq 3$  mg/L
- Have failed or be intolerant to previous bDMARD therapy for RA
- Currently treated with csDMARD therapy (restricted to MTX, chloroquine, hydroxychloroquine, sulfasalazine, or leflunomide)  $\geq 3$  months and on stable dose for  $\geq 4$  weeks

Major exclusion criteria:

- Prior exposure to any JAK inhibitor
- History of an inflammatory joint disease other than RA
- Laboratory values meeting the following criteria
  - AST or ALT  $> 2 \times$  ULN
  - eGFR  $< 40$  mL/min/1.73m<sup>2</sup>
  - WBC  $< 2,500/\mu\text{L}$
  - ANC  $< 1500/\mu\text{L}$
  - PLT  $< 100,000/\mu\text{L}$
  - ALC  $< 800/\mu\text{L}$
  - Hg  $< 10$  g/dL

The dose selection for UPA 15 mg and 30 mg once-daily oral tablets was based on extrapolation of preclinical efficacy models and analyses of PK, pharmacodynamic, safety, and efficacy data from the phase 1 studies in healthy volunteers and phase 2 studies in RA subjects. The doses selected for this study were expected to be efficacious with an acceptable safety profile.

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## Study Endpoints

The proportion of subjects achieving an ACR20 at Week 12 was used as the primary endpoint for improvement in signs and symptoms. The ACR response criteria consists of 7 components:

- Swollen joint count (66 joints)
- Tender joint count (68 joints)
- Subject global assessment of pain (VAS 100mm)
- Subject global assessment of disease activity (VAS 100mm)
- Physician global assessment of disease activity (VAS 100mm)
- Subject assessment of physical function using HAQ
- CRP

The ACR20 definition of response specifies a 20% improvement over baseline in swollen and tender joints and in 3 out of 5 of the remaining core data set measures. For the primary endpoint, assessment of the ACR20 occurred at Week 12. The choice of the primary endpoint is appropriate to assess a clinically meaningful benefit of UPA and consistent with Agency guidelines.

Key secondary endpoints were selected to capture clinically meaningful endpoints used to support the findings of the primary endpoint and were ranked as change from baseline to Week 12 in DAS28-CRP, Health Assessment Questionnaire-Disability Index (HAQ-DI), low disease activity as measured by DAS28-CRP, and change from baseline in Short Form-36 (SF36) physical components summary (PCS). Other clinically important secondary endpoints included change from baseline to Week 12 in ACR50/ACR70, morning stiffness and FACIT-F. Further discussion of the secondary endpoints can be found in Section 7.1.2. Analysis of other key secondary endpoints can be found in Dr. Koh's review.

## Statistical Analysis Plan

### Primary Endpoint:

Comparison of the primary endpoint was made between each UPA dose group and the combined PBO groups using the Cochran-Mantel-Haenszel test adjusted for main stratification factors. For the primary analysis, Non-Responder Imputation was used. The analysis was repeated using Observed Cases. Supportive analysis was also conducted on the Per Protocol Analysis Set. The primary efficacy analyses were also performed in demographic subgroups including age, sex, weight, body mass index, race, and geographical region to assess the consistency of the treatment effect. Additional subgroup analyses based on baseline disease characteristics and stratification factors were also conducted

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#### Secondary Endpoints:

For binary endpoints, frequencies and percentages were reported for each treatment group. Similar analyses as for the primary endpoint were conducted. For the major RA continuous endpoints DAS28 and HAQ-DI change from baseline at Week 12, statistical inference was conducted using analysis of covariance (ANCOVA) coupled with multiple imputation for missing data handling. Specifically, the ANCOVA model was to include treatment as the fixed factor, and the corresponding baseline value and the stratification factor prior bDMARD use as the covariates.

For other continuous endpoints, statistical inference was conducted using the Mixed Effect Model Repeat Measurement (MMRM) model with fixed effects of treatment, visit and treatment by-visit interaction, prior bDMARD use and baseline value as covariate. For both the MI and MMRM analyses, the least square mean and 95% confidence interval (CI) were reported for each randomized treatment group; the LS mean treatment difference and associated 95% CI and p-value were reported comparing each UPA dose group with the combined PBO group. Both nominal p value and adjusted p-value through the graphical multiplicity procedure were provided.

#### **Protocol Amendments**

The current protocol had two major amendments and nine country-specific amendments. The majority of changes to the protocol were responses to regulatory feedback, clarifications and editorial changes. Country-specific protocol amendments did not affect interpretation of the results of the study. Major amendments as they relate to the US studies are as follows:

- Amendment 1 (29 February 2016, 427 subjects) included revisions to the inclusion criteria to clarify requirements of pregnancy testing and women of childbearing potential. Text was added to clarify contraception requirements for background RA medication and follicle stimulating hormone (FSH) testing for females. Criteria were added for adjusting or adding background medication at Week 24 if subjects did not achieve low disease activity as defined by CDAI. Text was added to clarify TB assessment and testing, ECG procedures, and the CDAI calculation.
- Amendment 2 (10 October 2016, 60 subjects) was updated to clarify that there were different primary efficacy variables for different regulatory purposes. Revisions updated inclusion criteria text to accommodate geographic differences in MTX dosing, to remove failure of csDMARDs, and to be more in line with expected pharmacodynamics of these drugs and standard practice. Revisions were made to the exclusion criteria to clarify the highest risk for gastrointestinal perforation with IL-6 and JAK inhibitors is for the lower GI tract, to update laboratory values within the screening period to reflect normal laboratory value reference ranges in the elderly population, and to reflect lack of QTc prolongation with UPA. Guidance text was provided for washout of csDMARDs and permitted background RA therapy. Traditional Chinese medicine

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was added as prohibited. ECG and in vivo biomarkers at the final/premature discontinuation visit were added to the schedule of activities.

Reviewer's Comments:

The current study was well-designed, randomized, double-blinded, PBO-controlled and evaluated two doses of UPA in subjects with moderately to severely active RA receiving concomitant background therapy of csDMARDs and who had an inadequate response to a previous bDMARD or were intolerant to bDMARD therapy. The enrolled subjects represented a typically more difficult to treat patient population due to having failed several therapies with different mechanisms-of-action. The inclusion and exclusion criteria were acceptable and were consistent with RA subjects with moderately to severely active RA. The choice of a PBO control group was appropriate for the objectives of the study and the choice of concomitant csDMARDs were those that are commonly used in the US.

The Applicant's choice to use the proportion of subjects achieving an ACR20 at Week 12 as the primary endpoint and the HAQ-DI and DAS28 at Week 12 as major secondary endpoints, are adequate to assess clinically meaningful outcomes and have been validated and used in previous approvals of other drugs indicated for patients with moderate to severe RA and are recommended in the Agency's RA guidance document.

### 6.1.2. Study Results

#### **Compliance with Good Clinical Practices**

The Applicant has provided attestation that the study was conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of the clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice.

#### **Financial Disclosure**

A financial disclosure review was conducted for all five phase 3 studies. Because many investigators participated in more than one study, a combined review of the financial disclosures will be presented. Table 6 shows the total number of investigators identified in each of the phase 3 studies that were evaluated for financial disclosure based on the investigator information.

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**Table 6. All Five Phase 3 Studies: Total Number of Investigators in Registrational Studies**

<b>Study</b>	<b>Total Number of Investigators</b>	<b>Number of Principle Investigators</b>	<b>Number of Sub-investigators</b>
M13-542	674	153	521
M13-545	1205	236	969
M13-549	721	150	571
M14-465	1383	285	1098
M15-555	667	138	529

Adapted from Applicant's Financial Summary Table 1.

A total of 41 investigators had disclosable financial interests/arrangements. Each investigator's financial disclosure documentation was reviewed. For these investigators with disclosable financial interests/arrangements: none received compensation for conducting the study where the value could be influenced by the outcome of the study; no investigators received significant payments of other sorts; no investigators had proprietary interest in the product being tested held by the investigator; no investigator had significant equity interest in the Sponsor covered study.

These financial disclosures do not raise concerns regarding the integrity of the phase 3 studies as the Applicant took steps to minimize potential bias of clinical investigators with financial interests and arrangements by using proper study design and operations. The clinical studies were blinded to the study site personnel and the participating subjects through the primary endpoint collection for the studies. Each active dose of investigational drug product was identical in appearance to its matched PBO and each subject was randomly assigned to their treatment arm independent of the investigator and the study site. Additionally, the number of subjects enrolled at the individual investigator sites were small compared to the total number of subjects enrolled in the overall study.

### **Patient Disposition**

A total of 499 subjects were randomized and 498 subjects received study drug. One subject who failed screening was randomized in error and did not receive study drug. A total of 457 (92%) subjects completed study drug through Week 12 and 419 (84%) subjects completed study drug through Period 1 (Table 7).

**Table 7. Study M13-542: Subject Disposition (All Randomized Subjects)**

	PBO/UPA 15 mg QD (n=85)	PBO/UPA 30 mg QD (n=85)	UPA 15 mg QD (n=165)	UPA 30 mg QD (n=165)
<b>Treated</b>	85	84	165	165
<b>Completed Week 12, n (%)</b>	75 (88)	76 (91)	157 (96)	149 (90)
<b>Discontinued study through Week 12, n (%)</b>	10 (12)	9 (10)	7 (4)	16 (10)
<b>AE</b>	2 (2)	2 (2)	1 (1)	12 (7)
<b>Withdrawal by subject</b>	2 (2)	1 (1)	4 (2)	2 (1)
<b>Lost to follow-up</b>	2 (2)	1 (1)	0	0
<b>Lack of efficacy</b>	0	0	0	0
<b>Other</b>	4 (5)	4 (5)	2 (1)	2 (1)
<b>Discontinued study Week 12 to 24, n (%)</b>	3 (4)	2 (2)	4 (2)	14 (9)
<b>AE</b>	1 (1)	2 (2)	2 (1)	5 (3)
<b>Withdrawal by subject</b>	1 (1)	0	1 (1)	4 (2)
<b>Lost to follow-up</b>	0	0	0	1 (1)
<b>Lack of efficacy</b>	0	0	0	0
<b>Other</b>	1 (1)	0	1 (1)	4 (2)

Adapted from Applicant's M13-542 Study Report Table 3.

Through the first 12-weeks of the study, similar numbers of subjects in the PBO and UPA 30 mg groups discontinued study drug compared to a lower percentage of UPA 15 mg subjects. A greater number of UPA 30 mg subjects discontinued the study due to AE while "Other" was the largest category for PBO-treated subjects discontinuing. From Week 12 through Week 24, a larger percentage of subjects who were initially randomized to the UPA 30 mg group discontinued the study compared to the other treatment arms.

### Protocol Violations/Deviations

The most common reason for protocol deviations was related to not meeting inclusion/exclusion criteria. A total of 8/499 (2%) subjects entered the study without being on a stable dose of the required csDMARD concomitant treatment. A total of 7/499 (1%) subjects entered the study not meeting the protocol-specified duration of time for bDMARD discontinuation prior to baseline, and six subjects each entered the study not meeting the minimum disease activity criteria at screening and having a history of GI perforation or a history of associated GI diseases.

Overall, the total number of subjects with protocol violations at the time of the primary endpoint assessment was small and relatively balanced between treatment arms. These protocol deviations were not considered to have affected the overall assessment of study results.

### Table of Demographic Characteristics

As shown in Table 8, subjects' baseline demographics were similar between treatment arms.

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The average subject enrolled in the study was female, White, 57-years of age and clinically overweight, which is consistent with the US patient population.

**Table 8. Study M13-542: Subjects Baseline Demographics**

Demographic Parameters	PBO (N=169)	UPA 15 mg QD (N=164)	UPA 30 mg QD (N=165)
<b>Sex, n (%)</b>			
Male	26 (15)	27 (17)	27 (16)
Female	143 (85)	137 (84)	138 (84)
<b>Age, n (%)</b>			
Mean $\pm$ SD	58 $\pm$ 11	56 $\pm$ 11	57 $\pm$ 12
Median (min, max)	60 (24, 81)	57 (23, 81)	58 (28, 87)
<b>Age (years), n (%)</b>			
< 40 years	14 (8)	11 (7)	14 (9)
40-64	106 (63)	115 (70)	103 (62)
$\geq$ 65 years	49 (29)	38 (23)	48 (29)
<b>Race, n (%)</b>			
White	143 (85)	142 (87)	148 (90)
Black or African American	21 (12)	17 (10)	10 (6)
Asian	5 (3)	2 (1)	2 (1)
American Indian or Alaska Native	0	3 (2)	4 (2)
Native Hawaiian or Other Pacific Islander	0	0	1 (1)
<b>Ethnicity</b>			
Hispanic or Latino	24 (14)	34 (21)	28 (17)
Not Hispanic or Latino	145 (86)	130 (79)	137 (83)
<b>BMI (kg/m<sup>2</sup>)</b>			
Mean $\pm$ SD	30 $\pm$ 7	31 $\pm$ 7	30 $\pm$ 6
Median (min, max)	28 (15, 48)	31 (18, 64)	29 (17, 47)

Adapted from Applicant's Study M13-542 study report Table 4.

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Overall, the subjects enrolled in the study demonstrated moderately to severely active disease as evidenced by the average DAS28 score, swollen and tender joint counts, HAQ-DI and length of morning stiffness. Subjects' baseline disease characteristics and background RA-related therapy were similar between individual treatment arms (Table 9).

**Table 9. Study M13-542: Subjects Baseline Disease Characteristics**

Demographic Parameters	PBO (N=169)	UPA 15 mg QD (N=164)	UPA 30 mg QD (N=165)
<b>Duration of RA (years)</b>			
Mean ± SD	15 ± 9	12 ± 9	13 ± 10
Median (min, max)	12 (<1, 40)	10 (<1, 47)	10 (<1, 51)
<b>RF and anti-CCP, n (%)</b>			
Positive (RF + anti-CCP)	102 (60)	107 (66)	101 (61)
At least one negative	67 (40)	56 (34)	64 (39)
<b>DAS28 (CRP)</b>			
n	166	163	163
Mean ± SD	5.8 ± 1	5.9 ± 1	5.8 ± 1
Median (min, max)	6 (3, 8)	6 (4, 8)	6 (4, 8)
<b>Swollen Joint Count-66</b>			
Mean ± SD	16 ± 10	17 ± 11	17 ± 11
Median (min, max)	14 (4, 57)	14 (6, 62)	14 (6, 64)
<b>Tender Joint Count-68</b>			
Mean ± SD	29 ± 15	28 ± 16	27 ± 15
Median (min, max)	27 (6, 66)	25 (6, 68)	23 (6, 66)
<b>HAQ-DI</b>			
n	166	163	161
Mean ± SD	1.6 ± 0.6	1.7 ± 0.6	1.6 ± 0.6
Median (min, max)	1.6 (0, 3)	2 (0, 3)	1.6 (0, 3)
<b>CRP (mg/L)</b>			
Mean ± SD	16 ± 21	16 ± 19	16 ± 21
Median (min, max)	9 (0, 150)	9 (0, 129)	8 (1, 137)
<b>Morning Stiffness duration (minutes)</b>			
Mean ± SD	138 ± 179	140 ± 189	184 ± 285
Median (min, max)	120 (0, 1440)	90 (0, 1440)	120 (5, 1440)
<b>Failed at least one TNF inhibitor, n (%)</b>			
Yes	152 (90)	146 (89)	151 (92)
No	17 (10)	18 (11)	13 (8)
<b>Concomitant csDMARD at baseline, n (%)</b>			
MTX alone	122 (73)	118 (73)	124 (76)
MTX and other csDMARD	17 (10)	19 (12)	11 (7)
csDMARD other than MTX	29 (17)	24 (15)	29 (18)
<b>Oral corticosteroid dose (mg)</b>			
n	74	83	87
Mean ± SD	6 ± 2	6 ± 2	6 ± 6
Median (min, max)	5 (2.5, 10)	5 (1, 10)	5 (1, 55)

Adapted from Applicant's Study M13-542 study report Table 5.

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance was calculated as the number of tablets taken in Period 1. Mean treatment compliance was 100% in both the UPA 15 mg and 30 mg groups, respectively, and 100% in those subjects who switched from PBO to UPA 15 mg and 30 mg at Week 12.

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As shown in Table 9, over 80% of subjects in all treatment arms were receiving concomitant MTX with or without an additional csDMARD, which was limited to either chloroquine, hydroxychloroquine, sulfasalazine, or leflunomide, all of which are commonly used in the US to treat subjects with RA. The remaining approximately 20% of subjects were only treated with csDMARD that were not MTX.

### **Efficacy Results – Primary Endpoint**

As shown in Table 10, the primary endpoint analysis demonstrated a statistically significant difference between PBO and the individual UPA treatment arms. The average treatment effect size for the UPA 15 mg and UPA 30 mg treatment arms were 36% and 28%, respectively. There was no apparent additional benefit with the UPA 30 mg dose compared to the UPA 15 mg dose. In fact, these results demonstrate a greater response rate in UPA 15 mg-treated subjects compared with UPA 30 mg subjects.

**Table 10. Study M13-542: Proportion of Subjects Achieving ACR20 at Week 12**

	<b>PBO (N=169) n (%)</b>	<b>UPA 15 mg QD (N=164) n (%)</b>	<b>UPA 30 mg QD (N=165) n (%)</b>
ACR20	48 (28)	106 (65)	93 (56)
Difference (%), (95% CI)	-	36 (26, 46)	28 (18, 38)
Source: FDA Biostatistics Review for NDA 211675			

The primary endpoint analysis demonstrates a clinically meaningful benefit with UPA treatment for the improvement of the signs and symptoms of subjects with active RA despite concurrent csDMARD therapy and having failed treatment with at least one bDMARD. Additionally, UPA-treated subjects demonstrated greater improvements in all ACR components compared to PBO-treated subjects at Week 12 demonstrating that the results were not driven by any single component of the ACR response criteria (Table 11).

**Table 11. Study M13-542: Change from Baseline in ACR Components (excluding HAQ-DI)**

Treatment Arm	N	Baseline Mean (SD)	n	Visit Mean (SD)	Est Diff (95 % CI)	p-value
<b>CRP</b>						
PBO	169	16.3 (21.1)	151	13.8 (17.3)	-	-
UPA 15 mg QD	164	16.2 (18.6)	158	5.1 (14.1)	-8.8 (-11.7, -5.9)	<0.001
UPA 30 mg QD	165	16.0 (21.2)	152	4.8 (8.0)	-9.2 (-12.1, -6.3)	<0.001
<b>SJC (Out of 28)</b>						
PBO	169	11.4 (5.6)	151	6.4 (6.3)	-	-
UPA 15 mg QD	164	11.9 (5.8)	160	4.2 (4.7)	-2.5 (-3.7, -1.4)	<0.001
UPA 30 mg QD	165	11.6 (5.7)	154	4.9 (6.1)	-1.7 (-2.8, -0.5)	0.005
<b>SJC (Out of 66)</b>						
PBO	169	16.3 (9.6)	151	9.2 (10.2)	-	-
UPA 15 mg QD	164	17.0 (10.8)	160	6.0 (8.2)	-3.8 (-5.6, -1.9)	<0.001
UPA 30 mg QD	165	17.2 (11.4)	154	7.7 (11.4)	-2.3 (-4.1, -0.4)	0.016
<b>TJC (Out of 28)</b>						
PBO	169	15.9 (7.3)	151	9.8 (8.2)	-	-
UPA 15 mg QD	164	16.1 (7.3)	160	6.0 (7.1)	-4.1 (-5.5, -2.6)	<0.001
UPA 30 mg QD	165	15.4 (6.5)	154	6.1 (7.2)	-3.6 (-5.0, -2.1)	<0.001
<b>TJC (Out of 68)</b>						
PBO	169	28.5 (15.3)	151	18.5 (17.2)	-	-
UPA 15 mg QD	164	27.8 (16.3)	160	11.4 (14.3)	-6.8 (-9.6, -4.0)	<0.001
UPA 30 mg QD	165	27.3 (15.2)	154	11.4 (13.9)	-6.4 (-9.3, -3.6)	<0.001
<b>Physician Global</b>						
PBO	166	66.9 (16.9)	144	39.2 (25.1)	-	-
UPA 15 mg QD	163	68.7 (16.6)	159	28.9 (22.4)	-10.9 (-16.1, -5.7)	<0.001
UPA 30 mg QD	161	66.4 (15.6)	150	25.9 (21.7)	-13.3 (-18.5, -8.0)	<0.001
<b>Patient Global</b>						
PBO	161	66.3 (22.7)	150	53.6 (27.9)	-	-
UPA 15 mg QD	157	67.2 (19.6)	160	39.9 (26.5)	-13.9 (-19.7, -8.1)	<0.001
UPA 30 mg QD	157	64.7 (21.0)	154	35.2 (27.1)	-17.8 (-23.6, -11.9)	<0.001
<b>Patient Pain</b>						
PBO	166	68.9 (21.0)	150	55.2 (27.7)	-	-
UPA 15 mg QD	163	68.2 (19.8)	160	40.9 (27.6)	-13.8 (-19.6, -8.1)	<0.001
UPA 30 mg QD	161	65.3 (20.7)	154	35.3 (26.2)	-18.9 (-24.7, -13.0)	<0.001

Source: FDA Biometrics Review for NDA 211675

Results from sensitivity analyses on the Per Protocol Analysis set were consistent with the primary analysis. Subgroup analysis results using Nonresponder Imputation, were also consistent with the primary analysis.

## Efficacy Results – Secondary and other relevant endpoints

### HAQ-DI

Table 12 shows that at Week 12, subjects treated with UPA experienced a statistically significant and clinically meaningful change from baseline ( $\leq -0.3$ ) compared to subjects treated with PBO; however, there was no evidence of a dose-dependent increase in response between the UPA 15 mg and UPA 30 mg dosing groups. These data support the results of the primary endpoint demonstrating a clinical benefit of UPA treatment in subjects with RA.

**Table 12. Study M13-542: Change in HAQ-DI from Baseline to Week 12**

HAQ-DI Score	PBO	UPA 15 mg QD	UPA 30 mg QD
	<b>N=166</b>	<b>N=163</b>	<b>N=161</b>
Baseline (Mean $\pm$ SD)	1.6 $\pm$ 0.6	1.7 $\pm$ 0.6	1.6 $\pm$ 0.6
	<b>N=150</b>	<b>N=160</b>	<b>N=154</b>
Week 12 (Mean $\pm$ SD)	1.3 $\pm$ 0.7	1.2 $\pm$ 0.8	1.2 $\pm$ 0.7
Difference (%), (95% CI)	-	-0.2 (-0.3, -0.1)	-0.2 (-0.3, -0.1)
Source: FDA Biostatistics Review for NDA 211675			

Tipping point analyses were conducted to evaluate the robustness of the results for the change from baseline in HAQ-DI comparing UPA 15 mg and 30 mg with PBO. In study M13-542, PBO patients with missing HAQ-DI response at Week 12 would have to average at least 1-point improvement from baseline, together with missing UPA patients to average 0.5-point improvement from baseline in order to tip the conclusions, such that there would be no longer evidence of an effect (data not shown). This provides additional support to the primary analysis demonstrating the benefit of UPA treatment on HAQ-DI in subjects with RA.

### ACR20/ACR50/ACR70

Analysis of the ACR responses demonstrated a statistically significant increase in the improvement of signs and symptoms of subjects in the UPA groups compared to the PBO group (Table 13). Upadacitinib 30 mg-treated subjects achieved greater responses in ACR50 and ACR70 response compared to subjects in the UPA 15 mg group; however, as discussed with the analysis of the primary endpoint, a greater proportion of UPA 15 mg subjects achieved an ACR20.

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**Table 13. Study M13-542: Change in ACR20/ACR50/ACR70 from Baseline at Week 12**

	<b>PBO (N=169) n (%)</b>	<b>UPA 15 mg (N=164) n (%)</b>	<b>UPA 30 mg (N=165) n (%)</b>	<b>UPA 15 mg vs PBO Difference (%), (95% CI)</b>	<b>UPA 30 mg vs. PBO Difference (%), (95% CI)</b>
<b>ACR20</b>	48 (28)	106 (65)	93 (56)	36 (26, 46)	28 (18, 38)
<b>ACR50</b>	20 (12)	56 (34)	59 (36)	22 (14, 31)	24 (15, 33)
<b>ACR70</b>	11 (7)	19 (12)	38 (23)	5 (-1, 11)	17 (9, 24)

Source: FDA Biostatistics Review for NDA 211675

These data support the results of the primary endpoint and demonstrate a clinically meaningful effect of UPA compared to PBO in subjects with moderately to severely active RA.

### **DAS28-CRP**

A significantly greater mean change from baseline in DAS28-CRP at Week 12 was observed in the UPA treatment arms compared to PBO (Table 14). These data support the results of the primary endpoint demonstrating a clinically meaningful benefit of UPA treatment in subjects with RA; however, a dose-dependent increase in the DAS28-CRP response between the UPA 15 mg and UPA 30 mg dosing groups was not observed.

**Table 14. Study M13-542: Change in DAS28-CRP from Baseline to Week 12**

<b>DAS28-CRP Score</b>	<b>PBO</b>	<b>UPA 15 mg QD</b>	<b>UPA 30 mg QD</b>
	<b>N=166</b>	<b>N=163</b>	<b>N=163</b>
Baseline (Mean ± SD)	5.8 ± 1	5.9 ± 1	5.8 ± 1
	<b>N=147</b>	<b>N=157</b>	<b>N=149</b>
Week 12 (Mean ± SD)	4.7 ± 1.4	3.5 ± 1.3	3.5 ± 1.5
Difference (%), (95% CI)	-	-1.2 (-1.5, -0.9)	-1.1 (-1.4, -0.8)

Source: FDA Biostatistics Review for NDA 211675

### **DAS28-CRP <2.6**

DAS28-CRP responses <2.6 represent very low disease activity. In Study M13-542, a higher proportion of subjects treated with UPA 15 mg and 30 mg achieved DAS28-CRP <2.6 responses compared to PBO-treated subjects, 29% and 24% versus 9%, respectively. These results demonstrate a clinically meaningful benefit of UPA in decreasing disease activity in subjects with active RA. Similar to previous results, there was no increased benefit with higher doses of UPA 30 mg compared to UPA 15 mg.

**SF-36**

In study M13-542, the mean adjusted change from baseline in the SF-36 PCS score at Week 12 was significantly higher in subjects treated with UPA 15 mg and 30 mg compared to PBO-treated subjects (Table 15); however, there was only a minimal, non-significant change in the SF-36 MCS score. These results suggest a modest improvement in the SF-36 PCS score but no improvement of the SF-36 MCS score. The reader is directed to Dr. Koh’s review for a detailed analysis of the individual SF-36 domains.

**Table 15. Study M13-542: Change in SF-36 PCS and MCS Scores from Baseline to Week 12**

<b>SF-36 PCS Score</b>	<b>PBO</b>	<b>UPA 15 mg QD</b>	<b>UPA 30 mg QD</b>
	<b>N=166</b>	<b>N=163</b>	<b>N=162</b>
Baseline (Mean ± SD)	32 ± 7	31 ± 8	32 ± 7
	<b>N=147</b>	<b>N=157</b>	<b>N=149</b>
Week 12 (Mean ± SD)	35 ± 9	37 ± 10	39 ± 9
Difference (%), (95% CI)	-	3.1 (1, 5)	5 (3, 6)
<b>SF-36 MCS Score</b>			
	<b>N=166</b>	<b>N=163</b>	<b>N=162</b>
Baseline (Mean ± SD)	46 ± 13	44 ± 12	46 ± 12
	<b>N=147</b>	<b>N=157</b>	<b>N=149</b>
Week 12 (Mean ± SD)	49 ± 11	49 ± 12	49 ± 11
Difference (%), (95% CI)	-	1 (-1, 3)	0 (-2, 2)
Source: FDA Biostatistics Review for NDA 211675			

**Morning Stiffness**

As shown in Table 16, the mean change from baseline in duration of morning stiffness at Week 12 in subjects treated with UPA 15 mg or 30 mg decreased significantly compared to subjects treated with PBO. These results support a clinically relevant benefit of UPA in decreasing disease activity in subjects with active RA. Similar to previous results, there was no increased benefit with higher doses of UPA 30 mg compared to UPA 15 mg.

**Table 16. Study M13-542: Change in Morning Stiffness from Baseline to Week 12**

Morning Stiffness (minutes)	PBO	UPA 15 mg QD	UPA 30 mg QD
	<b>N=169</b>	<b>N=164</b>	<b>N=165</b>
Baseline (Mean ± SD)	138 ± 179	140 ± 190	185 ± 285
	<b>N=151</b>	<b>N=160</b>	<b>N=153</b>
Week 12 (Mean ± SD)	133 ± 249	68 ± 133	90 ± 203
Difference (%), (95% CI)	-	-64 (-104, -25)	-60 (-100, -19)

Source: FDA Biostatistics Review for NDA 211675

## 6.2. Study M13-549

### 6.2.1. Study Design

#### Overview and Objective

*“A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Dose of Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) and Have an Inadequate Response to csDMARDs”.*

The primary objective of Study M13-549 was to assess the safety and efficacy of UPA 15 mg and UPA 30 mg compared to PBO in subjects with moderately to severely active RA receiving stable doses of concomitant csDMARDs and who have had an inadequate response to csDMARDs. For the purposes of this study csDMARDs were restricted to MTX, chloroquine, hydroxychloroquine, sulfasalazine or leflunomide.

#### Trial Design

Study M13-549 was a phase 3 multicenter study conducted in two periods:

- Period 1 was a 12-week, randomized, double-blind, parallel-group, PBO-controlled period designed to compare the safety and efficacy of orally administered UPA 15 mg QD and 30 mg QD versus PBO for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to csDMARDs.

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- Period 2 was a blinded long-term extension period to evaluate the long-term safety, tolerability, and efficacy of UPA 30 mg QD and 15 mg QD in subjects with RA who had completed Period 1.

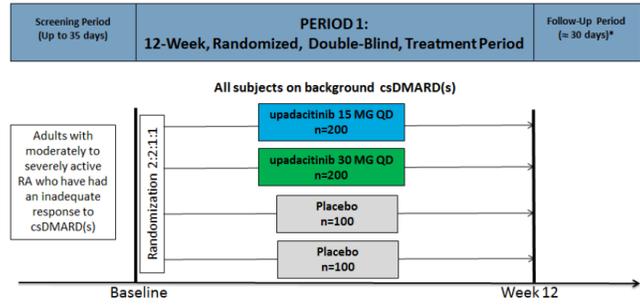
The study was designed to enroll approximately 600 subjects and actually enrolled 661 subjects at 150 study sites in 35 countries (Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Canada Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Ireland, Israel, Kazakhstan, Korea, Latvia, Lithuania, Mexico, New Zealand, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Switzerland, Taiwan, Ukraine, United Kingdom, United States). Subjects meeting eligibility criteria were randomized in a 2:2:1:1 ratio to one of four treatment groups:

- Group 1: UPA 30 mg PO QD (Day 1 to Week 12) → UPA 30 mg PO QD (remainder of study)
- Group 2: UPA 15 mg PO QD (Day 1 to Week 12) → UPA 15 mg PO QD (remainder of study)
- Group 3: PBO (Day 1 to Week 12) → UPA 30 mg PO QD (remainder of study)
- Group 4: PBO (Day 1 to Week 12) → UPA 15 mg PO QD (remainder of study)

Subjects entered the study on a stable dose of csDMARD(s) for  $\geq 4$  weeks prior to the first dose of study drug and remained on a stable dose until Week 24. Subjects with prior exposure to at most one bDMARD for RA were also eligible for enrollment in the study up to 20% of total study population and only after the required washout period was satisfied and if they had limited exposure ( $< 3$  months), or adequate response to bDMARD but had to discontinue that bDMARD due to intolerability (regardless of treatment duration). These subjects were stratified across all treatment groups. Subjects who were considered bDMARD inadequate responders, as determined by the investigator, were not eligible. Starting at Week 24, subjects who did not meet low disease activity by the clinical disease activity index criterion ( $CDAI \leq 10$ ) were able to have concomitant medication adjusted including the initiation/change of corticosteroids, NSAIDs, acetaminophen, or adding or increasing doses in up to two csDMARD. Starting at Week 24, at least 20% improvement in both tender joint count and swollen joint count was required to remain on study drug. Anyone who did not fulfill this criterion at two consecutive visits (starting at Week 24) were discontinued from study drug.

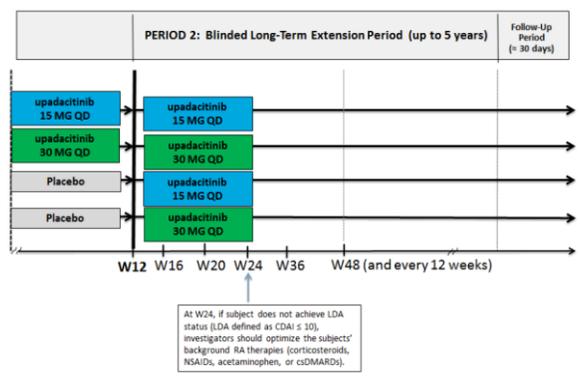
Subjects who completed the Week 12 visit entered Period 2 of the study, the blinded long-term extension of up to five years. Subjects who were assigned to UPA treatment groups in Period 1 continued to receive UPA 15 mg QD or 30 mg QD per original randomization assignment in a blinded manner. Subjects who were assigned to PBO for the first 12 weeks of Period 1 and subsequently switched to UPA 15 mg QD or 30 mg QD per their prespecified randomization assignments at Week 12, continued to receive the same dose of UPA per their original randomization assignment in a blinded manner. Figure 4 and Figure 5 illustrate the general schema of Study M13-542.

**Figure 4. Study M13-549: Period 1 Overview**



Adapted from Applicant's M13-549 Study Report Figure 1.

**Figure 5. Study M13-549: Period 2 Overview**



Adapted from Applicant's M13-549 Study Report Figure 2.

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### Major inclusion criteria:

- Male and female subjects  $\geq 18$  years-of-age
- Diagnosis of RA based on the 2010 ACR/EULAR criteria for a duration for  $\geq 3$  months
- $\geq 6$  swollen joints (based on 66 joint counts)
- $\geq 6$  tender joints (based on 68 joint counts)
- hsCRP  $\geq 3$  mg/L
- Have failed or be intolerant to previous csDMARD therapy for RA
- Currently treated with csDMARD therapy (restricted to MTX, chloroquine, hydroxychloroquine, sulfasalazine, or leflunomide)  $\geq 3$  months and on stable dose for  $\geq 4$  weeks

### Major exclusion criteria:

- Prior exposure to any JAK inhibitor
- History of an inflammatory joint disease other than RA
- Laboratory values meeting the following criteria
  - AST or ALT  $> 2 \times$  ULN
  - eGFR  $< 40$  mL/min/1.73m<sup>2</sup>
  - WBC  $< 2,500/\mu\text{L}$
  - ANC  $< 1500/\mu\text{L}$
  - PLT  $< 100,000/\mu\text{L}$
  - ALC  $< 800/\mu\text{L}$
  - Hg  $< 10$  g/dL

The dose selection for UPA 15 mg and 30 mg once-daily oral tablets was based on extrapolation of preclinical efficacy models and analyses of PK, pharmacodynamic, safety, and efficacy data from the phase 1 studies in healthy volunteers and phase 2 studies in RA subjects. The doses selected for this study were expected to be efficacious with an acceptable safety profile.

## Study Endpoints

The proportion of subjects achieving an ACR20 at Week 12 was used as the primary endpoint for improvement in signs and symptoms. The ACR response criteria consists of 7 components:

- Swollen joint count (66 joints)
- Tender joint count (68 joints)
- Subject global assessment of pain (VAS 100mm)
- Subject global assessment of disease activity (VAS 100mm)
- Physician global assessment of disease activity (VAS 100mm)
- Subject assessment of physical function using HAQ
- CRP

The ACR20 definition of response specifies a 20% improvement over baseline in swollen and tender joints and in 3 out of 5 of the remaining core data set measures. The choice of the primary

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endpoint is appropriate to assess a clinically meaningful benefit of UPA and consistent with Agency guidelines.

Key secondary endpoints were selected to capture clinically meaningful endpoints used to support the findings of the primary endpoint and were ranked as change from baseline to Week 12 in DAS28-CRP, HAQ-DI, low disease activity as measured by DAS28-CRP, and change from baseline in Short Form-36 (SF-36) physical components summary (PCS). Other clinically important secondary endpoints included change from baseline to Week 12 in ACR50/ACR70, and morning stiffness. Further discussion of the secondary endpoints can be found in Section 7.1.2. Analysis of other key secondary endpoints can be found in Dr. Koh's review.

### **Statistical Analysis Plan**

#### Primary Endpoint:

Comparison of the primary endpoint was made between each UPA dose group and the combined PBO groups using the Cochran-Mantel-Haenszel test adjusted for main stratification factors. For the primary analysis, Non-Responder Imputation was used. The analysis was repeated using Observed Cases. Supportive analysis was also conducted on the Per Protocol Analysis Set. The primary efficacy analyses were also performed in demographic subgroups including age, sex, weight, body mass index, race, and geographical region to assess the consistency of the treatment effect. Additional subgroup analyses based on baseline disease characteristics and stratification factors were also conducted.

#### Secondary Endpoints:

For binary endpoints, frequencies and percentages were reported for each treatment group. Similar analyses as for the primary endpoint were conducted. For the major RA continuous endpoints, and DAS28 and HAQ-DI change from baseline, statistical inference was to be conducted using analysis of covariance (ANCOVA) coupled with multiple imputation (MI) for missing data handling. Specifically, the ANCOVA model was to include treatment as the fixed factor, and the corresponding baseline value and the stratification factor prior bDMARD use (Yes/No) as the covariates. For other continuous endpoints, statistical inference was to be conducted using the Mixed Effect Model Repeat Measurement (MMRM) model, with the main stratification factor being prior bDMARD use (Yes/No). For both the MI and MMRM analyses, the least square (LS) mean and 95% confidence interval (CI) were to be reported for each randomized treatment group; the LS mean treatment difference and associated 95% CI and p-value were to be reported comparing each UPA dose group with the combined PBO group. Both nominal p-value and adjusted p-value through the graphical multiplicity procedure were to be provided.

### **Protocol Amendments**

The current protocol had three major amendments and seven country-specific amendments. The majority of changes to the protocol were responses to regulatory feedback, clarifications and editorial changes. Country-specific protocol amendments did not affect interpretation of the

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results of the study. Major amendments as they relate to the US studies are as follows:

- Amendment 1 (11 December 2015, 183 subjects) updated the study design to add a blinded long-term extension (Period 2); revised inclusion criteria; added the following exclusion criteria: subjects who are considered inadequate responders to bDMARD therapy; subjects with a history of gastrointestinal perforation or a history of associated gastrointestinal diseases; subjects with conditions that could interfere with drug absorption; subjects who have received an organ transplant; and subjects who had clinically relevant or significant ECG abnormalities; and added an interim data analysis after the completion of Period 1.
- Amendment 2 (01 April 2016, 453 subjects) added CDAI calculation at Week 24 to determine low disease activity. Clarified that starting at Week 24, subjects who did not show a 20% improvement in total joint count and swollen joint count compared to baseline at two consecutive visits should discontinue study drug.
- Amendment 3 (31 March 2017, 0 subjects) revised contraception recommendations for males including sperm donation time frame and clarified follicle-stimulating hormone testing requirements for females. Added and updated key secondary endpoints and additional endpoints. Updated statistical sections for accuracy and clarity.

### Reviewer's Comments:

The current study was well-designed, randomized, double-blinded, PBO-controlled and evaluated two doses of UPA in subjects with moderately to severely active RA receiving concomitant background therapy of csDMARDs and who had an inadequate response to previous csDMARD therapy. The enrolled subjects represented a typically more difficult to treat patient population due to having failed several therapies with different mechanisms-of-action. The inclusion and exclusion criteria were acceptable and were consistent with RA subjects with moderately to severely active RA. The choice of a PBO control group was appropriate for the objectives of the study and the choice of concomitant csDMARDs were those that are commonly used in the US.

The Applicant's choice to use the proportion of subjects achieving an ACR20 at Week 12 as the primary endpoint and the HAQ-DI and DAS28 at Week 12 as major secondary endpoints, are adequate to assess clinically meaningful outcomes and have been validated and used in previous approvals of other drugs indicated for patients with moderate to severe RA and are recommended in the Agency's RA guidance document.

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## 6.2.2. Study Results

### Compliance with Good Clinical Practices

The Applicant has provided attestation that the study was conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of the clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice.

### Financial Disclosure

A financial disclosure review was conducted for all five phase 3 studies. Because many investigators participated in more than one study, a combined review of the financial disclosures will be presented. Table 17 shows the total number of investigators identified in each of the phase 3 studies that were evaluated for financial disclosure based on the investigator information.

**Table 17. All Five Phase 3 Studies: Total Number of Investigators in Registrational Studies**

Study	Total Number of Investigators	Number of Principle Investigators	Number of Sub-investigators
M13-542	674	153	521
M13-545	1205	236	969
M13-549	721	150	571
M14-465	1383	285	1098
M15-555	667	138	529

Adapted from Applicant's Financial Summary Table 1.

A total of 41 investigators had disclosable financial interests/arrangements. Each investigator's financial disclosure documentation was reviewed. For these investigators with disclosable financial interests/arrangements: none received compensation for conducting the study where the value could be influenced by the outcome of the study; no investigators received significant payments of other sorts; no investigators had proprietary interest in the product being tested held by the investigator; no investigator had significant equity interest in the Sponsor covered study.

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These financial disclosures do not raise concerns regarding the integrity of the phase 3 studies as the Applicant took steps to minimize potential bias of clinical investigators with financial interests and arrangements by using proper study design and operations. The clinical studies were blinded to the study site personnel and the participating subjects through the primary endpoint collection for the studies. Each active dose of investigational drug product was identical in appearance to its matched PBO and each subject was randomly assigned to their treatment arm independent of the investigator and the study site. Additionally, the number of subjects enrolled at the individual investigator sites were small compared to the total number of subjects enrolled in the overall study.

### Patient Disposition

A total of 661 subjects were randomized and all subjects received study drug. A total of 618 (94%) subjects completed study drug through Week 12 (Table 18).

**Table 18. Study M13-549 : Subject Disposition (All Randomized Subjects)**

	<b>PBO (n=221)</b>	<b>UPA 15 mg QD (n=221)</b>	<b>UPA 30 mg QD (n=219)</b>
<b>Treated</b>	221	221	219
<b>Completed Week 12, n (%)</b>	208 (94)	213 (95)	201 (92)
<b>Discontinued study drug through Week 12, n (%)</b>	13 (6)	8 (4)	18 (8)
<b>AE</b>	5 (2)	5 (2)	8 (4)
<b>Withdrawal by subject</b>	2 (1)	5 (2)	6 (3)
<b>Lost to follow-up</b>	1 (1)	0	2 (1)
<b>Lack of efficacy</b>	4 (2)	0	0
<b>Other</b>	2 (1)	1 (1)	2 (1)

Adapted from Applicant's M13-549 Study Report Table 3.

Through the first 12-weeks of the study, similar numbers of subjects in the PBO and UPA groups discontinued study drug. A greater number of UPA 30 mg subjects discontinued the study due to AE while "lack of efficacy" was the largest category for PBO-treated subjects discontinuing.

### Protocol Violations/Deviations

The most common reason for protocol deviations was related to not meeting inclusion/exclusion criteria. The most common inclusion/exclusion criteria violations were related to all women of childbearing potential to have a negative serum pregnancy test at the Screening Visit; however, serum pregnancy tests were not performed at screening for all female subjects due to an error by the central lab. Serum pregnancy tests were performed only in females of childbearing potential, although the protocol required the test in all female subjects. A total of 52 of 661 subjects (8%) did not meet this inclusion criterion, however, all urine pregnancy tests at baseline were negative, and no pregnant subjects were randomized.

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Overall, the total number of subjects with protocol violations at the time of the primary endpoint assessment was small and relatively balanced between treatment arms. These protocol deviations were not considered to have affected the overall assessment of study results.

### Table of Demographic Characteristics

As shown in Table 19, subjects' baseline demographics were similar between treatment arms. The average subject enrolled in the study was female, White, 56 years of age and clinically overweight, which is consistent with the US patient population.

**Table 19. Study M13-549: Subjects Baseline Demographics**

Demographic Parameters	PBO (N=221)	UPA 15 mg QD (N=221)	UPA 30 mg QD (N=219)
<b>Sex, n (%)</b>			
Male	55 (25)	39 (18)	47 (22)
Female	166 (75)	182 (82)	172 (79)
<b>Age, n (%)</b>			
Mean ± SD	56 ± 12	55 ± 11	56 ± 11
Median (min, max)	58 (23, 86)	57 (26, 80)	57 (21, 80)
<b>Age (years), n (%)</b>			
< 40 years	21 (10)	23 (10)	22 (10)
40-64	145 (66)	153 (69)	145 (66)
≥ 65 years	55 (25)	45 (20)	52 (24)
<b>Race, n (%)</b>			
White	187 (85)	188 (85)	186 (85)
Black or African American	10 (5)	13 (6)	8 (4)
Asian	19 (9)	19 (9)	21 (10)
American Indian or Alaska Native	1 (1)	0	1 (1)
<b>Ethnicity</b>			
Hispanic or Latino	27 (12)	23 (10)	30 (14)
Not Hispanic or Latino	194 (88)	198 (90)	189 (86)
<b>BMI (kg/m<sup>2</sup>)</b>			
Mean ± SD	30 ± 7	30 ± 8	30 ± 7
Median (min, max)	28 (17, 51)	28 (17, 58)	29 (17, 51)

Adapted from Applicant's Study M13-542 study report Table 4.

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**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Overall, the subjects enrolled in the study demonstrated moderately to severely active disease as evidenced by the average DAS28 score, swollen and tender joint counts, HAQ-DI and duration of morning stiffness. Subjects' baseline disease characteristics and background RA-related therapy were similar between individual treatment arms (Table 20).

**Table 20. Study M13-549: Subjects Baseline Disease Characteristics**

Demographic Parameters	PBO (N=221)	UPA 15 mg QD (N=221)	UPA 30 mg QD (N=219)
<b>Duration of RA (years)</b>			
Mean ± SD	7 ± 7	7 ± 8	7 ± 8
Median (min, max)	4 (<1, 36)	4 (<1, 42)	4 (<1, 50)
<b>RF and anti-CCP, n (%)</b>			
Positive (RF + anti-CCP)	150 (68)	153 (70)	137 (63)
At least one negative	71 (32)	67 (31)	82 (37)
<b>DAS28 (CRP)</b>			
n	221	217	219
Mean ± SD	5.6 ± 0.8	5.7 ± 1	5.7 ± 0.9
Median (min, max)	5.6 (3.4, 7.3)	5.7 (3.1, 8.3)	5.7 (2.6, 8.2)
<b>Swollen Joint Count-66</b>			
Mean ± SD	15 ± 9	16 ± 10	16 ± 11
Median (min, max)	12 (3, 62)	13 (1, 61)	13 (6, 60)
<b>Tender Joint Count-68</b>			
Mean ± SD	25 ± 15	25 ± 14	26 ± 14
Median (min, max)	21 (2, 66)	22 (6, 64)	23 (6, 68)
<b>HAQ-DI</b>			
n	221	216	219
Mean ± SD	1.4 ± 0.6	1.5 ± 0.6	1.5 ± 0.6
Median (min, max)	1.5 (0, 3)	1.5 (0, 3)	1.6 (0, 3)
<b>CRP</b>			
Mean ± SD	13 ± 14	17 ± 19	15 ± 17
Median (min, max)	8 (0, 104)	9 (0, 108)	9 (1, 122)
<b>Morning Stiffness duration (minutes)</b>			
Mean ± SD	139 ± 214	152 ± 242	129 ± 156
Median (min, max)	90 (0, 1440)	90 (0, 1440)	90 (0, 1440)
<b>Prior biologic DMARD use, n (%)</b>			
Yes	29 (13)	27 (12)	28 (13)
No	192 (87)	194 (88)	191 (87)
<b>Concomitant csDMARD at baseline, n (%)</b>			
MTX alone	141 (64)	122 (56)	136 (62)
MTX and other csDMARD	49 (22)	47 (21)	39 (18)
csDMARD other than MTX	30 (14)	51 (23)	44 (20)
<b>Oral corticosteroid dose (mg)</b>			
n	106	96	103
Mean ± SD	6 ± 2.5	6 ± 2.4	6 ± 2.6
Median (min, max)	5 (2.5, 10)	5 (1, 10)	5 (<1, 12.5)

Adapted from Applicant's Study M13-549 study report Table 5.

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### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance was calculated as the number of tablets taken in Period 1. Mean treatment compliance was 99% and 98% in the UPA 15 mg and 30 mg groups, respectively, and 100% in the PBO group.

As shown in Table 20, over 80% of subjects in all treatment arms were receiving concomitant MTX with or without an additional csDMARD, which was limited to either chloroquine, hydroxychloroquine, sulfasalazine, or leflunomide, all of which are commonly used in the US to treat subjects with RA. The remaining approximate 20% of subjects were only treated with csDMARD that were not MTX.

### Efficacy Results – Primary Endpoint

As shown in Table 21, the primary endpoint analysis demonstrated a statistically significant difference between PBO and the individual UPA treatment arms. The average treatment effect size for the UPA 15 mg and UPA 30 mg treatment arms were 28% and 31%, respectively. The UPA 30 mg group demonstrated a small increase in the proportion of subjects achieving an ACR20 response compared to the UPA 15 mg group; however, the overall difference in effects is likely not to be clinically meaningful.

**Table 21. Study M13-549: Proportion of Subjects Achieving ACR20 at Week 12**

	<b>PBO (N=221) n (%)</b>	<b>UPA 15 mg QD (N=221) n (%)</b>	<b>UPA 30 mg QD (N=219) n (%)</b>
ACR20	79 (36)	141 (64)	145 (66)
Difference (%), (95% CI)	-	28 (19, 37)	31 (22, 39)

Source: FDA Biostatistics Review for NDA 211675

This analysis demonstrates a clinically meaningful benefit with UPA treatment for the improvement of the signs and symptoms of subjects with active RA despite concurrent csDMARD therapy and having failed prior treatment with csDMARDs. Additionally, UPA-treated subjects demonstrated greater improvements in all ACR components compared to PBO-treated subjects at Week 12 demonstrating that the results were not driven by any single component of the ACR response criteria (Table 22).

**Table 22. Study M13-549: Change from Baseline in ACR Components (excluding HAQ-DI)**

Treatment Arm	N	Baseline Mean (SD)	n	Visit Mean (SD)	Est Diff (95 % CI)	p-value
<b>CRP</b>						
PBO	221	12.6 (14.0)	207	13.2 (15.6)		
UPA 15 mg QD	221	16.6 (19.2)	209	4.5 (9.6)	-9.7 (-11.9, -7.6)	<0.001
UPA 30 mg QD	219	14.8 (16.9)	201	5.3 (8.6)	-8.4 (-10.5, -6.2)	<0.001
<b>SJC (Out of 28)</b>						
PBO	221	10.8 (5.1)	207	6.1 (5.9)		
UPA 15 mg QD	221	11.0 (5.4)	210	4.2 (5.7)	-2.0 (-2.9, -1.1)	<0.001
UPA 30 mg QD	219	11.2 (5.5)	201	3.2 (4.2)	-3.0 (-3.9, -2.1)	<0.001
<b>SJC (Out of 66)</b>						
PBO	221	15.4 (9.2)	207	8.9 (9.8)		
UPA 15 mg QD	221	16.0 (10.0)	210	6.4 (9.6)	-2.8 (-4.2, -1.4)	<0.001
UPA 30 mg QD	219	16.2 (10.6)	201	4.6 (6.4)	-4.5 (-5.8, -3.1)	<0.001
<b>TJC (Out of 28)</b>						
PBO	221	14.2 (6.6)	207	8.8 (7.9)		
UPA 15 mg QD	221	14.3 (6.7)	210	6.4 (7.4)	-2.5 (-3.7, -1.3)	<0.001
UPA 30 mg QD	219	15.0 (6.8)	201	5.3 (6.1)	-3.9 (-5.1, -2.7)	<0.001
<b>TJC (Out of 68)</b>						
PBO	221	24.7 (15.0)	207	16.3 (17.0)		
UPA 15 mg QD	221	25.2 (13.8)	210	11.9 (14.4)	-4.9 (-7.2, -2.7)	<0.001
UPA 30 mg QD	219	26.2 (14.3)	201	9.5 (11.4)	-7.6 (-9.9, -5.3)	<0.001
<b>Physician Global</b>						
PBO	221	64.4 (17.7)	201	40.9 (24.5)		
UPA 15 mg QD	216	64.3 (16.2)	205	26.1 (20.9)	-14.7 (-18.9, -10.6)	<0.001
UPA 30 mg QD	219	63.0 (18.0)	193	22.8 (18.9)	-18.3 (-22.5, -14.0)	<0.001
<b>Patient Global</b>						
PBO	211	60.3 (20.5)	206	49.8 (25.7)		
UPA 15 mg QD	209	63.1 (21.9)	210	32.3 (23.9)	-18.4 (-22.9, -13.9)	<0.001
UPA 30 mg QD	213	62.8 (20.3)	200	30.2 (22.6)	-20.2 (-24.7, -15.7)	<0.001
<b>Patient Pain</b>						
PBO	221	61.5 (20.8)	206	50.8 (25.6)		
UPA 15 mg QD	217	64.1 (19.5)	210	33.1 (24.3)	-18.8 (-23.3, -14.4)	<0.001
UPA 30 mg QD	219	64.0 (19.8)	200	30.1 (22.8)	-21.5 (-26.0, -17.0)	<0.001

Source: FDA Biometrics Review for NDA 211675

Results from sensitivity analyses on the Per Protocol Analysis set were consistent with the primary analysis (data not shown). Subgroup analysis results using Nonresponder Imputation,

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were also consistent with the primary analysis (data not shown).

### **Efficacy Results – Secondary and other relevant endpoints**

#### **HAQ-DI**

Table 23 shows that at Week 12, subjects treated with UPA experienced a statistically significant and clinically meaningful change ( $\leq -0.3$ ) from baseline compared to subjects treated with PBO; however, there was no evidence of a dose-dependent increase in response between the UPA 15 mg and UPA 30 mg dosing groups. These data support the results of the primary endpoint demonstrating a clinical benefit of UPA treatment in subjects with RA.

**Table 23. Study M13-549: Change in HAQ-DI from Baseline to Week 12**

<b>HAQ-DI Score</b>	<b>PBO</b>	<b>UPA 15 mg QD</b>	<b>UPA 30 mg QD</b>
	<b>N=221</b>	<b>N=216</b>	<b>N=219</b>
Baseline (Mean $\pm$ SD)	1.4 $\pm$ 0.6	1.5 $\pm$ 0.6	1.5 $\pm$ 0.6
	<b>N=206</b>	<b>N=210</b>	<b>N=200</b>
Week 12 (Mean $\pm$ SD)	1.1 $\pm$ 0.7	0.9 $\pm$ 0.7	0.9 $\pm$ 0.7
Difference (%), (95% CI)	-	-0.3 (-0.4, -0.3)	-0.3 (-0.4, -0.1)

Source: FDA Biostatistics Review for NDA 211675

Tipping point analyses were conducted to evaluate the robustness of the results for the change from baseline in HAQ-DI comparing UPA 15 mg and 30 mg with PBO and were found to support the observed results (data not shown).

#### **ACR20/ACR50/ACR70**

Analysis of the ACR responses demonstrated a statistically significant increase in the improvement of signs and symptoms of subjects in the UPA groups compared to the PBO group (Table 24). Upadacitinib 30 mg-treated subjects achieved greater responses in ACR20, ACR50 and ACR70 response compared to subjects in the UPA 15 mg group; however, the clinical meaningfulness of the relatively modest increased effect is questionable.

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**Table 24. Study M13-549: Change in ACR20/ACR50/ACR70 from Baseline at Week 12**

	<b>PBO (N=221) n (%)</b>	<b>UPA 15 mg (N=221) n (%)</b>	<b>UPA 30 mg (N=219) n (%)</b>	<b>UPA 15 mg vs PBO Difference (%), (95% CI)</b>	<b>UPA 30 mg vs. PBO Difference (%), (95% CI)</b>
<b>ACR20</b>	79 (36)	141 (64)	145 (66)	28 (19, 37)	31 (22, 39)
<b>ACR50</b>	33 (15)	84 (38)	95 (43)	23 (15, 31)	28 (20, 37)
<b>ACR70</b>	13 (6)	46 (21)	58 (27)	15, (9, 21)	21 (14, 27)

Source: FDA Biostatistics Review for NDA 211675

These data support the results of the primary endpoint and demonstrate a clinically meaningful effect of UPA compared to PBO in subjects with moderately to severely active RA.

### **DAS28-CRP**

A significantly greater mean change from baseline in DAS28-CRP at Week 12 was observed in the UPA treatment arms compared to PBO (Table 25). These data support the results of the primary endpoint demonstrating a clinical benefit of UPA treatment in subjects with RA; however, a dose-dependent increase in the DAS28-CRP response between the UPA 15 mg and UPA 30 mg dosing groups was not observed.

**Table 25. Study M13-549: Change in DAS28-CRP from Baseline to Week 12**

<b>DAS28-CRP Score</b>	<b>PBO</b>	<b>UPA 15 mg QD</b>	<b>UPA 30 mg QD</b>
	<b>N=221</b>	<b>N=217</b>	<b>N=219</b>
Baseline (Mean ± SD)	5.6 ± 0.8	5.7 ± 1	5.7 ± 0.9
	<b>N=206</b>	<b>N=206</b>	<b>N=200</b>
Week 12 (Mean ± SD)	4.5 ± 1.5	3.4 ± 1.4	3.3 ± 1.2
Difference (%), (95% CI)	-	-1.2 (-1.4, -0.9)	-1.3 (-1.6, -1.1)

Source: FDA Biostatistics Review for NDA 211675

### **DAS28-CRP <2.6**

DAS28-CRP responses <2.6 represent very low disease activity. In Study M13-549, a higher proportion of subjects treated with UPA 15 mg and 30 mg achieved DAS28-CRP <2.6 responses compared to PBO-treated subjects, 31% and 28% versus 10%, respectively. These results demonstrate a clinically meaningful benefit of UPA in decreasing disease activity in subjects with active RA. Similar to previous results, there was no increased benefit with higher doses of UPA 30 mg compared to UPA 15 mg.

**SF-36**

In study M13-549, the mean adjusted change from baseline in the SF-36 PCS score at Week 12 was significantly higher in subjects treated with UPA 15 mg and 30 mg compared to PBO-treated subjects (Table 26); however, there was only a minimal significant change in subjects treated with UPA 15 mg and no significant change in UPA 30 mg-treated subjects in the SF-36 MCS score. These results suggest a modest improvement in the SF-36 PCS score but no clinically meaningful improvement of the SF-36 MCS score. The reader is directed to Dr. Koh’s review for a detailed analysis of the individual SF-36 components.

**Table 26. Study M13-549: Change in SF-36 PCS and MCS Scores from Baseline to Week 12**

<b>SF-36 PCS Score</b>	<b>PBO</b>	<b>UPA 15 mg QD</b>	<b>UPA 30 mg QD</b>
	<b>N=221</b>	<b>N=219</b>	<b>N=217</b>
Baseline (Mean ± SD)	33 ± 8	33 ± 7	33 ± 8
	<b>N=207</b>	<b>N=211</b>	<b>N=199</b>
Week 12 (Mean ± SD)	37 ± 9	41 ± 9	42 ± 9
Difference (%), (95% CI) <sup>1</sup>	-	4 (3, 6)	5 (4, 7)
<b>SF-36 MCS Score</b>			
	<b>N=221</b>	<b>N=219</b>	<b>N=217</b>
Baseline (Mean ± SD)	47 ± 12	46 ± 11	46 ± 12
	<b>N=207</b>	<b>N=211</b>	<b>N=199</b>
Week 12 (Mean ± SD)	49 ± 11	50 ± 10	50 ± 10
Difference (%), (95% CI)	-	2 (0.5, 4)	1 (-0.5, 3)

Source: FDA Biostatistics Review for NDA 211675. <sup>1</sup>adjusted means

**Morning Stiffness**

As shown in Table 27, the mean change from baseline in duration of morning stiffness at Week 12 in subjects treated with UPA 15 mg or 30 mg decreased significantly compared to subjects treated with PBO. These results demonstrate a clinically meaningful benefit of UPA in decreasing disease activity in subjects with active RA. Similar to previous results, there was no clinically significant increased benefit observed with higher doses of UPA 30 mg compared to UPA 15 mg.

**Table 27. Study M13-549: Change in Morning Stiffness from Baseline to Week 12**

<b>Morning Stiffness (minutes)</b>	<b>PBO</b>	<b>UPA 15 mg QD</b>	<b>UPA 30 mg QD</b>
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	<b>N=216</b>	<b>N=217</b>	<b>N=215</b>
Baseline (Mean ± SD)	139 ± 214	152 ± 242	129 ± 156
	<b>N=202</b>	<b>N=207</b>	<b>N=197</b>
Week 12 (Mean ± SD)	98 ± 166	54 ± 114	43 ± 67
Difference (%), (95% CI)	-	-43 (-64, -22)	-49 (-71, -28)

Source: FDA Biostatistics Review for NDA 211675

Reviewer's Comments:

Study M13-549 was a well-conducted study with balanced subject cohorts, limited subject dropouts, and minimal protocol violations that allowed for reliable interpretation of the study results. The efficacy analysis of the primary endpoint clearly demonstrates a clinically meaningful treatment effect of UPA 15 and 30 mg compared to PBO regarding improvement of the signs and symptoms of subjects with moderately to severely active RA receiving concomitant background therapy of csDMARDs and who had an inadequate response to prior csDMARD therapy. The primary endpoint is fully supported by the results of the secondary endpoints.

Similar to the results observed in Study M13-542, the results of this study demonstrate a clinically meaningful benefit from treatment with UPA 15 and 30 mg but do not support a dose-dependent increase of clinical efficacy with the higher dose of UPA in this patient population. Consequently, the overall benefit-risk assessment for UPA 30 mg will need to be determined in the context of the overall safety evaluation.

**FACIT-F**

The mean change from baseline in FACIT-F at Week 12 in subjects treated with UPA 15 mg and 30 mg was nominally statistically significantly greater compared to subjects treated with PBO in study M13-549 (Table 28).

**Table 28. Study M13-549: Change in FACIT-F from Baseline to Week 12**

<b>FACIT-F</b>	<b>PBO</b>	<b>UPA 15 mg QD</b>	<b>UPA 30 mg QD</b>
	<b>N=221</b>	<b>N=216</b>	<b>N=217</b>
Baseline (Mean ± SD)	28 ± 12	28 ± 11	28 ± 13
	<b>N=207</b>	<b>N=211</b>	<b>N=199</b>
Week 12 (Mean ± SD)	32 ± 12	36 ± 10	36 ± 11
Difference (%), (95% CI)	-	5 (3, 7)	5 (3, 7)

Reviewer's Comments:

Study M13-549 was a well-conducted study with balanced subject cohorts, limited subject dropouts, and minimal protocol violations that allowed for reliable interpretation of the study results. The efficacy analysis of the primary endpoint clearly demonstrates a clinically meaningful treatment effect of UPA 15 and 30 mg compared to PBO regarding improvement of the signs and symptoms of subjects with moderately to severely active RA receiving concomitant background therapy of csDMARDs and who had an inadequate response to prior bDMARD therapy. The primary endpoint is fully supported by the results of the secondary endpoints.

Although these results demonstrate a clinically meaningful benefit from treatment with UPA 15 and 30 mg, these data overall do not support a dose-dependent increase of clinical efficacy with the higher dose of UPA in this patient population. Consequently, the overall benefit-risk assessment for UPA 30 mg will need to be determined in the context of the overall safety evaluation.

### **6.3. Study M14-465**

#### **6.3.1. Study Design**

##### **Overview and Objective**

*"A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who are on a Stable Background of Methotrexate (MTX) and Who Have an Inadequate Response to MTX (MTX-IR)"*

The primary objective of Study M14-465 was to assess the safety and efficacy of UPA 15 mg versus ADA and PBO in subjects with moderately to severely active RA on stable background MTX and who have had an inadequate response to MTX. Additionally, the study was designed to also compare the efficacy of UPA compared to PBO for the prevention of structural progression.

##### **Trial Design**

Study M14-465 was a phase 3 multicenter study conducted in two periods:

- Period 1 was a 48-week, randomized, double-blind, parallel-group, PBO-controlled and active comparator-controlled period designed to compare the safety and efficacy of orally administered UPA 15 mg QD versus PBO and versus ADA for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of MTX and had

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an inadequate response to MTX. Period 1 was also designed to compare the efficacy of UPA 15 mg versus PBO for the prevention of structural progression.

- Period 2 was a long-term extension to evaluate the safety, tolerability, and efficacy of UPA 15 mg in subjects with RA who had completed Period 1.

The study was designed to enroll approximately 1500 subjects and actually enrolled 1629 subjects at 286 study sites in 41 countries (Argentina, Australia, Belarus, Belgium, Bosnia and Herzegovina, Brazil, Bulgaria, Canada, Chile, Czech Republic, Estonia, France, Germany, Greece, Hong Kong, Hungary, Israel, Italy, Kazakhstan, Republic of Korea, Latvia, Lithuania, Malaysia, Mexico, New Zealand, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Serbia, Slovakia, South Africa, Spain, Taiwan, Turkey, Ukraine, United Kingdom, and United States). Subjects meeting eligibility criteria were randomized in a 2:2:1 ratio to one of three treatment groups:

- Group 1: UPA 15 mg PO QD
- Group 2: PBO
- Group 3: ADA 40 mg SC EOW

Subjects received both oral study drug QD (either UPA 15 mg or matching PBO) and subcutaneous study drug EOW (either ADA 40 mg or matching PBO) until the study was unblinded. At Week 26, all subjects receiving PBO were to be switched to UPA 15 mg regardless of response.

Subjects were to have been on MTX therapy for  $\geq 3$  months, on a stable MTX dose for  $\geq 4$  weeks prior to the first dose of study drug and were to remain on a stable dose throughout the study; the MTX dose could be decreased only for safety reasons. In addition, all subjects received oral folic acid throughout study participation. Subjects with prior exposure to at most one bDMARD (except ADA) for RA were also eligible for enrollment in the study up to 20% of total study population and only after the required washout period was satisfied. Subjects could also be included if they had limited exposure ( $< 3$  months), or adequate response to bDMARD but had to discontinue that bDMARD due to intolerability (regardless of treatment duration). These subjects were to be equally stratified across all treatment groups.

Starting at the Week 26 visit and thereafter, initiation or change in background RA medication including corticosteroids, non-steroidal anti-inflammatory drugs, and acetaminophen /paracetamol was allowed. Starting at Week 48 and thereafter, initiation of, or change in, conventional synthetic csDMARD was allowed (restricted to MTX, chloroquine, hydroxychloroquine, sulfasalazine, or leflunomide).

Rescue therapy was offered to subjects who met the following criteria:

PBO:

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- Subjects who did not achieve a  $\geq 20\%$  improvement in tender joint count and swollen joint count at Weeks 14, 18, or 22 compared to Baseline were to be switched to blinded UPA treatment.
- At Week 26, all remaining subjects were switched to blinded UPA treatment regardless of clinical response.

### ADA:

- Subjects who did not achieve a  $\geq 20\%$  improvement in tender joint count and swollen joint count at Weeks 14, 18, or 22 compared to Baseline were to be switched to blinded UPA treatment.
- At Week 26, all remaining subjects who did not achieve low disease activity defined as CDAI  $\leq 10$  at Week 26 were to be switched to blinded UPA treatment.

### UPA 15 mg:

- Subjects who did not achieve a  $\geq 20\%$  improvement in tender joint count and swollen joint count at Weeks 14, 18, or 22 compared to Baseline were to be switched to blinded ADA treatment.
- At Week 26, all remaining subjects who did not achieve low disease activity according to CDAI  $\leq 10$  at Week 26 were to be switched to blinded ADA treatment.

An unblinded analysis was conducted when all subjects were expected to have completed their Week 26 visit for the purpose of regulatory submission. To maintain integrity of the trial, study sites and subjects remained blinded for the duration of Period 1.

Each subject had a maximum of five scheduled visits for x-ray examination of their bilateral hands and feet during Period 1 (unless unscheduled repeat imaging was needed due to failure to meet the quality requirements) at Screening, Week 26, and Week 48 or Premature Discontinuation. Subjects who were non-responders at Week 14 and were switched to rescue therapy received an x-ray examination at Week 14; in addition, subjects who prematurely discontinued from study drug or the study from Week 36 and before Week 40 were to have an x-ray examination at the time of discontinuation.

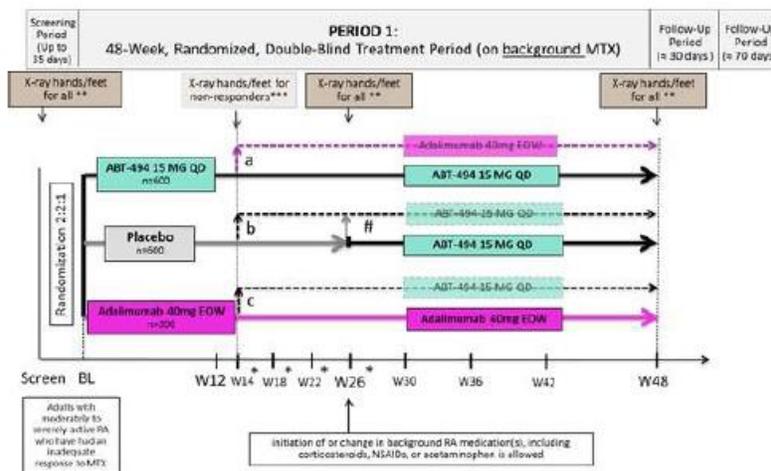
Joint x-rays were to be sent to the central imaging vendor designated by the Sponsor. The x-rays were to only be assessed by the imaging vendor for erosions and joint space narrowing and were not to be assessed for any other clinically significant findings that may have impacted a subject's health.

Subjects who complete Period 1 (Week 48) were eligible to enter the long-term extension Period 2 that will continue for up to five years. Subjects will continue study treatment as assigned in

Period 1. Subjects who are assigned to the UPA 15 mg treatment group at the end of Period 1 will continue to receive UPA 15 mg in a blinded manner. Similarly, subjects who are assigned to ADA at the end of Period 1 will continue to receive ADA in a blinded manner. When the last subject completes the last visit of Period 1, the subjects' respective study drug assignment will be dispensed in an open-label fashion until the completion of Period 2.

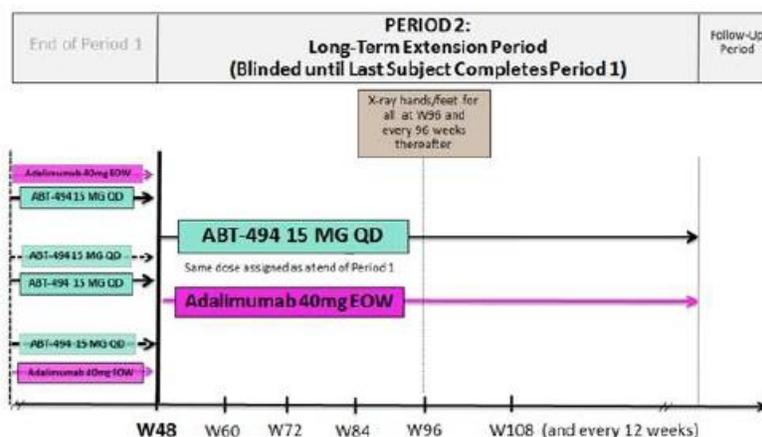
Figure 6 and Figure 7 show the study periods overviews of Study M14-465

**Figure 6. Study M14-465: Period 1 Overview**



Adapted from Applicant's M14-465 Study Report Figure 1.

Figure 7. Study M14-465: Period 2 Overview



Adapted from Applicant's M14-465 Study Report Figure 2.

Major inclusion criteria:

- Male and female subjects  $\geq 18$  years-of-age
- Diagnosis of RA based on the 2010 ACR/EULAR criteria for a duration for  $\geq 3$  months
- $\geq 6$  swollen joints (based on 66 joint counts)
- $\geq 6$  tender joints (based on 68 joint counts)
- hsCRP  $\geq 5$  mg/L
- Have failed or be intolerant to previous MTX therapy for RA
- Currently treated with MTX therapy  $\geq 3$  months and on stable dose for  $\geq 4$  weeks
- $\geq 3$  bone erosion on x-ray or  $\geq 1$  bone erosion and RF (+) or  $\geq 1$  bone erosion anti-CCP (+)

Major exclusion criteria:

- Prior exposure to any JAK inhibitor
- History of an inflammatory joint disease other than RA
- Laboratory values meeting the following criteria
  - AST or ALT  $> 2 \times$  ULN
  - eGFR  $< 40$  mL/min/1.73m<sup>2</sup>
  - WBC  $< 2,500/\mu\text{L}$
  - ANC  $< 1500/\mu\text{L}$
  - PLT  $< 100,000/\mu\text{L}$
  - ALC  $< 800/\mu\text{L}$
  - Hg  $< 10$  g/dL

The dose selection for UPA 15 mg once-daily oral tablets was based on extrapolation of preclinical efficacy models and analyses of PK, pharmacodynamic, safety, and efficacy data from the phase 1 studies in healthy volunteers and phase 2 studies in RA subjects. The doses selected for this study were expected to be efficacious with an acceptable safety profile.

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## Study Endpoints

The proportion of subjects achieving an ACR20 at Week 12 was used as the primary endpoint for improvement in signs and symptoms. The ACR response criteria consists of 7 components:

- Swollen joint count (66 joints)
- Tender joint count (68 joints)
- Subject global assessment of pain (VAS 100mm)
- Subject global assessment of disease activity (VAS 100mm)
- Physician global assessment of disease activity (VAS 100mm)
- Subject assessment of physical function using HAQ
- CRP

The ACR20 definition of response specifies a 20% improvement over baseline in swollen and tender joints and in 3 out of 5 of the remaining core data set measures. For the primary endpoint, assessment of the ACR20 occurred at Week 12. The choice of the primary endpoint is appropriate to assess a clinically meaningful benefit of UPA and consistent with Agency guidelines.

Key secondary endpoints were selected to capture clinically meaningful endpoints used to support the findings of the primary endpoint and were ranked as change from baseline in DAS28-CRP at Week 12, change from baseline in mTSS score at Week 26, change from baseline in HAQ-DI at Week 12, ACR50 response at Week 12, change from baseline in Short Form-36 (SF-36) physical components summary (PCS) at Week 12, and the proportion of subjects achieving low disease activity as measured by DAS28-CRP at Week 12. Other clinically important secondary endpoints included change from baseline to Week 12 in morning stiffness and FACIT-F. Further discussion of the secondary endpoints can be found in Section 7.1.2. Analysis of other key secondary endpoints can be found in Dr. Koh's review.

## Statistical Analysis Plan

### Primary Endpoint:

Comparison of the primary endpoint was made between each UPA dose group and the combined PBO groups using the Cochran-Mantel-Haenszel test adjusted for main stratification factors. For the primary analysis, Non-Responder Imputation was used. The analysis was repeated using Observed Cases. Supportive analysis was also conducted on the Per Protocol Analysis Set. The primary efficacy analyses were also performed in demographic subgroups including age, sex, weight, body mass index, race, and geographical region to assess the consistency of the treatment effect. Additional subgroup analyses based on baseline disease characteristics and stratification factors were also conducted.

### Secondary Endpoints:

For binary endpoints, frequencies and percentages were reported for each treatment group. Similar analyses as for the primary endpoint were conducted. Additionally, for ACR50 response

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rate, analysis was conducted to test the non-inferiority of UPA versus ADA using the 95% confidence interval (CI) of treatment difference against a noninferiority margin of 10%. Superiority of UPA versus ADA was tested using the Cochran-Mantel-Haenszel test adjusting for stratification factor prior bDMARD use. For the major RA continuous endpoints DAS28 and HAQ-DI change from Baseline, statistical inference was conducted using analysis of covariance (ANCOVA) coupled with Multiple Imputation (MI) for missing data handling. Specifically, the ANCOVA model included treatment as the fixed factor, and the corresponding Baseline value and the stratification factor prior bDMARD use as the covariates. For other continuous endpoints, statistical inference was conducted using the Mixed Effect Model Repeat Measurement (MMRM) model with the main stratification factor being prior bDMARD use. From both the MI and MMRM analyses, the least square (LS) mean and 95% CI were to be reported for each randomized treatment group; the LS mean treatment difference and associated 95% CI and p-value were to be reported comparing the UPA group with the PBO group. For change from Baseline in patient's global assessment of pain and change from Baseline in HAQ-DI, superiority of UPA versus ADA was tested.

mTSS-Related Secondary Endpoints: Linear extrapolation was used for all mTSS-related endpoints. Analysis based on As Observed data was also performed. In the linear extrapolation analysis, the Week 26 data was imputed via linear extrapolation using x-ray data from the Baseline window and the Week 14 window for the following subjects: subjects rescued to a different study drug at Week 14, subjects who prematurely discontinued study drug prior to Week 18, and subjects otherwise missing x-ray data in the Week 26 window but have available x-ray data in the Week 14 window. For the proportion of subjects with no radiographic progression, frequencies and percentages were reported for each treatment group. Similar analyses as for the primary endpoint were conducted, with the exception that linear extrapolation was used for imputation. For change from Baseline in mTSS, statistical inference was conducted using the ANCOVA model with treatment and prior bDMARD use as the fixed factors and the corresponding baseline value as the covariates. In the event that data severely deviated from the normal distribution, non-parametric analyses such as the Wilcoxon rank sum test may have been considered for treatment comparison. From the linear extrapolation analysis, the point estimate and 95% CI were to be reported for each randomized treatment group; the point estimate, 95% CI, and p-value were to be reported comparing the UPA group with the PBO group.

Additional Clinical Efficacy Variables: For binary endpoints, frequencies and percentages were reported for each randomized treatment group. Similar analyses as for the primary endpoint were conducted. For the primary analysis, nonresponder imputation was used. In addition, subjects who met the rescue criteria at either Week 14, 18 or 22 were treated as non-responders at visits after rescue treatment switching. For subjects who meet the rescue criteria at Week 26, data after rescue treatment switching were overwritten by the last response prior to rescue. As observed data were also summarized using frequencies and percentages. For continuous variables, statistical inference was conducted using ANCOVA with treatment and prior bDMARD

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use as the fixed factor and the corresponding Baseline value as the covariate. For subjects who met the rescue criteria at either Week 14, 18, 22, or 26, data after rescue treatment switching was overwritten by Last Observation Carried Forward for the primary analysis.

## Protocol Amendments

The current protocol had five major amendments, nine country-specific amendments and two global administrative changes. The majority of changes to the protocol were responses to regulatory feedback, clarifications and editorial changes. Country-specific protocol amendments did not affect interpretation of the results of the study. Major amendments as they relate to the US studies, and the number of subjects enrolled under each amendment, are as follows:

Amendment 1 (11 December 2015, 13 subjects) changed the duration of Period 1 from 52 weeks to 48 weeks. Added the following: long-term extension period (Period 2); stable dose of MTX requirements; csDMARD background therapy other than MTX would not be allowed during Period 1; rescue criteria; study visits for rescue therapy; discontinuation procedures; contraception recommendations and pregnancy testing; requirement for a 12-lead ECG and physical exam at Week 48; addition of international normalized ratio and FSH laboratory tests; instructions for chest x-ray requirements; use of external DMC; interim analysis after completion of the Week 26 and Week 48 visits. Updated primary, secondary, and other efficacy variables; x-ray study visits; hsCRP value requirement at screening; contraception requirements; randomization stratification; AST and ALT specific toxicity management guidelines. Clarified language regarding independent joint assessors; hsCRP level requirement; and the AE collection period. Added the following exclusion criteria: females who are considering becoming pregnant during the study or for approximately 150 days after the last dose of study drug; males who are considering fathering a child or donating sperm during the study or for approximately 90 days after the last dose of study drug; and subjects who are considered inadequate responders to bDMARD therapy as determined by the Investigator, have a history of gastrointestinal perforation or a history of associated gastrointestinal diseases, have a history of demyelinating disease, have received an organ transplant, or had clinically relevant or significant ECG abnormalities.

- Amendment 2 (08 January 2016, 509 subjects) corrected study visits for blood samples for exploratory research and validation studies.
- Amendment 3 (01 April 2016, 785 subjects) updated rescue therapy criteria at Week 26. Clarified that starting at Week 48, subjects who failed to show at least 20% improvement in tender joint count and swollen joint count compared to baseline at two consecutive visits should discontinue study drug treatment.
- Amendment 4 (11 January 2017, 291 subjects) added the following: oral traditional Chinese medicine is prohibited; requirement to perform pregnancy testing if FSH results are consistent with pre-menopausal status. Updated the following: the key secondary endpoints to match a head-to-head comparison of UPA to ADA; the list of additional endpoints; text to allow concomitant

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medication modifications at Week 26; required duration of contraception to reflect new data obtained from chronic animal toxicology studies and that additional local contraception requirements may apply; pregnancy and sperm donation waiting periods following oral study drug administration; and clinical laboratory tests to remove creatine kinase-muscle/brain, and add minimum residual B-cell panel, antinuclear antibodies/dsDNA (reflex) antibodies, and HIV testing. Clarified the following: rescue therapy; central imaging; re-screening labs and Premature Discontinuation Visits for subjects who prematurely discontinue from study drug; exceptions for administering live vaccines; that all remaining subjects who had not been previously rescued and have not reached low disease activity will be rescued at Week 26; pregnancy testing; HIV testing; independent joint assessor; TB test; TB prophylaxis, x-rays of the hands and feet, and chest x-ray; that ECG will be performed at the final visit of Period 1 only if the subject does not enter Period 2 or if the subject discontinues from the study; statistical analysis details; and assumptions used for sample size determination. Made the following updates to inclusion criteria: updated MTX dosing information; updated requirements for stable doses of NSAIDs, acetaminophen, oral corticosteroids, or inhaled corticosteroids; included discontinuation requirements for oral traditional Chinese medicine; and clarified pregnancy testing requirement. Made the following updates to exclusion criteria: updated Exclusion Criterion 8 to include chronic and invasive infections and added HIV infection definition; updated follow-up period from 90 days to 30 days in Exclusion Criterion 7; updated Exclusion Criterion 11 to clarify that the 70-day follow-up period pertains to the subcutaneous study drug; and updated Exclusion Criterion 21 to reflect normal reference range in the elderly population.

- Amendment 5 (01 December 2017, 0 subjects) defined key secondary endpoints as ranked. Implemented a supplemental eCRF for thrombotic events. Added management language for subjects with Hepatitis B core antibody positive and negative HBV DNA at Screening and laboratory values during the study which may indicate active hepatitis. Updated the following: safety collection requirements for subjects that are treated with commercial ADA after end of study treatment; text to align with permitted background corticosteroid requirements; herpes zoster vaccine language for subject safety prior to and after study drug; duration of contraception recommendations for males; AEs of special interest that will be monitored during the study to align in content and presentation with the current version of the product safety statistical analysis plan. Clarified the following: that the long-term extension period is blinded until the last subject completes Period 1; tender and swollen joint count improvement requirements starting at Week 48 to remain on study drug; requirements for contraception for females if child-bearing potential status changes during the course of the study; the frequency of the Latent TB Risk Assessment Form completion; that an annual ECG is required for all subjects; indeterminate QuantiFERON-TB test results; that annually is considered every 48 weeks; requirements for recording lab abnormalities as AEs; efficacy variables; that starting at Week 48, at least 20% improvement in both SJC and TJC compared to

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Baseline is required to remain on study drug; who will remain blinded at study time points; that subjects should discontinue study drug for an ECG abnormality that is considered clinically significant with reasonable possibility that the event is related to study drug; toxicity management for ALT, AST, INR, serum creatinine, and elevated CPK values; imputation method and safety analysis details; and that for CPK and serum creatinine, NCI-CTCAE grading would be used.

Reviewer's Comments:

The current study was well-designed, randomized, double-blinded, PBO-controlled and active-controlled evaluating UPA 15 mg in subjects with moderately to severely active RA with erosive disease receiving concomitant background therapy of MTX and who had an inadequate response to prior MTX therapy. The enrolled subjects represented a typically more difficult patient population to treat due to having failed therapy with MTX and having erosive disease. The inclusion and exclusion criteria were acceptable and were consistent with RA subjects with moderately to severely active RA. The choice of a PBO control and active control group was appropriate for the objectives of the study and the choice of concomitant MTX was appropriate as a commonly used DMARD in the US.

The Applicant's choice to use the proportion of subjects achieving an ACR20 at Week 12 as the primary endpoint and the change from baseline in mTSS score, HAQ-DI and DAS28 at Week 12 as major secondary endpoints, are adequate to assess clinically meaningful outcomes and have been validated and used in previous approvals of other drugs indicated for patients with moderate to severe RA and are recommended in the Agency's RA guidance document.

### 6.3.2. Study Results

#### **Compliance with Good Clinical Practices**

The Applicant has provided attestation that the study was conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of the clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice.

#### **Financial Disclosure**

A financial disclosure review was conducted for all five phase 3 studies. Because many investigators participated in more than one study, a combined review of the financial disclosures will be presented. Table 29 shows the total number of investigators identified in each of the phase 3 studies that were evaluated for financial disclosure based on the investigator information.

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**Table 29. All Five Phase 3 Studies: Total Number of Investigators in Registrational Studies**

<b>Study</b>	<b>Total Number of Investigators</b>	<b>Number of Principle Investigators</b>	<b>Number of Sub-investigators</b>
M13-542	674	153	521
M13-545	1205	236	969
M13-549	721	150	571
M14-465	1383	285	1098
M15-555	667	138	529

Adapted from Applicant's Financial Summary Table 1.

A total of 41 investigators had disclosable financial interests/arrangements. Each investigator's financial disclosure documentation was reviewed. For these investigators with disclosable financial interests/arrangements: none received compensation for conducting the study where the value could be influenced by the outcome of the study; no investigators received significant payments of other sorts; no investigators had proprietary interest in the product being tested held by the investigator; no investigator had significant equity interest in the Sponsor covered study.

These financial disclosures do not raise concerns regarding the integrity of the phase 3 studies as the Applicant took steps to minimize potential bias of clinical investigators with financial interests and arrangements by using proper study design and operations. The clinical studies were blinded to the study site personnel and the participating subjects through the primary endpoint collection for the studies. Each active dose of investigational drug product was identical in appearance to its matched PBO and each subject was randomly assigned to their treatment arm independent of the investigator and the study site. Additionally, the number of subjects enrolled at the individual investigator sites were small compared to the total number of subjects enrolled in the overall study.

### **Patient Disposition**

A total of 1629 subjects were randomized, and 1628 subjects received study drug. One subject who was randomized to the UPA group was administered one subcutaneous PBO injection at baseline prior to prematurely discontinuing from the study. The subject did not take any oral study drug and was assigned to the PBO group for the safety analysis but remained in the Full Analysis set for efficacy analysis. A total of 1540 subjects (95%) subjects completed study drug through Week 14 and 1483 (91%) subjects completed study drug (or rescue therapy) through Week 26 (Table 30).

**Table 30. Study M14-465: Subject Disposition (All Randomized Subjects)**

	<b>PBO (N=651)</b>	<b>ADA 40 mg EOW (N=327)</b>	<b>UPA 15 mg QD (N=651)</b>
<b>Completed study drug Week 14, n (%)</b>	620 (95)	300 (92)	620 (95)
<b>Discontinued study drug through Week 14, n (%)</b>	31 (5)	27 (8)	31 (5)
<b>AE</b>	10 (2)	15 (5)	15 (2)
<b>Withdrawal by subject</b>	14 (2)	9 (3)	9 (1)
<b>Lost to follow-up</b>	4 (1)	1 (<1)	3 (1)
<b>Lack of efficacy</b>	1 (<1)	0	0
<b>Other</b>	2 (<1)	2 (1)	4 (1)

Adapted from Applicant's M14-465 Study Report Table 4.

Through the first 14 weeks of the study, similar percentages of subjects in the PBO and UPA 15 mg groups discontinued study drug compared to a higher percentage of ADA subjects. A greater number of ADA subjects discontinued the study due to AE compared to the other two treatment arms. Overall, relatively few subjects discontinued from the study during the 14-week controlled period.

A higher percentage of PBO subjects received rescue therapy after the Week 14, Week 18, and Week 22 visits compared to subjects randomized to UPA or ADA (Table 31). Overall, a higher percentage of subjects randomized to ADA received rescue therapy through Week 26 in comparison to subjects randomized to UPA (Table 31).

**Table 31. Study M14-465: Percentage of Subjects Rescued at Each Visit by Randomization Treatment Arm**

<b>Rescue Visit</b>	<b>PBO (N=651) n (%)</b>	<b>ADA 40 mg (N=327) n (%)</b>	<b>UPA 15 mg (N=651) n (%)</b>
<b>Week 14</b>	231 (36)	56 (17)	78 (12)
<b>Week 18</b>	48 (7)	14 (4)	29 (5)
<b>Week 22</b>	26 (4)	7 (2)	18 (3)
<b>Week 26</b>	-	82 (25)	126 (19)

Adapted from Applicant's M14-465 Study Report Table 6.

### Protocol Violations/Deviations

The most common inclusion/exclusion criteria violations were related to all women of childbearing potential to have a negative serum pregnancy test at the Screening Visit; however, serum pregnancy tests were not performed at screening for all female subjects due to an error by the central lab. Serum pregnancy tests were performed only in females of childbearing potential, although the protocol required the test in all female subjects. A total of 88 of 1629 subjects (5%) did not meet this inclusion criterion. No pregnant subjects were randomized.

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Overall, the total number of subjects with protocol violations at the time of the primary endpoint assessment was small and relatively balanced between treatment arms. These protocol deviations were not considered to have affected the overall assessment of study results.

### Table of Demographic Characteristics

As shown in Table 32, subjects' baseline demographics were similar between treatment arms. The average subject enrolled in the study was female, White, 54-years of age and clinically overweight, which is consistent with the US patient population.

**Table 32. Study M14-465: Subjects Baseline Demographics**

Demographic Parameters	PBO (N=651)	ADA 40 mg (N=327)	UPA 15 mg (N=651)
<b>Sex, n (%)</b>			
Male	139 (21)	68 (21)	130 (20)
Female	512 (79)	259 (79)	521 (80)
<b>Age, n (%)</b>			
Mean ± SD	54 ± 12	54 ± 12	54 ± 12
Median (min, max)	55 (19, 86)	54 (19, 83)	55 (20, 83)
<b>Age (years), n (%)</b>			
< 40 years	91 (14)	39 (12)	81 (12)
40-64	437 (67)	232 (71)	439 (67)
≥ 65 years	123 (19)	56 (17)	131 (20)
<b>Race, n (%)</b>			
White	561 (86)	292 (89)	576 (89)
Black or African American	38 (6)	17 (5)	33 (5)
Asian	39 (6)	15 (5)	31 (5)
American Indian or Alaska Native	2 (<1)	1 (<1)	1 (<1)
Native Hawaiian or Other Pacific Islander	1 (<1)	0	0
<b>Ethnicity</b>			
Hispanic or Latino	206 (32)	106 (32)	215 (33)
Not Hispanic or Latino	445 (68)	221 (68)	436 (67)
<b>BMI (kg/m<sup>2</sup>)</b>			
Mean ± SD	29 ± 6	29 ± 7	29 ± 7
Median (min, max)	28 (16, 55)	27 (16, 57)	28 (17, 68)

Adapted from Applicant's Study M14-465 study report Table 7.

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**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Overall, the subjects enrolled in the study demonstrated moderately to severely active disease as evidenced by the mean DAS28 score, swollen and tender joint counts, HAQ-DI and duration of morning stiffness. Subjects' baseline disease characteristics and background RA-related therapy were similar between individual treatment arms (Table 33).

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**Table 33. Study M14-465: Subjects Baseline Disease Characteristics**

Demographic Parameters	PBO (N=651)	ADA 40 mg (N=327)	UPA 15 mg (N=651)
<b>Duration of RA (years)</b>			
Mean ± SD	8 ± 8	8 ± 8	8 ± 8
Median (min, max)	6 (<1, 50)	6 (<1, 51)	6 (<1, 43)
<b>RF and anti-CCP, n (%)</b>			
Positive (RF + anti-CCP)	475 (73)	241 (74)	480 (74)
At least one negative	174 (27)	86 (26)	171 (26)
Negative RF and anti-CCP	80 (12)	39 (12)	85 (13)
<b>DAS28 (CRP)</b>			
n	649	324	647
Mean ± SD	5.8 ± 1	5.9 ± 1	5.8 ± 1
Median (min, max)	6 (2, 8)	6 (3, 9)	6 (2, 8)
<b>Swollen Joint Count-66</b>			
Mean ± SD	16 ± 9	16 ± 9	17 ± 10
Median (min, max)	14 (3, 55)	14 (4, 64)	13 (1, 61)
<b>Tender Joint Count-68</b>			
Mean ± SD	26 ± 14	26 ± 15	26 ± 15
Median (min, max)	23 (6, 68)	23 (6, 68)	23 (5, 66)
<b>HAQ-DI</b>			
n	649	325	646
Mean ± SD	1.6 ± 0.6	1.6 ± 0.6	1.6 ± 0.6
Median (min, max)	1.6 (0, 3)	1.8 (0, 3)	1.8 (0, 3)
<b>CRP</b>			
Mean ± SD	18 ± 22	20 ± 22	18 ± 22
Median (min, max)	11 (0, 198)	12 (0, 142)	10 (0, 174)
<b>Morning Stiffness duration (minutes)</b>			
Mean ± SD	142 ± 170	146 ± 185	142 ± 188
Median (min, max)	120 (0, 1440)	105 (0, 1440)	90 (0, 1440)
<b>Failed at least one TNF inhibitor, n (%)</b>			
Yes	152 (90)	146 (89)	151 (92)
No	17 (10)	18 (11)	13 (8)
<b>Concomitant MTX dose at baseline, n (%)</b>			
N	650	326	650
Mean ± SD	17 ± 4	17 ± 4	17 ± 4
Median (min, max)	15 (7.5, 25)	15 (10, 25)	15 (10, 25)
<b>Oral corticosteroid dose (mg)</b>			
n	391	202	388
Mean ± SD	6 ± 2	7 ± 2	6 ± 2
Median (min, max)	5 (<1, 12.5)	5 (2, 10)	5 (<1, 12.5)
<b>Baseline mTSS</b>			
n	649	326	644
Mean ± SD	36 ± 52	35 ± 47	34 ± 50
Median (min, max)	15 (0, 325)	16 (0, 250)	14 (0, 305)

Adapted from Applicant's Study M13-542 study report Table 8.

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### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Mean treatment compliance of oral study drug (UPA and PBO) through Week 26 was 99%, 99%, and 99% for subjects randomized to UPA, ADA, and PBO, respectively. Mean treatment compliance of subcutaneous study drug (ADA and PBO) through Week 26 was 99%, 99%, and 99% for subjects randomized to UPA, ADA, and PBO, respectively.

As shown in Table 33, approximately 99% of subjects in all treatment arms were receiving concomitant MTX at an average dose of 15 mg weekly, which is a dose commonly used in the US to treat subjects with RA and generally believed to be effective.

### Efficacy Results – Primary Endpoint

As shown in Table 34, the primary endpoint analysis demonstrated a statistically significant difference between PBO and the UPA 15 mg and ADA treatment arms. The average treatment effect size for the UPA 15 mg and ADA treatment arms were 34% and 27%, respectively. These results also demonstrate a greater proportion of UPA 15 mg-treated subjects achieved an ACR20 response versus ADA-treated subjects; however, given the limitations of the study, no firm conclusions can be drawn regarding the superiority of UPA compared to ADA.

**Table 34. Study M14-465: Proportion of Subjects Achieving ACR20 at Week 12**

	PBO (N=651) n (%)	ADA 40 mg (N=327) n (%)	UPA 15 mg (N=651) n (%)
ACR20	237 (36)	206 (63)	459 (71)
Difference (%), (95% CI)	-	27 (20, 33)	34 (29, 39)

Source: FDA Biostatistics Review for NDA 211675

This analysis demonstrates a clinically meaningful benefit with UPA treatment for the improvement of the signs and symptoms of subjects with active RA despite concomitant MTX therapy and having failed treatment with MTX. Additionally, UPA-treated subjects demonstrated greater improvements in all ACR components compared to PBO-treated subjects at Week 12 demonstrating that the results were not driven by any single component of the ACR response criteria (Table 35).

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**Table 35. Study M14-465: Change from Baseline in ACR Components (excluding HAQ-DI)**

Treatment Arm	N	Baseline Mean (SD)	n	Visit Mean (SD)	Est Diff (95 % CI)	p-value
<b>CRP</b>						
PBO	651	18.0 (21.5)	595	16.2 (19.8)		
ADA 40 mg EOW	327	19.8 (21.5)	299	9.3 (15.8)	-7.3 (-9.4, -5.2)	<0.001
UPA 15 mg QD	651	17.9 (22.5)	590	5.5 (10.9)	-10.7 (-12.4, -9.0)	<0.001
<b>SJC (Out of 28)</b>						
PBO	651	11.8 (5.3)	625	6.7 (5.8)		
ADA 40 mg EOW	327	11.7 (5.5)	314	4.3 (4.5)	-2.4 (-3.0, -1.8)	<0.001
UPA 15 mg QD	651	11.4 (5.6)	624	3.5 (4.5)	-3.1 (-3.6, -2.6)	<0.001
<b>SJC (Out of 66)</b>						
PBO	651	16.2 (9.0)	625	9.3 (8.9)		
ADA 40 mg EOW	327	16.3 (9.2)	314	5.9 (6.5)	-3.4 (-4.3, -2.5)	<0.001
UPA 15 mg QD	651	16.6 (10.3)	624	5.2 (7.4)	-4.3 (-5.0, -3.5)	<0.001
<b>TJC (Out of 28)</b>						
PBO	651	15.4 (6.8)	625	9.7 (7.9)		
ADA 40 mg EOW	327	15.1 (7.0)	314	6.6 (6.6)	-3.0 (-3.8, -2.1)	<0.001
UPA 15 mg QD	651	15.0 (6.9)	624	5.3 (6.2)	-4.3 (-5.0, -3.6)	<0.001
<b>TJC (Out of 68)</b>						
PBO	651	26.0 (14.3)	625	16.4 (14.6)		
ADA 40 mg EOW	327	26.4 (15.2)	314	11.7 (12.7)	-4.8 (-6.3, -3.4)	<0.001
ADA 40 mg EOW	651	26.4 (15.1)	624	9.9 (12.6)	-6.8 (-8.0, -5.6)	<0.001
<b>Physician Global</b>						
PBO	649	1.6 (0.6)	623	1.3 (0.7)		
ADA 40 mg EOW	325	1.6 (0.6)	314	1.1 (0.7)	-0.2 (-0.3, -0.1)	<0.001
UPA 15 mg QD	646	1.6 (0.6)	623	1.0 (0.7)	-0.3 (-0.4, -0.3)	<0.001
<b>Patient Global</b>						
PBO	620	66.0 (18.2)	613	40.8 (24.7)		
ADA 40 mg EOW	305	65.1 (17.6)	304	29.4 (20.5)	-11.2 (-14.3, -8.2)	<0.001
UPA 15 mg QD	616	65.6 (17.1)	614	26.8 (21.4)	-14.0 (-16.5, -11.5)	<0.001
<b>Patient Pain</b>						
PBO	649	63.8 (21.5)	623	48.3 (24.5)		
ADA 40 mg EOW	324	65.8 (21.1)	314	41.0 (24.7)	-7.9 (-11.1, -4.7)	<0.001
UPA 15 mg QD	647	64.3 (21.8)	623	33.4 (24.2)	-15.0 (-17.6, -12.4)	<0.001

Source: FDA Biometrics Review for NDA 211675

Results from sensitivity analyses on the Per Protocol Analysis set were consistent with the primary analysis. Subgroup analysis results using Nonresponder Imputation, were also consistent

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with the primary analysis.

### **Efficacy Results – Secondary and other relevant endpoints**

#### **HAQ-DI**

Table 36 shows that at Week 12, subjects treated with UPA experienced a statistically significant and clinically meaningful change from baseline ( $\leq -0.3$ ) compared to subjects treated with PBO. Changes in HAQ-DI were similar between the UPA 15 mg and ADA dosing groups. These data support the results of the primary endpoint demonstrating a clinical benefit of UPA treatment in subjects with RA.

**Table 36. Study M14-465: Change in HAQ-DI from Baseline to Week 12**

<b>HAQ-DI Score</b>	<b>PBO N=650</b>	<b>UPA 15 mg N=645</b>	<b>ADA 40 mg N=325</b>
Baseline (Mean $\pm$ SD)	1.6 $\pm$ 0.6	1.6 $\pm$ 0.6	1.6 $\pm$ 0.6
	<b>N=617</b>	<b>N=617</b>	<b>N=309</b>
Week 12 (Mean $\pm$ SD)	1.3 $\pm$ 0.7	1.0 $\pm$ 0.7	1.1 $\pm$ 0.7
Difference (%), (95% CI)	-	-0.3 (-0.4, -0.3)	-0.2 (-0.3, -0.1)

Source: FDA Biostatistics Review for NDA 211675

Tipping point analyses were conducted to evaluate the robustness of the results for the change from baseline in HAQ-DI comparing UPA 15 mg and ADA with PBO and were found to support the observed results (data not shown).

#### **ACR20/ACR50/ACR70**

Analysis of the ACR responses demonstrated a statistically significant increase in the improvement of signs and symptoms of subjects in the UPA and ADA groups compared to the PBO group (Table 37). Upadacitinib 15 mg-treated subjects achieved greater responses in ACR20, ACR50 and ACR70 responses compared to subjects in the ADA mg group.

**Table 37. Study M14-465: Change in ACR20/ACR50/ACR70 from Baseline at Week 12**

	<b>PBO (N=651) n (%)</b>	<b>UPA 15 mg (N=651) n (%)</b>	<b>ADA (N=327) n (%)</b>	<b>UPA 15 mg vs PBO Difference (%), (95% CI)</b>
<b>ACR20</b>	237 (36)	459 (71)	206 (63)	34 (29, 39)
<b>ACR50</b>	97 (15)	294 (45)	95 (29)	30 (26, 35)
<b>ACR70</b>	32 (5)	162 (25)	44 (14)	20 (16, 24)

Source: FDA Biostatistics Review for NDA 211675

These data support the results of the primary endpoint and demonstrate a clinically meaningful effect of UPA compared to PBO in subjects with moderately to severely active RA.

### DAS28-CRP

A significantly greater mean change from baseline in DAS28-CRP at Week 12 was observed in the UPA treatment arm and the ADA compared to PBO (Table 38). In contrast to what was observed in the primary endpoint analysis, there was a trend to greater decreases in active disease in ADA-treated subjects compared to UPA-treated subjects. Overall, these data support the results of the primary endpoint demonstrating a clinical benefit of UPA treatment in subjects with RA.

**Table 38. Study M14-465: Change in DAS28-CRP from Baseline to Week 12**

<b>DAS28-CRP Score</b>	<b>PBO</b>	<b>ADA 40 mg</b>	<b>UPA 15 mg</b>
	<b>N=649</b>	<b>N=324</b>	<b>N=647</b>
Baseline (Mean ± SD)	5.8 ± 0.9	5.9 ± 1	5.8 ± 1
	<b>N=595</b>	<b>N=295</b>	<b>N=586</b>
Week 12 (Mean ± SD)	4.7 ± 1.4	3.8 ± 1.4	3.3 ± 1.2
Difference (%), (95% CI)	-	-0.9 (-1.0, -0.7)	-1.3 (-1.5, -1.2)

Source: FDA Biostatistics Review for NDA 211675

### DAS28-CRP <2.6

DAS28-CRP responses <2.6 represent very low disease activity. In Study M14-465, a higher proportion of subjects treated with UPA 15 mg and ADA achieved DAS28-CRP responses compared to PBO-treated subjects (29% and 18% versus 6%, respectively). A much larger percentage of UPA-treated subjects achieved low disease activity compared to ADA-treated subjects suggesting UPA has a more robust clinical effect compared to ADA; however, given the limitations of this single study, no firm conclusions can be drawn regarding the superiority of UPA compared to ADA. Overall, the results demonstrate a clinically meaningful benefit of UPA in

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decreasing disease activity, as assessed by measures of signs and symptoms, in subjects with active RA.

### SF-36

In study M14-465, the mean adjusted changes from baseline in the SF-36 PCS and MCS scores at Week 12 were significantly higher in subjects treated with UPA 15 mg and ADA compared to PBO-treated subjects (Table 39). These results suggest a modest improvement in the SF-36 PCS and MCS scores with UPA 15 mg and ADA. The reader is directed to Dr. Koh’s review for a detailed analysis of the individual SF-36 components.

**Table 39. Study M14-465: Change in SF-36 PCS and MCS Scores from Baseline to Week 12**

<b>SF-36 PCS Score</b>	<b>PBO</b>	<b>ADA 40 mg</b>	<b>UPA 15 mg</b>
	<b>N=647</b>	<b>N=327</b>	<b>N=648</b>
Baseline (Mean ± SD)	33 ± 7	32 ± 7	33 ± 7
	<b>N=632</b>	<b>N=322</b>	<b>N=634</b>
Week 12 (Mean ± SD)	37 ± 8	39 ± 9	41 ± 9
Difference (%), (95% CI)	-	3 (2, 4)	4 (4, 5)
<b>SF-36 MCS Score</b>			
	<b>N=647</b>	<b>N=327</b>	<b>N=648</b>
Baseline (Mean ± SD)	43 ± 11	43 ± 12	43 ± 11
	<b>N=632</b>	<b>N=322</b>	<b>N=634</b>
Week 12 (Mean ± SD)	46 ± 11	48 ± 10	49 ± 10
Difference (%), (95% CI)	-	2 (1, 3)	3 (2, 4)
Source: FDA Biostatistics Review for NDA 211675			

### Morning Stiffness

#### As shown in

Table 40, the mean change from baseline in duration of morning stiffness at Week 12 in subjects treated with UPA 15 mg or ADA decreased significantly compared to subjects treated with PBO. These results demonstrate a clinically meaningful benefit of UPA in decreasing disease activity in subjects with active RA and was comparable to the effect observed with subjects treated with ADA.

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**Table 40. Study M14-465: Change in Morning Stiffness from Baseline to Week 12**

<b>Morning Stiffness (minutes)</b>	<b>PBO</b>	<b>ADA 40 mg</b>	<b>UPA 15 mg</b>
	<b>N=651</b>	<b>N=324</b>	<b>N=649</b>
Baseline (Mean ± SD)	142 ± 170	146 ± 185	142 ± 188
	<b>N=625</b>	<b>N=314</b>	<b>N=625</b>
Week 12 (Mean ± SD)	92 ± 135	61 ± 105	48 ± 95
Difference (%), (95% CI)	-	-32 (-46, -19)	-43 (-54, -32)
Source: FDA Biostatistics Review for NDA 211675			

#### **FACIT-F**

The mean change from baseline in FACIT-F at Week 12 in subjects treated with UPA 15 mg and ADA was statistically significantly greater compared to subjects treated with PBO in study M14-465 (Table 41).

**Table 41. Study M14-465: Change in Morning Stiffness from Baseline to Week 12**

<b>FACIT-F</b>	<b>PBO</b>	<b>ADA 40 mg</b>	<b>UPA 15 mg</b>
	<b>N=644</b>	<b>N=325</b>	<b>N=646</b>
Baseline (Mean ± SD)	27 ± 11	26 ± 11	27 ± 11
	<b>N=632</b>	<b>N=322</b>	<b>N=632</b>
Week 12 (Mean ± SD)	32 ± 12	34 ± 11	35 ± 11
Difference (%), (95% CI)	-	3 (2, 5)	4 (2, 5)
Source: FDA Biostatistics Review for NDA 211675			

#### **Inhibition of Radiographic Progression**

The ability for UPA treatment to slow progression of radiographic damage was assessed by the Applicant using the change from baseline in mTSS score at Week 26. Independent verification of the data was conducted by Dr. Koh and the data that follows is based on his analyses.

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The distribution of baseline radiograph scores and the proportion of subjects with no observed joint erosions was similar between treatment arms (Table 42).

**Table 42. Study M14-465: Baseline Radiograph Scores and Components.**

		<b>Placebo (N=651)</b>	<b>UPA 15 MG QD (N=651)</b>	<b>ADA 40 MG EOW (N=327)</b>
<b>mtSS</b>	<i>Mean (SD)</i>	35.9 (51.7)	34.0 (50.1)	34.5 (47.1)
	<i>Min -Max</i>	0.0 - 324.5	0.0 - 304.5	0.0 - 249.5
	<i>n</i>	(n=649)	(n=644)	(n=326)
<b>Erosion Score</b>	<i>Mean (SD)</i>	17.0 (27.4)	16.5 (26.4)	15.4 (23.1)
	<i>Min -Max</i>	0.0 - 192.0	0.0 - 168.0	0.0 - 129.0
	<i>n</i>	(n=649)	(n=644)	(n=326)
<b>Joint Space Narrowing</b>	<i>Mean (SD)</i>	18.9 (26.1)	17.5 (25.1)	19.2 (25.8)
	<i>Min -Max</i>	0.0 - 134.5	0.0 - 136.5	0.0 - 125.0
	<i>n</i>	(n=649)	(n=644)	(n=326)
<b>Proportion with mTSS = 0</b>	<i>Count (%)</i>	79 (12%)	90 (14%)	44 (13%)
Source: FDA Biostatistics Review for NDA 211675				

As seen in Table 43, 26% of the randomized subjects underwent radiograph evaluation at Week 14 with the majority of the subjects coming from the placebo group. Of these subjects, less than 1% of these subjects had discontinued randomized treatment prior to Week 14. At Week 26, 90% of the subjects remaining in the study, regardless of discontinuation of randomized or rescue treatment, had an evaluable radiograph collected within the visit window.

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**Table 43. Study M14-645: Disposition of Patients with mTSS Evaluated during the First 26 Weeks**

	Placebo (N=651)	UPA 15 MG QD (N=651)	ADA 40 MG EOW (N=327)	All (N=1629)
<b>Baseline</b>				
<b>Patients with evaluable mTSS</b>	649 (100%)	644 (99%)	326 (100%)	1619 (99%)
Patients with $\geq 1$ post-baseline mTSS value	608 (93%)	599 (92%)	298 (91%)	1505 (92%)
Patients without post-baseline mTSS value	41 (6%)	45 (7%)	28 (9%)	114 (7%)
<b>Patients missing mTSS at baseline</b>	2 (0%)	7 (1%)	1 (0%)	10 (1%)
<b>Week 14</b>				
<b>Patients with evaluable mTSS</b>	243 (37%)	110 (17%)	67 (20%)	420 (26%)
<i>Patients without baseline mTSS</i>	2	5	1	8
On randomized treatment (prior to rescue)	238 (37%)	105 (16%)	63 (19%)	406 (25%)
Discontinued randomized treatment <sup>a</sup>	5 (1%)	5 (1%)	4 (1%)	14 (1%)
<b>Week 26</b>				
<b>Patients with evaluable mTSS</b>	588 (90%)	588 (90%)	291 (89%)	1467 (90%)
<i>Patients without baseline mTSS</i>	1	6	1	8
On randomized treatment (never rescued)	295 (45%)	465 (71%)	211 (65%)	971 (60%)
Discontinued randomized treatment	7 (1%)	6 (1%)	7 (2%)	20 (1%)
Remained on rescue treatment <sup>b</sup>	282 (43%)	113 (17%)	73 (22%)	468 (29%)
Discontinued rescue treatment <sup>b</sup>	4 (1%)	4 (1%)	-	8 (0%)
<b>Patients without mTSS</b>	63 (10%)	63 (10%)	36 (11%)	162 (10%)
Discontinued rescue/randomized treatment <sup>c</sup>	18 (3%)	22 (3%)	4 (1%)	44 (3%)
Discontinued study participation	43 (7%)	39 (6%)	32 (10%)	114 (7%)
On either rescue/randomized treatment	2 (<1%)	2 (<1%)	-	4 (<1%)

Source: FDA Biostatistics Review for NDA 211675.

Results for the components of the mTSS, i.e., erosion and joint space narrowing scores, were statistically significant at Week 26, with similar trends towards benefit for UPA 15 mg relative to PBO (Table 44). The conclusions of Dr. Koh's results were similar to those based on the Applicant's analysis that included all radiographs collected following discontinuation of randomized treatment (Table 45).

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**Table 44. Study M14-465: Applicant’s Primary Analysis of the Mean Change from Baseline in mTSS and Components at Week 26 using Linear Extrapolation for Patients Rescued**

Treatment Arm	N	Baseline Mean (SD)	n	Change from Baseline Mean (SD)	Vs Placebo		Vs Adalimumab	
					Est Difference (95% CI)	P-value	Est Difference (95% CI)	P-value
<b>mTSS</b>								
Placebo	649	35.9 (51.7)	599	0.9 (3.5)				
UPA 15 mg QD	644	34.0 (50.1)	593	0.2 (1.6)	-0.67 (-0.97, -0.37)	<0.001	0.14 (-0.23, 0.51)	0.45
ADA 40 mg EOW	326	34.5 (47.1)	296	0.1 (2.4)	-0.82 (-1.2, -0.45)	<0.001		
<b>Erosion Score</b>								
Placebo	649	17.0 (27.4)	599	0.5 (2.2)				
UPA 15 mg QD	644	16.5 (26.4)	593	0.1 (0.8)	-0.41 (-0.58, -0.24)	<0.001	0.009 (-0.2, 0.22)	0.93
ADA 40 mg EOW	326	15.4 (23.1)	296	0.0 (0.9)	-0.42 (-0.63, -0.21)	<0.001		
<b>Joint Space Narrowing</b>								
Placebo	649	18.9 (26.1)	599	0.5 (2.4)				
UPA 15 mg QD	644	17.5 (25.1)	593	0.1 (1.1)	-0.36 (-0.56, -0.17)	<0.001	0.08 (-0.16, 0.32)	0.50
ADA 40 mg EOW	326	19.2 (25.8)	296	0.0 (1.0)	-0.45 (-0.69, -0.21)	<0.001		

Source: FDA Biostatistics Review for NDA 211675.

**Table 45. Study M14-465: Sensitivity Analysis for the Mean Change from Baseline in mTSS and Components at Week 24 Including After Rescue**

Treatment Arm	N	Baseline Mean (SD)	n	Change from Baseline Mean (SD)	Est Difference (95% CI)	P-value	Est Difference (95% CI)	P-value
<b>mTSS</b>								
Placebo	649	35.9 (51.7)	588	36.7 (51.5)				
UPA 15 mg QD	644	34.0 (50.1)	588	35.4 (51.1)	-0.56 (-0.83, -0.29)	<0.001	0.16 (-0.17, 0.49)	0.34
ADA 40 mg EOW	326	34.5 (47.1)	291	35.2 (48.0)	-0.72 (-1.1, -0.39)	<0.001		
<b>Erosion Score</b>								
Placebo	649	17.0 (27.4)	588	17.4 (27.6)				
UPA 15 mg QD	644	16.5 (26.4)	588	17.2 (27.1)	-0.35 (-0.49, -0.21)	<0.001	0.01 (-0.16, 0.18)	0.91
ADA 40 mg EOW	326	15.4 (23.1)	291	15.9 (23.7)	-0.36 (-0.53, -0.18)	<0.001		
<b>JSN</b>								
Placebo	649	18.9 (26.1)	588	19.3 (25.8)				
UPA 15 mg QD	644	17.5 (25.1)	588	18.2 (25.6)	-0.28 (-0.46, -0.1)	0.002	0.08 (-0.13, 0.3)	0.45
ADA 40 mg EOW	326	19.2 (25.8)	291	19.4 (26.2)	-0.36 (-0.58, -0.15)	0.001		

Source: FDA Biostatistics Review for NDA 211675.

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Table 46 shows the proportions of subjects with no radiographic progression, as measured by an observed change from baseline  $\leq 0$  at Week 26. These results were consistent with the key radiograph results based on the treatment policy estimand, providing additional supportive evidence of the efficacy.

**Table 46. Study M14-465: Proportion of Subjects with No Change in mTSS Score at Week 26**

Treatment Arm	n	Excluding Data after Rescue (LE)			n	Using All Data Collected after Rescue		
		Resp (%)	EstCI	Pvalue		Resp (%)	EstCI	Pvalue
<b>mTSS</b>								
Placebo	599	455 (76%)			587	451 (77%)		
UPA 15 mg QD	593	495 (83%)	7.5% (3.0% - 12.1%)	0.001	582	483 (83%)	6.2% (1.6% - 10.7%)	0.009
ADA 40 mg EOW	296	257 (87%)	10.9% (5.7% - 16.0%)	<0.001	290	251 (87%)	9.7% (4.5% - 14.9%)	<0.001
<b>Erosion Score</b>								
Placebo	599	498 (83%)			587	491 (84%)		
UPA 15 mg QD	593	536 (90%)	7.2% (3.4% - 11.1%)	<0.001	582	526 (90%)	6.7% (2.9% - 10.6%)	<0.001
ADA 40 mg EOW	296	269 (91%)	7.7% (3.3% - 12.2%)	0.002	290	265 (91%)	7.7% (3.3% - 12.1%)	0.002
<b>Joint Space Narrowing</b>								
Placebo	599	500 (83%)			587	488 (83%)		
UPA 15 mg QD	593	528 (89%)	5.6% (1.7% - 9.5%)	0.005	582	516 (89%)	5.5% (1.5% - 9.5%)	0.007
ADA 40 mg EOW	296	273 (92%)	8.8% (4.5% - 13.0%)	<0.001	290	265 (91%)	8.2% (3.8% - 12.7%)	0.001
Source: FDA Biostatistics Review for NDA 211675; Abbreviations: UPA=upadacitinib; QD=once daily; MTX=methotrexate; ADA=adalimumab; EOW=every other week; SD=standard deviation; CI=confidence interval; mTSS=modified total sharp score.								

Further sensitivity analyses supported the primary finding that UPA was able to inhibit radiographic progression in subjects with moderately to severely active RA. The reader is referred to Dr. Koh's review for a detailed discussion of the data and sensitivity analyses.

**Reviewer's Comments:**

Study M14-465 was a well-conducted study with balanced subject cohorts, limited subject dropouts, and minimal protocol violations that allowed for reliable interpretation of the study results. The efficacy analysis of the primary endpoint clearly demonstrates a clinically meaningful treatment effect of UPA 15 compared to PBO regarding improvement of the signs and symptoms of subjects with moderately to severely active RA receiving concomitant background therapy of MTX and who had an inadequate response to prior MTX therapy. The primary endpoint is fully supported by the results of the secondary endpoints.

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The results of the primary endpoint and key secondary endpoints from this study suggest that UPA may have greater efficacy compared to ADA in treating the signs and symptoms of RA. However, this is only a single study that was not specifically designed to assess superiority of UPA versus ADA. More clinical data would be required for the Applicant to make a claim of superiority. Additionally, the overall benefit-risk assessment for UPA 15 mg compared to treatment with ADA would need to be determined in the context of the relative safety profiles of each drug.

## **6.4. Study M15-555**

### **6.4.1. Study Design**

#### **Overview and Objective**

*“A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) Monotherapy to Methotrexate (MTX) in Subjects with Moderately to Severely Active Rheumatoid Arthritis with Inadequate Response to MTX”*

The primary objective of Study M15-555 was to assess the safety and efficacy of UPA 15 mg monotherapy and UPA 30 mg monotherapy compared to continuing MTX monotherapy in subjects with moderately to severely active RA who had an inadequate response to prior MTX treatment.

#### **Trial Design**

Study M15-555 was a phase 3 multicenter study conducted in two periods:

- Period 1 was a 14-week, randomized, double-blind, parallel-group, controlled period designed to compare the safety and efficacy of orally administered UPA 15 mg QD and 30 mg QD versus continuing MTX alone for the treatment of signs and symptoms of subjects with moderately to severely active RA who had a previous inadequate response to MTX.
- Period 2 was a blinded long-term extension period (226-weeks) to evaluate the long-term safety, tolerability, and efficacy of UPA 30 mg QD and 15 mg QD in subjects with RA who had completed Period 1.

The study was designed to enroll approximately 600 subjects and actually enrolled 648 subjects at 138 study sites in 24 countries (Argentina, Austria, Belgium, Bulgaria, Chile, Czech Republic, Estonia, Greece, Hungary, Israel, Italy, Japan, Mexico, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Serbia, South Africa, Spain, Turkey, Ukraine, United States). Subjects meeting eligibility criteria were randomized in a 2:2:1:1 ratio to one of four treatment groups:

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- Group 1: UPA 30 mg PO QD (Period 1) → UPA 30 mg PO QD (Period 2)
- Group 2: UPA 15 mg PO QD (Period 1) → UPA 15 mg PO QD (Period 2)
- Group 3: MTX (Period 1) → UPA 30 mg PO QD (Period 2)
- Group 4: MTX (Period 1) → UPA 15 mg PO QD (Period 2)

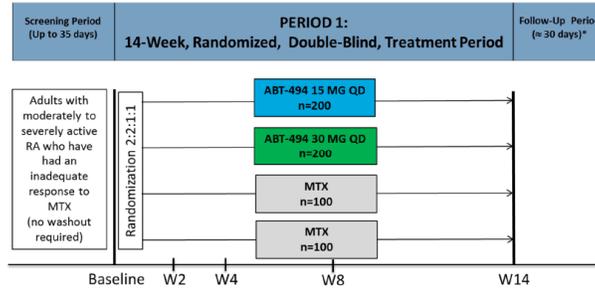
Subjects were treated with MTX therapy for  $\geq 3$  months, on a stable MTX dose for  $\geq 4$  weeks prior to the first dose of study drug and were to remain on a stable dose throughout the study; the MTX dose may have been decreased only for safety reasons. In addition, all subjects were to take a received oral folic acid throughout study participation.

Starting at the Week 26 visit and thereafter, initiation or change in background RA medication including corticosteroids, non-steroidal anti-inflammatory drugs, and acetaminophen /paracetamol was allowed. Starting at Week 48 and thereafter, initiation of, or change in, conventional synthetic csDMARD was allowed (restricted to MTX, chloroquine, hydroxychloroquine, sulfasalazine, or leflunomide).

Starting at Week 26, subjects who did not meet low disease activity by the clinical disease activity index criterion ( $CDAI \leq 10$ ) were able to have concomitant medication adjusted including the initiation/change of corticosteroids, NSAIDs, acetaminophen, or adding or increasing doses in up to two csDMARD. Starting at Week 26, at least 20% improvement in both tender joint count and swollen joint count was required to remain on study drug. Anyone who did not fulfill this criterion at two consecutive visits was discontinued from study drug.

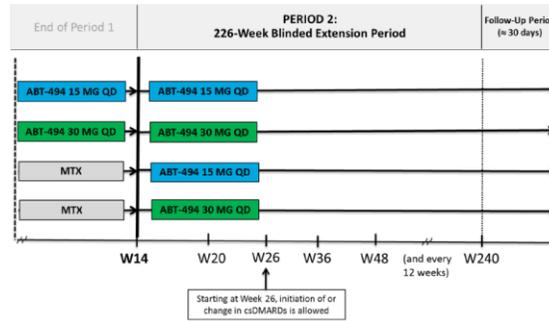
Subjects who completed the Week 14 visit entered Period 2 of the study, the blinded long-term extension of 226 weeks. Subjects who were assigned to UPA treatment groups in Period 1 continued to receive UPA 15 mg QD or 30 mg QD per original randomization assignment in a blinded manner. Subjects who were assigned to PBO for the first 12 weeks of Period 1 and subsequently switched to UPA 15 mg QD or 30 mg QD per their prespecified randomization assignments at Week 12, continued to receive the same dose of UPA per their original randomization assignment in a blinded manner. Figure 8 and Figure 9 illustrate the general schema of Study M15-555.

Figure 8. Study M15-555: Period 1 Overview



Adapted from Applicant's M15-555 Study Report Figure 1.

Figure 9. Study M15-555: Period 2 Overview



Adapted from Applicant's M15-555 Study Report Figure 2.

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### Major inclusion criteria:

- Male and female subjects  $\geq 18$  years-of-age
- Diagnosis of RA based on the 2010 ACR/EULAR criteria for a duration for  $\geq 3$  months
- $\geq 6$  swollen joints (based on 66 joint counts)
- $\geq 6$  tender joints (based on 68 joint counts)
- hsCRP  $\geq 3$  mg/L
- Have failed or be intolerant to previous MTX therapy for RA

### Major exclusion criteria:

- Prior exposure to any JAK inhibitor
- Prior exposure to any bDMARD
- History of an inflammatory joint disease other than RA
- Laboratory values meeting the following criteria
  - AST or ALT  $> 2$  x ULN
  - eGFR  $< 40$  mL/min/1.73m<sup>2</sup>
  - WBC  $< 2,500/\mu\text{L}$
  - ANC  $< 1500/\mu\text{L}$
  - PLT  $< 100,000/\mu\text{L}$
  - ALC  $< 800/\mu\text{L}$
  - Hg  $< 10$  g/dL

The dose selection for UPA 15 mg and 30 mg once-daily oral tablets was based on extrapolation of preclinical efficacy models and analyses of PK, pharmacodynamic, safety, and efficacy data from the phase 1 studies in healthy volunteers and phase 2 studies in RA subjects. The doses selected for this study were expected to be efficacious with an acceptable safety profile.

## Study Endpoints

The proportion of subjects achieving an ACR20 at Week 14 was used as the primary endpoint for improvement in signs and symptoms. The ACR response criteria consists of 7 components:

- Swollen joint count (66 joints)
- Tender joint count (68 joints)
- Subject global assessment of pain (VAS 100mm)
- Subject global assessment of disease activity (VAS 100mm)
- Physician global assessment of disease activity (VAS 100mm)
- Subject assessment of physical function using HAQ
- CRP

The ACR20 definition of response specifies a 20% improvement over baseline in swollen and tender joints and in 3 out of 5 of the remaining core data set measures. For the primary endpoint, assessment of the ACR20 occurred at Week 14. The choice of the primary endpoint is

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appropriate to assess a clinically meaningful benefit of UPA and consistent with Agency guidelines.

Key secondary endpoints were selected to capture clinically meaningful endpoints used to support the findings of the primary endpoint and were ranked as change from baseline to Week 12 in DAS28-CRP, HAQ-DI, change from baseline in Short Form-36 (SF-36) physical components summary (PCS), and low disease activity as measured by DAS28-CRP. Other clinically important secondary endpoints included change from baseline to Week 12 in ACR50/ACR70, and morning stiffness. Further discussion of the secondary endpoints can be found in Section 7.1.2. Analysis of other key secondary endpoints can be found in Dr. Koh's review.

### **Statistical Analysis Plan**

#### Primary Endpoint:

Comparison of the primary endpoint was made between each UPA dose group and the combined PBO groups using the Cochran-Mantel-Haenszel test adjusted for main stratification factors. For the primary analysis, Non-Responder Imputation was used. Supportive analysis was also conducted on the Per Protocol Analysis Set. The primary efficacy analyses were also performed in demographic subgroups including age, sex, weight, body mass index, race, and geographical region to assess the consistency of the treatment effect. Additional subgroup analyses based on baseline disease characteristics and stratification factors were also conducted.

#### Secondary Endpoints:

For binary endpoints, frequencies and percentages were reported for each treatment group. Similar analyses as for the primary endpoint were conducted. For the major RA continuous endpoints DAS28 and HAQ-DI change from baseline at Week 12, statistical inference was conducted using analysis of covariance (ANCOVA) coupled with multiple imputation for missing data handling. Specifically, the ANCOVA model was to include treatment as the fixed factor, and the corresponding baseline value and the stratification factor of geographic region as the covariates. For other continuous endpoints, statistical inference was conducted using the Mixed Effect Model Repeat Measurement (MMRM) model with fixed effects of treatment, visit and treatment by-visit interaction, prior bDMARD use and baseline value as covariate. For both the MI and MMRM analyses, the least square mean and 95% confidence interval (CI) were reported for each randomized treatment group; the LS mean treatment difference and associated 95% CI and p-value were reported comparing each UPA dose group with the combined PBO group. Both nominal p value and adjusted p-value through the graphical multiplicity procedure were provided.

For binary endpoints, point estimate and 95% CI using normal approximation were to be provided for the response rate for each randomized treatment group. Point estimate, 95% CI, and p-value were to be provided for the treatment comparison between each UPA dose group and the

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combined MTX group using the Cochran-Mantel-Haenszel test adjusting for stratification factor of geographic region. Only the nominal p-value was to be provided, and the 95% CI was to be based on normal approximation. NRI was to be used as primary analysis and Observed Cases was to be used as sensitivity analysis. For continuous endpoints, the LS mean, and 95% CI were to be reported for each randomized treatment group. The LS mean treatment difference and associated 95% CI and p-values between each UPA dose group and the combined MTX group were to be provided using MMRM model with fixed effects of treatment, visit and treatment-by-visit interaction, geographic region, and Baseline value as covariate.

## Protocol Amendments

The current protocol had three major amendments, four country-specific amendments, five global administrative changes and three country-specific administrative changes. The majority of changes to the protocol were responses to regulatory feedback, clarifications and editorial changes. Country-specific protocol amendments did not affect interpretation of the results of the study. Major amendments as they relate to the US studies are as follows:

- Amendment 1 (21 January 2016, 0 subjects) updated the study design and plan to change the duration of Period 1 from to 14 weeks and added a blinded long-term extension (Period 2). Added a 15 mg treatment group. Increased the number of study centers and number of subjects to be enrolled. Described how the blind will be maintained. Added discontinuation procedures. Updated procedures for laboratory samples during the screening period and defined screen failure. Added follow-up procedures. Updated MTX therapy and hsCRP value requirements at Screening. Identified patient questionnaires to be completed. Added INR, follicle stimulating hormone, and varicella zoster virus specific IgG to clinical chemistry lab tests. Updated randomization and randomization stratification. Added language regarding the Week 14 interim analysis. Added text to describe the addition of an external DMC. Updated the AST or ALT specific toxicity management guidelines. Added the following exclusion criteria: females who are considering becoming pregnant during the study or for approximately 180 days after the last dose of study drug; male subject who is considering fathering a child or donating sperm during the study or for approximately 180 days after the last dose of study drug; subjects with a history of GI perforation or a history of associated GI diseases; subjects with conditions that could interfere with drug absorption; subjects who have been the recipient of an organ transplant; subjects who had clinically relevant or significant ECG abnormalities.
- Amendment 2 (28 February 2016, 283 subjects) updated RA classification criteria serum pregnancy testing requirements. Added criteria for adjusting or adding background medication at Week 26 if subjects do not achieve low disease activity as defined by CDAI.
- Amendment 3 (06 October 2016, 166 subjects) updated exclusion criteria to reflect normal reference range in the elderly population and the lack of

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corrected QT interval prolongation with UPA. Added text to follow MTX local label for concomitant treatment contraindications.

Reviewer's Comments:

The current study was well-designed, randomized, double-blinded and active comparator-controlled to assess two doses of UPA monotherapy versus continuing MTX monotherapy in subjects with moderately to severely active RA who had an inadequate response to prior MTX therapy. The inclusion and exclusion criteria were acceptable and were consistent with RA subjects with moderately to severely active RA. The choice of control group was appropriate for the objectives of the study and the choice of MTX as the comparator was appropriate as a commonly used DMARD in the US.

The Applicant's choice to use the proportion of subjects achieving an ACR20 at Week 14 as the primary endpoint and the HAQ-DI and DAS28 at Week 14 as major secondary endpoints, are adequate to assess clinically meaningful outcomes and have been validated and used in previous approvals of other drugs indicated for patients with moderate to severe RA and are recommended in the Agency's RA guidance document.

## 6.4.2. Study Results

### **Compliance with Good Clinical Practices**

The Applicant has provided attestation that the study was conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of the clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice.

### **Financial Disclosure**

A financial disclosure review was conducted for all five phase 3 studies. Because many investigators participated in more than one study, a combined review of the financial disclosures will be presented. Table 47 shows the total number of investigators identified in each of the phase 3 studies that were evaluated for financial disclosure based on the investigator information.

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**Table 47. All Five Phase 3 Studies: Total Number of Investigators in Registrational Studies**

<b>Study</b>	<b>Total Number of Investigators</b>	<b>Number of Principle Investigators</b>	<b>Number of Sub-investigators</b>
M13-542	674	153	521
M13-545	1205	236	969
M13-549	721	150	571
M14-465	1383	285	1098
M15-555	667	138	529

Adapted from Applicant's Financial Summary Table 1.

A total of 41 investigators had disclosable financial interests/arrangements. Each investigator's financial disclosure documentation was reviewed. For these investigators with disclosable financial interests/arrangements: none received compensation for conducting the study where the value could be influenced by the outcome of the study; no investigators received significant payments of other sorts; no investigators had proprietary interest in the product being tested held by the investigator; no investigator had significant equity interest in the Sponsor covered study.

These financial disclosures do not raise concerns regarding the integrity of the phase 3 studies as the Applicant took steps to minimize potential bias of clinical investigators with financial interests and arrangements by using proper study design and operations. The clinical studies were blinded to the study site personnel and the participating subjects through the primary endpoint collection for the studies. Each active dose of investigational drug product was identical in appearance to its matched PBO and each subject was randomly assigned to their treatment arm independent of the investigator and the study site. Additionally, the number of subjects enrolled at the individual investigator sites were small compared to the total number of subjects enrolled in the overall study.

### **Patient Disposition**

A total of 648 subjects were randomized and all received study drug. One subject who failed screening was randomized in error and did not receive study drug. A total of 598 (92%) subjects completed study drug through Week 14 (Table 48).

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**Table 48. Study M15-555: Subject Disposition (All Randomized Subjects)**

	<b>MTX (n=216)</b>	<b>UPA 15 mg (n=217)</b>	<b>UPA 30 mg (n=215)</b>
<b>Completed Week 14, n (%)</b>	197 (91)	199 (92)	202 (94)
<b>Discontinued study drug through Week 14, n (%)</b>	19 (9)	19 (8)	13 (6)
<b>AE</b>	5 (2)	6 (3)	6 (3)
<b>Withdrawal by subject</b>	7 (3)	7 (3)	5 (2)
<b>Lost to follow-up</b>	0	4 (2)	2 (1)
<b>Lack of efficacy</b>	4 (2)	1 (1)	0
<b>Other</b>	3 (1)	0	0

Adapted from Applicant's M15-555 Study Report Table 3.

Through the first 14-weeks of the study, similar proportions of subjects in the MTX and UPA groups discontinued study drug. The reasons for discontinuation were also similar between the treatment arms.

### **Protocol Violations/Deviations**

The most common reason for protocol deviations was related to not meeting inclusion/exclusion criteria with the overall total percentage for any specific inclusion or exclusion criteria violation less than two percent. There were also protocol deviations related to a subject receiving the wrong treatment from Week 4 through Week 8 and a subject who was enrolled and treated with UPA 30 mg during Period 1 despite meeting exclusion criteria for an absolute lymphocyte count < 850/ $\mu$ L.

Overall, the total number of subjects with protocol violations at the time of the primary endpoint assessment was small and relatively balanced between treatment arms. These protocol deviations were not considered to have affected the overall assessment of study results.

### **Table of Demographic Characteristics**

As shown in Table 49, subjects' baseline demographics were similar between treatment arms. The average subject enrolled in the study was female, White, 54-years of age and clinically overweight, which is consistent with the US patient population.

**Table 49. Study M15-555: Subjects Baseline Demographics**

Demographic Parameters	MTX (N=216)	UPA 15 mg QD (N=217)	UPA 30 mg QD (N=215)
<b>Sex, n (%)</b>			
Male	37 (17)	43 (20)	45 (21)
Female	179 (83)	174 (80)	170 (79)
<b>Age, n (%)</b>			
Mean ± SD	55 ± 11	55 ± 12	53 ± 13
Median (min, max)	57 (25, 80)	56 (20, 79)	55 (22, 80)
<b>Age (years), n (%)</b>			
< 40 years	23 (11)	28 (13)	31 (14)
40-64	148 (69)	147 (68)	141 (66)
≥ 65 years	45 (21)	42 (19)	43 (20)
<b>Race, n (%)</b>			
White	176 (82)	173 (80)	180 (84)
Black or African American	11 (5)	15 (7)	9 (4)
Asian	24 (11)	24 (11)	21 (10)
American Indian or Alaska Native	3 (1)	4 (2)	3 (1)
Multiple	2 (1)	1 (1)	2 (1)
<b>Ethnicity</b>			
Hispanic or Latino	50 (23)	52 (24)	54 (25)
Not Hispanic or Latino	166 (77)	165 (76)	161 (75)
<b>BMI (kg/m<sup>2</sup>)</b>			
Mean ± SD	29 ± 7	28 ± 6	29 ± 7
Median (min, max)	28 (16, 58)	28 (17, 52)	28 (17, 52)

Adapted from Applicant's Study M15-555 study report Table 4.

Overall, the subjects enrolled in the study demonstrated moderately to severely active disease as evidenced by the average DAS28 score, swollen and tender joint counts, HAQ-DI and duration of morning stiffness. Subjects' baseline disease characteristics and background RA-related therapy were similar between individual treatment arms (Table 50).

**Table 50. Study M15-555: Subjects Baseline Disease Characteristics**

Demographic Parameters	MTX (N=216)	UPA 15 mg QD (N=217)	UPA 30 mg QD (N=215)
<b>Duration of RA (years)</b>			
Mean ± SD	6 ± 7	8 ± 9	7 ± 7
Median (min, max)	3 (<1, 36)	4 (<1, 54)	4 (<1, 42)
<b>RF and anti-CCP, n (%)</b>			
Positive (RF + anti-CCP)	135 (63)	142 (65)	131 (61)
At least one negative	81 (38)	75 (35)	84 (39)
<b>DAS28 (CRP)</b>			
n	216	217	215
Mean ± SD	5.6 ± 1	5.6 ± 1	5.6 ± 1
Median (min, max)	5.5 (2, 8)	5.6 (3, 8)	5.5 (3, 8)
<b>Swollen Joint Count-66</b>			
Mean ± SD	17 ± 12	16 ± 11	17 ± 10
Median (min, max)	14 (6, 66)	13 (6, 64)	14 (3, 59)
<b>Tender Joint Count-68</b>			
Mean ± SD	25 ± 16	25 ± 15	25 ± 15
Median (min, max)	20 (6, 68)	20 (6, 68)	22 (3, 67)
<b>HAQ-DI</b>			
n	216	216	215
Mean ± SD	1.5 ± 0.7	1.5 ± 0.7	1.5 ± 0.7
Median (min, max)	1.6 (0, 3)	1.5 (0, 3)	1.5 (0, 3)
<b>CRP (mg/L)</b>			
Mean ± SD	15 ± 17	14 ± 16	16 ± 21
Median (min, max)	8 (0, 128)	8 (0, 122)	9 (0, 136)
<b>Morning Stiffness duration (minutes)</b>			
Mean ± SD	153 ± 222	144 ± 215	134 ± 153
Median (min, max)	90 (0, 1440)	90 (0, 1830)	90 (0, 1440)
<b>Concomitant MTX dose at baseline, n (%)</b>			
N	215	215	213
Mean ± SD	17 ± 4	17 ± 4	17 ± 5
Median (min, max)	15 (8, 25)	15 (8, 25)	15 (8, 25)
<b>Oral corticosteroid dose (mg)</b>			
n	115	112	96
Mean ± SD	6 ± 3	6 ± 3	6 ± 2
Median (min, max)	5 (1, 10)	5 (2, 15)	5 (1, 10)

Adapted from Applicant's Study M15-555 study report Table 5.

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Mean treatment compliance was 99%, 99%, and 97% for UPA 15 mg, UPA 30 mg and MTX, respectively; and 98%, 98%, and 95% for matching PBO in the UPA 15 mg, UPA 30 mg, and MTX groups through Week 14, respectively. As shown in Table 50, over 99% of subjects in all treatment arms were receiving concomitant MTX and approximately 6 mg of oral corticosteroid.

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### Efficacy Results – Primary Endpoint

As shown in Table 51, the primary endpoint analysis demonstrated a statistically significant difference between MTX and the individual UPA treatment arms. The average treatment effect size for the UPA 15 mg and UPA 30 mg treatment arms were 27% and 30%, respectively. There was no additional clinically meaningful benefit with the UPA 30 mg dose compared to the UPA 15 mg dose.

**Table 51. Study M15-555: Proportion of Subjects Achieving ACR20 at Week 14**

	<b>MTX (N=216) n (%)</b>	<b>UPA 15 mg QD (N=217) n (%)</b>	<b>UPA 30 mg QD (N=215) n (%)</b>
ACR20	89 (41)	147 (68)	153 (71)
Difference (%), (95% CI)	-	27 (18, 36)	30 (21, 39)

Source: FDA Biostatistics Review for NDA 211675

This analysis demonstrates a clinically meaningful benefit with UPA monotherapy treatment for the improvement of the signs and symptoms of subjects with active RA despite having failed treatment with MTX. Additionally, UPA-treated subjects demonstrated greater improvements in all ACR components compared to PBO-treated subjects at Week 14 demonstrating that the results were not driven by any single component of the ACR response criteria (Table 52).

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**Table 52. Study M15-555: Change from Baseline in ACR Components (excluding HAQ-DI)**

Treatment Arm	N	Baseline Mean (SD)	n	Visit Mean (SD)	Est Diff (95 % CI)	p-value
<b>CRP</b>						
MTX	216	14.5 (17.3)	196	12.8 (21.7)		
UPA 15 mg QD	217	14.0 (16.5)	197	3.7 (7.8)	-9.1 (-11.9, -6.3)	<0.001
UPA 30 mg QD	215	16.3 (20.8)	199	5.0 (12.0)	-8.3 (-11.1, -5.4)	<0.001
<b>SJC (Out of 28)</b>						
MTX	216	11.3 (6.0)	197	6.1 (6.3)		
UPA 15 mg QD	217	11.1 (5.8)	199	3.8 (4.8)	-2.0 (-2.9, -1.1)	<0.001
UPA 30 mg QD	215	11.6 (5.7)	203	3.1 (4.5)	-3.0 (-3.9, -2.2)	<0.001
<b>SJC (Out of 66)</b>						
MTX	216	16.9 (11.5)	197	9.4 (11.1)		
UPA 15 mg QD	217	16.4 (10.9)	199	5.7 (8.6)	-3.2 (-4.6, -1.9)	<0.001
UPA 30 mg QD	215	16.9 (10.2)	203	4.6 (7.0)	-4.8 (-6.1, -3.4)	<0.001
<b>TJC (Out of 28)</b>						
MTX	216	14.5 (7.4)	197	8.4 (7.8)		
UPA 15 mg QD	217	14.2 (6.8)	199	5.5 (6.2)	-2.7 (-3.9, -1.5)	<0.001
UPA 30 mg QD	215	14.2 (7.5)	203	4.3 (5.7)	-3.9 (-5.1, -2.7)	<0.001
<b>TJC (Out of 68)</b>						
MTX	216	25.2 (16.0)	197	14.7 (15.7)		
UPA 15 mg QD	217	24.5 (15.1)	199	9.8 (12.5)	-4.4 (-6.6, -2.3)	<0.001
UPA 30 mg QD	215	24.8 (15.2)	203	7.5 (10.7)	-7.0 (-9.1, -4.8)	<0.001
<b>Physician Global</b>						
MTX	216	62.1 (17.5)	193	36.9 (24.1)		
UPA 15 mg QD	216	65.7 (18.5)	193	25.3 (20.4)	-12.8 (-17.1, -8.6)	<0.001
UPA 30 mg QD	215	62.6 (17.8)	192	21.9 (19.5)	-14.8 (-19.1, -10.5)	<0.001
<b>Patient Global</b>						
MTX	200	59.6 (21.8)	195	48.2 (25.7)		
UPA 15 mg QD	209	62.2 (22.3)	199	36.8 (27.3)	-12.3 (-17.2, -7.5)	<0.001
UPA 30 mg QD	202	59.4 (22.8)	201	29.7 (23.8)	-18.5 (-23.3, -13.7)	<0.001
<b>Patient Pain</b>						
MTX	216	62.5 (21.3)	195	48.1 (25.1)		
UPA 15 mg QD	216	62.3 (22.5)	199	35.4 (26.4)	-12.8 (-17.5, -8.1)	<0.001
UPA 30 mg QD	215	61.9 (22.1)	201	28.8 (23.7)	-19.3 (-24.0, -14.6)	<0.001

Source: FDA Biometrics Review for NDA 211675

Results from sensitivity analyses on the Per Protocol Analysis set were consistent with the primary analysis. Subgroup analysis results using Nonresponder Imputation, were also consistent

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with the primary analysis.

## Efficacy Results – Secondary and other relevant endpoints

### HAQ-DI

Table 53 shows that at Week 14, subjects treated with UPA experienced a statistically significant and clinically meaningful change from baseline ( $\leq -0.3$ ) compared to subjects treated with MTX; however, there was no evidence of a dose-dependent increase in response between the UPA 15 mg and UPA 30 mg dosing groups. These data support the results of the primary endpoint demonstrating a clinical benefit of UPA treatment in subjects with RA.

**Table 53. Study M15-555: Change in HAQ-DI from Baseline to Week 14**

HAQ-DI Score	MTX	UPA 15 mg QD	UPA 30 mg QD
	<b>N=216</b>	<b>N=216</b>	<b>N=215</b>
Baseline (Mean $\pm$ SD)	1.5 $\pm$ 0.7	1.5 $\pm$ 0.7	1.5 $\pm$ 0.7
	<b>N=195</b>	<b>N=199</b>	<b>N=201</b>
Week 14 (Mean $\pm$ SD)	1.2 $\pm$ 0.7	0.8 $\pm$ 0.87	0.8 $\pm$ 0.7
Difference, (95% CI)	-	-0.3 (-0.4, -0.2)	-0.4 (-0.5, -0.3)

Source: FDA Biostatistics Review for NDA 211675

Tipping point analyses were conducted to evaluate the robustness of the results for the change from baseline in HAQ-DI comparing UPA 15 mg and 30 mg with MTX and were found to support the observed results (data not shown).

### ACR20/ACR50/ACR70

Analysis of the ACR responses demonstrated a statistically significant increase in the improvement of signs and symptoms of subjects in the UPA groups compared to the MTX group (Table 54). Upadacitinib 30 mg-treated subjects achieved greater responses in ACR20, ACR50 and ACR70 response compared to subjects in the UPA 15 mg group.

**Table 54. Study M15-555: Change in ACR20/ACR50/ACR70 from Baseline at Week 14**

	<b>MTX (N=216) n (%)</b>	<b>UPA 15 mg (N=217) n (%)</b>	<b>UPA 30 mg (N=215) n (%)</b>	<b>UPA 15 mg vs MTX Difference (%), (95% CI)</b>	<b>UPA 30 mg vs. MTX Difference (%), (95% CI)</b>
<b>ACR20</b>	89 (41)	147 (68)	153 (71)	27 (18, 36)	30 (21, 39)
<b>ACR50</b>	33 (15)	91 (42)	112 (52)	27 (19, 35)	37 (29, 45)
<b>ACR70</b>	6 (3)	49 (23)	71 (33)	20 (14, 26)	30 (24, 37)

Source: FDA Biostatistics Review for NDA 211675

These data support the results of the primary endpoint and demonstrate a clinically meaningful effect of UPA compared to PBO in subjects with moderately to severely active RA.

#### **DAS28-CRP**

A significantly greater mean change from baseline in DAS28-CRP at Week 14 was observed in the UPA treatment arms compared to MTX (Table 55). These data support the results of the primary endpoint demonstrating a clinical benefit of UPA treatment in subjects with RA. While there was a small dose-dependent increase in the DAS28-CRP response between the UPA 15 mg and UPA 30 mg dosing groups, the effect is not likely to be clinically significant.

**Table 55. Study M15-555: Change in DAS28-CRP from Baseline to Week 14**

<b>DAS28-CRP Score</b>	<b>MTX</b>	<b>UPA 15 mg QD</b>	<b>UPA 30 mg QD</b>
	<b>N=216</b>	<b>N=216</b>	<b>N=215</b>
Baseline (Mean ± SD)	5.6 ± 1	5.6 ± 0.9	5.6 ± 1.1
	<b>N=194</b>	<b>N=195</b>	<b>N=198</b>
Week 14 (Mean ± SD)	4.4 ± 1.4	3.3 ± 1.4	3 ± 1.3
Difference, (95% CI)	-	-1.1 (-1.3, -0.9)	-1.4 (-1.7, -1.2)

Source: FDA Biostatistics Review for NDA 211675

#### **DAS28-CRP <2.6**

DAS28-CRP responses <2.6 represent very low disease activity. In Study M15-555, a higher proportion of subjects treated with UPA 15 mg and 30 mg achieved DAS28-CRP responses compared to MTX-treated subjects 28% and 40% versus 8%, respectively. These results demonstrate a clinically meaningful benefit of UPA in decreasing disease activity in subjects with

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active RA. Approximately 12% more subjects treated with UPA 30 mg achieved a DAS28 score <2.6 compared to UPA 15 mg-treated subjects, which is likely a clinically meaningful effect of the higher UPA dose using this measure of disease activity.

### SF-36

In study M15-555, the mean adjusted changes from baseline in the SF-36 PCS and MCS scores at Week 14 were significantly higher in subjects treated with UPA 15 mg and UPA 30 mg compared to MTX-treated subjects (Table 56). These results suggest a modest improvement in the SF-36 PCS and MCS scores with UPA 15 mg and 30 mg. The reader is directed to Dr. Koh’s review for a detailed analysis of the individual SF-36 components.

**Table 56. Study M15-555: Change in SF-36 PCS and MCS Scores from Baseline to Week 14**

<b>SF-36 PCS Score</b>	<b>MTX</b>	<b>UPA 15 mg QD</b>	<b>UPA 30 mg QD</b>
	<b>N=216</b>	<b>N=217</b>	<b>N=214</b>
Baseline (Mean ± SD)	33 ± 7	33 ± 8	34 ± 8
	<b>N=195</b>	<b>N=200</b>	<b>N=202</b>
Week 14 (Mean ± SD)	37 ± 8	41 ± 9	44 ± 9
Difference, (95% CI)	-	4 (3, 5)	6 (4, 7)
<b>SF-36 MCS Score</b>			
	<b>N=216</b>	<b>N=217</b>	<b>N=214</b>
Baseline (Mean ± SD)	45 ± 11	44 ± 11	45 ± 12
	<b>N=195</b>	<b>N=200</b>	<b>N=202</b>
Week 14 (Mean ± SD)	48 ± 11	49 ± 10	50 ± 11
Difference, (95% CI)	-	3 (1, 4)	3 (1, 4)

Source: FDA Biostatistics Review for NDA 211675

### Morning Stiffness

As shown in Table 57, the mean change from baseline in duration of morning stiffness at Week 14 in subjects treated with UPA 15 mg or 30 mg decreased significantly compared to subjects treated with MTX. These results demonstrate a clinically meaningful benefit of UPA in decreasing disease activity in subjects with active RA. There was a dose-dependent decrease in the average duration of morning stiffness between the UPA 30 mg and UPA 15 mg groups.

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**Table 57. Study M15-555: Change in Duration of Morning Stiffness from Baseline to Week 14**

Duration of Morning Stiffness (minutes)	MTX	UPA 15 mg QD	UPA 30 mg QD
	<b>N=215</b>	<b>N=217</b>	<b>N=214</b>
Baseline (Mean ± SD)	153 ± 222	144 ± 215	134 ± 153
	<b>N=196</b>	<b>N=199</b>	<b>N=202</b>
Week 14 (Mean ± SD)	102 ± 190	56 ± 111	43 ± 81
Difference, (95% CI)	-	-42 (-67, -17)	-49 (-74, -24)

Source: FDA Biostatistics Review for NDA 211675

Reviewer’s Comments:

Study M15-555 was a well-conducted study with balanced subject cohorts, limited subject dropouts, and minimal protocol violations that allowed for reliable interpretation of the study results. The efficacy analysis of the primary endpoint clearly demonstrates a clinically meaningful treatment effect of UPA 15 and 30 mg monotherapy compared to MTX monotherapy for improvement of the signs and symptoms of subjects with moderately to severely active RA who had an inadequate response to prior MTX therapy. The primary endpoint is fully supported by the results of the secondary endpoints.

Similar to the results observed in Study M13-542, the results of this study demonstrate a clinically meaningful benefit from treatment with UPA 15 and 30 mg but overall do not support a dose-dependent increase of clinical efficacy with the higher dose of UPA in this patient population. Consequently, the overall benefit-risk assessment for UPA 30 mg will need to be determined in the context of the overall safety evaluation.

## 6.5. Study M13-545

### 6.5.1. Study Design

#### Overview and Objective

*“A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) Once Daily Monotherapy to Methotrexate (MTX) Monotherapy in MTX-Naïve Subjects with Moderately to Severely Active Rheumatoid Arthritis”*

The primary objective of Study M13-545 was to assess the safety and efficacy of UPA 7.5 mg (Japan only), UPA 15 mg and UPA 30 mg versus MTX monotherapy in MTX-naïve subjects with moderately to severely active RA. The UPA 7.5 mg treatment arm was only conducted in Japan

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and will not be included in this efficacy analyses.

### **Trial Design**

Study M13-545 was a phase 3 multicenter study conducted in two periods:

- Period 1 was a 48-week, randomized, double-blind, parallel-group, active comparator-controlled study designed to compare the safety and efficacy of orally administered UPA 15 mg QD and 30 mg QD versus MTX monotherapy for the treatment of signs and symptoms and prevention of structural progression of subjects with moderately to severely active RA.
- Period 2 was a blinded long-term extension period (192-weeks) to evaluate the long-term safety, tolerability, and efficacy of UPA 15 mg QD and 30 mg QD in subjects with RA who had completed Period 1.

The study was designed to enroll approximately 975 subjects and actually enrolled 1002 subjects at 236 study sites in 43 countries (Argentina, Australia, Belarus, Belgium, Bosnia, Brazil, Bulgaria, Canada, Chile, China, Colombia, Croatia, Czech Republic, Estonia, Germany, Guatemala, Hong Kong, Hungary, Ireland, Israel, Italy, Japan, Kazakhstan, Latvia, Lithuania, Mexico, New Zealand, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Slovakia, Slovenia, South Africa, Spain, Switzerland, Taiwan, Tunisia, Turkey, Ukraine, United Kingdom, United States). Subjects meeting eligibility criteria were randomized in a 1:1:1 ratio to one of three treatment groups for Groups 2, 3 and 4:

- Group 1: UPA 7.5 mg PO QD (N=75; Japan only)
- Group 2: UPA 15 mg PO QD (Period 1) → UPA 15 mg PO QD (Period 2)
- Group 3: UPA 30 mg PO QD (Period 1) → UPA 30 mg PO QD (Period 2)
- Group 4: MTX (Period 1) → MTX PO QD (Period 2)

Subjects who were assigned to UPA 15 mg or 30 mg were to start on their respective UPA dose at baseline. Subjects who were assigned to the MTX treatment group were to start oral MTX treatment at 10 mg/week and were to be titrated up to 20 mg/week (increase by 5 mg every 4 weeks), as tolerated, by Week 8 (minimum 15 mg/week final dose required, with documentation of intolerance of >15 mg/week). After completion of MTX (or PBO) titration, a single dose reduction of study drug (by 5 mg) was allowed for safety reasons, up to Week 26, as long as the subject remained on ≥15 mg/week of MTX (or matching PBO) weekly. All subjects received oral folic acid (or equivalent) throughout study participation.

Rescue therapy was defined for Weeks 12 through 24, Week 26, and Weeks 36 through 40. Starting at the Week 48 Visit and thereafter, initiation of or change in background RA medications,

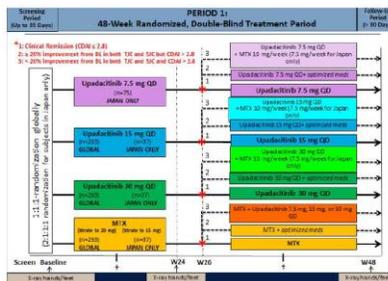
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including corticosteroids, NSAIDs, acetaminophen/paracetamol, and csDMARDs was allowed as per local label.

An unblinded analysis was conducted after all subjects had completed Week 24 for the purpose of regulatory submission. To maintain integrity of the trial and avoid introduction of bias, study sites and subjects were to remain blinded for the duration of Period 1. Additional unblinded analyses may be conducted after the first unblinded analysis for regulatory purposes.

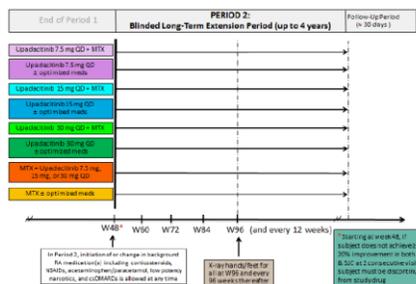
Subjects who completed the Week 48 visit were eligible to enter the long-term extension, Period 2. Subjects continued study treatment per assignment at the end of Period 1 in a blinded fashion. When the last subject completes the last visit of Period 1, study drug assignment in both periods may be unblinded and subjects will then be dispensed study drug in an open-label fashion until the completion of Period 2. All subjects will continue study treatment to which they were assigned at the time of study unblinding. Figure 10 and Figure 11 illustrate the general schema of Study M13-545.

**Figure 10. Study M13-545: Period 1 Overview**



Adapted from Applicant's M13-545 Study Report Figure 1.

**Figure 11. Study M13-545: Period 2 Overview**



Adapted from Applicant's M13-545 Study Report Figure 2.

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### Major inclusion criteria:

- Male and female subjects  $\geq 18$  years-of-age
- Diagnosis of RA based on the 2010 ACR/EULAR criteria for a duration for  $\geq 3$  months
- $\geq 6$  swollen joints (based on 66 joint counts)
- $\geq 6$  tender joints (based on 68 joint counts)
- hsCRP  $\geq 5$  mg/L
- $\geq 1$  bone erosion on x-ray OR RF (+) and anti-CCP (+)
- Have been naïve to MTX therapy

### Major exclusion criteria:

- Prior exposure to any JAK inhibitor
- Prior exposure to any bDMARD
- History of an inflammatory joint disease other than RA
- Laboratory values meeting the following criteria
  - AST or ALT  $> 2$  x ULN
  - eGFR  $< 40$  mL/min/1.73m<sup>2</sup>
  - WBC  $< 2,500/\mu\text{L}$
  - ANC  $< 1500/\mu\text{L}$
  - PLT  $< 100,000/\mu\text{L}$
  - ALC  $< 800/\mu\text{L}$
  - Hg  $< 10$  g/dL

The dose selection for UPA 15 mg and 30 mg once-daily oral tablets was based on extrapolation of preclinical efficacy models and analyses of PK, pharmacodynamic, safety, and efficacy data from the phase 1 studies in healthy volunteers and phase 2 studies in RA subjects. The doses selected for this study were expected to be efficacious with an acceptable safety profile.

## Study Endpoints

The proportion of subjects achieving an ACR50 at Week 12 was used as the primary endpoint for improvement in signs and symptoms. The ACR response criteria consists of 7 components:

- Swollen joint count (66 joints)
- Tender joint count (68 joints)
- Subject global assessment of pain (VAS 100mm)
- Subject global assessment of disease activity (VAS 100mm)
- Physician global assessment of disease activity (VAS 100mm)
- Subject assessment of physical function using HAQ
- CRP

The ACR50 definition of response specifies a 50% improvement over baseline in swollen and tender joints and in 3 out of 5 of the remaining core data set measures. For the primary endpoint, assessment of the ACR50 occurred at Week 12. The choice of the primary endpoint is

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appropriate to assess a clinically meaningful benefit of UPA compared to MTX in MTX-naïve subjects as the expected treatment effect of the active comparator is likely to be large and differences in clinical benefit are more likely to be observed at the larger ACR percentage of improvement. Use of the ACR50 is consistent with Agency guidelines.

Key secondary endpoints were selected to capture clinically meaningful endpoints used to support the findings of the primary endpoint and were ranked as change from baseline in DAS28-CRP at Week 12, change from baseline in HAQ-DI at Week 12, change from baseline in mTSS score as Week 26, change from low disease activity as measured by DAS28-CRP at Week 12, change from baseline in Short Form-36 (SF-36) physical components summary (PCS) at Week 12, and. Other clinically important secondary endpoints included change from baseline to Week 12 in morning stiffness and FACIT-F. Further discussion of the secondary endpoints can be found in Section 7.1.2. Analysis of other key secondary endpoints can be found in Dr. Koh's review.

## **Statistical Analysis Plan**

### Primary Endpoint:

For ACR20 and ACR50 at Week 12, and clinical response based on DAS28 at Week 24, point estimate and 95% CI of the response rate for each randomized treatment group was provided. Comparisons of the primary endpoint were made between each UPA dose group and the MTX group using the Cochran-Mantel-Haenszel test adjusting for geographic region. Point estimate, 95% CI and p-value for the treatment comparison were presented. Both nominal p-values constructed using the Cochran-Mantel-Haenszel test and adjusted p-value through the graphical multiplicity procedure were provided. For the primary analysis, non-responder imputation was used. Subjects who meet the joint count rescue criteria at Week 16 or 20 were treated as non-responders at Week 24 for the primary analysis.

For mean change from baseline in mTSS at Week 24, both linear extrapolation and as observed as observed analyses were conducted. Linear extrapolation results were used for the purpose of multiplicity control. To analyze the mean change from baseline in mTSS at Week 24, the point estimate and 95% CI were reported for each randomized treatment group. Between-group comparisons for each UPA treatment group and the MTX group were performed using ANCOVA model with treatment and geographic region as the fixed factors and the corresponding baseline value as the covariate. Both nominal p-value and adjusted p-value through the graphical multiplicity procedure were provided.

The analysis of ACR20 and ACR50 at Week 12 was to be repeated using Observed Cases and the analysis of CR at Week 24 was repeated using As Observed as a sensitivity analysis without any imputation. These analyses were conducted on the FAS based on randomized treatment groups. Supportive NRI analysis for ACR20, ACR50 and CR and supportive linear extrapolation and as observed analysis for change from baseline in mTSS were also conducted on the Per Protocol

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Analysis Set. Primary efficacy analyses (except mTSS) were also performed in demographic subgroups including age, sex, weight, body mass index, race, and geographical region to assess the consistency of the treatment effect. Additional subgroup analyses based on baseline disease characteristics were also conducted.

### Secondary Endpoints:

For Week 12 binary endpoints, similar NRI and OC analyses as for the primary endpoint of ACR20 and ACR50 at Week 12 were conducted. For non-mTSS Week 24 binary endpoints, similar NRI and as observed analyses as for the primary endpoint of CR at Week 24 were conducted. For the analysis of the proportion of subjects with no radiographic progression at Week 24, both linear extrapolation and AO analyses were conducted. Linear extrapolation results were used for the purpose of multiplicity control. Point estimate and 95% CI of the response rate for each randomized treatment group were provided. Comparisons were made between each UPA dose group and the MTX group using the Cochran-Mantel-Haenszel test adjusting for geographic region. Point estimate, 95% CI and p-value for the treatment comparison were presented.

For all continuous key secondary endpoints other than mTSS, statistical inference was conducted using analysis of covariance (ANCOVA) coupled with MI for missing data handling. Specifically, the ANCOVA model included treatment and geographic region as the fixed factors and the corresponding baseline value as the covariates. The LS mean, and 95% CI were reported for each randomized treatment group; the LS mean treatment difference and associated 95% CI and p-value were reported comparing each UPA dose group with the MTX group. For subjects who met the rescue criteria at Week 16 or 20, data after rescue was overwritten by last observation carried forward. Both nominal p-value and adjusted p-value through the graphical multiplicity procedure were provided for primary and ranked key secondary endpoints. For other secondary endpoints, only nominal p-values were provided.

For continuous variables, statistical inference at each visit was conducted using analysis of covariance (ANCOVA) with treatment and geographic region as the fixed factors and the corresponding baseline value as the covariate. Only nominal p-values were provided. For subjects who met the rescue criteria defined by not achieving 20% improvement in TJC/SJC (for Week 12 through Week 24) in two consecutive visits, or subjects who met the rescue switching criteria at Week 26 defined by not reaching CDAI CR and not achieving 20% improvement in TJC/SJC), data after rescue was overwritten by LOCF for the primary analysis.

### **Protocol Amendments**

The current protocol had five major amendments, six country-specific amendment and two global administrative changes. The majority of changes to the protocol were responses to regulatory feedback, clarifications and editorial changes. Country-specific protocol amendments did not affect interpretation of the results of the study. Major amendments as they relate to the US studies are as follows:

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- Amendment 1 (15 January 2016, 2 subjects) added frequency of MTX administration. Updated text to reflect the change in study duration, to change the study design to include a 48-week randomized, double-blind treatment period (Period 1), and to add a long-term extension (Period 2). Described how the blind will be maintained. Added language regarding study drug dose reduction and the initiation of or change in background RA medication. Added the following exclusion criteria: females who are considering becoming pregnant during the study or for approximately 180 days after the last dose of study drug; male subject who is considering fathering a child or donating sperm during the study or for approximately 180 days after the last dose of study drug; subjects with a history of gastrointestinal perforation or a history of associated gastrointestinal diseases; subjects with conditions that could interfere with drug absorption; subjects who have been the recipient of an organ transplant; subjects who had clinically relevant or significant ECG abnormalities. Clarified permitted RA therapies during Period 1. Added permitted RA therapies during Period 2. Added criteria for rescue therapy at Week 26. Clarified informed consent details. Clarified TB testing procedures during Periods 1 and 2. Added efficacy assessments for the long-term extension, Period 2. Added text to reflect current discontinuation procedures. Clarified that subjects will receive both two capsules once weekly (MTX or matching PBO) and one tablet QD (UPA or matching PBO) to maintain the double blind. Added language regarding blinding and the Week 24 interim analysis. Clarified that administration of both daily and weekly study drug must be stopped if study drug treatment is interrupted or withdrawn in Periods 1 or 2. Updated rules regarding study drug interruption for Period 1 to reflect the change in study duration and added for the long-term extension, Period 2. Updated the AST or ALT specific toxicity management guidelines.
- Amendment 2 (29 February 2016, 126 subjects) updated text to provide clarification for discontinuation criteria. Updated Inclusion Criterion 9 text to clarify pregnancy testing and women of childbearing potential. Updated text to clarify RA optimization therapies. Added criteria for adjusting or adding background medication at Week 26 if subjects do not achieve low disease activity as defined by CDAI or do not achieve >20% improvement from baseline in both tender joint count and swollen joint count. Updated text to clarify Independent Joint Assessor. Updated text to clarify TB assessment and testing. Added text that all subjects to have ECG performed at screening and every 48 weeks.

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- Amendment 3 (31 May 2016, 199 subjects) added criteria for rescue therapy between Weeks 12 and 24 and between Weeks 36 and 40 if subjects do not achieve  $\geq 20\%$  improvement from baseline in both tender and swollen joint counts. Updated text to clarify exceptions for rescue therapy. Added text to follow MTX local label for concomitant treatment contraindications.
- Amendment 4 (18 August 2016, 534) updated Inclusion Criterion 2 text to select subject population based on duration of symptoms consistent with RA. Updated text to clarify when to administer live vaccines and to provide examples of inactivated vaccines. Added text to describe the addition of MTX for Week 26 rescue therapy. Added requirement to perform pregnancy testing if follicle-stimulating hormone results are consistent with premenopausal status. Updated text to account for local contraception requirements. Added text to clarify different primary efficacy variable for different regulatory purposes. Updated time points for key secondary variables to allow for rescue therapy at Week 12.
- Amendment 5 (26 December 2017, 0 subjects) clarified who will remain blinded during Period 1 and that additional unblinded analyses may be conducted after the first unblinded analysis for regulatory purposes. Clarified that study drug dose changes are not permitted during unblinded Period 2. Clarified 30-day follow-up visit when subject withdraws consent during Period 1 and Period 2. Clarified use of grapefruit and updated the list of examples of commonly used strong cytochrome (CYP)3A inhibitors and inducers. Clarified that live vaccines must not be administered at least 30 days after last dose of study drug. Added clarification on requirements for contraception for females if childbearing potential status changes during the course of the study. Updated to clarify TB testing requirements during the study. Revised to prevent unnecessary initiation of TB prophylaxis in subjects with indeterminate QuantiFERON-TB test results by allowing local testing. Updated text for primary variables, ranked key secondary endpoints, other key secondary endpoints, additional endpoints, Period 2 variables to be aligned with the statistical analysis plan. Clarified that study drug dose changes are not permitted during unblinded Period 2. Updated Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting text per sponsor guideline. Clarified that subject should discontinue study drug for an ECG abnormality that is considered clinically significant with reasonable possibility that the event is related to study drug. Clarified all abnormal lab tests that are considered clinically significant by the investigator should be followed to a satisfactory resolution. Clarified toxicity management for ALT, AST, and INR. Added wording for management of subjects with hepatitis B core (HBcAb) Ab+ and

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negative HBV DNA at screening and laboratory values during study which may indicate active hepatitis. Clarified procedures for elevated creatine phosphokinase value but without any clinical signs and symptoms to allow continuation of treatment.

Reviewer's Comments:

The current study was well-designed, randomized, double-blinded, active-controlled (MTX monotherapy) and evaluated two doses of UPA in MTX-naïve subjects with moderately to severely active RA. The enrolled subjects represented newly diagnosed subjects, or those who were not yet treated with the accepted first-line therapy MTX. The inclusion and exclusion criteria were acceptable and were consistent with RA subjects with moderately to severely active RA. The choice of control group was appropriate for the objectives of the study and the choice of MTX was appropriate as the first-line standard of care DMARD used in the USA.

The Applicant's choice to use the proportion of subjects achieving an ACR20 at Week 12 as the primary endpoint and the change from baseline in mTSS score, HAQ-DI and DAS28 at Week 12 as major secondary endpoints, are adequate to assess clinically meaningful outcomes and have been validated and used in previous approvals of other drugs indicated for patients with moderate to severe RA and are recommended in the Agency's RA guidance document.

### 6.5.2. Study Results

#### **Compliance with Good Clinical Practices**

The Applicant has provided attestation that the study was conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of the clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice.

#### **Financial Disclosure**

A financial disclosure review was conducted for all five phase 3 studies. Because many investigators participated in more than one study, a combined review of the financial disclosures will be presented. Table 58 shows the total number of investigators identified in each of the phase 3 studies that were evaluated for financial disclosure based on the investigator information.

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**Table 58. All Five Phase 3 Studies: Total Number of Investigators in Registrational Studies**

<b>Study</b>	<b>Total Number of Investigators</b>	<b>Number of Principle Investigators</b>	<b>Number of Sub-investigators</b>
M13-542	674	153	521
M13-545	1205	236	969
M13-549	721	150	571
M14-465	1383	285	1098
M15-555	667	138	529

Adapted from Applicant's Financial Summary Table 1.

A total of 41 investigators had disclosable financial interests/arrangements. Each investigator's financial disclosure documentation was reviewed. For these investigators with disclosable financial interests/arrangements: none received compensation for conducting the study where the value could be influenced by the outcome of the study; no investigators received significant payments of other sorts; no investigators had proprietary interest in the product being tested held by the investigator; no investigator had significant equity interest in the Sponsor covered study.

These financial disclosures do not raise concerns regarding the integrity of the phase 3 studies as the Applicant took steps to minimize potential bias of clinical investigators with financial interests and arrangements by using proper study design and operations. The clinical studies were blinded to the study site personnel and the participating subjects through the primary endpoint collection for the studies. Each active dose of investigational drug product was identical in appearance to its matched PBO and each subject was randomly assigned to their treatment arm independent of the investigator and the study site. Additionally, the number of subjects enrolled at the individual investigator sites were small compared to the total number of subjects enrolled in the overall study.

### **Patient Disposition**

A total of 947 subjects were randomized and 945 subjects received study drug. One subject who failed screening was randomized in error and did not receive study drug. A total of 840 (89%) subjects completed study drug through Week 24 (Table 59).

**Table 59. Study M13-545: Subject Disposition (All Randomized Subjects)**

	<b>MTX (n=315)</b>	<b>UPA 15 mg (n=317)</b>	<b>UPA 30 mg (n=315)</b>
<b>Randomized but not dosed</b>	1 (<1)	0	1 (<1)
<b>Completed Week 24, n (%)</b>	268 (85)	290 (92)	282 (90)
<b>Discontinued study drug through Week 24, n (%)</b>	46 (15)	27 (9)	31 (10)
<b>AE</b>	13 (4)	13 (4)	12 (4)
<b>Withdrawal by subject</b>	15 (5)	8 (3)	11 (4)
<b>Lost to follow-up</b>	3 (1)	4 (1)	2 (1)
<b>Lack of efficacy</b>	10 (3)	0	3 (1)
<b>Other</b>	5 (2)	2 (1)	3 (1)

Adapted from Applicant's M13-545 Study Report Table 3.

Through the first 24-weeks of the study, a higher proportion of MTX-treated subjects discontinued the study compared to subjects in the UPA 15 mg and 30 mg groups, who discontinued study drug at comparable rates. The most commonly reported reasons for MTX-subjects discontinuing study drug was due to withdrawal of consent, AEs and lack of efficacy. Subjects treated with UPA 15 mg or 30 mg discontinued study drug at similar percentages regarding AEs and withdrawal of consent. The overall numbers of AEs leading to discontinuation was similar between the three treatment arms.

### **Protocol Violations/Deviations**

The most common reason for protocol deviations was related to not meeting inclusion/exclusion criteria. Specifically, 10/947 (1%) subjects did not meet the inclusion criteria that they have  $\geq 6$  swollen and tender joints. The overall percentage of all other inclusion or exclusion criteria violation was <1%. Overall, the total number of subjects with protocol violations at the time of the primary endpoint assessment was small and relatively balanced between treatment arms. These protocol deviations were not considered to have affected the overall assessment of study results.

### **Table of Demographic Characteristics**

As shown in Table 60, subjects' baseline demographics were similar between treatment arms. The average subject enrolled in the study was female, White, 55-years of age and clinically overweight, which is consistent with the US patient population.

**Table 60. Study M13-545: Subjects Baseline Demographics**

Demographic Parameters	MTX (N=314)	UPA 15 mg QD (N=317)	UPA 30 mg QD (N=314)
<b>Sex, n (%)</b>			
Male	74 (24)	76 (24)	74 (24)
Female	240 (76)	241 (76)	240 (76)
<b>Age, n (%)</b>			
Mean ± SD	53 ± 13	52 ± 13	55 ± 13
Median (min, max)	55 (21, 82)	53 (22, 83)	56 (18, 85)
<b>Age (years), n (%)</b>			
< 40 years	50 (16)	60 (19)	34 (11)
40-64	206 (66)	204 (64)	212 (68)
≥ 65 years	58 (19)	53 (17)	68 (22)
<b>Race, n (%)</b>			
White	256 (82)	256 (81)	254 (81)
Black or African American	12 (4)	8 (3)	13 (4)
Asian	37 (12)	35 (11)	34 (11)
American Indian or Alaska Native	2 (1)	8 (3)	7 (2)
Native Hawaiian or other Pacific Islander	2 (1)	3 (1)	1 (<1)
Multiple	5 (2)	7 (2)	5 (2)
<b>Ethnicity</b>			
Hispanic or Latino	102 (33)	107 (34)	107 (34)
Not Hispanic or Latino	212 (68)	210 (66)	207 (66)
<b>BMI (kg/m<sup>2</sup>)</b>			
Mean ± SD	28 ± 6	28 ± 6	28 ± 7
Median (min, max)	27 (16, 54)	27 (17, 52)	27 (13, 72)

Adapted from Applicant's Study M13-545 study report Table 4.

Overall, the subjects enrolled in the study demonstrated moderately to severely active disease as evidenced by the average DAS28 score, swollen and tender joint counts, HAQ-DI and duration of morning stiffness. Subjects' baseline disease characteristics and background RA-related therapy were similar between individual treatment arms (Table 61).

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**Table 61. Study M13-545: Subjects Baseline Disease Characteristics**

Demographic Parameters	MTX (N=314)	UPA 15 mg QD (N=317)	UPA 30 mg QD (N=314)
<b>Duration of RA (years)</b>			
Mean ± SD	3 ± 5	3 ± 5	3 ± 6
Median (min, max)	0.5 (<1, 38)	0.5 (<1, 37)	0.6 (<1, 44)
<b>RF and anti-CCP, n (%)</b>			
Positive (RF + anti-CCP)	213 (68)	230 (73)	212 (68)
At least one negative	101 (32)	87 (27)	101 (32)
<b>DAS28 (CRP)</b>			
n	314	317	311
Mean ± SD	5.9 ± 1	5.9 ± 1	5.8 ± 1
Median (min, max)	5.8 (3, 8)	5.9 (3, 8)	5.7 (3, 8)
<b>Swollen Joint Count-66</b>			
Mean ± SD	17 ± 11	17 ± 10	16 ± 10
Median (min, max)	14 (5, 60)	14 (6, 58)	13 (0, 59)
<b>Tender Joint Count-68</b>			
Mean ± SD	26 ± 16	25 ± 14	25 ± 15
Median (min, max)	22 (3, 68)	22 (4, 68)	21 (2, 68)
<b>HAQ-DI</b>			
n	314	317	311
Mean ± SD	1.6 ± 0.7	1.6 ± 0.7	1.5 ± 0.7
Median (min, max)	1.6 (0, 3)	1.6 (0, 3)	1.5 (0, 3)
<b>CRP (mg/L)</b>			
Mean ± SD	21 ± 22	23 ± 27	19 ± 23
Median (min, max)	14 (0, 149)	14 (0, 207)	10 (0, 159)
<b>Morning Stiffness duration (minutes)</b>			
Mean ± SD	129 ± 134	169 ± 227	136 ± 166
Median (min, max)	90 (0, 1440)	120 (0, 1440)	90 (0, 1440)
<b>Oral corticosteroid dose (mg)</b>			
n	162	146	137
Mean ± SD	6 ± 2	6 ± 3	7 ± 3
Median (min, max)	5 (1, 12.5)	5 (1, 30)	5 (1, 20)

Adapted from Applicant's Study M13-545 study report Table 5.

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Through Week 24, mean treatment compliance was 98%, 98%, and 99% for UPA 15 mg, UPA 30 mg and MTX, respectively; and 99%, 98%, and 100% for matching PBO in the UPA 15 mg, UPA 30 mg, and MTX groups, respectively.

As shown in Table 61, between 43% and 52% of subjects were treated with oral corticosteroids with an average dose of approximately 6 mg of prednisone (or equivalent).

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### Efficacy Results – Primary Endpoint

As shown in Table 62, the primary endpoint analysis demonstrated a statistically significant difference between MTX and the individual UPA treatment arms. The average treatment effect size for the UPA 15 mg and UPA 30 mg treatment arms were 24% and 28%, respectively. There was a small dose-dependent increase in the proportion of UPA 30 mg-treated subjects achieving an ACR50 but the clinical meaningfulness of the numeric difference in ACR50 response is uncertain.

**Table 62. Study M13-545: Proportion of Subjects Achieving ACR50 at Week 12**

	<b>MTX (N=314) n (%)</b>	<b>UPA 15 mg QD (N=317) n (%)</b>	<b>UPA 30 mg QD (N=314) n (%)</b>
ACR50	89 (28%)	165 (52%)	177 (56%)
Difference (%), (95% CI)	-	24 (16, 31)	28 (21, 35)
Source: FDA Biostatistics Review for NDA 211675.			

This analysis demonstrates a clinically meaningful benefit with UPA treatment for the improvement of the signs and symptoms of MTX-naïve subjects with active RA compared to MTX monotherapy. Additionally, UPA-treated subjects demonstrated greater improvements in all ACR components compared to PBO-treated subjects at Week 12 demonstrating that the results were not driven by any single component of the ACR response criteria (Table 63).

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**Table 63. Study M13-545: Change from Baseline in ACR Components (excluding HAQ-DI) at Week 12**

Treatment Arm	N	Baseline Mean (SD)	n	Visit Mean (SD)	Est Diff (95 % CI)	p-value
<b>CRP</b>						
MTX	314	21.2 (22.1)	292	10.9 (14.9)		
UPA 15 mg QD	317	23.0 (27.4)	302	4.2 (8.8)	-6.2 (-8.3, -4.2)	<0.001
UPA 30 mg QD	314	19.4 (22.6)	298	5.0 (15.6)	-5.0 (-7.0, -2.9)	<0.001
<b>SJC (Out of 28)</b>						
MTX	314	11.8 (6.0)	291	4.5 (5.3)		
UPA 15 mg QD	317	11.8 (5.8)	303	3.4 (4.3)	-1.0 (-1.7, -0.4)	0.001
UPA 30 mg QD	314	11.4 (5.7)	301	2.8 (3.8)	-1.4 (-2.1, -0.8)	<0.001
<b>SJC (Out of 66)</b>						
MTX	314	16.9 (10.6)	291	6.4 (8.3)		
UPA 15 mg QD	317	16.9 (10.3)	303	4.5 (6.6)	-1.7 (-2.6, -0.8)	<0.001
UPA 30 mg QD	314	15.7 (9.7)	301	3.9 (5.5)	-2.0 (-2.9, -1.1)	<0.001
<b>TJC (Out of 28)</b>						
MTX	314	15.3 (7.2)	291	7.1 (7.3)		
UPA 15 mg QD	317	15.0 (6.9)	303	5.1 (6.1)	-1.9 (-2.8, -1.0)	<0.001
UPA 30 mg QD	314	14.8 (7.2)	301	4.4 (5.4)	-2.5 (-3.3, -1.6)	<0.001
<b>TJC (Out of 68)</b>						
MTX	314	26.4 (16.1)	291	12.8 (14.6)		
UPA 15 mg QD	317	25.4 (14.4)	303	8.6 (11.6)	-3.8 (-5.3, -2.2)	<0.001
UPA 30 mg QD	314	25.2 (15.0)	301	7.6 (10.0)	-4.5 (-6.0, -2.9)	<0.001
<b>Physician Global</b>						
MTX	216	62.1 (17.5)	193	36.9 (24.1)		
UPA 15 mg QD	216	65.7 (18.5)	193	25.3 (20.4)	-12.8 (-17.1, -8.6)	<0.001
UPA 30 mg QD	215	62.6 (17.8)	192	21.9 (19.5)	-14.8 (-19.1, -10.5)	<0.001
<b>Patient Global</b>						
MTX	314	1.6 (0.7)	289	1.1 (0.7)		
UPA 15 mg QD	317	1.6 (0.7)	303	0.8 (0.7)	-0.3 (-0.4, -0.2)	<0.001
UPA 30 mg QD	311	1.5 (0.7)	301	0.7 (0.7)	-0.3 (-0.4, -0.2)	<0.001
<b>Patient Pain</b>						
MTX	314	65.8 (21.5)	289	41.6 (25.0)		
UPA 15 mg QD	317	66.6 (22.0)	303	31.2 (24.3)	-9.8 (-13.6, -6.1)	<0.001
UPA 30 mg QD	311	64.9 (21.6)	301	28.0 (25.1)	-12.6 (-16.4, -8.8)	<0.001
Source: FDA Biometrics Review for NDA 211675.						

Results from sensitivity analyses on the Per Protocol Analysis set were consistent with the

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primary analysis. Subgroup analysis results using Nonresponder Imputation, were also consistent with the primary analysis.

### **Efficacy Results – Secondary and other relevant endpoints**

#### **HAQ-DI**

Table 64 shows that at Week 12, subjects treated with UPA experienced a statistically significant and clinically meaningful change from baseline ( $\leq -0.3$ ) compared to subjects treated with MTX; however, there was no evidence of a dose-dependent increase in response between the UPA 15 mg and UPA 30 mg dosing groups. These data support the results of the primary endpoint demonstrating a clinical benefit of UPA treatment in subjects with RA.

**Table 64. Study M13-545: Change in HAQ-DI from Baseline to Week 12**

<b>HAQ-DI Score</b>	<b>MTX</b>	<b>UPA 15 mg QD</b>	<b>UPA 30 mg QD</b>
	<b>N=314</b>	<b>N=317</b>	<b>N=311</b>
Baseline (Mean $\pm$ SD)	1.6 $\pm$ 0.7	1.6 $\pm$ 0.7	1.5 $\pm$ 0.7
	<b>N=278</b>	<b>N=302</b>	<b>N=298</b>
Week 12 (Mean $\pm$ SD)	1.1 $\pm$ 0.7	0.8 $\pm$ 0.87	0.7 $\pm$ 0.7
Difference (%), (95% CI)	-	-0.3 (-0.4, -0.2)	-0.3 (-0.4, -0.2)

Source: FDA Biostatistics Review for NDA 211675

Tipping point analyses were conducted to evaluate the robustness of the results for the change from baseline in HAQ-DI comparing UPA 15 mg and 30 mg with MTX and were found to support the observed results (data not shown).

#### **ACR20/ACR50/ACR70**

Analysis of the ACR responses demonstrated a statistically significant increase in the improvement of signs and symptoms of subjects in the UPA groups compared to the MTX group (Table 65). Upadacitinib 30 mg-treated subjects achieved numerically greater responses in ACR20, ACR50 and ACR70 response compared to subjects in the UPA 15 mg group; however, the clinical meaningfulness of the overall increased effect is questionable.

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**Table 65. Study M13-545: Change in ACR20/ACR50/ACR70 from Baseline at Week 12**

	<b>MTX (N=315) n (%)</b>	<b>UPA 15 mg (N=317) n (%)</b>	<b>UPA 30 mg (N=315) n (%)</b>	<b>UPA 15 mg vs MTX Difference (%), (95% CI)</b>	<b>UPA 30 mg vs. MTX Difference (%), (95% CI)</b>
<b>ACR20</b>	170 (54)	240 (76)	242 (77)	22 (14, 29)	23 (16, 30)
<b>ACR50</b>	89 (28)	165 (52)	177 (56)	24 (16, 31)	28 (21, 35)
<b>ACR70</b>	44 (14)	103 (33)	116 (37)	19 (12, 25)	23 (16, 30)

Source: FDA Biostatistics Review for NDA 211675.

These data support the results of the primary endpoint and demonstrate a clinically meaningful effect of UPA compared to PBO in subjects with moderately to severely active RA.

#### **DAS28-CRP**

A significantly greater mean change from baseline in DAS28-CRP at Week 12 was observed in the UPA treatment arms compared to MTX (Table 66). These data support the results of the primary endpoint demonstrating a clinical benefit of UPA treatment in subjects with RA. The treatment effect size as compared to control was similar between the two UPA treatment arms.

**Table 66. Study M13-545: Change in DAS28-CRP from Baseline to Week 12**

<b>DAS28-CRP Score</b>	<b>MTX</b>	<b>UPA 15 mg QD</b>	<b>UPA 30 mg QD</b>
	<b>N=315</b>	<b>N=317</b>	<b>N=311</b>
Baseline (Mean ± SD)	5.9 ± 1	5.9 ± 1	5.8 ± 1
	<b>N=290</b>	<b>N=303</b>	<b>N=297</b>
Week 12 (Mean ± SD)	4.0 ± 1.4	3.2 ± 1.4	3 ± 1.3
Difference (%), (95% CI)	-	-0.9 (-1.1, -0.7)	-1.0 (-1.2, -0.7)

Source: FDA Biostatistics Review for NDA 211675.

#### **DAS28-CRP <2.6**

DAS28-CRP responses <2.6 represent very low disease activity. In Study M13-545, a higher proportion of subjects treated with UPA 15 mg and 30 mg achieved DAS28-CRP responses compared to MTX-treated subjects 36% and 41% versus 13%, respectively. These results demonstrate a clinically meaningful benefit of UPA in decreasing disease activity in subjects with active RA compared to MTX monotherapy. Approximately 5% more subjects treated with UPA 30

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mg achieved a DAS28 score <2.6 compared to UPA 15 mg-treated subjects, demonstrating a dose-dependent effect of uncertain clinical significance.

### SF-36

In study M15-545, the mean adjusted changes from baseline in the SF-36 PCS and MCS scores at Week 12 were significantly higher in subjects treated with UPA 15 mg and UPA 30 mg compared to MTX-treated subjects (Table 67). These results suggest a modest improvement in the SF-36 PCS and MCS scores with UPA 15 mg and 30 mg. The reader is directed to Dr. Koh's review for a detailed analysis of the individual SF-36 components.

**Table 67. Study M13-545: Change in SF-36 PCS and MCS Scores from Baseline to Week 12**

<b>SF-36 PCS Score</b>	<b>MTX</b>	<b>UPA 15 mg QD</b>	<b>UPA 30 mg QD</b>
	<b>N=313</b>	<b>N=315</b>	<b>N=312</b>
Baseline (Mean ± SD)	33 ± 8	33 ± 8	34 ± 7
	<b>N=299</b>	<b>N=306</b>	<b>N=306</b>
Week 12 (Mean ± SD)	39 ± 9	43 ± 10	44 ± 9
Difference (%), (95% CI)	-	5 (3, 6)	5 (3, 6)
<b>SF-36 MCS Score</b>			
	<b>N=313</b>	<b>N=315</b>	<b>N=312</b>
Baseline (Mean ± SD)	43 ± 11	43 ± 11	43 ± 12
	<b>N=299</b>	<b>N=306</b>	<b>N=306</b>
Week 12 (Mean ± SD)	47 ± 11	49 ± 10	49 ± 11
Difference (%), (95% CI)	-	2 (1, 4)	2 (1, 4)

Source: FDA Biostatistics Review for NDA 211675.

### Morning Stiffness

As shown in Table 68, the mean change from baseline in duration of morning stiffness at Week 12 in subjects treated with UPA 15 mg or 30 mg decreased significantly compared to subjects treated with MTX. These results demonstrate a clinically meaningful benefit of UPA over MTX monotherapy in decreasing disease activity in subjects with active RA. There was a dose-dependent decrease in the average duration of morning stiffness between the UPA 30 mg and UPA 15 mg groups.

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**Table 68. Study M13-545: Change in Morning Stiffness from Baseline to Week 12**

<b>Morning Stiffness (minutes)</b>	<b>MTX</b>	<b>UPA 15 mg QD</b>	<b>UPA 30 mg QD</b>
	<b>N=314</b>	<b>N=316</b>	<b>N=313</b>
Baseline (Mean ± SD)	128 ± 134	169 ± 228	136 ± 167
	<b>N=291</b>	<b>N=303</b>	<b>N=301</b>
Week 12 (Mean ± SD)	72 ± 144	44 ± 70	34 ± 49
Difference (%), (95% CI)	-	-33 (-48, -18)	-39 (-54, -24)
Source: FDA Biostatistics Review for NDA 211675			

#### **FACIT-F**

The mean change from baseline in FACIT-F at Week 12 in subjects treated with UPA 15 mg and 30 mg was statistically significantly greater compared to subjects treated with MTX in Study M13-545 (Table 69).

**Table 69. Study M13-545: Change in FACIT-F from Baseline to Week 12**

<b>FACIT-F</b>	<b>PBO</b>	<b>ADA 40 mg</b>	<b>UPA 15 mg</b>
	<b>N=314</b>	<b>N=316</b>	<b>N=310</b>
Baseline (Mean ± SD)	27 ± 12	26 ± 12	28 ± 11
	<b>N=300</b>	<b>N=308</b>	<b>N=306</b>
Week 12 (Mean ± SD)	34 ± 11	37 ± 11	37 ± 11
Difference (%), (95% CI)	-	4 (2, 5)	3 (2, 5)
Source: FDA Biostatistics Review for NDA 21167.			

#### **Inhibition of Radiographic Progression**

The ability for UPA treatment to slow progression of radiographic damage was assessed by the Applicant using the change from baseline in mTSS score at Week 24. Independent verification of the data was conducted by Dr. Koh and the data that follows is based on his analyses.

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The distribution of baseline radiograph scores and the proportion of subjects with no observed joint erosions was similar between treatment arms (Table 70).

**Table 70. Study M13-545: Baseline Radiograph Scores and Components**

	<b>MTX (N=314)</b>	<b>UPA 15 MG (N=317)</b>	<b>UPA 30 MG (N=314)</b>	<b>All (N=945)</b>
<b>mtSS</b>	13.3 (30.5)	18.1 (38.2)	17.2 (38.3)	16.2 (35.9)
	0.0 - 260.5	0.0 - 206.5	0.0 - 243.5	0.0 - 260.5
	(n=309)	(n=309)	(n=309)	(n=927)
<b>Erosion Score</b>	6.1 (15.5)	8.6 (19.3)	8.0 (18.9)	7.6 (18.0)
	0.0 - 147.0	0.0 - 123.0	0.0 - 126.5	0.0 - 147.0
	(n=309)	(n=309)	(n=309)	(n=927)
<b>Joint Space Narrowing</b>	7.2 (16.1)	9.6 (20.1)	9.3 (20.3)	8.7 (19.0)
	0.0 - 113.5	0.0 - 103.0	0.0 - 118.0	0.0 - 118.0
	(n=309)	(n=309)	(n=309)	(n=927)
<b>Proportion with mTSS = 0</b>	100 (32%)	108 (34%)	103 (33%)	311 (33%)
Source: FDA Biostatistics Review for NDA 211675.				

As seen in Table 71, 87% of the randomized subjects underwent radiograph evaluation at Week 24 with similar proportions of subjects across study arms.

**Table 71. Study M13-545: Disposition of Patients with mTSS Evaluated during the First 24 Weeks**

	MTX (N=314)	UPA 15 MG QD (N=317)	UPA 30 mg (N=314)	All (N=945)
<b>Baseline</b>				
<b>Patients with evaluable mTSS</b>	309 (98%)	309 (97%)	309 (98%)	927 (98%)
<b>Patients missing mTSS at baseline</b>	5 (2%)	8 (3%)	5 (2%)	18 (2%)
<b>Week 12</b>				
<b>Patients with evaluable mTSS</b>	2 (1%)	2 (1%)	1 (<1%)	5 (1%)
<i>Patients without baseline mTSS</i>	1	1	1	3
On randomized treatment (prior to rescue)	2 (1%)	2 (1%)	1 (<1%)	5 (1%)
Discontinued randomized treatment <sup>a</sup>	-	-	-	-
<b>Week 24</b>				
<b>Patients with evaluable mTSS</b>	268 (85%)	281 (89%)	273 (87%)	822 (87%)
<i>Patients without baseline mTSS</i>	1	1	1	3
On randomized treatment	241 (77%)	265 (84%)	266 (85%)	772 (82%)
On rescued treatment	21 (7%)	14 (4%)	4 (1%)	39 (4%)
Discontinued randomized treatment	6 (2%)	2 (1%)	3 (1%)	11 (1%)
<b>Patients without mTSS</b>	46 (15%)	36 (11%)	41 (13%)	123 (13%)
Discontinued rescue/randomized treatment <sup>b</sup>	3 (1%)	1 (<1%)	5 (2%)	9 (1%)
Discontinued study participation	37 (12%)	24 (8%)	23 (7%)	84 (9%)
Ongoing	-	-	1 (<1%)	1 (<1%)
On either rescue/randomized treatment	6 (2%)	11 (3%)	12 (4%)	29 (3%)

Source: FDA Biostatistics Review for NDA 211675. a. Prior to Week 14; b. subjects were rescued to different study treatment prior to Week 26 but after Week 14.

Results for the mTSS and its components, i.e., erosion and joint space narrowing scores, were statistically significant at Week 24, with similar trends towards benefit for both UPA groups relative to MTX (Table 72). The conclusions of Dr. Koh's results were similar to those based on the Applicant's analysis that included all radiographs collected following discontinuation of randomized treatment (Table 73). Moreover, there was a small numeric benefit of UPA 30 mg compared to UPA 15 mg; however, the clinical relevance is uncertain.

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**Table 72. Study M13-545: Applicant’s Primary Analysis of the Mean Change from Baseline in mTSS and Components at Week 24 using Linear Extrapolation for Patients Rescued**

Treatment Arm	N	Baseline Mean (SD)	n	Mean Change from baseline (SD)	Est Diff (95% CI)	P-value
<b>mTSS</b>						
MTX	309	13.3 (30.5)	264	0.7 (2.8)		
UPA 15 mg QD	309	18.1 (38.2)	279	0.1 (1.4)	-0.53 (-0.8, -0.2)	0.001
UPA 30 mg QD	309	17.2 (38.3)	270	0.1 (1.2)	-0.59 (-0.9, -0.3)	<0.001
<b>Erosion Score</b>						
MTX	309	6.1 (15.5)	264	0.3 (1.5)		
UPA 15 mg QD	309	8.6 (19.3)	279	0.0 (0.5)	-0.29 (-0.4, -0.1)	<0.001
UPA 30 mg QD	309	8.0 (18.9)	270	0.0 (0.3)	-0.34 (-0.5, -0.2)	<0.001
<b>Joint Space Narrowing</b>						
MTX	309	7.2 (16.1)	264	0.3 (1.7)		
UPA 15 mg QD	309	9.6 (20.1)	279	0.1 (0.9)	-0.23 (-0.4, -0.02)	0.03
UPA 30 mg QD	309	9.3 (20.3)	270	0.1 (1.1)	-0.24 (-0.5, -0.03)	0.02
Source: FDA Biostatistics Review for NDA 211675.						

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**Table 73. Study M13-545: Sensitivity Analysis for the Mean Change from Baseline in mTSS and Components at Week 24 Including After Rescue**

Treatment Arm	N	Baseline Mean (SD)	n	Change from Baseline Mean (SD)	Est Difference (95% CI)	P-value
<b>mTSS</b>						
MTX	309	13.3 (30.5)	267	0.6 (2.8)		
UPA 15 mg QD	309	18.1 (38.2)	280	0.1 (1.4)	-0.52 (-0.8, -0.2)	0.001
UPA 30 mg QD	309	17.2 (38.3)	272	0.1 (1.2)	-0.58 (-0.9, -0.3)	<0.001
<b>Erosion Score</b>						
MTX	309	6.1 (15.5)	267	0.3 (1.4)		
UPA 15 mg QD	309	8.6 (19.3)	280	0.0 (0.5)	-0.29 (-0.4, -0.1)	<0.001
UPA 30 mg QD	309	8.0 (18.9)	272	0.0 (0.3)	-0.33 (-0.5, -0.2)	<0.001
<b>JSN</b>						
MTX	309	7.2 (16.1)	267	0.3 (1.7)		
UPA 15 mg QD	309	9.6 (20.1)	280	0.1 (0.9)	-0.23 (-0.4, -0.02)	0.03
UPA 30 mg QD	309	9.3 (20.3)	272	0.1 (1.1)	-0.24 (-0.4, -0.03)	0.03
Source: FDA Biostatistics Review for NDA 211675.						

Table 74 shows the proportions of subjects with no radiographic progression, as measured by an observed change from baseline  $\leq 0$  at Week 24. These results were consistent with the key radiograph results based on the treatment policy estimand, providing additional supportive evidence of the efficacy of both dosing regimens of upadacitinib.

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**Table 74. Study M13-545: Proportion of Subjects with No Change in mTSS Score at Week 24**

Treatment Arm	n	Excluding Data after Rescue (Linear Extrapolation)			n	Using All Data Collected after Rescue		
		Resp (%)	EstCI	Pvalue		Resp (%)	EstCI	Pvalue
<b>mTSS</b>								
MTX	264	205 (78%)			267	208 (78%)		
UPA 15 mg QD	279	244 (87%)	9.8% (3.5%, 16.2%)	0.002	280	245 (88%)	9.6% (3.3%, 15.9%)	0.003
UPA 30 mg QD	270	241 (89%)	11.6% (5.4%, 17.8%)	<0.001	272	243 (89%)	11.4% (5.3%, 17.6%)	<0.001
<b>Erosion Score</b>								
MTX	264	217 (82%)			267	220 (82%)		
UPA 15 mg QD	279	259 (93%)	10.6% (5.1%, 16.2%)	<0.001	280	260 (93%)	10.5% (5.0%, 15.9%)	<0.001
UPA 30 mg QD	270	257 (95%)	13.0% (7.7%, 18.3%)	<0.001	272	259 (95%)	12.8% (7.6%, 18.0%)	<0.001
<b>Joint Space Narrowing</b>								
MTX	264	230 (87%)			267	233 (87%)		
UPA 15 mg QD	279	255 (91%)	4.3% (-0.9%, 9.5%)	0.11	280	256 (91%)	4.2% (-1.0%, 9.3%)	0.12
UPA 30 mg QD	270	248 (92%)	4.7% (-0.5%, 9.9%)	0.07	272	250 (92%)	4.6% (-0.5%, 9.8%)	0.08

Source: FDA Biostatistics Review for NDA 211675.

Further sensitivity analyses supported the primary finding that UPA was able to inhibit radiographic progression in subjects with moderately to severely active RA (data not shown). The reader is referred to Dr. Koh’s review for a detailed discussion of the data and sensitivity analyses.

**Reviewer’s Comments:**

Study M15-545 was a well-conducted study with balanced subject cohorts, limited subject dropouts, and minimal protocol violations that allowed for reliable interpretation of the study results. The efficacy analysis of the primary endpoint clearly demonstrates a clinically meaningful treatment effect of UPA 15 and 30 mg monotherapy compared to MTX monotherapy for improvement of the signs and symptoms of subjects with moderately to severely active RA and who were naïve to MTX therapy. The primary endpoint is fully supported by the results of the secondary endpoints.

Similar to the results observed in Study M13-542, the results of this study demonstrate a clinically meaningful benefit from treatment with UPA 15 and 30 mg but do not support a dose-dependent increase of clinical efficacy with the higher dose of UPA in this patient population. Consequently, the overall benefit-risk assessment for UPA 30 mg will need to be determined in the context of the overall safety evaluation.

## 7. Integrated Review of Effectiveness

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### 7.1. Assessment of Efficacy Across Trials

Analysis of the primary and secondary endpoints provides statistically strong and consistent support for the efficacy of UPA. Subgroup and sensitivity analyses further support the clinical benefits for the to-be-marketed dose of UPA 15 mg QD. Analysis of the efficacy data did not demonstrate a consistent additional benefit with UPA 30 mg treatment compared to the lower dose in these studies. Discussion of the evidence for the individual efficacy claims appear below.

#### 7.1.1. Primary Endpoints

The five phase 3 studies provide the principal evidence demonstrating the clinical efficacy of UPA in subjects with moderately to severely active RA either as monotherapy or while receiving concomitant csDMARD therapy. Moreover, the studies were conducted using a broad population of subjects that reflect the types of patients that are typically seen in the clinical setting. For example, Study M13-545 enrolled MTX-naïve subjects, while the other four studies enrolled subjects who were inadequate responders to csDMARDs and bDMARDs.

All of the studies used the proportion of subjects achieving an ACR20 at Week 12 or 14 (except for Study M13-545 which used the ACR50). The ACR20 definition of response specifies a 20% improvement over baseline in swollen and tender joints and in 3 out of 5 of the remaining core data set measures. The choice of the primary endpoint is appropriate to assess a clinically meaningful benefit of UPA and is consistent with Agency guidelines.

In all five studies, a statistically significant greater proportion of UPA-treated subjects achieved the prespecified ACR response compared to subjects treated with PBO or an active comparator (Table 75). Subjects treated with UPA 15 mg or UPA 30 mg demonstrated treatment effect sizes that ranged between 24% to 36% and 27% to 31%, respectively, compared to the respective control arm. As discussed in more detail below, a dose-response effect was not readily apparent between the two UPA arms based on the primary endpoint results.

**Table 75. All Five Phase 3 Studies: Summary of Primary Efficacy Endpoint Results**

Treatment Arm	N	ACR20	Diff (%) (95% CI)
<b>M13-542</b>			
PBO	169	48 (28%)	
UPA 15 mg	164	106 (65%)	36 (26-46)
UPA 30 mg	165	93 (56%)	28 (18-38)
<b>M13-549</b>			
PBO	221	79 (36%)	
UPA 15 mg	221	141 (64%)	28 (19-37)
UPA 30 mg	219	145 (66%)	31 (22-39)
<b>M14-465</b>			
PBO	651	237 (36%)	
UPA 15 mg	651	456 (71%)	34 (29-39)
ADA 40 mg	327	206 (63%)	27 (20-33)
<b>M15-555</b>			
MTX	216	89 (41%)	
UPA 15 mg	217	147 (68%)	27 (18-36)
UPA 30 mg	215	153 (71%)	30 (21-39)
<b>M13-545 (ACR50)</b>			
MTX	314	89 (28%)	
UPA 15 mg	317	165 (52%)	24 (16-31)
UPA 30 mg	314	177 (56%)	28 (21-35)
Source: FDA Biostatistics Review for NDA 211675.			

Overall, the primary efficacy results demonstrated a clinically meaningful effect of UPA and support the indication that UPA therapy reduces the signs and symptoms of RA in subjects with moderately to severely active disease and who are either MTX-naïve or who have failed csDMARDs and/or a bDMARD.

### 7.1.2. Secondary and Other Endpoints

#### HAQ-DI

The claim of improvement in physical function described in the RA guidance document is intended to recognize clinical benefits regarding the disabling changes that occur over time in untreated patients. The HAQ-DI is a self-administered questionnaire that measures the degree of difficulty a person has in accomplishing tasks in eight functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, errands and chores) over the previous week. Responses in each functional area are scored from 0, indicating no difficulty, to 3, indicating inability to

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perform a task in that area. The minimum clinically important difference cut-off for HAQ-DI is  $\leq -0.22$ .

The principal evidence demonstrating that UPA treatment improves physical function in subjects with RA is provided by data from the controlled periods of the five phase 3 studies. All five studies demonstrated a greater proportion of subjects treated with UPA 15 mg or UPA 30 mg achieved a clinically significant improvement in HAQ-DI score ( $\leq -0.3$ ) from baseline compared to the respective UPA-treated groups (Table 76).  $\geq$

**Table 76. All Five Phase 3 Studies: Summary of Change from Baseline in HAQ-DI**

Treatment Arm	N	Baseline Mean (SD)	n	Visit Mean (SD)	Adj Mean Diff (95% CI)	P-value
<b>M13-542</b>						
Placebo	166	1.6 (0.6)	150	1.3 (0.7)		
UPA 15 mg QD	163	1.7 (0.6)	160	1.2 (0.8)	-0.2 (-0.3, -0.1)	0.002
UPA 30 mg QD	161	1.6 (0.6)	154	1.2 (0.7)	-0.2 (-0.3, -0.1)	<0.001
<b>M13-549</b>						
Placebo	221	1.4 (0.6)	206	1.1 (0.7)		
UPA 15 mg QD	216	1.5 (0.6)	210	0.9 (0.7)	-0.3 (-0.4, -0.2)	<0.001
UPA 30 mg QD	219	1.5 (0.6)	200	0.9 (0.7)	-0.3 (-0.4, -0.2)	<0.001
<b>M14-465</b>						
Placebo	650	1.6 (0.6)	617	1.3 (0.7)		
UPA 15 mg QD	645	1.6 (0.6)	617	1.0 (0.7)	-0.3 (-0.4, -0.3)	<0.001
ADA 40 mg EOW	325	1.6 (0.6)	309	1.1 (0.7)	-0.2 (-0.3, -0.1)	<0.001
<b>M15-555</b>						
MTX	216	1.5 (0.7)	195	1.2 (0.7)		
UPA 15 mg QD	216	1.5 (0.7)	199	0.8 (0.7)	-0.3 (-0.5, -0.2)	<0.001
UPA 30 mg QD	215	1.5 (0.7)	201	0.8 (0.7)	-0.4 (-0.5, -0.3)	<0.001
<b>M13-545</b>						
MTX	314	1.6 (0.7)	278	1.1 (0.7)		
UPA 15 mg QD	317	1.6 (0.7)	302	0.8 (0.7)	-0.3 (-0.4, -0.2)	<0.001
UPA 30 mg QD	311	1.5 (0.7)	298	0.7 (0.7)	-0.3 (-0.4, -0.2)	<0.001

Source: FDA Biostatistics Review for NDA 211675;

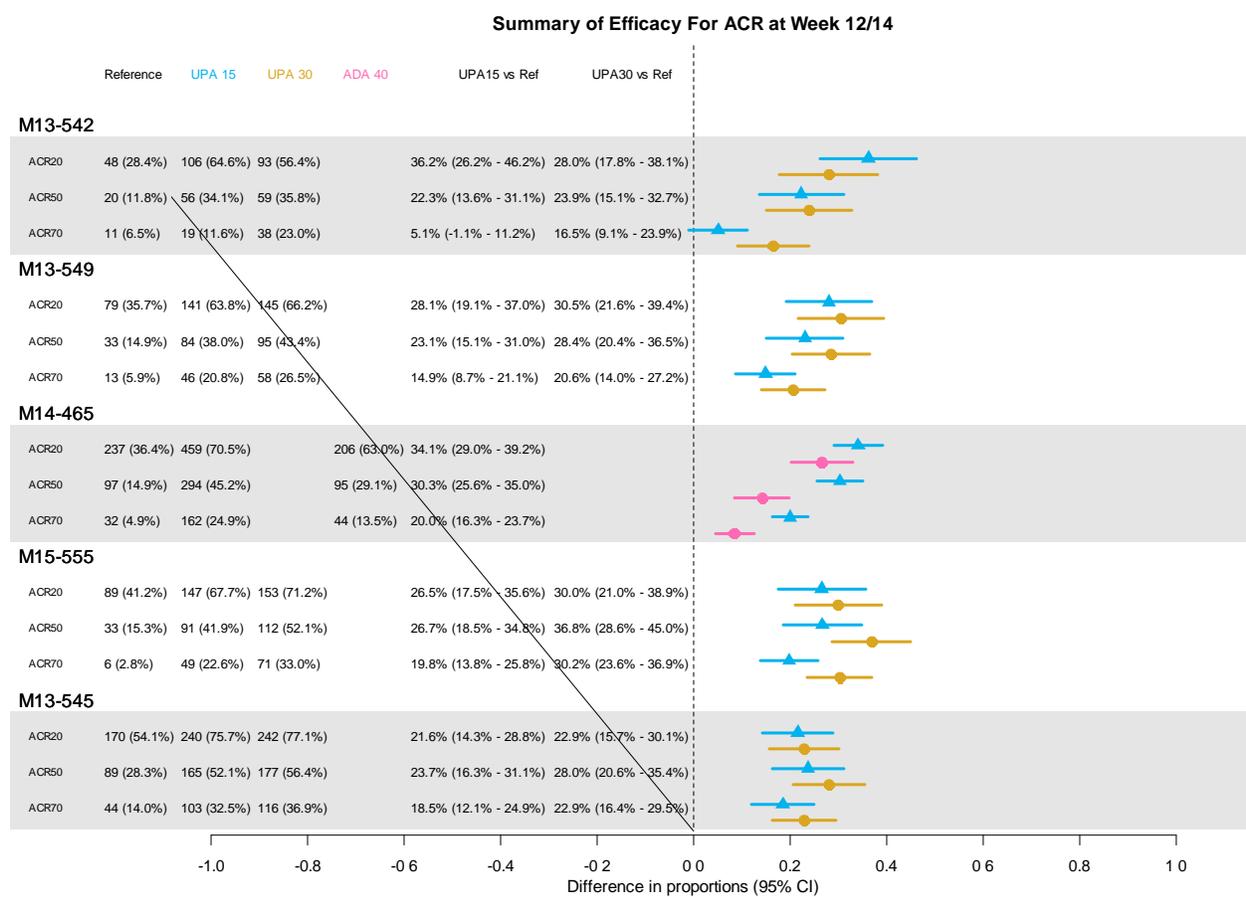
***Reviewer's Comment:***

The Applicant is seeking a labeling claim regarding the improvement of physical function. These data demonstrate that UPA therapy improves physical function in a clinically meaningful manner in the subject population studied and supports the primary endpoint of improving signs and symptoms of RA. This reviewer agrees with inclusion of the HAQ-DI data in the UPA label.

**ACR20/50/70**

Greater ACR response rates were also analyzed during the phase 3 studies to assess the degree of improvement of the signs and symptoms in subjects. Figure 12 shows the ACR20/50/70 response rates of subjects enrolled in each of the five phase 3 studies compared to their respective control.

**Figure 12. All Five Phase 3 Studies: Summary of ACR 20/50/70 Responses**



Source: FDA Biostatistics Review for NDA 211675; Abbreviations: ACR=American College of Rheumatology; MTX=methotrexate; UPA=upadacitinib; QD=once daily; CI=confidence intervals; EOW=every other week; ADA=adalimumab

Consistent with the data observed in the primary endpoint analyses, the proportion of subjects achieving higher ACR responses were greater in UPA-treated subjects compared to PBO- or active comparator-treated subjects. Subjects treated with UPA 30 mg consistently had a higher proportion of subjects with greater ACR responses compared to the UPA 15 mg group; however, given the relatively small increase in benefit, the degree of clinical meaningfulness is uncertain.

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Reviewer's Comment:

The Applicant is seeking inclusion of these data in the UPA label as the results are clinically relevant to a prescribing healthcare provider. This reviewer agrees that the data should be included in the label and that the results support the primary endpoint of improving signs and symptoms of RA.

**DAS28-CRP and DAS28-CRP <2.6**

The prespecified secondary endpoints also included the DAS28-CRP score which in contrast to the ACR criteria measures the level of disease activity rather than the proportion of subjects achieving a specified level of improvement. The DAS28 is a continuous measure and is a composite of 4 variables: 28 tender joint count, 28 swollen joint count, ESR and subject assessment of disease activity measure on a VAS of 100 mm. Scores for disease activity are defined as high ( $>5.1$ ); low ( $\leq 3.2$ ); clinically significant improvement (change  $\geq 1.2$ ), and remission ( $<2.6$ ). It is important to note that the DAS28 usage of remission does not meet the Agency's definition of remission since subjects can have active swollen and tender joints and still meet the DAS28 criteria of remission. In addition, while the definition of remission described in the RA guidance document specifies no radiographic progression, the DAS-based definition of remission does not include an assessment of radiographic progression.

According to the DAS28-CRP criteria, a greater proportion of subjects receiving UPA compared to subjects receiving PBO or active comparator, achieved clinical improvement and had low disease activity (Table 77).

**Table 77. All Five Phase 3 Studies: Summary of Change from Baseline in DAS28-CRP**

Treatment Arm	N	Baseline Mean (SD)	n	Visit Mean (SD)	Adj Mean Diff (95% CI)	P-value
<b>M13-542</b>						
Placebo	166	5.8 (1.0)	147	4.7 (1.4)		
UPA 15 mg QD	163	5.9 (0.9)	157	3.5 (1.3)	-1.2 (-1.5, -0.9)	<0.001
UPA 30 mg QD	163	5.8 (0.9)	149	3.5 (1.5)	-1.1 (-1.4, -0.8)	<0.001
<b>M13-549</b>						
Placebo	221	5.6 (0.8)	206	4.5 (1.5)		
UPA 15 mg QD	217	5.7 (1.0)	206	3.4 (1.4)	-1.2 (-1.4, -0.9)	<0.001
UPA 30 mg QD	219	5.7 (0.9)	200	3.3 (1.2)	-1.3 (-1.6, -1.1)	<0.001
<b>M14-465</b>						
Placebo	649	5.8 (0.9)	595	4.7 (1.4)		
UPA 15 mg QD	647	5.8 (1.0)	586	3.3 (1.3)	-1.3 (-1.5, -1.2)	<0.001
ADA 40 mg EOW	324	5.9 (1.0)	295	3.8 (1.4)	-0.9 (-1.0, -0.7)	<0.001
<b>M15-555</b>						
MTX	216	5.6 (1.0)	194	4.4 (1.4)		
UPA 15 mg QD	216	5.6 (0.9)	195	3.3 (1.4)	-1.1 (-1.3, -0.9)	<0.001
UPA 30 mg QD	215	5.6 (1.1)	198	3.0 (1.3)	-1.4 (-1.7, -1.2)	<0.001
<b>M13-545</b>						
MTX	315	5.9 (1.0)	290	4.0 (1.4)		
UPA 15 mg QD	317	5.9 (1.0)	303	3.2 (1.4)	-0.9 (-1.1, -0.7)	<0.001
UPA 30 mg QD	311	5.8 (1.0)	297	3.0 (1.3)	-1.0 (-1.2, -0.7)	<0.001
Source: FDA Biostatistics Review for NDA 211675.						

Although the Agency does not recognize the term “remission” as it relates to DAS28 scores <2.6, we do recognize that scores below 2.6 represent very low disease activity and is an admirable goal of treatment in RA patients. To that end, the Applicant analyzed the proportion of subjects achieving a DAS28-CRP <2.6 at the time of the primary endpoint assessment. As shown in Table 78, a greater proportion of subjects treated with UPA achieved DAS28-CRP scores <2.6 compared to their respective controls.

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**Table 78. All Five Phase 3 Studies: Summary of Subjects Achieving DAS28-CRP<2.6**

Treatment Arm	Total	DAS28(CRP) <2.6	
		Response	Diff (%) [95 % CI]
<b>M13-542</b>			
Placebo	169	16 (9%)	
UPA 15 mg QD	164	47 (29%)	19.2% (11.0%, 27.4%)
UPA 30 mg QD	165	39 (24%)	14.2% (6.3%, 22.0%)
<b>M13-549</b>			
Placebo	221	22 (10%)	
UPA 15 mg QD	221	68 (31%)	20.8% (13.6%, 28.1%)
UPA 30 mg QD	219	62 (28%)	18.4% (11.2%, 25.5%)
<b>M14-465</b>			
Placebo	651	40 (6%)	
UPA 15 mg QD	651	187 (29%)	22.6% (18.6%, 26.5%)*
ADA 40 mg EOW	327	59 (18%)	11.9% (7.3%, 16.5%)**
<b>M15-555</b>			
MTX	216	18 (8%)	
UPA 15 mg QD	217	61 (28%)	19.8% (12.8%, 26.8%)
UPA 30 mg QD	215	87 (40%)	32.1% (24.6%, 39.7%)
<b>M13-545</b>			
MTX	314	42 (13%)	
UPA 15 mg QD	317	113 (36%)	22.3% (15.8%, 28.7%)
UPA 30 mg QD	314	128 (41%)	27.4% (20.8%, 34.0%)
Source: FDA Biostatistics Review for NDA 211675. *UPA 15 mg vs. Placebo; **ADA 40 mg vs. UPA 15 mg			

**Reviewer's Comment:**

The Applicant is seeking to add DAS28-CRP scores and proportions of subjects reaching DAS28-CRP <2.6 to the UPA label. Given that the DAS28 score is used clinically as a measure of disease activity and is consistent with the Agency's guidance document, this reviewer agrees with its inclusion in the product labeling. Additionally, these data further support the primary endpoint of improving signs and symptoms of RA.

**SF-36**

The SF-36 is a validated patient-reported instrument that assesses the general health-related quality of life of subjects over eight domains of a patient's functional health and well-being, namely physical functioning and mental health. It can also be summarized into two summary scores: the physical component summary (PCS) and mental component summary (MCS). The range is from 0 to 100, with higher scores indicating better outcomes.

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In all five phase 3 studies, subjects treated with UPA demonstrated statistically significant improvement in SF-36 PCS scores (Table 79). A clear UPA dose-response effect was not noted.

**Table 79. All Five Phase 3 Studies: Summary of Change from Baseline of SF-36 PCS**

Treatment Arm	N	Baseline Mean (SD)	n	Visit Mean (SD)	Adjusted Mean Diff (95% CI)	P-value
<b>M13-542</b>						
Placebo	166	31.6 (7.2)	147	34.6 (9.3)		
UPA 15 MG QD	163	30.6 (7.8)	157	37.1 (10.1)	3.1 (1.4, 4.8)	<0.001
UPA 30 MG QD	162	31.5 (7.3)	149	38.7 (9.4)	4.5 (2.8, 6.2)	<0.001
<b>M13-549</b>						
Placebo	221	33.1 (7.7)	207	36.8 (9.2)		
UPA 15 MG QD	219	33.4 (7.4)	211	41.3 (8.9)	4.4 (3.0, 5.8)	<0.001
UPA 30 MG QD	217	32.6 (7.9)	199	41.8 (8.9)	5.1 (3.6, 6.5)	<0.001
<b>M14-465</b>						
Placebo	647	32.5 (6.8)	632	36.6 (8.0)		
UPA 15 mg QD	648	32.5 (7.3)	634	40.8 (9.1)	4.3 (3.5, 5.1)	<0.001
ADA 40 mg EOW	327	32.2 (7.0)	322	38.9 (8.7)	2.5 (1.6, 3.5)	<0.001
<b>M15-555</b>						
MTX	216	33.3 (7.3)	195	37.1 (8.1)		
UPA 15 MG QD	217	33.3 (7.9)	200	41.3 (9.1)	4.2 (2.8, 5.7)	<0.001
UPA 30 MG QD	214	33.9 (7.8)	202	43.6 (9.1)	6.2 (4.7, 7.6)	<0.001
<b>M13-545</b>						
MTX	313	33.1 (7.5)	299	38.8 (8.9)		
UPA 15 MG QD	315	32.7 (7.7)	306	43.0 (9.7)	4.5 (3.3, 5.8)	<0.001
UPA 30 MG QD	312	33.7 (7.2)	306	43.7 (8.5)	4.6 (3.3, 5.8)	<0.001
Source: FDA Biostatistics Review for NDA 211675.						

Statistically significant improvement in the SF-36 MCS measure was universally demonstrated in all phase 3 studies (Table 80). Both UPA doses failed to demonstrate a meaningful improvement in the MCS score in Study M13-542 and the UPA 30 mg group in Study M13-549 did not demonstrate a significant change from baseline compared to PBO.

**Table 80. All Five Phase 3 Studies: Summary of Change from Baseline of SF-36 MCS**

Treatment Arm	N	Baseline Mean (SD)	n	Visit Mean (SD)	Adjusted Mean Diff (95% CI)	P-value
<b>M13-542</b>						
Placebo	166	45.9 (12.6)	147	49.2 (11.2)		
UPA 15 MG QD	163	44.0 (11.7)	157	49.0 (12.1)	1.0 (-0.8, 2.9)	0.28
UPA 30 MG QD	162	45.9 (12.3)	149	49.3 (11.4)	-0.2 (-2.1, 1.7)	0.82
<b>M13-549</b>						
Placebo	221	46.5 (11.7)	207	48.5 (11.4)		
UPA 15 MG QD	219	45.9 (10.9)	211	50.1 (9.9)	2.0 (0.5, 3.6)	0.01
UPA 30 MG QD	217	46.1 (12.0)	199	49.8 (10.4)	1.1 (-0.5, 2.7)	0.18
<b>M14-465</b>						
Placebo	647	43.0 (11.0)	632	46.2 (11.1)		
UPA 15 mg QD	648	43.0 (10.6)	634	48.8 (10.1)	2.7 (1.8, 3.6)	<0.001
ADA 40 mg EOW	327	42.7 (10.6)	322	47.7 (10.1)	1.7 (0.5, 2.8)	0.004
<b>M15-555</b>						
MTX	216	45.1 (11.0)	195	47.5 (10.6)		
UPA 15 MG QD	217	44.1 (11.3)	200	49.4 (10.2)	2.5 (0.9, 4.1)	0.002
UPA 30 MG QD	214	44.5 (11.5)	202	50.0 (10.7)	2.7 (1.1, 4.3)	<0.001
<b>M13-545</b>						
MTX	313	43.2 (10.7)	299	46.9 (10.5)		
UPA 15 MG QD	315	42.5 (10.6)	306	48.6 (10.3)	2.1 (0.7, 3.5)	0.003
UPA 30 MG QD	312	43.3 (11.6)	306	48.9 (10.8)	2.1 (0.7, 3.5)	0.003

Source: FDA Biostatistics Review for NDA 211675.

**Reviewer's Comment:**

The Applicant is seeking to add SF-36 PCS and MCS scores to the UPA label. The SF-36 represents a validated patient reported outcome score and is consistent with the Agency's guidance document. This reviewer agrees with inclusion of the SF-36 data in the product labeling.

**Morning Stiffness**

Patients with RA frequently describe morning stiffness as a problematic symptom that may be predictive of functional impairment among RA patients<sup>4</sup>. Measurement of morning stiffness was comprised of two items. The first item measures the severity of morning stiffness using an 11-point numerical rating scale, where 0 is defined as "no morning stiffness" and 10 is defined as "worst possible morning stiffness." The second item measures the duration of morning stiffness

<sup>4</sup> Yazici Y et al. J Rheumatol Sep;31(9):1723-6

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by asking patients the length of time, in hours and/or minutes, that it takes to "get as limber as possible."

(b) (4)



In all phase 3 studies, subjects treated with UPA experienced a statistically significant and improvement in morning stiffness (Table 81).

**Table 81. All Five Phase 3 Studies: Summary of Change from Baseline in Morning Stiffness**

Treatment Arm	N	Baseline Mean (SD)	n	Visit Mean (SD)	Est Diff (95% CI)	P-value
<b>M13-542</b>						
Placebo	169	138.4 (179)	151	133.1 (249)		
UPA 15 mg QD	164	140.4 (190)	160	68.3 (133)	-64.4 (-104.1, -24.7)	0.001
UPA 30 mg QD	165	184.5 (285)	153	89.8 (203)	-59.5 (-99.7, -19.3)	0.004
<b>M13-549</b>						
Placebo	216	138.9 (214)	202	95.7 (166)		
UPA 15 mg QD	217	152.4 (242)	207	54.3 (114)	-43.0 (-64.2, -21.7)	<0.001
UPA 30 mg QD	215	128.6 (156)	197	43.2 (67)	-49.4 (-70.9, -27.9)	<0.001
<b>M14-465</b>						
Placebo	651	142.4 (170)	625	91.8 (135)		
UPA 15 mg QD	649	141.5 (188)	625	47.9 (95)	-42.9 (-54.0, -31.7)	<0.001
ADA 40 mg EOW	324	146.1 (185)	314	61.0 (105)	-32.1 (-45.8, -18.5)	<0.001
<b>M15-555</b>						
MTX	215	153.0 (222)	196	102.3 (190)		
UPA 15 mg QD	217	144.2 (215)	199	55.8 (111)	-44.5 (-69.2, -19.8)	<0.001
UPA 30 mg QD	214	133.9 (153)	202	43.2 (81)	-54.4 (-79.0, -29.8)	<0.001
<b>M13-545</b>						
MTX	314	128.1 (134)	291	71.9 (144)		
UPA 15 mg QD	316	168.9 (228)	303	43.9 (69)	-33.2 (-48.3, -18.1)	<0.001
UPA 30 mg QD	313	136.4 (167)	301	33.7 (49)	-39.0 (-54.0, -23.9)	<0.001

Source: FDA Biostatistics Review for NDA 211675.

**Reviewer's Comment:**

(b) (4)

In a broader context, the general improvement in morning stiffness is clinically useful and supports the primary endpoint that UPA improves the signs and symptoms of RA in a clinically meaningful manner.

**FACIT-F**

Studies have found that fatigue is an independent predictor of physical functioning and disease activity in RA patients and that experiencing fatigue significantly affects patient's health-related quality of life. The FACIT-F consists of 13 items, which are assessed on a five-point Likert scale, with the following categories: not at all = 0 points; a little bit = 1 point; somewhat = 2 points; quite a bit = 3 points; very much = 4 points. The total score ranges from 0 to 52. High scores

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represent less fatigue. The minimal clinically important difference cut-off reported in RA population for FACIT-F is 4 points and normative value is 43.6.

FACIT-F is a commonly used tool to measure fatigue in RA clinical studies because the items have broad coverage of the concept of fatigue. The COA team reviewed the Applicant’s rationale and data for including FACIT-F scores in the UPA label and found the measure to be fit-for-purpose. Studies M13-542, M14-465 and M13-545 assessed the FACIT-F score. In each of the studies, UPA-treated subjects achieved statistically significant improvement in fatigue as measured by an increase in FACIT-F scores (Table 82). There did not appear to be a dose-dependent improvement in FACIT-F scores with higher doses of UPA.

**Table 82. Studies M13-542, M14-465, M13-545: Summary of Change from Baseline in FACIT-F Scores**

Treatment Arm	N	Baseline Mean (SD)	n	Visit Mean (SD)	Est Diff (95% CI)	P-value
<b>M13-542</b>						
Placebo	221	28.3 (11.5)	207	31.6 (11.8)		
UPA 15 mg QD	216	28.1 (11.1)	211	36.0 (10.4)	4.8 (3.2, 6.5)	<0.001
UPA 30 mg QD	217	27.5 (12.6)	199	36.4 (11.4)	4.9 (3.2, 6.5)	<0.001
<b>M14-465</b>						
Placebo	644	27.0 (11.1)	632	31.5 (11.6)		
UPA 15 mg QD	646	26.9 (11.1)	632	35.3 (10.5)	4.0 (3.0, 5.0)	<0.001
ADA 40 mg EOW	325	26.2 (11.4)	322	33.8 (11.3)	2.7 (1.5, 3.9)	<0.001
<b>M13-545</b>						
MTX	314	26.6 (11.7)	300	33.6 (11.3)		
UPA 15 mg QD	316	26.4 (11.9)	308	37.0 (10.8)	3.6 (2.2, 5.1)	<0.001
UPA 30 mg QD	310	27.8 (11.1)	306	37.4 (10.7)	3.2 (1.7, 4.7)	<0.001
Source: FDA Biostatistics Review for NDA 211675.						

**Reviewer’s Comment:**

The Applicant is seeking to add FACIT-F scores to the UPA label. The Agency’s COA team has reviewed the evidence and agrees that the FACIT-F is fit-for-purpose and can be included in the label. This reviewer agrees with the COA team and after review of the data believes that UPA-treated subjects demonstrated an improvement in fatigue as demonstrated by increased FACIT-F scores and should be included in the product labeling.

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### **Inhibition of Radiographic Progression**

Radiographic progression of structural joint damage was measured using the Van der Heijde mTSS. The mTSS is an established instrument that quantifies and sums the extent of bone erosions and joint space narrowing. The range of the mTSS is from 0 to 448, with a higher score indicating more radiographic damage. The subcomponents of erosion score and joint space narrowing score are as follows:

- Erosion score: A total of 44 joints of the hands, wrists and feet were assessed for bone erosions. The range of the erosion score is from 0 to 280, with higher score indicating more erosions.
- Joint space narrowing score: A total of 42 joints of the hands, wrists and feet are assessed for joint space narrowing. The range of the joint space narrowing score is from 0 to 168, with a higher score indicating more joint space narrowing.

Studies M14-465 and M13-545 assessed UPA ability to inhibit radiographic progression using the mTSS. The primary analysis for this review was performed by Dr. Koh who conducted independent analyses and subsequently used to verify the Applicant's analyses. The reader is directed to Dr. Koh's review for a detailed discussion of the radiographic analyses.

In Study M14-465, subjects treated with UPA 15 mg demonstrated inhibition of radiographic progression at Week 26 as measured by a lower mTSS score compared to PBO-treated subjects and similar to ADA-treated subjects (Table 83). The benefit of UPA treatment was also seen in the individual components of the mTSS score, i.e., erosion and joint space narrowing scores.

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**Table 83. Study M14-465: Applicant's Primary Analysis of the Mean Change from Baseline in mTSS and Components at Week 26**

Treatment Arm	N	Baseline Mean (SD)	n	Change from Baseline Mean (SD)	Vs Placebo		Vs Adalimumab	
					Est Difference (95% CI)	P-value	Est Difference (95% CI)	P-value
<b>mTSS</b>								
Placebo	649	35.9 (51.7)	599	0.9 (3.5)				
UPA 15 mg QD	644	34.0 (50.1)	593	0.2 (1.6)	-0.67 (-0.97, -0.37)	<0.001	0.14 (-0.23, 0.51)	0.45
ADA 40 mg EOW	326	34.5 (47.1)	296	0.1 (2.4)	-0.82 (-1.2, -0.45)	<0.001		
<b>Erosion Score</b>								
Placebo	649	17.0 (27.4)	599	0.5 (2.2)				
UPA 15 mg QD	644	16.5 (26.4)	593	0.1 (0.8)	-0.41 (-0.58, -0.24)	<0.001	0.009 (-0.2, 0.22)	0.93
ADA 40 mg EOW	326	15.4 (23.1)	296	0.0 (0.9)	-0.42 (-0.63, -0.21)	<0.001		
<b>Joint Space Narrowing</b>								
Placebo	649	18.9 (26.1)	599	0.5 (2.4)				
UPA 15 mg QD	644	17.5 (25.1)	593	0.1 (1.1)	-0.36 (-0.56, -0.17)	<0.001	0.08 (-0.16, 0.32)	0.50
ADA 40 mg EOW	326	19.2 (25.8)	296	0.0 (1.0)	-0.45 (-0.69, -0.21)	<0.001		

Source: FDA Biostatistics Review for NDA 211675.

Similarly, for Study M13-545, subjects treated with UPA 15 mg also demonstrated inhibition of radiographic progression at Week 24 as measured by a lower mTSS score compared to MTX-treated subjects (Table 84). Treatment with UPA 30 mg did not appear to have an increased clinically meaningful effect. The benefit of UPA treatment was also seen in the individual components of the mTSS score, i.e., erosion and joint space narrowing scores.

**Table 84. Study M13-545: Applicant’s Primary Analysis of the Mean Change from Baseline in mTSS and Components at Week 24**

Treatment Arm	N	Baseline Mean (SD)	n	Mean Change from baseline (SD)	Est Diff (95% CI)	P-value
<b>mTSS</b>						
MTX	309	13.3 (30.5)	264	0.7 (2.8)		
UPA 15 mg QD	309	18.1 (38.2)	279	0.1 (1.4)	-0.53 (-0.8, -0.2)	0.001
UPA 30 mg QD	309	17.2 (38.3)	270	0.1 (1.2)	-0.59 (-0.9, -0.3)	<0.001
<b>Erosion Score</b>						
MTX	309	6.1 (15.5)	264	0.3 (1.5)		
UPA 15 mg QD	309	8.6 (19.3)	279	0.0 (0.5)	-0.29 (-0.4, -0.1)	<0.001
UPA 30 mg QD	309	8.0 (18.9)	270	0.0 (0.3)	-0.34 (-0.5, -0.2)	<0.001
<b>Joint Space Narrowing</b>						
MTX	309	7.2 (16.1)	264	0.3 (1.7)		
UPA 15 mg QD	309	9.6 (20.1)	279	0.1 (0.9)	-0.23 (-0.4, -0.02)	0.03
UPA 30 mg QD	309	9.3 (20.3)	270	0.1 (1.1)	-0.24 (-0.5, -0.03)	0.02
Source: FDA Biostatistics Review for NDA 211675.						

**Reviewer’s Comment:**

The Applicant is seeking to add inhibition of radiographic progression to the UPA label. Overall the data from the two studies demonstrate UPA 15 mg is effective in inhibiting the radiographic progression of erosive disease as measured by the mTSS. Analysis of radiographic inhibition is included in the Agency RA Guidance document and the Applicant used established methods to collect and analyze the data. I agree with inclusion of this data in the UPA label as it is clinically relevant and will help guide clinicians in the care of patients with RA who have, or are susceptible, to developing erosive disease.

**7.1.3. Subpopulations**

Subgroup analyses based on age, gender, weight, BMI, race, geographic region, baseline rheumatoid factor status, baseline anti-CCP antibody status, background cDMARDs at baseline and prior bDMARD intolerance, were conducted for ACR20 responses at Week 12 using pooled data from the “PBO-Controlled UPA 15 mg” analysis set (Studies M13-542, M13-549 and M14-465) and the “PBO-Controlled UPA 15 mg and UPA 30 mg” analysis set (M13-542, M13-549). Results from these analyses demonstrated similar degrees of UPA efficacy across the range of demographic and baseline disease characteristics (data not shown).

**7.1.4. Dose and Dose-Response**

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The totality of the efficacy data throughout all five phase 3 clinical studies failed to demonstrate a consistent dose-response or increased benefit from treatment of subjects with UPA 30 mg compared to UPA 15 mg. Moreover, in the clinical endpoints where UPA 30 mg was more effective, the overall therapeutic effect size was small compared to UPA 15 mg and the additional clinical benefit is difficult to justify given the increased safety risk associated with UPA 30 mg compared to the lower dose.

Given these results, the Applicant is only requesting approval of the UPA 15 mg QD dose. The clinical studies all demonstrated the to-be-marketed dose of UPA 15 mg, as monotherapy or in combination with csDMARDs, to have a clinically meaningful effect in subjects with moderately to severely active RA and who are MTX-naïve or have failed csDMARDs and/or bDMARD therapy.

#### **7.1.5. Onset, Duration, and Durability of Efficacy Effects**

In all five phase 3 studies, subjects treated with UPA 15 mg and 30 mg demonstrated a relatively quick onset of action as evidenced by statistically significant greater ACR20 responses compared to their respective control group by the first postbaseline visits (Table 85). These data demonstrate that approximately one-quarter of UPA-treated subjects with active RA experience a clinically meaningful improvement in symptoms within the first two weeks of starting therapy.

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**Table 85. All Five Phase 3 Studies: ACR20 Responses at Postbaseline Visit 1**

Time Point Treatment	N	Responder % (95% CI)	Response Rate Difference (UPA-Control)	
			Point Estimate (95% CI)	p-value
<b>Study M13-542</b>				
Week 1				
PBO	169	11 (6, 15)		
UPA 15 mg	164	27 (21, 34)	17 (9, 25)	<0.001
UPA 30 mg	165	25 (18, 31)	14 (6, 22)	<0.001
<b>Study M13-549</b>				
Week 1				
PBO	221	9 (5, 12)		
UPA 15 mg	221	22 (17, 28)	14 (7, 20)	<0.001
UPA 30 mg	219	28 (22, 34)	20 (13, 27)	<0.001
<b>Study M14-465</b>				
Week 2				
PBO	651	14 (11, 17)		
UPA 15 mg	651	34 (30, 37)	20 (15, 24)	<0.001
ADA 40 mg	327	33 (28, 38)		
<b>Study M13-545</b>				
Week 2				
MTX	314	16 (12, 20)		
UPA 15 mg	317	40 (35, 46)	24 (17, 31)	<0.001
UPA 30 mg	314	48 (42, 53)	31 (24, 38)	<0.001
<b>Study M15-555</b>				
Week 2				
MTX	216	7 (4, 10)		
UPA 15 mg	217	33 (27, 39)	26 (19, 33)	<0.001
UPA 30 mg	215	43 (37, 50)	36 (29, 44)	<0.001

Source: Applicant's Summary of Clinical Efficacy, Table 11

Persistence of clinical activity was analyzed in each of the five phase 3 clinical studies. A high percentage of subjects remained enrolled in the studies through the last study visit that included Week 60 for Studies M13-542 (74%) and M13-549 (78%); and through Week 48 for Studies M13-465 (87%), M13-545 (80%) and M15-555 (84%).

Subjects who were originally randomized to the UPA 15 mg group in Studies M13-542, M13-549, M14-465, M13-545 and M15-555 maintained ACR20 responses of 77%, 85%, 65%, 74% and 80% at the time of the last study visit before data cutoff. Similar results were observed for subjects

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initially randomized to UPA 30 mg. These data demonstrate a durability of effect for UPA 15 mg and 30 mg in subjects with active RA over the course of approximately one year.

Taken together, analysis of the ACR20 responses in the five phase 3 studies demonstrates UPA to have a clinically meaningful rapid onset of activity by one to two weeks from the time of starting therapy and a persistence of effect lasting at least one year after initiation of treatment.

## **7.2. Additional Efficacy Considerations**

### **7.2.1. Considerations on Benefit in the Postmarket Setting**

The Applicant conducted five well-controlled studies that enrolled a broad population of subjects with moderately to severely active RA including subjects who were naïve to MTX, those who had an inadequate response to MTX and/or csDMARDs, and subjects who were refractory to one or more bDMARDs. Additionally, the baseline demographics and disease characteristics are representative of subjects in the US. However, as with most clinical trials, selection of subjects was optimized to capture the maximum treatment effect size by only including subjects with moderate to severely active disease while limiting comorbidities to provide the most favorable safety profile.

In the postmarketing setting, UPA is likely to be prescribed to a wider range of patients, namely subjects with less severe disease and more comorbidities. This may alter the overall benefit-risk assessment of UPA in these subjects. Thus, while UPA is clinically efficacious, including in subjects who are MTX-naïve, the known risks of UPA based on this review leads the Agency to recommend UPA therapy after patients have failed MTX.

## **7.3. Integrated Assessment of Effectiveness**

The Applicant has submitted substantial evidence meeting the evidentiary standard for the clinical effectiveness of UPA 15 mg based on the results from five well-controlled phase 3 studies that enrolled a broad population of subjects who were representative of the target US patient population. Study M13-545 enrolled subjects who were naïve to MTX, while Studies M13-542, M13-549, M14-465 and M15-555 enrolled subjects who were inadequate responders to MTX and/or csDMARDs and refractory/intolerant to bDMARDs, thus, representing a more difficult to treat patient population as they had already failed generally accepted first-line and/or second line-therapy. The studies all used validated and well-established primary and secondary endpoints that were designed to capture clinically meaningful changes in patients' disease activity.

The primary endpoint assessed the proportion of subjects achieving an ACR20 at Week 12 or 14 (except for Study M13-545 which used the ACR50). This endpoint was appropriate and consistent

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with Agency's guidelines to assess the clinical effectiveness of UPA in subjects with RA. As discussed in Section 6, each of the studies achieved statistical significance for the primary endpoint with an average treatment effect size ranging between 24% and 36% for subjects treated with UPA 15 mg, the to-be-marketed dose. This degree of treatment effect size clearly demonstrates a clinically meaningful benefit to patients by improving the signs and symptoms of RA. UPA 30 mg was also assessed in Studies M13-549, M13-542, M13-545, and M15-555. In the clinical endpoints where UPA 30 mg was more effective, the overall therapeutic effect size was small compared to UPA 15 mg and the additional clinical benefit is difficult to justify given the increased safety risk associated with UPA 30 mg compared to the lower dose.

Secondary endpoints were chosen to support the primary endpoint and to assess other potential treatment benefits to patients with RA. These endpoints measured the change from baseline for the improvement of physical function (HAQ-DI), inhibition of radiographic progression (mTSS), achievement of low disease activity (ACR 50/70 and DAS28-CRP <2.6), improvement in general health status (SF-36), and improvement in fatigue (FACIT-F). As discussed in Section 6, analyses for each of these secondary endpoints demonstrated a statistically significant and clinically meaningful benefit of treatment with UPA 15 mg.

Approximately 25% of subjects experienced a clinically meaningful benefit from the initiation of UPA 15 mg within the first one to two weeks of therapy. Additionally, subjects treated with UPA 15 mg continued to experience a clinical benefit after one-year of therapy demonstrating the durability of the treatment effect.

In summary, the Applicant has submitted substantial evidence of UPA's effectiveness that meets the statutory evidentiary standard. The effectiveness of UPA 15 mg was demonstrated to produce a clinically meaningful benefit in subjects with moderately to severely active RA either as monotherapy or in combination with MTX or csDMARDs in subjects who were MTX-naïve, or who had an inadequate response to MTX, csDMARDs and/or bDMARDs. The results of my analysis support the Applicant's proposed indication.

## 8. Review of Safety

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### 8.1. Safety Review Approach

This safety review is focused on identifying potential signals of UPA-related AEs as they relate to the treatment of patients with RA. As outlined in Table 5 and discussed in Section 5.2, the majority of the data for this safety review is derived from the five phase 3 studies which were designed to assess the safety profile of once daily UPA dosing as monotherapy and as combination therapy with MTX or other csDMARDs. The phase 3 studies were designed to assess the safety of two doses of UPA (15 mg and 30 mg) compared to PBO, MTX and ADA. The studies enrolled a broad population of patients with moderately to severely active RA who were either naïve to MTX, had an IR to MTX or csDMARDs, or had an IR or were intolerant to bDMARDs.

The phase 2 studies assessed dose-ranging of the immediate-release UPA formulation using the twice daily dosing regimen of UPA in RA subjects with an IR to MTX (Study M13-537) or IR to TNF inhibitors (Study M13-550). Study M13-538 was a bioavailability study that compared the immediate-release and extended-release formulations to support the selection of the extended-release formulations of UPA 15 mg and 30 mg QD dosing for the phase 3 studies. The phase 2 studies were not used in the primary safety analysis but provided additional data when assessing all subject exposure to UPA.

Upadacitinib is a member of the JAK-inhibitor class of drugs that includes tofacitinib and baricitinib. In addition to being potent immunosuppressants, these drugs have been associated with what appear to be class-specific AEs. Consequently, this safety review focused special interest of AEs of serious infection, opportunistic infections, herpes zoster, malignancy, hepatic disorders, gastrointestinal perforation, anemia, neutropenia, lymphopenia, creatine phosphate kinase (CPK) elevation, renal dysfunction, major adverse cardiovascular events (MACE) and venous thromboembolic events (VTE).

During the phase 3 studies, each study subject remained on the same UPA dose during the long-term extension period that they had received during randomization in the controlled period and no UPA dose change was allowed in order to optimize the safety assessment for each dose. Placebo-treated subjects were randomized to receive one of the two doses of UPA after the completion of the controlled period and were not allowed to change the dose of UPA during the long-term period. To prevent missing data in the ITT analysis set, subjects who withdrew early from the study, unless withdrawing consent, were permitted to continue to participate in the study. Each phase 3 study had its own long-term extension period, which subsequently led to the five phase 3 studies having different cutoff dates for the data included in the Integrated Summary of Safety.

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Each study had an independent external Data Monitoring Committee (DMC) that reviewed unblinded safety data at regular intervals during the conduct of the study and provided recommendations to continue, modify or terminate the respective study. In addition to the DMC, the Applicant convened an independent external Cardiovascular Adjudication Committee (CAC) that reviewed and adjudicated all potential cardiovascular events including VTEs and deaths.

All analysis for the safety review were performed on the predefined Safety Analysis Sets, which included all subjects who received at least one dose of study drug. All subjects were assigned to the “as treated” treatment group based on the actual treatment they received regardless of the treatment to which they were initially randomized. Except for one subject from Study M14-465, the “as treated” group for the initial treatment was the same as the randomized treatment group.

Safety analyses included all subjects enrolled in the UPA development program with emphasis on the pooled data from the phase 3 studies. To best identify potential safety signals, the Agency requested the Applicant to submit analyses based on UPA dose and comparator during the controlled periods and long-term extension periods of the phase 3 studies. These six analysis sets will be referred to extensively in Section 8 and include the following:

- Integrated controlled-period analysis sets:
  - The “PBO-Controlled UPA 15 mg” analysis set consists of data from Studies M13-542, M13-549 and M14-465. All three of these studies randomized subjects to a PBO and UPA 15 mg group during the 12-week controlled period of the studies. This analysis set allows for the direct comparison of AEs between the proposed marketed dose of UPA 15 mg and PBO treatment arms.
  - The “PBO-Controlled UPA 15 mg and 30 mg” analysis set consists of data from Studies M13-542 and M13-549. These two studies randomized subjects to one of three treatment arms PBO, UPA 15 mg or UPA 30 mg during the 12-week controlled period of the studies. This analysis set allows for the relative comparison of the two UPA doses to assess for a dose-dependent effect of UPA as well as the comparison to PBO-treated subjects.
  - The “MTX-Controlled” analysis set included data from Studies M13-545 and M15-555. These studies randomized subjects to receive either MTX, UPA 15 mg or UPA 30 mg during the 12- or 14-week controlled period, respectively. These studies again allowed for the relative comparison of the two UPA doses to assess for a dose-dependent effect as well as the comparison to MTX-treated subjects. Pooling of these two studies was deemed acceptable despite having Study M13-545 enrolled MTX-naïve subjects and Study M15-555 enrolled MTX-IR subjects.
- Integrated long-term analysis sets:

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- The “Any Phase 3 UPA 15 mg” analysis set consists of data from all five phase 3 studies, M13-542, M13-549, M13-545, M15-555 and M14-465. These studies all followed subjects treated with UPA 15 mg either from the time of randomization or from the time of crossover following the end of the controlled periods up to one year.
- The “Any Phase 3 UPA 15 mg and 30 mg” analysis set consists of Studies M13-542, M13-546, M13-545 and M15-555. These studies followed subjects treated with UPA 15 mg or UPA 30 mg either from the time of randomization or from the time of crossover following the end of the controlled periods up to one year.
- The “Any RA UPA” analysis set consists of all subjects enrolled in the phase 2 and phase 3 studies. For this analysis set, the Applicant pooled subjects treated with the immediate-release formulation used in the phase 2 studies and the respective extended-release formulations used in the phase 3 studies. Since the Applicant demonstrated the bioequivalence between the BID dosing of the immediate-release formulation and the daily extended-release formulation in Study M13-538, pooling of these subjects was deemed acceptable for the safety analyses.

Study M14-465 which included PBO, UPA 15 mg and ADA treatment arms was analyzed separately to compare the relative safety of UPA 15 mg versus subjects treated with ADA and PBO in the controlled period and long-term periods of the study.

For this review, each safety section is analyzed separately by the controlled period and the long-term period. The controlled period utilized the “PBO-Controlled UPA 15 mg”, “PBO-Controlled UPA 15 mg and 30 mg”, and “MTX-controlled” analysis sets to evaluate the types and frequencies of AEs between the UPA groups and their respective control groups. Additionally, this data was reviewed to assess whether UPA induced a dose-dependent effect regarding AEs.

Review of the long-term period utilized the “Any Phase 3 UPA 15 mg”, “Any Phase 3 UPA 15 mg and 30 mg” and “Any RA UPA” analysis sets to compare the type and frequency of AEs between UPA 15 mg and 30 mg doses over the long-term treatment period. Relative safety was also analyzed in those studies that maintained subjects on active control beyond the control period.

## **8.2. Review of the Safety Database**

### **8.2.1. Overall Exposure**

As shown in Table 86, 4443 subjects received at least one dose of UPA in the phase 2 or phase 3 studies, and of these subjects, 2972 (67%) were exposed to UPA for at least 48 weeks. A total of 2630 subjects who were enrolled in the phase 3 studies received at least one dose of UPA 15 mg, the proposed dose for marketing, for a mean of 369 days. It is important to note that the majority

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of the long-term data in this Application is derived from subjects exposed to UPA for 48 weeks or less, thus, caution is required when interpreting the data of certain AEs that may occur with exposure to UPA for longer periods, e.g., malignancies, VTEs and MACE.

**Table 86. Number and Percentage of Subjects Exposed to Study Drug by Duration Intervals (“Any RA UPA” Analysis Set)**

	<b>UPA 6 mg            BID/15 mg QD            (N=2819)            n (%)</b>	<b>UPA 12mg            BID/30 mg QD            (N=1309)            n (%)</b>	<b>Any UPA            (N=4443)            n (%)</b>
≥4 weeks (28 days)	2776 (99)	1286 (98)	4373 (98)
≥12 weeks (84 days)	2673 (95)	1206 (92)	4205 (95)
≥24 weeks (168 days)	2415 (85)	1057 (81)	3852 (87)
≥36 weeks (252 days)	2032 (72)	1013 (77)	3413 (77)
≥48 weeks (336 days)	1710 (61)	908 (69)	2972 (67)
≥72 weeks (504 days)	680 (24)	382 (29)	1361 (31)
≥96 weeks (672 days)	188 (7)	60 (5)	520 (12)
Mean Duration (days)	383	388	433

Adapted from Applicant’s ISS Table 2.3 6.1 and Table 2.3 6.2

**8.2.2. Relevant characteristics of the safety population:**

Subject demographics and baseline disease characteristics are detailed for each individual study in Section 6. Overall, the average subject was overweight, White, female, and 55 years of age with moderately to severely active RA despite treatment with MTX. Over 83% of subjects lived in North America, Eastern Europe or South/Central America. The patient demographics and baseline disease characteristics of the UPA development program are representative of the expected US target population and the results of the study appear to be extrapolatable to the broader population.

**8.2.3. Adequacy of the safety database:**

The five phase 3 studies were designed to assess the safety of two doses of UPA (15 mg and 30 mg) compared to PBO, MTX and ADA with 12 or 14-week controlled periods followed by long-term extension studies. The studies enrolled a sufficiently large and broad population of patients with moderately to severely active RA who were either naïve to MTX, had an IR to MTX or other csDMARDs (restricted to chloroquine, hydroxychloroquine, sulfasalazine or leflunomide), and were IR or intolerant to bDMARDs. Furthermore, four of the five studies were conducted while the subjects were receiving concomitant MTX/csDMARD, which is the likely clinical scenario when the drug is marketed. The subject demographics and baseline disease characteristics are

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representative of the targeted patient population for the proposed indication. The phase 3 studies, in conjunction with the data from the phase 2 studies, provides an adequately sized safety database on which to identify potential safety signals of UPA.

Given UPA's mechanism of action and the potential for AEs with longer durations of treatment, the overall safety database is limited to some extent by the small number of subjects treated with UPA for longer periods of time than one year; however, this limitation should not affect the ability to conclude an overall determination of the risk-benefit assessment of UPA for the treatment of RA.

### **8.3. Adequacy of Applicant's Clinical Safety Assessments**

#### **8.3.1. Issues Regarding Data Integrity and Submission Quality**

Overall, the data integrity and submission quality of the current application was excellent. The submission was complete, well-organized, easily navigable in electronic format and the data consistent between case report tabulations, case report forms and narrative summaries for individual subjects. Review of the study sites using the site selection tool did not identify any potential problems with safety reporting.

#### **8.3.2. Categorization of Adverse Events**

Overall, the Applicant's process for recording, coding and categorizing AEs was acceptable.

All treatment-emergent AEs were summarized using MedDRA (version 19.1). The number and proportion of subjects reporting treatment-emergent AEs were summarized by MedDRA primary system organ class (SOC) and preferred term (PT). The exposure-adjusted TEAE rate per 100 PY of exposure was also summarized. For both short-term and long-term analysis sets, exposure-adjusted event rates (EAERs) and exposure-adjusted incidence rates (EAIRs) were utilized; EAERs were used when summarizing long-term AEs and EAIRs were used for AEs which typically occur as single instances or for composite endpoints of interrelated events (i.e., malignancies, MACE, and VTE).

Treatment-emergent AEs were defined as those that began or worsened in severity after the first dose of study drug but no more than 30 days after the last dose of study drug. A subject with more than one treatment-emergent AE reported for the same PT is counted only once for that term. For assessing the severity of AEs, investigators were to classify treatment-emergent AEs according to the Rheumatology Common Terminology Criteria (CTC; Outcome Measures in Rheumatology [OMERACT]). The number and percentage of subjects experiencing treatment-emergent AEs were summarized for each treatment group for the following AE categories:

- All AEs

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- All severe AEs
- All reasonably possibly related AEs
- All SAEs
- Frequent AEs (reported in 5% of subjects or more in any treatment group)
- Frequent reasonably possibly related AEs (reported in 5% of subjects or more in any treatment group)
- Discontinuations due to AEs
- Death

The AEs of special interest (including but not limited to infection, opportunistic infection, herpes zoster, TB, gastrointestinal perforations, malignancies, MACE, renal dysfunction, anemia, increased CPK, and drug-related hepatic disorders) were summarized. Event rate (per 100 patient years) for AEs of special interest were also summarized for the combined safety analyses. All AEs leading to discontinuation of study drug will be presented.

Changes from baseline by visit, and changes from baseline to minimum value, maximum value, and final values in continuous laboratory data, and vital signs will be summarized by treatment group. For the controlled period analysis, baseline values are defined as the last non-missing measurements recorded on or before the date of the first dose of study drug. For combined safety analysis of the controlled and long-term periods, baseline values were defined as the last non-missing measurements recorded on or before the date of the first dose of UPA. The laboratory data was categorized as low, normal, or high based on the normal ranges of the laboratory utilized. The shift tables tabulated the number and percentage of subjects with baseline values below/within/above the normal range versus minimum/maximum/final values below/within/above the normal range.

## **8.4. Safety Results**

### **8.4.1. Deaths**

Patients with RA have an increased risk of mortality compared to an age and gender matched general population with a standard mortality ratio between 1.2 and 2.7<sup>5,6,7</sup>. Severity of disease and a non-response to MTX appear to be risk factors for increased mortality<sup>5</sup>. Cardiovascular disease is the most common cause of death in patients with RA<sup>7,8</sup> and studies from the USA and

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<sup>5</sup> Gabriel SE et al Arthritis Rheum 2003 Jan;48(1):54-58

<sup>6</sup> Symmons DP et al J Rheumatol 1998 Jun;25(6):1027-7

<sup>7</sup> Sokka T et al Clin Exp Rheumatol 2008 Sep-Oct;26(Suppl 51):S35-61

<sup>8</sup> Solomon DH et al Arthritis Rheum 2006 Dec;54(12):3790-3798

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Europe demonstrated that approximately 50% of all deaths in the RA population were attributed to cardiovascular deaths<sup>9,10</sup>.

All deaths in the UPA development program were adjudicated by a CAC to assess for a cardiovascular or non-cardiovascular cause of death. Table 87 and Table 88 show the EAERs of all deaths (treatment-emergent and non-treatment emergent) during the controlled periods and long-term periods across the global phase 3 RA studies, respectively.

**Table 87. Death EAER Per 100 PY: Controlled Period Prior to Treatment Switching (Phase 3 Safety Analysis Set)**

	<b>PBO (N=1042) n/PY (n/100 PY)</b>	<b>MTX (N=530) n/PY (n/100 PY)</b>	<b>ADA (N=327) n/PY (n/100 PY)</b>	<b>UPA 15 mg QD (N=1569) n/PY (n/100 PY)</b>	<b>UPA 30 mg QD (N=913) n/PY (n/100 PY)</b>
Deaths	2/257 (0.8)	1/122 (0.8)	1/86 (1.2)	1/386 (0.3)	4/211 (1.9)

Adapted from Applicant's ISS Table 2.4\_7.1.1

**Table 88. Death EAER Per 100 PY: Long-Term Period All Exposure (Phase 3 Safety Analysis Set)**

	<b>MTX (N=314) n/PY (n/100 PY)</b>	<b>ADA (N=579) n/PY (n/100 PY)</b>	<b>UPA 15 mg QD (N=2630) n/PY (n/100 PY)</b>	<b>UPA 30 mg QD (N=1204) n/PY (n/100 PY)</b>
Deaths	1/314 (0.3)	4/468 (0.9)	14/2651 (0.5)	14/1362 (1)

Adapted from Applicant's ISS Table 2.4\_9.1.1.1.8, Table 2.4\_11.1.1.2.2.1, Table 2.4\_4.1.1.8.1, Table 2.4\_5.1.1.8.1

The data from both the controlled and long-term periods of the Phase 3 safety analysis set demonstrates that UPA 15 mg-treated subjects have similar EAERs of death as subjects treated with PBO, MTX and ADA. Conversely, the UPA 30 mg group has a greater EAER of death as compared to the UPA 15 mg group in both the controlled and long-term periods of the analysis sets. Additionally, the EAER of deaths for UPA 30 mg group is greater than the MTX group and similar to the long-term EAER of the ADA group in both the controlled and long-term periods.

<sup>9</sup> Maradit-Kremers H et al Arthritis Rheum 2005 Mar;52(3):722-32

<sup>10</sup> Wallberg-Jonsson S et al J Rheumatol 1997 Mar;24(3):445-51

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There was a total of 42 deaths (33 treatment-emergent and 9 non-treatment emergent) reported in the phase 2 and phase 3 RA studies, including Study M14-663. Thirty-three (25 treatment-emergent) deaths occurred in the UPA treatment arms: UPA 15 mg (n=14); UPA 30 mg (n=16), UPA 6 mg BID (n=4) and UPA 12 mg BID (n=1). Review of the individual death narratives based on study drug and dosing is summarized as follows:

- UPA 6 mg BID/15 mg QD (n=18)
  - Cardiovascular-related deaths (n=12)
    - Sudden Death/Unexplained deaths (n=6)
    - Myocardial Infarction (n=3)
    - Congestive Heart Failure (n=2)
    - Cerebrovascular Accident (n=1)
  - Respiratory System (n=3)
    - Acute Respiratory Distress Syndrome (n=1)
    - Infection (n=1)
    - Pulmonary Embolism (n=1)
  - Malignancy (n=3)
    - Lung (n=1)
    - Hodgkin's Lymphoma (n=1)
    - Melanoma (n=1)
- UPA 12 mg BID/30 mg QD (n=17)
  - Cardiovascular System (n=9)
    - Sudden Death/Unexplained (n=3)
    - Myocardial Infarction (n=5)
    - Aortic Aneurysm Rupture (n=1)
  - Respiratory System (n=2)
    - Respiratory Failure (n=1)
    - Pulmonary Embolism (n=1)
  - Infection (n=3)
    - Peritonitis (n=1)
    - Meningitis (n=1)
    - Pneumonia (n=1)
  - Malignancy (n=3)
    - Rectal/Colon (n=2)
    - Adenoma of unknown primary source (n=1)
- ADA 40 mg EOW (n=4)
  - Mixed Connective Tissue Disease (n=1)
  - Congestive Heart Failure (n=1)
  - Colon cancer (n=1)
  - Traumatic brain injury (n=1)
- PBO (n=2)
  - Sudden death/Unexplained (n=1)
  - Pneumocystis jirovecii pneumonia (n=1)
- MTX (n=1)
  - Myocardial Infarction (n=1)

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### Controlled Period

Two PBO-treated subjects experienced AEs that led to death (sudden death and pneumocystis jirovecii pneumonia) in the “PBO-controlled UPA 15 mg” analysis set and no UPA 15 mg-treated subjects died.

In the “PBO-controlled UPA 15 mg and 30 mg” analysis set, no subjects died in either the PBO or UPA 15 mg groups and there was one death due to congestive heart failure and pulmonary embolism (PE) reported in the UPA 30 mg group, which was adjudicated as a non-cardiovascular death due to unconfirmed D-dimer results.

Deaths were reported in the MTX (n=1), UPA 15 mg (n=1) and UPA 30 mg (n=3) treatment arms during the three-months of exposure in the “MTX-Controlled” analysis set. With exposure up to six months, the EAERs of deaths were 0.5 E/100 PY in the MTX group, 0.4 E/100 PY in the UPA 15 mg group and 1.2 E/100 PY in the UPA 30 mg group among subjects with no treatment switching. During the 26-week controlled period of Study M14-465, the EAER of death in the UPA 15 mg and ADA groups was 0 and 1.5 E/100 PY, respectively. No deaths occurred while subjects were treated with UPA 15 mg after switching from PBO or after switching from ADA.

### Long-Term Period

In the long-term “Any Phase 3 UPA 15 mg” analysis set the EAER of deaths for the UPA 15 mg group was 0.3 E/100 PY.

In the long-term “Any Phase 3 UPA 15 mg and 30 mg” analysis set the EAER of deaths was 0.4 E/100 PY for the UPA 15 mg group and 0.8 E/100 PY for the UPA 30 mg group.

In the long-term analysis of Study M13-545, EAERs of death for the MTX, UPA 15 mg and UPA 30 mg groups were 0.3 E/100 PY, 1.2 E/100 PY and 2.1 E/100 PY, respectively.

Through the data cutoff for Study M14-465, EAER of death in the UPA 15 mg and ADA groups was 0.4 E/100 PY and 0.9 E/100 PY, respectively.

The EAERs of death for UPA 15 mg and UPA 30 mg was 0.4 E/100 PY and 0.8 E/100 PY from review of the long-term data for “Any RA UPA” analysis set.

Two additional deaths were reported in subjects treated with UPA 30 mg for Study M14-663, one case each of respiratory failure and aortic aneurysm rupture.

The Applicant performed a standard mortality ratio (SMR) analysis using the World Health Organization country-age-gender specific death data for the general population that generated an SMR estimate of 0.58 (95% CI: 0.37, 0.85) for the 25 treatment-emergent deaths in the UPA groups. The expected number of deaths on UPA was 43 compared to the 25 observed.

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Reviewer's Comment:

The overall mortality rate of the UPA-treated subjects was consistent with rates in the general population when matched by country, age and gender. There were no specific safety signals identified regarding causes of death and no temporal relationship was identified between duration of UPA treatment and time of death. There was a higher EAER of death in subjects treated with UPA 30 mg compared to UPA 15 mg; however, the overall numbers of deaths were small, and it is difficult to draw firm conclusions from the data. Moreover, only the UPA 15 mg dose is being proposed for approval and the overall EAER of deaths of UPA 15 mg was similar to PBO during the controlled period and MTX control during the long-term period.

The most common cause of deaths of subjects treated with UPA were cardiovascular related, which is consistent with the overall RA population. All adjudicated cardiovascular deaths occurred in subjects with underlying cardiovascular risk factors.

#### 8.4.2. Serious Adverse Events

##### Controlled Period

Among the "PBO-controlled UPA 15 mg" analysis set, a greater proportion of UPA 15 mg-treated subjects experienced SAEs compared to PBO-treated subjects, 3.4% versus 1.8%, respectively. The EAERs of SAEs was 16 E/100 PY for the UPA 15 mg group and 9 E/100 PY in the PBO group. The majority of SAEs were reported in individual subjects in any treatment group, except for appendicitis, gastroenteritis, viral infection and wrist fracture each reported in two subjects treated with UPA 15 mg; pneumocystis jirovecii pneumonia and gastroenteritis were reported in two subjects and three subjects in the PBO group, respectively.

In the "PBO-Controlled UPA 15 mg and 30 mg" analysis set, the percentages of subjects with SAEs was lowest in the PBO group (1.3%) and higher in the UPA 15 mg and UPA 30 mg groups (4.7% and 4.9%, respectively). The EAERs of SAEs for the PBO, UPA 15 mg and UPA 30 mg treatment arms were 7 E/100 PY, 23 E/100 PY and 28 E/100 PY, respectively. The majority of SAEs were reported in one subject each in the three treatment arms except for wrist fracture (n=2, UPA 15 mg), pneumonia (n=2, UPA 30 mg) and prostate cancer (n=2, UPA 30 mg).

With exposure up to three months in the "MTX-Controlled" analysis set, the percentage of subjects with SAEs was similar among the MTX, UPA 15 mg and UPA 30 mg groups at 2.3%, 3% and 3.6%, respectively. The majority of SAEs were reported in one subject each in the groups except for acute cholecystitis (n=2, MTX), cholelithiasis (n=2, UPA 30 mg), pneumonia (n=3, UPA 30 mg).

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Up to Week 26 of Study M14-465, the EAER of SAEs was greatest in the ADA group (22 E/100 PY) and lower in the UPA 15 mg (13 E/100 PY) and PBO (11 E/100 PY) groups.

### Long-Term Period

In the long-term “Any Phase 3 UPA 15 mg” analysis set, the EAER of SAEs was 15 E/100 PY with the most frequent SAE reported being pneumonia. The EAER of SAEs was stable with continued treatment of UPA 15 mg. There was no increase in EAER of SAEs over the course of 24 months: 0 to 6 months, 13E n/100 PY; 6 to 12 months, 9 n/100 PY; >12 months, 9 n/100 PY.

In long-term “PBO-Controlled UPA 15 mg and 30 mg” analysis set, the EAERs of SAEs in subjects treated with UPA 15 mg and UPA 30 mg was 17 E/100 PY and 21 E/100 PY, respectively. The SAE with the highest EAER in the UPA treatment arms was pneumonia (1 E/100 PY and 2 E/100 PY, respectively). The EAER of SAEs was stable throughout the treatment duration and no increase in EAER of SAEs.

For the long-term analysis of Study M13-545, the EAERs of SAEs were comparable between the UPA 15 mg (14 E/100 PY) and UPA 30 mg (15 E/100 PY) groups of which both were higher than the MTX control group (12 E/100 PY). The most frequently reported SAE was pneumonia for the MTX, UPA 15 mg and UPA 30 mg groups at 1 E/100 PY, 1 E/100 PY and 2 E/100 PY, respectively. Through the data cutoff date for Study M14-465, the EAER of SAEs was 13 E/100 PY during any exposure to UPA 15 mg and 16 E/100 PY during any ADA exposure. The most frequent SAE in UPA-treated subjects was pneumonia and for ADA-treated subjects was osteoarthritis, worsening RA and pulmonary embolism.

In the “Any RA UPA” analysis set, the EAERs of SAEs for UPA 6 mg BID/15 mg QD-treated subjects were 14 E/100 PY and 21 E/100 PY for UPA 12 mg BID/30 mg QD subjects.

Safety narratives were reviewed, and no specific safety signals were identified regarding the types of SAEs or a temporal relationship between duration of UPA treatment and time of SAE onset.

### Reviewer’s Comment:

Overall, there was a greater percentage of subjects experiencing an SAE in subjects treated with UPA 15 mg compared to PBO-treated subjects. This greater percentage of SAEs was dose-dependent with higher proportions of UPA 30 mg-treated subjects reporting SAEs compared to subjects treated with UPA 15 mg or PBO. The dose-dependent increase in SAEs was also demonstrated in the long-term period analysis with higher EAERs of SAEs in UPA 30 mg-treated subjects. The types of SAEs were similar between treatment arms and the majority of events were reported in single subjects within an individual study and with no SAE occurring in more than three subjects. No safety signals were identified regarding an unexpected type of SAE and

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there was no clear temporal relationship between the duration of UPA treatment and onset of SAE.

### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

#### Controlled Period

Upadacitinib 15 mg-treated subjects had a small but higher proportion of AEs leading to discontinuation of study drug compared to PBO-treated subjects (3% versus 2%, respectively) in the “PBO-Controlled UPA 15 mg” analysis set. The majority of AEs leading to discontinuation of study drug were reported as single occurrences in each group except for anemia (n=2), vertigo (n=2), bronchitis (n=2), elevated ALT (n=2), elevated AST (n=3), increased serum creatinine (n=2) and headache (n=2) in the UPA 15 mg treatment arm; and worsening RA (n=2) and pneumocystis jirovecii pneumonia (n=2) in the PBO treatment arm. Overall, there were no meaningful differences between study arms in the types of AEs leading to discontinuation.

In the “PBO-Controlled UPA 15 mg and 30 mg” analysis set, the percentage of AEs leading to discontinuation was lowest in the UPA 15 mg group (3%) compared to the PBO (4%) and UPA 30 mg (7%) groups. There were no meaningful differences between treatment arms in the types of AEs leading to study drug discontinuation. Most AEs were reported by a single subject except for pneumonia (n=4), prostate cancer (n=2) and depression (n=2) in the UPA 30 mg group and worsening RA (n=6) in the PBO group.

The proportion of subjects with AEs leading to discontinuation of study drug was similar between the MTX (3%), UPA 15 mg (3%) and UPA 30 mg (3%) groups in the “MTX-Controlled” analysis set with up to three-months exposure. The majority of AEs leading to discontinuation of study drug were reported as single occurrences in each group except for ALT elevation which was reported in two subjects from each treatment arm.

Through Week 14 of Study M14-465, prior to any rescue therapy, the percentage of subjects with AEs leading to discontinuation of study drug was highest in the ADA group (5%) compared to the UPA 15 mg (3%) and PBO (2%) groups. Consistent results were seen through Week 26. There were no meaningful differences between treatment arms in the types of AEs leading to study drug discontinuation.

#### Long-Term Period

The EAER of AEs leading to discontinuation was 8 E/100 PY in the long-term “Any Phase 3 UPA 15 mg” analysis set with pneumonia being the most frequently reported AE.

In the long-term “PBO-controlled UPA 15 mg and 30 mg” analysis set, the proportion of subjects with AEs leading to discontinuation of study drug for the UPA 15 mg group was 9 E/100 PY

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compared to the UPA 30 mg group at 13 E/100 PY. The most frequent AE leading to discontinuation in both UPA treatment arms was pneumonia.

Through the study cutoff for Study M13-545, the EAERs of AEs leading to discontinuation of study drug were comparable across the MTX, UPA 15 mg and UPA 30 mg groups, 9 E/100 PY, 11 E/100 PY and 11 E/100 PY, respectively. The types of AEs were similar between treatment arms with the most frequently reported AEs being ALT, AST and liver function test increases (1 E/100 PY) in the MTX group. No AE leading to study drug discontinuation occurred at a rate greater than 1 E/100 PY in either UPA group.

Through the study cutoff for Study M14-465, the EAER of AEs leading to discontinuation of study drug was lower in the UPA 15 mg group (7 E/100 PY) compared to the ADA group (11 E/100 PY). The types of AEs were similar between treatment arms.

Analysis of the long-term “Any RA UPA” dataset further showed the dose-dependent increase of AEs leading to discontinuation of study drug in subjects treated with UPA 15 mg and UPA 30 mg, 8 E/100 PY and 13 E/100 PY, respectively.

Reviewer’s Comment:

The percentages of AEs leading to discontinuation of study drug was similar between subjects in the UPA 15 mg groups and PBO and MTX groups during the controlled periods of the five phase 3 studies. However, subjects treated with UPA 30 mg experienced a higher percentage of AEs that led to study drug discontinuation compared to either the UPA 15 mg or PBO group. These results are consistent with the overall trend seen in the safety data that demonstrates a dose-dependent increase of AEs with UPA treatment. In general, there were no meaningful differences between treatment arms in the types of AEs leading to study drug discontinuation.

#### 8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

##### 8.4.4.1 Overview of Adverse Events

###### Controlled Period

As shown in Table 89, the overall percentage of AEs was higher in UPA-treated subjects compared to PBO-treated subjects, 56% vs 48%, respectively. Similar trends were observed for SAEs and AEs leading to discontinuation of study drug. No deaths were reported in UPA-treated subjects and two deaths were reported in the PBO treatment arm.

**Table 89. Overview of Treatment-Emergent AEs: Controlled Period Comparing PBO vs. UPA 15mg Prior to Treatment Switching (PBO-Controlled UPA 15 mg Analysis Set)**

	PBO	UPA 15 mg QD
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	(N=1042) n (%)	(N=1035) n (%)
AEs	504 (48)	580 (56)
SAEs	19 (2)	35 (3)
AEs leading to discontinuation of study drug	21 (2)	29 (3)
Deaths	2 (<1)	0

Adapted from Applicant's ISS Table 2.4 1.1.1.1

Comparing doses of UPA 15 mg and 30 mg versus PBO-treated subjects demonstrated a dose-dependent increase in the percentages of AEs, SAEs and AEs leading to discontinuation of study drug (Table 90). There was one death reported in the UPA 30 mg treatment arm and no deaths in the UPA 15 mg and PBO treatment arms.

**Table 90. Overview of Treatment-Emergent AEs: Controlled Period Comparing PBO vs. UPA 15mg and 30 mg Prior to Treatment Switching (PBO-Controlled UPA 15 mg and 30 mg Analysis Set)**

	PBO (N=390) n (%)	UPA 15 mg QD (N=385) n (%)	UPA 30 mg QD (N=384) n (%)
AEs	203 (52)	218 (57)	230 (60)
SAEs	5 (1)	18 (5)	19 (5)
AEs leading to discontinuation of study drug	16 (4)	11 (3)	28 (7)
Deaths	0	0	1 (<1)

Source: Sponsor's ISS Table 2.4 2.1.1.1

In the MTX-controlled Studies M13-545 and M15-555 with exposure through three months, i.e., prior to pre-defined treatment switching, a higher proportion of subjects treated with UPA reported AEs, SAEs and AEs leading to discontinuation in a dose-dependent manner as shown in Table 91. These findings are consistent with those of the PBO-controlled studies. One death occurred in the PBO and UPA 15 mg dosing groups and three deaths occurred in the UPA 30 mg group. Although the data are confounded due to subjects switching treatment groups, analyses of EAER of AEs, SAEs and AEs leading to study drug discontinuation in these studies through six months demonstrated a similar frequency and dose-dependent increase of AEs with UPA-treated subjects compared to subjects treated MTX (data not shown).

**Table 91. Overview of Treatment-Emergent AEs: Controlled Period Comparing PBO vs. UPA 15mg and 30 mg Prior to Treatment Switching (MTX-Controlled UPA 15 mg and 30 mg Analysis Set)**

	MTX/csMTX (N=530) n (%)	UPA 15 mg QD (N=534) n (%)	UPA 30 mg QD (N=529) n (%)
AEs	256 (48)	265 (50)	280 (53)
SAEs	12 (2)	16 (3)	19 (4)
AEs leading to discontinuation of study drug	14 (3)	18 (3)	14 (3)
Deaths	1 (<1)	1 (<1)	3 (1)
Source: Sponsor's ISS Table 2.4 3.1.1.1			

Through the controlled-period of Study M14-465, subjects treated with UPA 15 mg or ADA 40 mg reported higher percentages of AEs, SAEs and AE leading to discontinuation compared to PBO-treated subjects. The overall number of AEs were similar between the UPA and ADA groups; however, ADA-treated subjects experienced a higher frequency of SAEs and AEs leading to discontinuation of study drug. There were no deaths in the UPA treatment group during the controlled period of the study but there were two deaths in each of the PBO and ADA treatment arms.

### Long-Term Period

Analysis of the "Any Phase 3 UPA 15 mg and 30 mg" analysis set (Studies M13-542, M13-545, M13-549, M15-555) demonstrated that the EAERs of AEs, SAEs and AEs leading to discontinuations were higher in the UPA 30 mg treatment arm compared to the UPA 15 mg treatment arm (Table 92). There was a higher number of deaths in subjects treated with UPA 30 mg compared to UPA 15 mg.

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**Table 92. Overview of TEAEs EAERs per 100 PY: Long-Term Exposure for Phase 3 Studies Comparing UPA 15 mg and 30 mg (Any Phase 3 UPA 15 mg and 30 mg Analysis Set)**

	<b>UPA 15 mg QD (N=1213) (PY=1411) E (E/100 PY)</b>	<b>UPA 30 mg QD (N=1204) (PY=1365) E (E/100 PY)</b>
AEs	4540 (322)	5033 (369)
SAEs	238 (17)	291 (21)
AEs leading to discontinuation of study drug	132 (9)	182 (13)
Deaths	6 (<1)	11 (1)

Adapted from Applicant's ISS Table 2.4 5.1.1.1.1

The "All Study Drug Exposure" analysis set, which included any subjects exposed to ADA or UPA, showed a higher frequency of EAERs of AEs, SAEs and AEs leading to study drug discontinuation in both ADA- and UPA-treated subjects compared to PBO. The EAER of overall AEs were similar between the ADA and UPA treatment arms (388 E/100 PY vs. 386 E/100 PY, respectively); however, ADA-treated subjects experienced higher rates of SAEs and AEs leading to discontinuation of study drug compared to UPA-treated subjects, 19 E/100 PY and 20 E/100 PY vs. 12 E/100 PY and 13 E/100 PY, respectively).

Analysis of all UPA-treated subjects (UPA 6 mg BID/15 mg QD vs. UPA 12 mg BID/30 mg QD) during the phase 2 and 3 studies of the Applicant's development program demonstrated a similar dose-dependent increase of all TEAEs (Table 93) as that observed in the phase 3 studies.

**Table 93. Overview of TEAEs EAERs per 100 PY: Long-Term Exposure for All Phase 2 and Phase 3 Studies (Any RA UPA Analysis Set)**

	<b>UPA 6 mg BID/15 mg QD (N=2819) (PY=2953) E (E/100 PY)</b>	<b>UPA 12mg BID/30 mg QD (N=1309) (PY=1389) E (E/100 PY)</b>
AEs	8280 (280)	5164 (372)
SAEs	424 (14)	292 (21)
AEs leading to discontinuation of study drug	243 (8)	185 (13)
Deaths	11 (<1)	11 (1)

Adapted from Applicant's ISS Table 2.4 6.1.1.1

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Analysis of the overall safety database demonstrated that UPA-treated subjects experienced a greater proportion of AEs and SAEs compared to PBO-treated subjects. This effect was dose-dependent as evidenced by the small but repeatedly higher proportions of UPA 30 mg-treated subjects experiencing AEs compared to subjects treated with UPA 15 mg in both the controlled and long-term periods of the phase 3 studies. During the controlled periods, similar percentages of subjects reported AEs leading to discontinuation of study drug in both UPA groups; however, analysis of the long-term period demonstrated a higher proportion of UPA 30 mg-treated subjects compared to UPA 15 mg-treated subjects discontinued study drug due to an AE. There was a higher EAER of death in subjects treated with UPA 30 mg compared to UPA 15 mg during the long-term period; however, the overall numbers of deaths were small, and it is difficult to draw firm conclusions from the data.

#### 8.4.4.2 Common Adverse Events

##### Controlled Period

Table 94 shows the frequency of AEs, defined by Preferred Term (PT), which occurred in  $\geq 2\%$  of subjects and occurred in a greater proportion of UPA-treated subjects during the controlled periods of Studies M13-542, M13-549, and M14-465. The most frequently reported AEs for subjects treated with UPA 15 mg were upper respiratory tract infections (URI), nasopharyngitis, urinary tract infection (UTI), nausea, headache, bronchitis, diarrhea, increased ALT/AST/CPK serum laboratory values, hypertension, cough and back pain. There were no AEs that occurred in  $\geq 10\%$  of subjects in either treatment arm.

**Table 94. TEAEs Reported in  $\geq 2\%$  of Subjects During the Controlled Period Comparing PBO vs. UPA 15 mg Prior to Treatment Switching (PBO-Controlled UPA 15 mg Analysis Set)**

MedDRA Preferred Term (PT)	PBO (N=1042) n (%)	UPA 15 mg QD (N=1035) n (%)
Upper respiratory tract infection	38 (4)	53 (5)
Nasopharyngitis	33 (3)	46 (4)
Urinary tract infection	34 (3)	42 (4)
Nausea	23 (2)	36 (4)
Headache	38 (4)	33 (3)
Bronchitis	21 (2)	32 (3)
Diarrhea	26 (3)	30 (3)
ALT increase	27 (3)	28 (3)
CPK increase	9 (1)	26 (3)
Hypertension	22 (2)	24 (2)
Cough	10 (1)	23 (2)
AST increase	21 (2)	21 (2)
Back pain	14 (1)	21 (2)

Adapted from Applicant's ISS Table 2.4\_1.2.1.5

The most frequent AEs by SOC that were reported in  $\geq 4\%$  of UPA 15 mg treated subjects and more frequent than PBO-treated subjects were infections and infestations (27%); gastrointestinal

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disorders (11%); investigations (10%); blood and lymphatic disorders (5%); metabolism and nutrition disorders (5%); respiratory, thoracic and mediastinal disorders (5%); and general disorders and administrative site conditions (4%).

Analysis of AEs comparing doses of UPA 15 mg and 30 mg versus PBO-treated subjects in Studies M13-542 and M13-549 demonstrated similar types and frequencies of AEs as in the UPA 15 mg-controlled studies discussed above with UPA-treated subjects reporting a greater frequency of AEs compared to PBO-treated subjects but similar frequencies between UPA treatment arms (Table 95). The most common AEs reported with UPA 15 mg were UTI (94%), URI (3%) and nausea (3%). Subjects treated with UPA 30 mg more commonly reported increased serum CPK (5%), UTI (4%), URI (4%) and headache (3%). Subjects treated with PBO alone during the controlled period reported URI (4%), worsening RA (3%) and UTI (3%) as the most common AEs.

**Table 95. TEAEs Reported in ≥2% of Subjects During the Controlled Period Comparing PBO vs. UPA 15 mg and 30 mg Prior to Treatment Switching (PBO-Controlled UPA 15 mg and 30 mg Analysis Set)**

<b>MedDRA Preferred Term</b>	<b>PBO (N=390) n (%)</b>	<b>UPA 15 mg QD (N=385) n (%)</b>	<b>UPA 30 mg QD (N=384) n (%)</b>
Upper respiratory tract infection	22 (6)	25 (7)	23 (6)
Nasopharyngitis	20 (5)	19 (5)	22 (6)
Urinary tract infection	18 (5)	23 (6)	15 (4)
Nausea	11 (3)	22 (6)	10 (3)
Bronchitis	9 (2)	11 (3)	9 (2)
CPK increase	0	7 (2)	9 (2)
Neutropenia	0	7 (2)	9 (2)
Fatigue	5 (1)	4 (1)	9 (2)
Pyrexia	0	6 (2)	8 (2)

Adapted from Applicant's ISS Table 2.4 2.2.1.5

Similar results were observed in the controlled period of the MTX active comparator studies M13-545 and M15-555 demonstrating similar types and frequencies of AEs and with UPA-treated subjects reporting a greater frequency of AEs compared to MTX-treated subjects but similar frequencies between UPA treatment arms (data not shown).

The most common AEs reported during the controlled-period of Study M14-465 were similar to those reported during the controlled periods of the other four clinical phase 3 studies with subjects in the UPA 15 mg treatment arm experiencing a greater frequency of nasopharyngitis (4%), URI (4%), increases in serum ALT (4%) and bronchitis (3%). Overall, the types of AEs in ADA-treated subjects were consistent with those included in the current ADA package insert.

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### Long-Term Period

Analysis of the types and frequency of AEs in the “Any Phase 3 UPA 15 mg and 30 mg” analysis set, as well as, the “all study drug exposure” analysis set were similar to those observed during the PBO-controlled UPA 15 mg and 30 mg analysis (data not shown).

Analysis of AEs by SOC demonstrated that infections and infestations, gastrointestinal disorders, and investigations were the most commonly reported types of AEs in the PBO, UPA 15 mg and 30 mg treatment arms. The overall pattern of the most common AEs with long-term treatment of UPA 15 mg and 30 mg was similar to that observed in the first three months of the controlled periods of the clinical studies.

#### Reviewer’s Comment:

The most frequent AEs by SOC that were reported in a greater proportion of UPA 15 mg-treated subjects were infections and infestations (27%), gastrointestinal disorders (11%) and investigations (10%). Upper respiratory tract infections were the most commonly reported AE in the infections and infestations SOC. Nausea was the most common AE reported in the gastrointestinal SOC and elevations in CPK was the most commonly reported AE in the investigations SOC. Overall, the types of AEs were similar to those reported in RA patients treated with immunosuppressant therapy and similar to other JAK inhibitors. No unique safety signal was identified.

#### **8.4.4.3 Adverse Drug Reactions for Labeling**

Assessment of the Applicant’s analysis of adverse drug reactions (ADR) for UPA followed the guidelines described in Council for International Organizations of Medical Sciences (CIOMS) Working Groups III and V Guidelines for Preparing Core Clinical-Safety Information on Drugs' (CIOMS Working Groups III and V 1999).

In general, the decision to consider an AE as an ADR was based on the totality of evidence and on levels of evidence taking the following considerations: disproportionate number of reports between PBO and UPA, observed dose-related effect, consistency of the findings across studies, similar trend among medically related events, temporal relationship, dechallenge/rechallenge information for relevant event reports, preclinical data and biological plausibility based on mechanism of action and/or class effect.

All AEs by MedDRA coded to PTs in the “PBO-controlled UPA 15 mg and 30 mg” analysis set (Studies M13-549, M13-542) were examined regardless of the investigator causality assessment.

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AEs that occurred in  $\geq 1\%$  of subjects in the UPA 15 mg and 30 groups and at a higher rate compared to the PBO group were identified.

Additionally, if any AE rate was found to be greater on UPA 15 mg but not on UPA 30 mg, and the AE rate in UPA 15 mg was greater than PBO in the PBO-controlled UPA 15 mg analysis set (Studies M13-549, M14-465, M13-542), the event was considered for inclusion as an ADR. AEs that were determined to have biologic plausibility from JAK inhibition were also evaluated and considered for inclusion as an ADR. Table 96 shows the ADRs that were identified based on the analysis of AEs and medical review are presented for the 12-week controlled period of pooled clinical studies from the “PBO-controlled UPA 15 mg” analysis set.

**Table 96. Proposed Adverse Drug Reactions Occurring in the UPA 15 mg and PBO Groups (“PBO-Controlled UPA 15 mg” Analysis Set).**

MedDRA Preferred Term	PBO (N=1042) n (%)	UPA 15 mg QD (N=1035) n (%)
Upper respiratory tract infection	99 (10)	140 (14)
Nausea	23 (2)	36 (4)
CPK increase	9 (1)	26 (3)
Cough	10 (1)	23 (2)
Neutropenia	2 (<1)	19 (2)
Pyrexia	0	12 (1)
Hypercholesterolemia	2 (<1)	7 (1)

Adapted from Applicant’s ISS Table 2.4 1.2.1.1 and Table 2.4 1.2.16

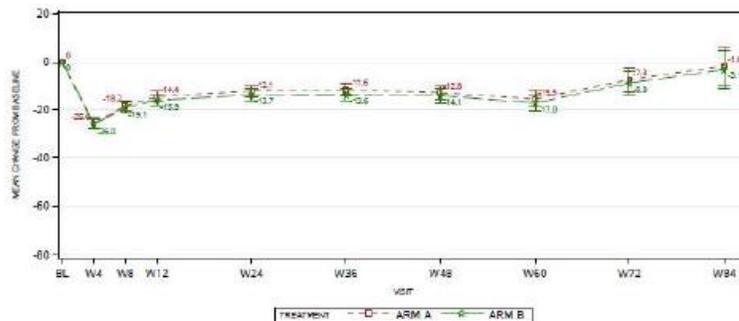
#### 8.4.5. Laboratory Findings

##### 8.4.6.1 Hematology

Adverse events related to hemoglobin, neutrophils and lymphocytes are discussed in Section 8.5. Consequently, only clinical changes in platelets will be discussed in the current section.

There was a larger decrease in mean platelet counts at Week 4 in the UPA 15 mg group compared to the PBO group,  $-27 \times 10^9/L$  versus  $-0.5 -27 \times 10^9/L$ , respectively, in the “PBO-controlled UPA 15 mg” analysis set. Platelet counts slowly increased by Week 12 but still remained below baseline values (Figure 13).

**Figure 13. Mean Change from Baseline in Platelets Over Time (Any Phase 3 UPA 15 mg Analysis Set)**



Adapted from Applicant's ISS Figure 2.5\_4.5.1

No UPA-treated subjects in the “PBO-Controlled UPA 15 mg” or “PBO-Controlled UPA 15 mg and 30 mg” analysis sets experienced a Grade 2, 3 or 4 change in platelet counts. In the “MTX-controlled” analysis set, there was one UPA 15 mg-treated subject who experienced a Grade 2 decrease in platelet counts and one UPA 30 mg-treated subject who experienced a Grade 4 decrease in platelet count over a 16-day period after initiating UPA. The same UPA 30 mg-treated subject experienced the concomitant AEs of pneumonia, sepsis, renal insufficiency and respiratory insufficiency on Day 15 and died secondary to septic shock on Day 16.

There were no Grade 2, 3 or 4 changes in platelet counts in UPA-treated subjects through Week 26 of Study M14-465.

In the controlled-period analysis sets, shift analyses from baseline to postbaseline showed that the percentages of subjects who had platelet counts  $<600 \times 10^9/L$  at baseline and had a postbaseline platelet count  $>600 \times 10^9/L$  were low and similar between PBO, MTX and UPA treatment arms. Analysis of the long-term period analysis sets of the phase 3 studies were consistent with the values observed during the controlled-periods.

Very few subjects experienced an AE related to thrombocytopenia or thrombocytosis in any treatment arm in either of the three controlled-period analysis sets and the rates were similar between the UPA 15 mg, UPA 30 mg and PBO groups (data not shown). Similar results were observed during the long-term periods of the same studies.

The EAERs of platelet-related AEs were low and similar between the UPA 15 mg and ADA groups through the data cutoff of Study M14-465.

Through the data cutoff for Study M13-545 the EAER of thrombocytopenia was higher in the UPA 30 mg group compared to the UPA 15 mg group or MTX arm, 0.9 E/100 PY, 0 E/100 PY and 0.3

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E/100 PY; however, the overall number of subjects reporting thrombocytopenia in Study M13-545 was small.

Reviewer's Comments:

In general, there were no clinically meaningful differences in platelet counts identified in subjects treated with UPA compared to subjects treated with PBO, MTX or ADA during the controlled periods of the phase 3 studies. In the long-term analyses, changes in platelet counts were similar between UPA 15 mg, ADA- and MTX-treated subjects. Changes in platelet counts did not appear to be dose-dependent in the controlled and long-term analyses. There was no apparent correlation between changes in platelet counts and the development of VTE.

#### 8.4.6.2 Chemistry

Adverse events of abnormal chemistry values ALT, AST, creatinine and CPK are discussed in Section 8.5. This section will focus on the clinically relevant elevation in lipid profiles related to UPA treatment.

As discussed in Section 8.5.13, RA patients have an increased risk of cardiovascular disease compared to the general population. Elevation of total cholesterol (TC) and low-density lipoprotein-C (LDL-C) are correlated with a higher risk of cardiovascular events in the general population; however, a "lipid paradox" has been observed in patients with RA who have an increased cardiovascular risk at low lipid levels<sup>11</sup>.

Lower lipid levels are also found in other inflammatory conditions, suggesting systemic inflammation is likely a factor driving the decrease in lipid levels. Effective treatment of RA by csDMARDs and bDMARDs has been observed to increase or re-normalize lipid levels. The level of increase in lipid levels varies among different RA therapies, with JAK inhibitors and anti-IL-6 therapies showing the greatest increase. A meta-analysis of tofacitinib did not demonstrate an increase in cardiovascular disease risk despite increases in LDL-C, compared to other RA therapies<sup>12</sup>. In a Phase 4 study designed to evaluate if increased lipid levels lead to increased rates of MACE, tocilizumab, an anti-IL6 receptor antibody which increases lipids by 12%, did not significantly increase MACE rates in comparison to etanercept, an anti-TNF agent<sup>13</sup>

An UPA-induced dose-dependent increase of lipids was observed during phase 2 studies. In the phase 3 program, TC, LDL-C, high density lipoprotein-C (HDL-C), apoB and apoA1 were measured to further assess the effect of UPA on lipids. Triglycerides were also measured during the study but since fasting was not required prior to blood sampling, the results may be confounded and

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<sup>11</sup> Robertson J et al. Nat Rev Rheumatol 2013 Sep;9(9):513-23

<sup>12</sup> Charles-Schoeman C et al. Semin Arthritis Rheum 2016 Aug;46(1):71-80.

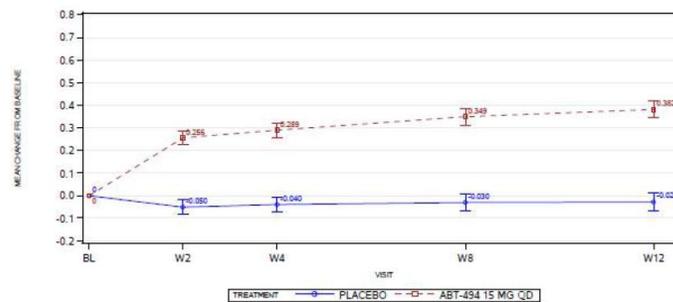
<sup>13</sup> Giles JT et al. ACR/ARHP Annual Meeting 2016 Oct; Abst No. 3L

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difficult to interpret. In the phase 3 studies, approximately 29% of subjects had elevated LDL-C ( $\geq 3.36$  mmol/L) and 58% had lower HDL-C ( $\leq 1.55$  mmol/L) at baseline.

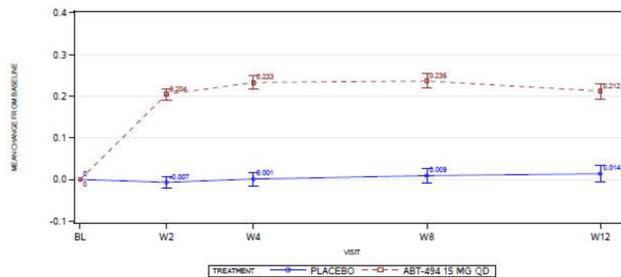
In the “PBO-Controlled UPA 15 mg” analysis set, the mean changes in lipid parameters from baseline to Week 12 were higher in the UPA 15 mg group compared to the PBO group (Figure 14 and Figure 15). At Week 12, the mean ratios of TC/HDL-C and LDL-C/HDL-s remained similar for the PBO and UPA 15 mg group (data not shown).

**Figure 14. Mean Change from Baseline in LDL-C Over Time (PBO-Controlled UPA 15 mg Analysis Set)**



Adapted from Applicant's ISS Figure 2.5\_1.1.6

**Figure 15. Mean Change from Baseline in HDL-C Over Time PBO-Controlled UPA 15 mg Analysis Set**

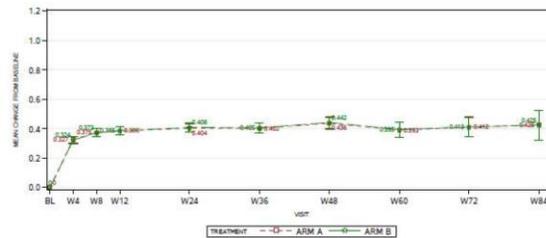


Adapted from Applicant's ISS Figure 2.5\_1.1.6

The mean change from baseline in LDL-C and HDL-C for UPA 15 mg-treated subjects peaked by Week 8 and then plateaued through Week 84 (Figure 16 and Figure 17).

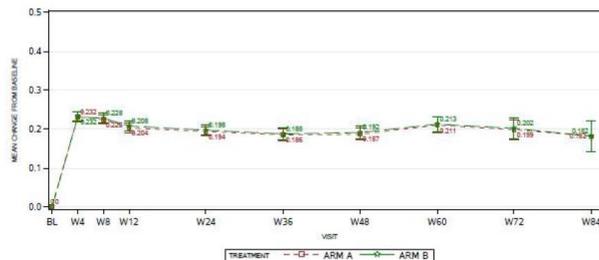
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**Figure 16. Mean Change from Baseline in LDL-C Over Time (Any Phase 3 UPA 15 mg Analysis Set)**



Adapted from Applicant's ISS Figure 2.5\_4.5.1

**Figure 17. Mean Change from Baseline in HDL-C Over Time (Any Phase 3 UPA 15 mg Analysis Set)**



Adapted from Applicant's ISS Figure 2.5\_4.5.1

Shift analyses were performed on the “PBO-Controlled UPA 15 mg” analysis set using National Cholesterol Education Program ATP III lipid categories. Total cholesterol shift analysis showed 10% and 2% of subjects shifted from <5.2 mmol/L (desirable) at baseline to  $\geq 6.2$  mmol/L (high) in UPA 15 mg-treated subjects versus PBO, respectively. HDL-C shift analysis demonstrated that >90% UPA 15 mg-treated subjects and 88% of PBO-treated subjects had favorable HDL levels ( $\geq 1$  mmol/L) at baseline and remained in that category. LDL-C shift analysis demonstrated 9% and 2% of subjects shifted from <3.4 mmol/L (optimal to near optimal) at baseline to  $\geq 4.1$  mmol/L (high to very high) in the UPA 15mg group versus PBO, respectively.

Approximately 11% of subjects in the “Any Phase 3 UPA 15 mg” analysis set reported statin use at baseline. These subjects showed a trend toward smaller mean increases in TC and LDL-C and stable HDL-C levels. Nine subjects in the UPA 15 mg group and five subjects in the PBO group-initiated statin therapy during the PBO-controlled periods of the phase 3 studies. A trend of reduced LDL-C was noted.

Review of the “PBO-Controlled UPA 15 mg and 30 mg” analysis set demonstrated an increase of TC, LDL-C and HDL-C levels in both UPA treatment arms without an apparent dose-dependent effect as both groups demonstrated similar increases in lipids (data not shown).

Reviewer's Comments:

UPA treatment was associated with an increase in lipid parameters in a manner consistent with other JAK inhibitors. The increased lipid concentrations did not affect the overall atherogenic indices as evidenced by ratios of TC/HDL-C and LDL-C/HDL-C. The observed lipid elevations were responsive to statin therapy in the limited number of subjects who initiated statin therapy and there was no relationship identified between subjects with elevated lipids and MACE in the phase 3 studies.

#### 8.4.6. Vital Signs

Except for weight gain, the overall mean changes in vital signs with UPA treatment were minimal and are not considered to be clinically meaningful (data not shown). Moreover, changes in vital signs were similar between the UPA 15 mg and 30 mg groups and PBO, MTX, and ADA groups.

A greater percentage of UPA-treated subjects experienced an increase in weight compared to PBO, MTX and ADA-treated subjects. The percentages of subjects gaining weight on UPA therapy were similar between dosing groups. There were four reports from the same investigator sites of subjects with serious weight gain, two subjects treated with UPA 15 mg and two subjects with UPA 30 mg. The increased weight gain was approximately 10 kg from baseline in all four subjects and occurred between Day 141 to 337 of study drug. No UPA dose was changed but two subjects discontinued study drug due to the weight gain.

#### 8.4.7. QT

Extensive monitoring and evaluation of ECG parameters including exposure-response analyses during the UPA Phase 1 program showed no evidence of UPA effects on cardiac conduction, including no effect on QT/QTc interval. Consequently, based on the compiled evidence from the Phase 1 studies, the Agency agreed that additional thorough QT studies for UPA were not required.

### 8.5. Analysis of Submission-Specific Safety Issues

#### 8.5.1. Adverse Events of Special Interest: Serious Infections

Patients with RA have been shown to have an approximately 1.5-times higher risk of infection than in the general population and those RA patients treated with immunosuppressive therapy have an approximately two-fold greater risk<sup>14,15</sup>.

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<sup>14</sup> Doran MF et al. Arthritis Rheum 2002 Sep;46(9):2294-300.

<sup>15</sup> Bernatsky S et al. Rheumatology 2007 Jul;46(7):1157-60.

JAK inhibitors block signaling of multiple cytokines, some of which are important in the activation, function and proliferation of lymphocytes. Consequently, JAK inhibitor therapy in RA patients are likely to be associated with an increased risk of infections. Data from several clinical trials and observational registries showed a rate of serious infection in RA patients treated with biologics and JAK inhibitors ranged between 1.9 to 4.2 E/100 PY.

### Controlled Period

As shown in Table 97, the percentage of subjects with serious infections was approximately two-fold higher in UPA 15 mg-treated subjects compared to PBO-treated subjects, 1.2% vs. 0.6%, respectively. Serious infections reported in  $\geq 2$  subjects treated with UPA 15 mg were appendicitis, gastroenteritis and viral infection, while gastroenteritis and pneumocystis jirovecii pneumonia were most frequent in the PBO treatment arm.

**Table 97. TEAEs of Serious Infections in Subjects During the Controlled Period Comparing PBO vs. UPA 15 mg Prior to Treatment Switching (PBO-Controlled UPA 15 mg Analysis Set)**

<b>MedDRA Preferred Term</b>	<b>PBO (N=1042) n (%)</b>	<b>UPA 15 mg QD (N=1035) n (%)</b>
Any Serious Infection	6 (0.6)	12 (1.2)
Appendicitis	0	2 (0.2)
Bronchiolitis	0	1 (<0.1)
Bronchitis bacterial	1 (<0.1)	0
Enterocolitis infectious	0	1 (<0.1)
Fallopian tube abscess	0	1 (<0.1)
Gastroenteritis	3 (0.3)	2 (0.2)
Influenza	0	1 (<0.1)
Kidney infection	0	1 (<0.1)
Lower respiratory tract infection	0	1 (<0.1)
Lung infection	0	1 (<0.1)
Peritonitis	0	1 (<0.1)
Pneumocystis jirovecii pneumonia	2 (0.2)	0
Pneumonia	1 (<0.1)	0
Sepsis	1 (<0.1)	0
Urosepsis	0	1 (<0.1)
Viral infection	0	2 (0.2)

Adapted from Applicant's ISS Table 2.4 1.3.1.5 and ISS Table 2.4 1.1.2.1

Subjects treated with UPA 15 mg and 30 mg demonstrated a dose-dependent increase in the percentages of subjects with serious infections compared to PBO-treated subjects. The overall

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percentage of subjects with a serious infection was similar between PBO- and UPA 15 mg-treated subjects (0.3% vs. 0.5%, respectively) but substantially greater in subjects treated with UPA 30 mg (1.8%). The only serious infection reported in  $\geq 2$  subjects in a group was pneumonia in the UPA 30 mg treatment arm. A total of six (1.6%) subjects treated with UPA 30 mg had a serious infection that led to discontinuation of study drug and included two cases of pneumonia and one case each of ophthalmic herpes zoster, herpes zoster, varicella and staphylococcal wound infection.

A similar dose-response relationship was observed during three months of the MTX-controlled studies as that observed in the PBO-controlled studies. The percentage of subjects with a serious infection was similar between MTX- and UPA 15 mg-treated subjects (0.4% vs. 0.6%, respectively) but substantially greater in subjects treated with UPA 30 mg (1.5%). In the same analysis set with exposure up to 24-weeks, the EAERs of serious infections were higher in the UPA 15 mg and 30 mg arms (4.4 E/100 PY and 4.8 E/100 PY, respectively) compared to the active controlled MTX arm (2.5 E/100 PY) among subjects who did not switch treatment arms.

Through the controlled period of Study M14-465, prior to subjects switching treatment groups, the EAERs of serious infections were similar between the UPA 15 mg and ADA 40 mg EOW treatment arms (5 E/100 PY vs. 4 E/100 PY, respectively) but greater than PBO-treated subjects (3 E/100 PY). This trend continued even after subjects switched to either the UPA or ADA treatment arms, 4 E/100 PY vs. 4 E/100 PY, respectively.

### Long-Term Period

Analysis of the phase 3 UPA 15 mg and 30 mg analysis set (Studies M13-542, M13-545, M13-549, M15-555) showed a higher proportion of serious infections in the UPA 30 mg treatment arm compared to the UPA 15 mg treatment arm (Table 98). The most common serious infections in UPA 15 mg-treated subjects were pneumonia, bronchitis and cellulitis. The most common serious infections in subjects treated with UPA 30 mg were pneumonia, sepsis, herpes zoster, bronchitis and influenza. Three subjects treated with UPA 30 mg died due to serious infection (meningitis, peritonitis and sepsis/pneumonia).

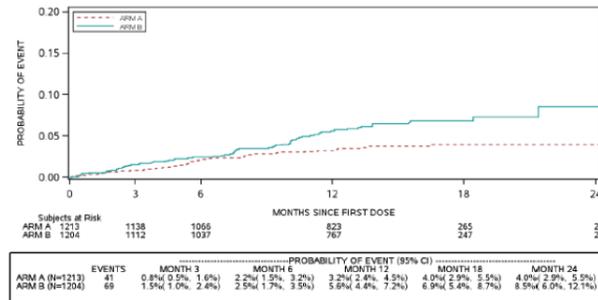
**Table 98. TEAEs of Serious Infections EAERs per 100 PY: Long-Term Exposure for Phase 3 Studies Comparing UPA 15 mg and 30 mg (Any Phase 3 UPA 15 mg and 30 mg Analysis Set)**

<b>MedDRA Preferred Term</b>	<b>UPA 15 mg QD (N=1213) (PY=1411) E (E/100 PY)</b>	<b>UPA 30 mg QD (N=1204) (PY=1365) E (E/100 PY)</b>
Any Serious Infection	51 (4)	85 (6)
Bronchitis	4 (0.3)	5 (0.4)
Cellulitis	3 (0.2)	4 (0.3)
Diverticulitis	1 (<0.1)	3 (0.2)
Gastroenteritis	0	3 (0.2)
Herpes zoster	0	5 (0.4)
Influenza	2 (0.1)	5 (0.4)
Pneumonia	13 (0.9)	23 (1.7)
Pyelonephritis	1 (<0.1)	2 (0.1)
Sepsis	1 (<0.1)	7 (0.5)
Upper respiratory infection	0	2 (0.1)
Urinary tract infection	2 (0.1)	4 (0.3)
Wound infection staphylococcal	0	4 (0.3)

Adapted from Applicant's ISS Table 2.4 5.4.1.2.1

A Kaplan-Meier analysis for serious infections for the “Any Phase 3 UPA 15 mg and 30 mg” analysis set (Studies M13-542, M13-545, M13-549, M15-555) demonstrated a higher risk of serious infections in the UPA 30 mg treatment arm and suggested that the risk of subjects experiencing a serious infection on UPA 15 mg remained constant over the 24-month treatment period while increasing in subjects treated with UPA 30 mg (Figure 17).

**Table 99. Kaplan-Meier Curve for TEAEs of Serious Infections: Long-Term Exposure for UPA 15 mg and 30 mg (Any Phase 3 UPA 15 mg Analysis Set)**



Long-term analysis of the UPA 15 mg dose across all five phase 3 studies showed that serious infections occurred at a rate of 4 E/100 PY with the most common infections being pneumonia, appendicitis, bronchitis, cellulitis, gastroenteritis and sepsis. A total of 32 serious infections that occurred in the UPA 15 mg arm led to discontinuation of study drug and one serious infections led to death (pneumonia).

The number of serious infections through the study cutoff date for Study M13-545 continued to demonstrate an UPA dose-dependent effect with the EAER of serious infections: MTX monotherapy (3 E/100 PY) vs. UPA 15 mg (4 E/100 PY) and UPA 30 mg (5 E/100 PY).

In Study M14-465, the EAERs of serious infections from all subjects (including those who switched treatments) were similar between the UPA 15 mg and ADA groups; however, analysis of those subjects who did not switch treatments, and consequently were remained on their originally assigned dose, demonstrated a lower rate of serious infections in subjects treated with UPA 15 mg (4 E/100 PY) compared to ADA-treated subjects (6 E/100 PY).

Review of the “Any RA UPA” analysis set for serious infections was consistent with results from the phase 3 studies demonstrating types infections consistent with the RA patient population, with pneumonia being the most frequently reported serious infection.

Subjects with a positive hepatitis B core antibody (HBcAb) test at screening could enter the phase 3 studies if there was no evidence of active hepatitis B virus (HBV) disease, (subjects with positive anti-HBc antigen required HBV DNA PCR testing). A total of 395/4443 (9%) subjects had a positive HBcAb test at screening in the phase 2 and phase 3 studies.

One UPA-treated subject in the “Any RA UPA” analysis set and one UPA-treated subject from Study M14-663 experienced a SAE of HBV reactivation.

- Subject (b) (6) (Study M13-549; UPA 30 mg) was a 65-year-old female with a history of cholelithiasis and cholecystectomy due to infection and receiving

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treatment for her RA with leflunomide and methylprednisolone experienced HBV reaction. The subject was HBcAb-positive, but negative for HBV DNA and HBsAg, at screening. On Day 421 of UPA treatment, the subject presented with ALT and AST > 8 x ULN. Further evaluation revealed a positive HBsAg and HBV DNA > 1.7 x 10<sup>8</sup> IU/mL. Chronic hepatitis with HBV cytolytic flare reactivation was reported. The subject was treated with entecavir, arginine, phospholipids, amioplasma and ursodeoxycholic acid and discontinued the study.

- Subject (b) (6) (Study M14-663; UPA 15 mg) was a 78-year-old female with a history of Sjogren's syndrome and receiving treatment with MTX and prednisolone for her RA when she experienced HBV reactivation. On Day 337 of UPA treatment, HBV DNA increased. Transaminase levels remained within normal ranges throughout the duration of the study. The subject was treated with entecavir and a repeat test on Day 386 revealed HBV DNA was no longer available. The subject was discontinued from the study.

Two additional cases of UPA-treated subjects presenting with positive HBV tests were reported in the "Any RA UPA" analysis set but were considered nonserious AEs. Review of the cases suggested that the two incidents did not constitute HBV reactivation.

Reviewer's Comments:

A higher rate of serious infections was observed in a dose-dependent manner of UPA-treated subjects compared to control subjects across all analysis sets.

Overall, there was a greater percentage of subjects experiencing a serious infection when treated with UPA 15 mg compared to PBO-treated subjects. This greater percentage of serious infections was dose-dependent with higher proportions of UPA 30 mg-treated subjects reporting serious infections compared to subjects treated with UPA 15 mg or PBO. The dose-dependent increase in serious infections was also demonstrated in the long-term period analysis with higher EAERs of serious infection in UPA 30 mg-treated subjects. The types of serious infections were similar between treatment arms and no clear temporal relationship between the duration of UPA treatment and onset of serious infection was identified. Additionally, there were two definitive cases of HBV reactivation reported in UPA-treated subjects during the phase 2 and phase 3 program. Consequently, the UPA USPI should contain information regarding risks of serious infections and potential HBV reactivation.

**8.5.2. Adverse Events of Special Interest: Opportunistic Infections: Excluding Tuberculosis**

Controlled Period

Analysis of the "PBO-controlled UPA 15 mg" analysis set showed a similar proportion of opportunistic infections in PBO- and UPA 15 mg-treated subjects (Table 100). All opportunistic

infections in the UPA 15 mg group were nonserious mucosal candidiasis including four cases of oral candidiasis and one case of esophageal candidiasis. Three cases of opportunistic infections occurred in the PBO arm: one case of oral candidiasis and two serious cases of pneumocystis jirovecii pneumonia (one death and one discontinuation of study drug).

**Table 100. TEAEs of Opportunistic Infections in Subjects During the Controlled Period Comparing PBO vs. UPA 15mg Prior to Treatment Switching (PBO-Controlled UPA 15 mg Analysis Set)**

<b>MedDRA Preferred Term</b>	<b>PBO (N=1042) n (%)</b>	<b>UPA 15 mg QD (N=1035) n (%)</b>
Any Opportunistic Infection	3 (0.3)	5 (0.5)
Esophageal candidiasis	0	1 (<0.1)
Oral candidiasis	1 (<0.1)	4 (0.4)
Pneumocystis jirovecii pneumonia	2 (0.2)	0

Adapted from Applicant's ISS Table 2.4 1.1.2.1 and ISS Table 2.4 1.3.1.6

Rates of opportunistic infections from the controlled periods of Studies M13-542 and M13-549 demonstrated a higher number of opportunistic infections in subjects treated with UPA 30 mg compared to UPA 15 mg and PBO groups, n=6, (1.6%); n=2 (0.5%) and n=1 (0.3%), respectively. All opportunistic infections reported were oral candidiasis except for one case of varicella zoster pneumonia reported in a subject treated with UPA 30 mg.

A higher number of subjects treated with UPA 30 mg developed opportunistic infections compared with UPA 15 mg or MTX-controlled subjects (n=4, n=0 and n=1, respectively) during the three months of the controlled periods from Studies M13-545 and M15-555. Opportunistic infections included oral candidiasis, oropharyngeal candidiasis, positive cytomegalovirus test and fungal esophagus. In the analysis through the six-month time point of Study M13-545, subjects demonstrated few additional opportunistic infections with only one case of cryptococcal pneumonia in the UPA 15 mg group.

Through Week 14 of Study M14-465 the number of opportunistic infections were similar in the PBO (n=2, 0.3%), UPA 15 mg (n=3, 0.5%) and ADA (n=1, 0.3%) groups, respectively. Opportunistic infections included esophageal candidiasis (UPA 15 mg, n=1), oral candidiasis (UPA 15 mg, n=2; ADA, n=1) and pneumocystis jirovecii pneumonia (PBO, n=2). Additional opportunistic infections from Week 14 through Week 26 occurred in the UPA group (oral candidiasis) and PBO group (one case each of oral candidiasis and fungal esophagitis).

### Long-Term Period

Analysis of the phase 3 UPA 15 mg and 30 mg analysis set (Studies M13-542, M13-545, M13-549, M15-555) demonstrated a dose-dependent increase in opportunistic infections with a greater

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number of UPA 30 mg-treated reporting an opportunistic infection compared to subjects treated with UPA 15 mg (Table 101). The higher EAER of opportunistic infections in the UPA 30 mg group was largely driven by the number of oral candidiasis events.

**Table 101. TEAEs of Opportunistic Infections EAERs per 100 PY: Long-Term Exposure for Phase 3 Studies Comparing UPA 15 mg and 30 mg (Any Phase 3 UPA 15 mg and 30 mg Analysis Set)**

<b>MedDRA Preferred Term</b>	<b>UPA 15 mg QD (N=1213) (PY=1411) E (E/100 PY)</b>	<b>UPA 30 mg QD (N=1204) (PY=1365) E (E/100 PY)</b>
Any Serious Infection	8 (0.6)	24 (1.8)
Cryptococcosis	0	1 (<0.1)
Herpes zoster disseminated	0	1 (<0.1)
Esophageal candidiasis	1 (<0.1)	1 (<0.1)
Oral candidiasis	5 (0.4)	12 (0.9)
Oropharyngeal candidiasis	1 (<0.1)	2 (0.1)
Pneumonia cryptococcal	1 (<0.1)	1 (<0.1)
Varicella zoster pneumonia	0	1 (<0.1)
Investigations		
Cytomegalovirus test positive	0	5 (0.4)

Adapted from Applicant's ISS Table 2.4 5.4.1.3.1

Through the long-term exposure period for Study M13-545, subjects receiving UPA 30 mg had a higher EAER of opportunistic infections compared to the UPA 15 mg and PBO groups (1.8 E/100 PY, 0.6 E/100 PY and 0, respectively).

Similar to the results described with serious infections, the EAERs of opportunistic infections in all subjects from Study M14-465 demonstrated relatively similar EAERs between the UPA 15 mg and ADA groups; however, analysis of those subjects who did not switch treatments, and consequently were remained on their originally assigned dose, demonstrated a lower rate of serious infections in subjects treated with UPA 15 mg (0.6 E/100 PY compared to ADA-treated subjects (1.7 E/100 PY).

Review of the "Any RA UPA" analysis set was consistent with results from the phase 3 studies demonstrating an increased number of opportunistic infections with higher dose of UPA. The following is a list of all opportunistic infections that occurred during the UPA phase 2 and 3 studies (excluding TB which is discussed separately): esophageal candidiasis (n=6), cytomegalovirus test positive (n=2), fungal esophagitis (n=2), pneumocystis jirovecii pneumonia (n=2), pneumonia cryptococcal (n=2), disseminated herpes zoster (n=2), disseminated histoplasmosis (n=1), bronchopulmonary aspergillosis (n=1), coccidioidomycosis (n=1) and varicella zoster pneumonia (n=1).

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Reviewer's Comments:

During the controlled periods of the phase 3 studies, the percentages of opportunistic infections was similar between subjects treated with UPA 15 mg and subjects who received PBO or MTX in the control groups. A greater percentages of opportunistic infections was observed in UPA 30 mg-treated subjects compared to UPA 15 mg-treated subjects over the same time periods. In the long-term analysis of Studies M14-465 and M13-545, the rates of opportunistic infections were similar between the UPA 15 mg, ADA and MTX groups. Rates of opportunistic infections were higher in the UPA 30 mg group as compared to the UPA 15 mg group in the long-term analysis of Study 13-545. The most common opportunistic infections were nonserious mucosal candidiasis infections in the controlled and long-term periods.

**8.5.3. Adverse Events of Special Interest: Tuberculosis**

All subjects enrolled in the Applicant's global phase 3 development program were screened for TB infection using the QuantiFERON-TB Gold test. The purified protein derivative (PPD) skin test was utilized only when a QuantiFERON-TB Gold test was not possible at a study site. Subjects with evidence of TB or who met TB exclusionary parameters were excluded from the study. Subject with latent TB were allowed to enroll in the study after initiating appropriate prophylactic treatment at least two weeks prior to the first administration of study drug. Annual TB screening was performed for subjects.

Approximately 11% of subjects tested positive for TB at the time of screening across all phase 2 and 3 studies (Table 102).

**Table 102. Baseline Screening for Tuberculosis (Any RA UPA Analysis Set)**

	UPA 6 mg BID/15 mg QD (N=2819) n (%)	UPA 12mg BID/30 mg QD (N=1309) n (%)	Any UPA (N=4443) n (%)
PPD skin test at screening			
Positive	19 (7)	6 (5)	27 (6)
Negative	260 (93)	111 (95)	414 (94)
Missing	2540	1192	4002
QuantiFERON-TB Gold Test at screening			
Positive	302 (12)	125 (11)	452 (11)
Negative	2241 (87)	1058 (89)	3527 (88)
Indeterminate	22 (1)	9 (1)	33 (1)
Missing	254	117	431
TB test results			
Positive	315 (11)	130 (10)	472 (11)
Negative	2471 (88)	1154 (88)	3878 (87)
Missing	33	25	93

Adapted from Applicant's ISS Table 2.2 6.1.3

In the "Any RA UPA" analysis set, which includes all phase 2 and phase 3 studies, the EAER of active/latent TB for all UPA doses was 2 E/100 PY, of which 8 events (0.2 E/100 PY) resulted in study discontinuation. The Applicant's review of the data identified six cases of active TB: five subjects receiving UPA (<0.1 E/100 PY) and one subject receiving ADA. Of the five subjects receiving UPA, three were treated with UPA 15 mg and two with UPA 30 mg at the time of their event. Three of the subjects that had positive TB testing at screening were treated with isoniazid: one subject treated for greater than six months and two subjects treated for less than six months.

Of the five UPA-treated subjects, two manifested extra-pulmonary TB with one case each involving the female genital tract/peritoneum and mediastinal lymph nodes. The one ADA subject presented with pulmonary TB. The six active cases of TB were reported from study sites in South Africa, Tunisia, Hungary, Japan, Guatemala and Estonia. No subject deaths were reported as a result of TB infection.

#### 8.5.4. Adverse Events of Special Interest: Herpes Zoster

Herpes zoster occurs from the reactivation of endogenous latent varicella-zoster virus infection within the sensory ganglia and is a common disease with approximately one-million new cases in

the US annually. While age is the most important risk factor for the development of herpes zoster, patients with underlying autoimmune diseases and those treated with immunosuppressive therapies are also at increased risk of infection<sup>16,17</sup>. Veetil et al<sup>18</sup> showed an increased incidence rate of herpes zoster in the RA population compared to the general population, 1.2 E/100 PY versus 0.5 E/100 PY, respectively.

### Controlled Period

While UPA 15 mg-treated subjects reported a higher percentage of herpes zoster compared to PBO-treated subjects, the overall number of cases were low during the PBO-controlled periods of Studies M13-542, M13-549 and M14-465 (Table 103). One case of herpes zoster led to discontinuation of study drug, but no cases were classified as a SAE. The calculated EAERs of herpes zoster during the controlled periods in the UPA 15 mg and PBO groups were 2.7 E/100 PY and 1.2 E/100 PY, respectively.

**Table 103. TEAEs of Herpes Zoster in Subjects During the Controlled Period Comparing PBO vs. UPA 15mg Prior to Treatment Switching (PBO-Controlled UPA 15 mg Analysis Set)**

<b>MedDRA Preferred Term</b>	<b>PBO (N=1042) n (%)</b>	<b>UPA 15 mg QD (N=1035) n (%)</b>
Any herpes zoster	3 (0.3)	7 (0.7)
Herpes zoster	2 (0.2)	7 (0.7)
Varicella	1 (<0.1)	0

Adapted from Applicant's ISS Table 2.4 1.1.2.1 and ISS Table 2.4 1.3.1.17

Analysis of the PBO-controlled UPA 15 mg and 30 mg analysis set demonstrated that the percentage of subjects with herpes zoster was the same in the PBO (0.5%) and UPA 15 mg (0.5%) treatment arms but higher in the UPA 30 mg (1.6%), which included one case each of varicella pneumonia, ophthalmic herpes zoster and a primary varicella infection. Three UPA 30 mg-treated subjects reported herpes zoster-related SAEs (ophthalmic herpes zoster, herpes zoster and primary varicella infection) that led to discontinuation of study drug.

A similar dose-response relationship was observed in UPA 15 mg- and UPA 30 mg-treated subjects who reported a higher percentage of herpes zoster compared to the MTX-control group, 6 (1.1%), 8 (1.5%) and 2 (0.4%), respectively, through the three-month MTX-controlled periods of Studies M13-545 and M15-555. In the MTX-controlled analysis set with exposure up to 6

<sup>16</sup> Smitten AL et al. Arthritis Rheum 2007 Dec 15;57(8):1431-8

<sup>17</sup> Curtis JR et al. Ann Rheum Dis 2016 Oct;75(10):1843-47

<sup>18</sup> Veetil BM et al Arthritis Care Res 2013 Jun;65(6):854-61

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months, the EAERs of herpes zoster were and highest in the UPA 15 mg (5 E/100 PY) and UPA 30 mg (7 E/100 PY) groups compared to the MTX control arm (1 E/100 PY).

Through the PBO-controlled period of Study M14-465, the EAER of herpes zoster was higher in the UPA 15 mg group compared to the ADA (0.7% EAER) and PBO (1.2 E/100 PY) groups, prior to subjects switching treatment. This trend continued through the study cutoff day (after subjects had switched treatments) where the EAERs of herpes zoster was higher in the UPA 15 mg (3.1 E/100 PY) compared to ADA 40 mg (1.3 E/100 PY). Moreover, subjects who continued their originally assigned study drug and did not switch treatments during the study also demonstrated a higher EAER rate for UPA 15 mg-treated subjects compared to ADA-treated subject, 2.6 E/100 PY and 0.6 E/100 PY, respectively.

### Long-Term Period

In the long-term analysis set of UPA 15 mg that included all five phase 3 studies, 90 subjects experienced 99 cases of herpes zoster (3.7 E/100 PY). Approximately 75% of the events involved a single dermatome; however, there was one case of disseminated herpes zoster, two events of ophthalmic herpes zoster and five events of post-herpetic neuralgia. Four of these events were reported as SAEs and three subjects discontinued study drug. Subgroup analysis showed an increased rate of herpes zoster in Asia compared to other geographical regions and also a higher rate with increasing age overall.

Consistent with what was observed in the controlled periods, herpes zoster events occurred at higher rates in subjects treated with UPA 30 mg versus UPA 15 mg (Table 104).

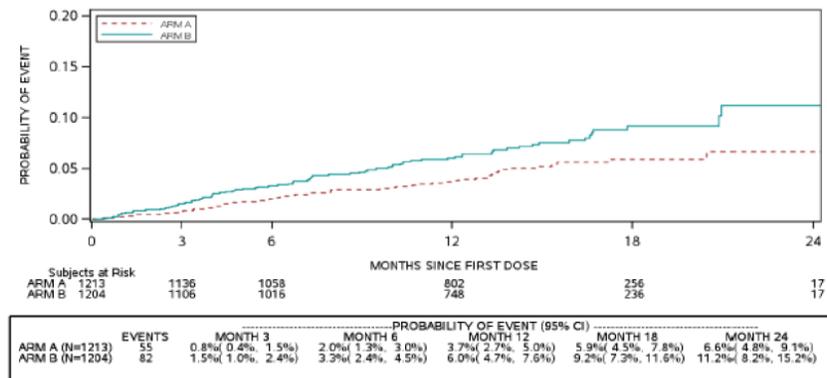
**Table 104. TEAEs of Herpes Zoster EAERs per 100 PY: Long-Term Exposure for Phase 3 Studies Comparing UPA 15 mg and 30 mg (Any Phase 3 UPA 15 mg and 30 mg Analysis Set)**

<b>MedDRA Preferred Term</b>	<b>UPA 15 mg QD (N=1213) (PY=1411) E (E/100 PY)</b>	<b>UPA 30 mg QD (N=1204) (PY=1365) E (E/100 PY)</b>
Any Herpes Zoster	61 (4)	96 (7)
Herpes zoster	57 (4)	86 (6)
Herpes zoster disseminated	0	1 (<0.1)
Ophthalmic herpes zoster	1 (<0.1)	1 (<0.1)
Varicella	1 (<0.1)	1 (<0.1)
Varicella zoster pneumonia	0	1 (<0.1)
Post-herpetic neuralgia	2 (0.1)	6 (0.4)

Adapted from Applicant's ISS Table 2.4 5.4.1.14.1

A Kaplan-Meier analysis for herpes zoster events in the Any Phase 3 UPA 15 mg and 30 mg analysis set suggests that the risk of subjects experiencing a herpes zoster event increased over the 24-month period (Figure 18).

**Figure 18. Kaplan-Meier Curve for TEAEs of Herpes Zoster: Long-Term Exposure for UPA 15 mg (Any RA UPA Analysis Set)**



Adapted from Applicant's ISS Figure 2.4 5.12.5.1

Consistent with increased frequency of herpes zoster events associated with UPA treatment during the controlled period, the long-term exposure through the study cutoff for Study M13-545 demonstrated higher EAERs of herpes zoster for subjects treated with UPA compared to MTX. Similarly, UPA 15 mg-treated subjects demonstrated higher EAERs of herpes zoster compared to ADA-treated subjects through the data cutoff date for Study M14-465 (2.6 E/100 PY and 0.6 E/100 PY, respectively).

Analysis of the "Any RA UPA" analysis set supported the finding of an UPA-related dose-dependent increase in the number of cases of herpes zoster (Table 105). Subjects continuously treated with UPA 6 mg BID/15 mg QD had approximately half the EAER compared to subjects continuously treated with UPA 12 mg BID/30 mg QD, 3.6 E/100 PY and 7 E/100 PY, respectively.

**Table 105. Summary of Extent of Involvement for Subjects with TEAEs Herpes Zoster for (Any RA UPA Analysis Set)**

	<b>UPA 6 mg            BID/15 mg QD            (N=97)            n (%)</b>	<b>UPA 12mg            BID/30 mg QD            (N=83)            n (%)</b>
Category Herpes Zoster Infection		
Single dermatome	67 (69)	62 (75)
Ophthalmic involvement	4 (4)	3 (4)
Meningoencephalopathic involvement	0	0
Unilateral involving multiple dermatomes	16 (17)	11 (13)
Herpes zoster oticus	2 (2)	0
Disseminated, cutaneous only	5 (5)	8 (10)
Disseminated, including noncutaneous	0	0
Missing	9 (9)	2 (2)
Adapted from Applicant's ISS Table 2.4 6.2.2.2		

**Reviewer's Comments:**

The rates of herpes zoster infection were higher in the UPA groups compared to PBO, MTX and ADA groups. There was a dose-dependent effect observed with higher rates of herpes zoster infections in subjects treated with UPA 30 mg compared to UPA 15 mg subjects. The majority of the zoster cases involved a single dermatome. Cases of ophthalmic zoster and disseminated cutaneous zoster but no cases of central nervous system (CNS) involvement were reported in both UPA groups.

**8.5.5. Adverse Events of Special Interest: Malignancy**

There is evidence that RA patients have a higher occurrence of certain malignancies compared to the general population<sup>19</sup>. The etiology of this finding may include immune dysregulation and/or chronic immune activation in RA patients. Lymphoproliferative disorders occur with increased frequency in patients with RA<sup>20</sup>. The lymphoma incidence increases the longer that active RA disease persists and correlates with the severity of disease activity<sup>21</sup>. In addition to lymphoma, RA patients are also at increased risk for lung cancer<sup>19</sup>. Malignancies that have not been shown to have an increased risk among RA patients include cervical cancer, prostate cancer and melanoma<sup>19</sup>.

<sup>19</sup> Simon TA et al. Arthritis Res Ther 2015 Aug 15;17:212

<sup>20</sup> Smitten AI et al. Arthritis Res Ther 2008;10(2):R45

<sup>21</sup> Nashitz JE and Rosner I Curr Opin Rheumatol 2008 Jan;20(1):100-105

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Age and sex standard incidence ratios (SIRs) of malignancies, excluding non-melanoma skin cancer (NMSC), vary between several RA registries and range between 0.5 to 0.9 E/100 PY<sup>22</sup>. In the long-term extension periods of RA clinical trials with bDMARD or JAK inhibitor treatment, malignancy excluding NMSC, ranged between 0.5 to 1.4 E/100 PY.

Non-melanoma skin cancers are common in the general population with more than 5.4 million cases of NMSCs treated in over 3.3 million people in the US in 2012<sup>23</sup>. The worldwide incidence of NMSC varies widely and Australia has the highest reported rate, with more than 1,000 per 100,000 person-years for basal cell carcinoma (2,448 E/100,000 PY), followed by Europe (129 E/100,000 PY in men, and 91 E/100,000 PY in women) and the US (450 E/ 100,000 PY)<sup>24</sup>. The reported rates for NMSC in RA clinical trials range between 0.3 to 0.6 E/100 PY<sup>25,26</sup>.

### Controlled Period

Overall, the number of malignancies reported during the PBO- or active-controlled periods of the UPA phase 3 studies were small and definitive conclusions could not be drawn regarding the rates of malignancies during this short time period.

A total of two malignancies were reported during the PBO-controlled UPA 15 mg dataset: two subjects in the PBO group (basal cell carcinoma, n=1; cervical carcinoma, n=1) and one subject in the UPA 15 mg group (malignant melanoma). Similarly, few malignancies were reported in the analysis of the PBO-controlled UPA 15 mg and 30 mg datasets with one UPA 15 mg-treated subject reporting a malignant melanoma (previously mentioned) and three UPA 30 mg-treated subjects (prostate cancer, n=2; B-cell small lymphocytic lymphoma/chronic lymphocytic leukemia, n=1). NMSCs were reported in two subjects treated with UPA 30 mg (basal cell carcinoma, n=1; squamous cell carcinoma, n=1).

A total of eight subjects reported malignancies through Week 24 of the MTX-controlled analysis datasets: MTX (n=2; ovarian cancer, basal cell carcinoma), UPA 15 mg (n=6; malignant melanoma, squamous cell carcinoma of the lung, uterine carcinoma in situ, non-Hodgkin's lymphoma, breast cancer) and UPA 30 mg (n=0). The EAIRs of malignancy, other than NMSC, in the UPA 15 mg, UPA 30 mg and MTX groups were 2 n/100 PY, 0.4 n/100 PY and 1 n/100 PY, respectively, in subjects with no treatment switching.

No malignancies other than NMSC in one subject each in the ADA and PBO treatment arms were reported through Week 26 of Study M14-465.

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<sup>22</sup> Askling J et al. *Ann Rheum Dis* 2016 Oct;75(10):1789-96

<sup>23</sup> Rogers HW et al. *JAMA Dermatol* 2015 Oct;151(10):1081-86

<sup>24</sup> Apalla et al. *Dermatol Pract Concept* 2017 Apr;7(2):1-6

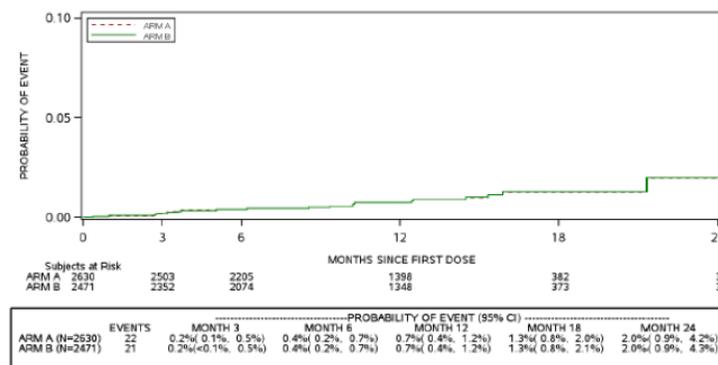
<sup>25</sup> Burmester GR et al. *Ann Rheum Dis* 2013 Apr;72(4):517-24

<sup>26</sup> Cohen SB et al. *Ann Rheum Dis* 2017 Jul;76(7):1253-62

## Long-Term Period

A total of 22 subjects with malignancies other than NMSC (0.8 n/100 PY) and eight subjects with NMSC (0.3 n/100 PY) were reported in the long-term analysis set of UPA 15 mg that included all five phase 3 studies. Single cases of different types of malignancies were reported except for basal cell carcinoma (n=5), invasive ductal breast carcinoma (n=3) and squamous cell skin cancer (n=3). The EAIR of malignancies other than NMSC and of NMSC in UPA 15 mg-treated subjects did not appear to increase overtime past 12 months (data not shown). Additionally, there was no clear signal in the time of onset to malignancy other than NMSC (Figure 19). In fact, ten of the malignancies other than NMSC were reported within six months of initiating UPA 15 mg.

**Figure 19. Kaplan-Meier Curve for Treatment-Emergent Malignancy Excluding NMSC: Long-Term Exposure for UPA 15 mg (Any Phase 3 UPA 15 mg Analysis Set)**



NOTE: ARM A = ABT-494 15 MG QD; ARM B = ABT-494 15MG QD NO ADA CROSS-OVER.  
 Adapted from Applicant's ISS Figure 2.4\_4.11.3.1

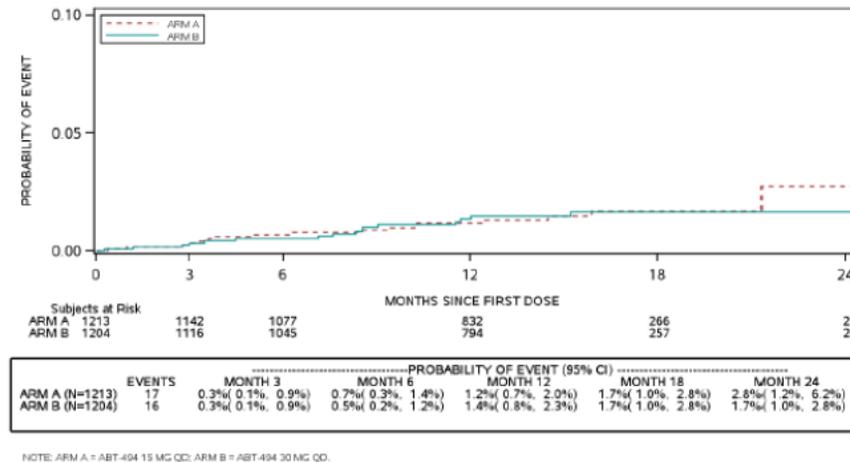
The Applicant performed a Standardized Incidence Ratio (SIR) analysis for malignancy excluding NMSC using age-gender specific malignancy data from the Surveillance, Epidemiology, and End Results (SEER) Registry Research Data 2000-2015 for the general population that generated an SIR estimate of 1.05 (95% CI: 0.66, 1.60) for the AE of malignancy in the UPA 15 mg treatment group. The expected number of malignancies other than NMSC in UPA 15 mg-treated subjects was 20.88 compared to the 22 cases of malignancy observed. Although limited by the relatively short observation period and limited number of subjects, these data suggest that there is no evidence that number of malignancies other than NMSC were greater with UPA 15 mg treatment than that expected for the general population.

The EAIRs of malignancies other than NMSC was the same for both UPA treatment arms, 1.2 n/100 PY, in the long-term analysis of Any Phase 3 UPA 15 mg and 30 mg datasets, which included Studies M13-542, M13-545, M13-549 and M15-555. Different types of malignancies with EAIRs  $\leq 0.1$  E/100 PY were most frequently reported, except for basal cell carcinoma (UPA 15 mg, 0.2 E/100 PY; UPA 30 mg, 0.4 E/100 PY), invasive ductal breast carcinoma (UPA 15 mg, 0.2 E/100 PY)

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and squamous cell skin cancer (UPA 30 mg, 0.6 E/100 PY). The risk of UPA-treated subjects developing malignancy other than NMSC did not meaningfully increase over time (Figure 20).

**Figure 20. Kaplan-Meier Curve for Treatment-Emergent Malignancy Excluding NMSC: Long-Term Exposure for UPA 15 mg and 30 mg (Any Phase 3 UPA 15 mg and 30 mg Analysis Set)**



Adapted from Applicant's ISS Figure 2.4\_5.12.3.1

Similarly, the overall risk of UPA-treated subjects developing a NMSC in the phase 3 studies did not appear to increase over time (data not shown).

The EAIRs of malignancies were similar between the UPA and MTX monotherapy groups. The EAIRs of malignancy other than NMSC for the UPA 15 mg, UPA 30 mg and MTX arms were 0.9 n/100 PY, 0.6 n/100 PY and 0.6 n/100 PY, respectively. NMSC was reported for one subject each in the UPA treatment arms and none in the MTX arm.

Among subjects in Study M14-465 who were treated with either UPA 15 mg or ADA and with no treatment switching during the study, the EAIR for malignancies other than NMSC was greater in ADA-treated subjects (0.6 n/100 PY) compared to UPA-treated subjects (0.2 n/100 PY). The EAIRs for NMSC was also greater in the ADA group (0.6 n/100 PY) versus the UPA 15 mg group (0.2 n/100 PY). Analysis of the all study drug exposure dataset, i.e., including subjects who switched treatment groups, the EAIRs of malignancies other than NMSC were similar between UPA 15 mg- and ADA-treated subjects, 0.4 n/100 PY vs. 0.6 n/100 PY, respectively, while the EAIRs of the NMSC were the same between treatment arms, 0.2 n/100 PY.

In the Any RA UPA analysis set, which included all phase 2 and phase 3 studies, the overall data did not reveal a discernable pattern of malignancies (Table 106); however, overall, there was a greater incidence of NMSC in the UPA-treated subjects compared to PBO and MTX control groups.

**Table 106. Types of Malignancies in UPA-Treated Subjects (Any RA UPA Analysis Set)**

Type of Malignancy	UPA 6 mg BID/15 mg QD (N=3143)	UPA 12mg BID/30 mg QD (N=1452)	UPA Other Doses (N=315)
Bladder	1	0	0
Breast	6	4	0
Ears, Nose and Throat	2	0	0
Gastrointestinal	4	4	0
Gynecological	2	2	0
Kidney	1	0	0
Lung	3	2	0
Lymphoma	3	1	0
Pancreas	1	0	0
Prostate	1	3	1
Skin	5	2	0
NMSC	13	16	0
Thyroid	1	0	0
Other	0	3	0

Adapted from Applicant's ISS Table 2.4 6.6.5 and Table 2.4 7.2.5

Patients with RA have a two-fold higher risk of lymphoma than the general population<sup>27</sup> and Askling et al<sup>28</sup> reported SIRs between 0.6-0.9/100 PY. Analysis of the Any RA UPA analysis set reported four subjects (<0.1 n/100 PY) with lymphoproliferative disorders. There were an additional two Japanese subjects from Study M14-663 who reported a single case each of Hodgkin's lymphoma and acute lymphocytic leukemia. Overall, the types of lymphoproliferative disorders and the incidence rate of lymphoma in the UPA program were within the expected range for the RA population.

**Reviewer's Comments:**

Malignancies were reported across all treatment arms in the short-term PBO-controlled, MTX-controlled and ADA-controlled datasets. The small number of events limits the comparison of malignancy rates among the groups. The long-term MTX-controlled and ADA-controlled datasets do not indicate an increased risk of malignancies other than NMSC with UPA treatment compared to treatment with either MTX or ADA. The types of malignancies reported in the UPA studies are consistent with that anticipated in a RA study population.

<sup>27</sup> Smedby KE et al. Cancer Epidemiol Biomarkers Prev 2006 Nov;15(11):2068-77.

<sup>28</sup> Askling J et al. Ann Rheum Dis 2016 Oct;75(10):1789-96

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Rates for malignancies were generally similar between the UPA 30 mg and 15 mg groups except for the rates of NMSC, which were higher in the UPA 30 mg group. No notable pattern regarding the types of malignancies was observed. Analysis of the long-term periods demonstrated that the incidence rate of malignancies other than NMSC in subjects receiving UPA 15 mg did not appear to increase over time. Across all UPA groups, the incidence rates of malignancies, excluding NMSC, for patients receiving UPA 15 mg were within the range expected for a population of patients with RA. The age-gender adjusted SIR for malignancies other than NMSC indicates that the malignancy risk with UPA 15 mg was within the expected range for the general population. However, the data are limited due to the majority of subjects only being exposed for one-year or less. It is not known whether an increase of malignancies could occur with long-term (>1 year) treatment with UPA, in light of safety signals from other drugs in the JAK inhibitor class.

#### 8.5.6. Adverse Events of Special Interest: Hepatic Disorders

##### Controlled Period

A greater mean increase in ALT and AST levels was observed in UPA 15 mg-treated subjects (5.4 U/L and 5 U/L, respectively) compared to PBO-treated subjects (0.8 U/L and 0.6 U/L, respectively) from baseline to Week 12 in the PBO-controlled UPA 15mg analysis set. In subjects treated with UPA 15 mg, ALT and AST levels increased during the initial four weeks of therapy and plateaued between Week 8 and 12. Additionally, a small increase in bilirubin was observed in the UPA 15 mg treatment arm compared to the PBO arm (1.1  $\mu\text{mol/L}$  vs. -0.1  $\mu\text{mol/L}$ , respectively).

As shown in Table 107, the majority of increases in ALT, AST and bilirubin levels were Grade 2 elevations (defined as 1.5 to <3 x ULN) and more frequent in the UPA 15 mg treatment arm compared to PBO. Higher grade elevations of hepatic enzymes also occurred in a greater proportion of UPA 15 mg-treated subjects but were overall less frequent than Grade 2 events. There were no subjects that met criteria for Hy's Law.

**Table 107. Hepatic Enzyme Elevations in Subjects During the Controlled Period Comparing PBO vs. UPA 15mg Prior to Treatment Switching (PBO-Controlled UPA 15 mg Analysis Set)**

Hepatic Enzyme Elevation Criteria (Unit)	PBO (N=1042) n (%)	UPA 15 mg QD (N=1035) n (%)
Alanine Aminotransferase (U/L)		
Grade 2 (1.5 to <3x ULN)	58/1037 (6)	89/1034 (9)
Grade 3 (3 to <8x ULN)	13/1037 (1)	18/1034 (2)
Grade 4 (>8x ULN)	2/1037 (0.2)	4/1034 (0.4)
Aspartate Aminotransferase (U/L)		
Grade 2 (1.5 to <3x ULN)	49/1037 (5)	54/1034 (5)
Grade 3 (3 to <8x ULN)	6/1037 (0.6)	13/1034 (1.3)
Grade 4 (>8x ULN)	1/1037 (<0/1)	3/1034 (0.3)
Alkaline Phosphatase (U/L)		
Grade 2 (1.5 to <3x ULN)	8/1037 (0.8)	4/1034 (0.4)
Grade 3 (3 to <5x ULN)	0	0
Grade 4 (>5x ULN)	0	0
Bilirubin (µmol/L)		
Grade 2 (1.4 to <1.9x ULN)	1/1037 (<0.1)	5/1034 (0.5)
Grade 3 (1.9 to <3x ULN)	1/1037 (<0.1)	2/1034 (0.2)
Grade 4 (>3x ULN)	0	0

Adapted from Applicant's ISS Table 2.5 1.2.1.2

The overall number of hepatic disorder AEs were similar between treatment arms and were comprised mostly of transaminase elevations as discussed above. Additionally, there was one case each of hepatic steatosis and serious hepatitis (ALT>10x ULN) in subjects treated with UPA 15 mg. In the case of serious hepatitis, study drug was interrupted from Day 45-62 and no further hepatic AE was reported. Following rechallenge, transaminase levels were generally within normal limits except for several instances of elevation <2x ULN. Three additional subjects discontinued UPA 15 mg during the PBO-controlled period of these studies due to a hepatic disorder AE. At the time of the Applicant's submission two cases had resolved and one was ongoing.

Through the controlled periods of the "PBO-controlled UPA 15 mg" analysis set, UPA 15 mg- and PBO-treated subjects had similar EAERs of hepatic disorder AEs, 25 E/100 PY and 23 E/100 PY, respectively.

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Comparison of ALT, AST and bilirubin levels from the “PBO-controlled UPA 15 mg and 30 mg” analysis set demonstrated similar mean increases in ALT, AST and bilirubin from baseline to Week 12 for the UPA 15 mg (4.6 U/L, 4.6 U/L and 0.9 µmol/L, respectively) and 30 mg (5.6 U/L, 5 U/L, 1.2 µmol/L, respectively) groups but greater than subjects treated with PBO (1.2 U/L, 1 U/L, -0.3 µmol/L, respectively). These data do not suggest a dose-dependent increase in UPA-induced transaminase levels during the controlled periods of Studies M13-542 and M13-549. The proportion of subjects with ALT $\geq$ 3x ULN was similar in all treatment arms during the controlled period of the studies (data not shown).

In the “MTX-controlled” analysis set, a greater mean change from baseline at Weeks 12 or 14 for ALT, AST and bilirubin was observed from UPA 15 mg (3 U/L, 4.3 U/L, 1.1 µmol/L, respectively) compared to MTX control (2.4 U/L, 1.5 U/L, 0.1 µmol/L, respectively). The percentage of subjects with ALT $\geq$ 3x ULN was approximately two-fold lower in UPA 15mg-treated subjects compared to the MTX group at both three months (0.8% vs 1.9%, respectively) and six months (1.7% vs 3.6%, respectively). Similar patterns were observed for serum AST levels. Additionally, elevations in ALT/AST  $\geq$ 3x ULN for the UPA 30 mg group were similar to MTX controls (data not shown). There were few subjects with reported elevations in bilirubin  $\geq$ 2x ULN and the percentages were comparable across all three treatment groups (data not shown).

The percentage of subjects with exposure up to three months reporting a hepatic disorder AE was similar for the UPA 15 mg and 30 mg groups but higher than the MTX group (3.6% and 3% vs. 1.9%, respectively). However, in the MTX-controlled analysis set with exposure up to six months the EAERs were higher in the MTX control group (23 E/100 PY) compared to UPA 15 mg (19 E/100 PY) and 30 mg (14 E/100 PY) in subjects with no treatment switching.

A greater mean increase from baseline through Week 26 for ALT, AST and bilirubin was observed for UPA 15 mg (6.7 U/L, 6.4 U/L, 1.3 µmol/L, respectively) compared to ADA (1.4 U/L, 2.1 U/L, 1.1 µmol/L, respectively) and PBO (0.4 U/L, 0.4 U/L, 0.2 µmol/L, respectively) through Week 26 of Study M14-465. Over the same time period, a higher percentage of subjects reported ALT and AST elevations  $\geq$ 3x ULN in the UPA 15 mg group (4.3% and 2.3%, respectively) compared to ADA (1.8% and 1.5%, respectively) and PBO (2.5% and 0.6%, respectively). There were no clinically significant differences in bilirubin concentrations between the three treatment arms and no subjects met criteria for Hy’s Law.

### Long-Term Period

Analysis of long-term treatment during the phase 3 UPA 15 mg and 30 mg analysis set (Studies M13-542, M13-545, M13-549, M15-555) demonstrated that changes from baseline through Week 84 for ALT, AST and bilirubin were similar between the UPA 15 mg and 30 mg treatment arms (data not shown). The percentages of subjects experiencing  $\geq$ 3x ULN increases in ALT or AST and  $\geq$ 2x ULN for bilirubin were low and similar in frequency between both UPA treatment arms

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(data not shown). Similarly, the EAERs of AEs of hepatic disorder were 12 E/100 PY and 13 E/100 PY for UPA 15 mg and 30 mg, respectively. These events were mostly due to transaminase elevations for both UPA treatment arms. The long-term EAERs for any serious hepatic disorder or hepatic disorders leading to discontinuation of study drug for UPA 15 mg were 0.2 E/100 PY and 0.7 E/100 PY, respectively and were similar for UPA 30 mg-treated subjects (0.1 E/100 PY and 1.1 E/100 PY, respectively).

The EAERs of hepatic disorders were similar for MTX, UPA 15 mg and UPA 30 mg subjects through the data cutoff for Study M13-545 at 20 E/100 PY, 19 E/100 PY and 16 E/100 PY, respectively.

Analysis of subjects in the all study drug exposure for Study M14-465 demonstrated a greater percentage of subjects experienced ALT or AST elevations  $\geq 3x$  ULN in the UPA 15 mg treatment arm (3.7% and 2.2%, respectively) compared to subjects in the ADA group (2.3% and 1.7%, respectively). Elevations in bilirubin were similar across treatment arms. Additionally, the EAER of any hepatic disorder AE was similar between the UPA 15 mg arm (19 E/100 PY) compared to the ADA arm (15 E/100 PY) among subjects who did not switch treatments during the study.

Analysis of the “Any RA UPA” analysis set shows that the overall number of subjects with an ALT or AST elevation of  $\geq 3x$  ULN, or bilirubin elevations of  $\geq 2x$  ULN were low and similar between the low and higher dose UPA treatment arms (Table 108).

**Table 108. Subjects with TEAEs for Liver-Related Enzyme Elevations (Any RA UPA Analysis Set)**

Hepatic Enzyme Elevation Criteria (Unit)	UPA 6 mg BID/15 mg QD (N=2819) n/N OBS (%)	UPA 12mg BID/30 mg QD (N=1309) n/N OBS (%)
ALT ≥3x ULN	93/2792 (3.3)	47/1300 (3.6)
ALT ≥5x ULN	32/2792 (1.1)	12/1300 (0.9)
ALT ≥10x ULN	8/2792 (0.3)	6/1300 (0.5)
ALT ≥20x ULN	2/2792 (<0.1)	1/1300 (<0.1)
AST ≥3x ULN	59/2792 (2.1)	24/1300 (1.8)
AST ≥5x ULN	19/2792 (0.7)	8/1300 (0.6)
AST ≥10x ULN	5/2792 (0.2)	4/1300 (0.3)
AST ≥20x ULN	1/2792 (<0.1)	1/1300 (<0.1)
TB ≥2x ULN	10/2792 (0.4)	4/1301 (0.3)
ALP ≥1.5x ULN	37/2792 (1.3)	14/1300 (1.1)
ALT and/or AST ≥3x ULN and TB ≥1.5x ULN	2/2792 (0.1)	2/1301 (0.2)
Adapted from Applicant's ISS Table 2.4 6.2.1.1		

A total of four subjects met criteria for Hy's Law.

- Subject (b) (6) (Study M13-537; UPA 12 mg BID) was a 56-year-old male subject on concomitant MTX who experienced mild transaminase elevations (ALT: 157 U/L, >3 x ULN; total bilirubin: 39 µmol/L, >2x ULN; INR, not reported) on Day 43 of treatment and study drug was discontinued. Four days later all liver test abnormalities either resolved or were resolving. Additional data was not available.
- Subject (b) (6) (Study M13-545; UPA 15 mg) was a 47-year-old female subject and with no concomitant MTX who experienced a Grade 3 increase in liver enzymes on Day 58 and continued to have fluctuating Grade 1-2 liver enzyme elevations until the final treatment day (Day 233) despite no UPA 15 mg dose interruptions or discontinuation. Of note, the subject was initiated on INH three weeks prior to Day 1 and continued until Day 282. INH is known to be capable of inducing hepatotoxicity with similar laboratory changes and may account for the hepatic-related laboratory elevations observed in this subject.
- Subject (b) (6) (Study M13-545; UPA 15 mg) was a 66-year-old male with a past medical history significant for malignant melanoma in 1993, and who was not on concomitant MTX, developed ALT and AST elevations on Day 110. The subject subsequently had further ALT/AST elevations and elevation of bilirubin.

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Metastatic melanoma with metastasis to the liver was subsequently diagnosed in this subject and is likely the source of the subjects elevated liver function tests.

- Subject (b) (6) (Study M13-549; UPA 30 mg) was a 65-year-old female who presented on Day 466, 29 days after the database lock with elevation of hepatic enzymes that met the criteria for Hy's Law. The subject was reported with Hepatitis B on Day 421. Peak ALT, AST and bilirubin levels were 1556 U/L, 1355 U/L and 225 µmol/L, respectively. The subject's elevated transaminase and bilirubin levels may be related to UPA and/or Hepatitis B reactivation.

One subject death was associated with hepatic enzyme elevation.

- Subject (b) (6) (Study M13-545; UPA 15 mg) was a 37-year-old female, without concomitant MTX, who developed bronchitis/pneumonia, high-output heart failure and dyspnea that lead to death. Laboratory testing revealed an AST-predominant, anicteric hepatitis. Given the overall clinical setting, the Applicant judged a cardiopulmonary cause of death with likely concomitant sepsis and heart failure that led to hypoperfusion of the liver resulting in the observed hepatic enzymatic laboratory abnormalities.

#### Reviewer's Comments:

Upadacitinib treatment resulted in a greater percentage of transaminase elevations compared to PBO-treated subjects. Transaminase elevations were similar between the UPA 15 mg and UPA 30 mg groups. Most of the transaminase elevations did not result in study drug discontinuation and resolved after discontinuation of UPA. No cases of drug-induced liver injury were identified.

#### **8.5.7. Adverse Events of Special Interest: Gastrointestinal Perforations**

A total of nine subjects in the "Any RA UPA" analysis set experienced 9 events (0.2 E/100 PY) identified as GI perforations based on an SMQ search: UPA 6 mg BID/15 mg QD (n=5) and UPA 12 mg BID /30 mg QD (n=4). No events of GI perforations were reported in subjects treated with PBO, MTX or ADA.

Review of the cases showed that three of the five events in UPA 6 mg BID/15 mg QD group did not appear to represent true GI perforation: peritonitis related to fallopian tube abscess; anal abscess in a subject with a history of perianal abscesses; and anal fistula in a subject with a history of two previous surgical anal fistula repairs. The remaining two cases of GI perforations included a ruptured appendix and an anal fistula that required surgical repair. All four cases of GI perforation in the higher dose UPA group were considered as GI perforations.

In Study M14-663, two subjects experienced three cases of GI perforation with one subject each reporting events in the UPA 15 mg (intestinal perforation) and UPA 30 mg treatment arms (anal fistula and perirectal abscess).

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Reviewer's Comments:

An increased frequency of gastrointestinal perforations has been reported with tofacitinib and baricitinib as well as the IL-6 inhibitor, tocilizumab. A total of six plausible UPA-related cases of gastrointestinal perforations were reported in the phase 3 studies compared to no cases in subjects treated with PBO, MTX or ADA. In light of the data from other JAK inhibitors, the data suggest that subjects treated with UPA are at an increased risk of developing gastrointestinal perforations. Based on the available data, the risk does not appear to be dose-dependent.

**8.5.8. Adverse Events of Special Interest: Anemia**

Anemia is common in patients with active RA due to chronic inflammation<sup>29</sup>. Treatment of the underlying inflammation has been associated with increases in hemoglobin values in patients receiving effective RA therapy. The impact of JAK inhibition on anemia is complex, due to potential beneficial effects of reducing inflammation and countering effects of reducing erythropoietin (EPO) signaling through JAK2/homodimer pairs.

Selective JAK1 inhibition was hypothesized to provide the potential to have an equivalent or greater impact on inflammation with a lesser impact on EPO signaling due to its higher selectivity for JAK1 compared to JAK2 isoforms. However, the physiologic impacts regarding the relative pharmacologic degree of selectivity to these JAK isoforms is unclear.

Controlled Period

Mean decreases in hemoglobin concentrations from baseline were similar between PBO and UPA 15 mg groups (-1.1 g/L and -1.5 g/L, respectively) during the controlled periods of Studies M13-542, M13-549 and M14-465. Additionally, the severity of anemia AEs was similar between treatment arms (Table 109). One PBO-treated subject and two UPA 15 mg-treated subjects who experienced an AE of anemia were discontinued from study drug.

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<sup>29</sup> Wilson A et al. Am J Med 2004 Apr 5;116 Suppl 7A:50S-57S

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**Table 109. Number of Subjects Meeting Criteria for Potentially Clinically Significant Values for Hemoglobin During the PBO-Controlled UPA 15mg Period (PBO-Controlled UPA 15 mg Analysis Set)**

Hemoglobin (g/L)	PBO (N=1042) n/N_OBS (%)	UPA 15 mg QD (N=1035) n/N_OBS (%)
Grade 2 (decreased 15 to <21)	85/1036 (8)	88/1034 (9)
Grade 3 (70 to <80 or decreased 21 to <30)	23/1036 (2)	30/1034 (3)
Grade 4 (<70 or decreased ≥30)	8/1036 (1)	4/1034 (<1)

Adapted from Applicant's ISS Table 2.5 1.2.1.1

Analysis of the “PBO-controlled UPA 15 mg and 30 mg” dataset from baseline to Week 12 demonstrated a dose-dependent decrease in hemoglobin: PBO (-1.2 g/L), UPA 15 mg (-1.9 g/L) and UPA 30 mg (-5.3 g/L). As shown in Table 110, the severity of anemia AEs were also dose-dependent. No AE of anemia led to discontinuation of study drug from this analysis set.

**Table 110. Number of Subjects Meeting Criteria for Potentially Clinically Significant Values for Hemoglobin During the PBO-Controlled UPA 15mg and UPA 30 mg Period (PBO-Controlled UPA 15 mg and 30 mg Analysis Set)**

Hemoglobin (g/L)	PBO (N=390) n/N_OBS (%)	UPA 15 mg QD (N=385) n/N_OBS (%)	UPA 30 mg QD (N=384) n/N_OBS (%)
Grade 2 (decreased 15 to <21)	31/386 (8)	25/384 (7)	58/381 (15)
Grade 3 (70 to <80 or decreased 21 to <30)	5/386 (1)	14/384 (4)	18/381 (5)
Grade 4 (<70 or decreased ≥30)	4/386 (1)	0/384	5/381 (1)

Adapted from Applicant's ISS Table 2.5 2.2.1.1

Analysis of the three-month MTX-controlled periods of Studies M13-545 and M15-555 showed mean hemoglobin changes of -0.7 g/L, 0.6 g/L and -2.6 g/L in the MTX, UPA 15 mg and UPA 30 mg groups, respectively. The percentage of subjects with Grade 3 hemoglobin decreases were similar between MTX (2%) and UPA 15 mg (2%) groups but higher among the UPA 30 mg (5%) group, again demonstrating a dose-dependent effect. No subjects discontinued study drug for AE of anemia. Similar results were observed in the “MTX-controlled” analysis set with exposure up to six months (data not shown).

Mean hemoglobin changes through Week 26 of Study M14-465 (prior to treatment switching) demonstrated increased hemoglobin concentrations for ADA (3 g/L) and UPA 15 mg (1.2 g/L) and a decrease in hemoglobin concentrations of PBO-treated subjects (-0.8 g/L). The percentage of

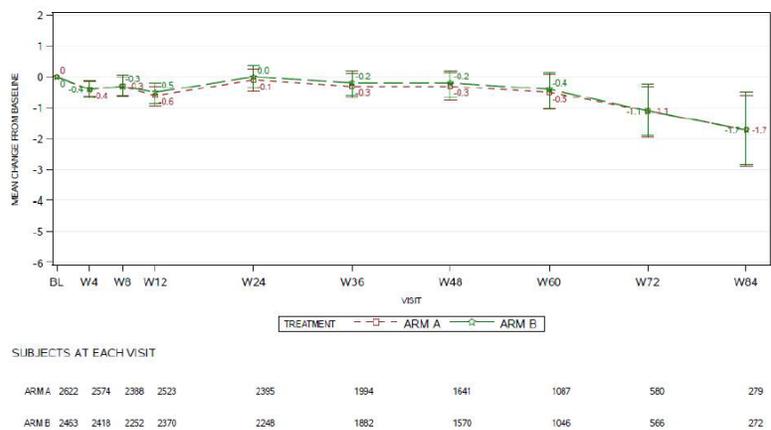
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Grade 3 hemoglobin decreases were generally similar between all treatment arms: PBO (3%), UPA 15 mg (4%) and ADA (2%). One subject who switched from ADA to UPA 15 mg discontinued study drug due to normocytic anemia after 236 days of UPA treatment.

### Long-Term Period

The long-term analysis of subjects treated with UPA 15 mg in all five phase 3 studies (“Any Phase 3 UPA 15 mg”) demonstrated a mean decrease in hemoglobin concentration of -1.8 g/L from baseline to Week 84. The mean hemoglobin concentrations decreased -0.5 g/L over the first 12 weeks of UPA 15 mg treatment then plateaued with continued treatment until approximately Week 60 when hemoglobin concentration further decreased by -1.7 g/L (Figure 21).

**Figure 21. Mean Change from Baseline in Hemoglobin Values Over Time: Long-Term Exposure (Any Phase 3 UPA 15 mg Analysis Set)**



Adapted from Applicant’s ISS Figure 2.5\_4.5.1

The percentages of UPA 15 mg-treated subjects with Grade 3 and Grade 4 decreases in hemoglobin over this period were 6% and 2%, respectively. There was a total of 39 subjects who experienced a Grade 4 hemoglobin decrease. The overall EAER of anemia AEs was calculated to be 4.6 E/100 PY.

Review of the long-term “Any Phase 3 UPA 15 mg and 30 mg” analysis set demonstrated mean hemoglobin decreases from baseline to Week 84 of -1.6 g/L and -3.1 g/L in the UPA 15 mg and UPA 30 mg groups, respectively. The percentage of subjects with Grade 3 and Grade 4 hemoglobin decreases was greater in the UPA 30 mg group (11% and 4%, respectively) compared to the UPA 15 mg group (7% and 2%, respectively).

Similar rates of anemia AEs were reported from the analysis of the long-term exposures for Study M13-545 for UPA 15 mg, UPA 30 mg and MTX with 6 E/100 PY, 6 E/100 PY and 5 E/100 PY. Similar

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results were observed for the long-term analysis of Study M14-465, which demonstrated similar EAERs of AEs of anemia between UPA 15 mg (4 E/100 PY) and ADA 4 E/100 PY).

Analysis of the “Any RA UPA” analysis set was significant for four SAEs of anemia:

- Subject (b) (6) (Study M13-549; UPA 15 mg QD) was a 42-year-old female with history of chronic anemia who was diagnosed with an exacerbation of her anemia on Day 288 requiring hospitalization. Diagnostic evaluation revealed two gastric erosions and the subjects received red blood cell transfusion. Dosing of UPA 15 mg was interrupted for 17 days and hemoglobin returned to baseline.
- Subject (b) (6) (Study M15-555; UPA 15 mg QD) was a 43-year-old female with a history of iron deficiency anemia who experienced an exacerbation of her anemia on Day 411 requiring hospitalization. Evaluation was significant for diagnosis of submucous leiomyoma of the uterus for which she underwent surgical resection. The dose of UPA 15 mg was interrupted during surgical treatment but the subject remained in the study and the last reported hemoglobin concentration was trending toward her baseline value.
- Subject (b) (6) (Study M14-465; UPA 15 mg QD) was a 53-year-old female diagnosed with a history of menorrhagia and abnormal uterine bleeding who presented with life-threatening anemia on Day 490 and hospitalized. On Study Day 493 she was diagnosed with endometrial adenocarcinoma of the uterus (Stage 1b) and UPA was discontinued.
- Subject (b) (6) (Study M14-465; UPA 15 mg QD) was a 45-year-old female who was diagnosed on Day 237 with SAEs of normochromic normocytic anemia, left eye uveitis, right leg cellulitis and bronchopulmonary aspergillosis at which time study drug was discontinued. On Day 240, the subject had a Grade 4 hemoglobin value of 65 g/L. The anemia was reported as resolved on Day 370.

A total of 15/4443 (0.3%) subjects in the “Any RA UPA” analysis set discontinued study drug due to an AE of anemia.

Reviewer’s Comments:

There were no clinically meaningful differences in changes in hemoglobin between UPA 15 mg-treated subjects and subjects in the PBO, MTX or ADA groups. Hemoglobin decreases and AEs of anemia were higher in the UPA 30 mg group than the UPA 15 mg group.

**8.5.9. Adverse Events of Special Interest: Neutropenia**

Controlled Period

There was a small mean decrease of neutrophil counts from baseline to Week 12 in UPA 15 mg-treated subjects ( $-0.9 \times 10^9/L$ ) compared to no change for PBO-treated subjects during the PBO-

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controlled periods of Studies M13-542, M13-549 and M14-465. A greater proportion of subjects in the UPA 15 mg group reported Grade 2, Grade 3 and Grade 4 decreases (4%, 1% and 1%, respectively) compared to PBO-treated subjects (1%, <1% and 0, respectively). A higher percentage of neutropenia AEs were observed in the UPA 15 mg group compared to the PBO group, 2% vs <1%, respectively. Although, there were no reports of SAEs related to neutropenia during the controlled period, one UPA 15 mg-treated subject discontinued study drug due to neutropenia. The EAER of AEs of neutropenia for the UPA 15 mg group was 9 E/100 PY compared with 1 E/100 PY in the PBO group.

There was a small but detectable dose-dependent increase in neutropenia with UPA treatment during the analysis of the “PBO-controlled periods of UPA 15 mg and 30 mg” dataset. Neutrophil counts decreased  $-0.9 \times 10^9/L$  and  $1 \times 10^9/L$  in the UPA 15 mg and UPA 30 mg groups, respectively, compared to  $-0.3 \times 10^9/L$  with the PBO group. Grade 2 and Grade 3 decreases in neutrophil counts were also greater in the UPA treatment arms in a dose-dependent manner compared to PBO (data not shown). Overall, neutropenia was reported in 2.6% of UPA 15 mg subjects and 3.1% of UPA 30 mg subjects and no neutropenia AE led to study discontinuation. For the controlled periods of the studies, the EAER for neutropenia AEs was higher in the UPA 30 mg QD group (17 E/100 PY) compared to the UPA 15 mg group (12 E/100 PY).

The mean decrease of neutrophil counts was greater in the UPA 15 mg and 30 mg groups ( $-1.3 \times 10^9/L$  and  $-1.2 \times 10^9/L$ , respectively) than in the MTX group ( $-0.6 \times 10^9/L$ ) during the three-month MTX-controlled periods of Studies M13-545 and M15-555. Similar to the PBO-controlled studies, there appeared to be small but detectable UPA dose-dependent increase in the number of subjects with Grade 3 and Grade 4 neutropenia (data not shown). Overall, UPA-treated subjects reported a greater proportion of AEs of neutropenia in the UPA 30 mg and 15 mg groups versus MTX: 3%, 2% and 1%, respectively. The same general trend of EAERs of neutrophil AEs were observed in the MTX-controlled analysis set with exposure up to six months with UPA 30 mg (8 E/100 PY), UPA 15 mg (5 E/100 PY) and MTX (2 E/100 PY).

Through Week 26 of Study M14-465, the mean change in neutrophil count from baseline was lower in the PBO group ( $-0.1 \times 10^9/L$ ) compared to UPA 15 mg ( $-1.2 \times 10^9/L$ ) and ADA ( $1.2 \times 10^9/L$ ). The percentage of Grade 3 neutrophil counts in the UPA 15 mg and ADA groups was 0.6% and 0.3%, respectively. The EAER of AEs of neutropenia were highest in the UPA 15 mg group (6 E/100 PY) compared to the ADA group (2 E/100 PY).

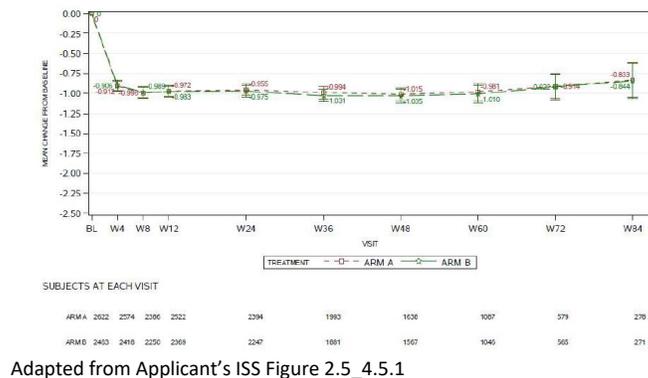
### Long-Term Period

The long-term analysis of the “Any Phase 3 UPA 15 mg” analysis set demonstrated an overall small decrease in mean neutrophil count of  $-0.8 \times 10^9/L$  from baseline to Week 84. The percentages of subjects with Grade 3 and Grade 4 decreased in neutrophil count of the UPA 15 mg group were 0.8% and 0.3% respectively.

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There was a total of seven UPA 15 mg-treated subjects with clinically significant shifts in their neutrophil counts: six subjects shifted once from baseline Grade 0 to postbaseline Grade 4 and one subject shifted from Grade 1 to Grade 4. In all seven subjects, the decrease of neutrophils occurred between three-weeks and three-months after the first dose of UPA and all neutrophil levels recovered to normal values. Two subjects had an associated infection, one tooth infection and one serious case of urosepsis. There were no SAEs of neutropenia and two AEs of neutropenia led to discontinuation of study drug. The EAER of AEs for neutropenia from all five phase 3 studies was 3 E/100 PY. Figure 22 shows the mean change from baseline in neutrophil counts in subjects treated with UPA 15 mg decreased over the initial eight weeks of treatment then plateaued with continued treatment.

**Figure 22. Plot of Mean Change from Baseline in Neutrophil Count Over Time: Long-Term Analysis (Any Phase 3 UP 15 mg Analysis Set)**



Consistent with the observations from the PBO-controlled periods, the long-term analysis of the “Any Phase 3 UPA 15 mg and 30 mg” dataset showed a small but detectable UPA dose-dependent decrease in neutrophil counts. The mean decreases from baseline to Week 84 in the UPA 15 mg and UPA 30 mg groups were  $-0.8 \times 10^9/L$  and  $-1.2 \times 10^9/L$ , respectively. Similarly, subjects in the UPA 30 mg group experienced a greater percentage of Grade 3 decreases in neutrophils compared to UPA 15 mg subjects (2% vs 1%, respectively) and similar percentages of Grade 4 decreases (<1%). The EAER of AEs of neutropenia was higher in the UPA 30 mg subjects compared to the UPA 15 mg group, 7 E/100 PY and 3 E/100 PY, respectively.

Analysis of the long-term exposure data for Study M13-545 demonstrated a dose-dependent decrease of neutrophils in UPA treated subjects with EAERs of 9 E/100 PY, 4 E/100 PY and 3 E/100 PY for subjects treated with UPA 30 mg, UPA 15 mg and MTX, respectively.

Through the data cutoff for Study M14-465, the EAERs of AEs of neutropenia for subjects with no treatment switching were greater in the UPA 15 mg group (3 E/100 PY) compared to subjects in the ADA group (2 E/100 PY).

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Review of the long-term “Any RA UPA” analysis set demonstrated a greater percentage of Grade 3 decreases in neutrophils were observed for subjects treated with UPA 12 mg BID/30 mg QD (2%) compared to UPA 6 mg BID/15 mg QD (1%), further suggesting a dose-dependent effect of UPA. Grade 4 events of decreased neutrophils were similar between the two treatment arms but there were relatively few events on which to draw definitive conclusions.

Overall there was 4/4443 (<0.1%) in the global phase 2 and phase 3 RA studies that discontinued study drug due to an AE of neutropenia. There was a total of 13 subjects in the “Any RA UPA” analysis set with cases of Grade 4 neutropenia of which ten subjects were without an associated infection and three subjects had an associated infection. Infections associated with Grade 4 neutropenia included nonserious tooth abscess, urinary tract infection s/p obstructive renal stone, and pneumonia complicated with sepsis resulting in death. No clear evidence of an association between cases of neutropenia and serious infections, opportunistic infections or herpes zoster was found on subset analyses.

Reviewer’s Comments:

Grade 2 and Grade 3 neutropenia were observed more frequently in the UPA 15 mg and 30 mg groups compared to subjects treated with PBO. Grade 4 neutrophil decreases were uncommon across the UPA groups. Neutrophil counts decreased over the first eight weeks of UPA treatment without further decreases over longer-term treatment. Neutrophil decreases occurred to a greater extent in the UPA 30 mg group compared to the 15 mg group. Adverse events of neutropenia were observed at a similar rate on UPA 15 mg compared to ADA and MTX treatment. No clear evidence of an association of serious infections, opportunistic infections or herpes zoster with a low neutrophil count was observed.

#### **8.5.10. Adverse Events of Special Interest: Lymphopenia**

##### Controlled Period

In the “PBO-controlled UPA 15 mg” analysis set, the mean absolute lymphocyte count increased from baseline to Week 12 in the UPA 15 mg group compared to the PBO group,  $0.07 \times 10^9/L$  versus  $0.01 \times 10^9/L$ , respectively. While the mean absolute lymphocyte counts increased, there were some subjects who experienced decreases with similar proportions of subjects in both the UPA 15 mg and PBO treatment arms. Most of the absolute lymphocyte count decreases were reported as Grade 2 or less (Table 111).

**Table 111. Number of Subjects Meeting Criteria for Potentially Clinically Significant Values for Lymphocytes During the PBO-Controlled UPA 15mg Analysis Set (PBO-Controlled 15 mg and 30 mg Analysis Set)**

<b>Lymphocytes (10<sup>9</sup>/L)</b>	<b>PBO (N=1042) n/N_OBS (%)</b>	<b>UPA 15 mg QD (N=1035) n/N_OBS (%)</b>
Grade 2 (1 to <1.5)	211/1036 (20)	204/1034 (20)
Grade 3 (0.5 to <1)	119/1036 (12)	140/1034 (14)
Grade 4 (<0.5)	7/1036 (1)	9/1034 (<1)
Adapted from Applicant's ISS Table 2.5 1.2.1.1		

Overall, the number of AEs of lymphopenia were reported in similar proportions of UPA 15 mg- and PBO-treated subjects (data not shown) and with similar EAERs of AEs, 5 E/100 PY in both groups. No SAEs related to decreased lymphocytes were reported. One subject in each of the UPA 15 mg and PBO groups discontinued study drug due to lymphopenia.

Analysis of the "PBO-controlled UPA 15 mg and 30 mg" dataset, AEs of lymphopenia were generally similar across PBO, UPA 15 mg and 30 mg treatment arms, 1%, 1% and 2% respectively. None of the events were reported as SAEs, however, one subject in the UPA 30 mg group was discontinued from study drug due to lymphopenia. The percentage of subjects meeting criteria for potentially clinically significant values of lymphopenia and the EAER of AEs of lymphopenia was similar across treatment arms (data not shown).

The percentage of subjects with Grade 3 and Grade 4 lymphopenia in the "MTX-controlled" analysis set was lower for UPA 15 mg compared UPA 30 mg and MTX (Table 112). Among subjects with no switching of treatments, the EAER of AE of lymphopenia was lower in the UPA 15 mg and UPA 30 mg groups compared to MTX-treated subjects, 2 E/100 PY, 4 E/100 PY and 6 E/100 PY, respectively.

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**Table 112. Number of Subjects Meeting Criteria for Potentially Clinically Significant Values for Lymphocytes: MTX-Controlled Analysis Set (MTX-Controlled 15 mg and 30 mg Analysis Set)**

<b>Lymphocytes (10<sup>9</sup>/L)</b>	<b>MTX (N=530) n/N_OBS (%)</b>	<b>UPA 15 mg QD (N=534) n/N_OBS (%)</b>	<b>UPA 30 mg QD (N=529) n/N_OBS (%)</b>
Grade 2 (1 to <1.5)	122/526 (23)	79/530 (15)	118/523 (23)
Grade 3 (0.5 to <1)	48/526 (9)	30/530 (6)	50/523 (10)
Grade 4 (<0.5)	2/526 (<1)	0/530	3/523 (<1)
Source: Sponsor's ISS Table 2.5 3.2.1.1			

Small mean increases in lymphocytes were observed through Week 26 of Study M14-465 in subjects treated with ADA (0.3 x 10<sup>9</sup>/L), UPA 15 mg (0.1 x 10<sup>9</sup>/L) and PBO (0.02 x 10<sup>9</sup>/L). The percentage of subjects with Grade 3 and Grade 4 lymphopenia was higher in the UPA 15 mg group (18% and 1%, respectively) than ADA (6% and 0%, respectively) and comparable to PBO (15 % and 1%, respectively). The EAERs of AE of lymphopenia was approximately 4 E/100 PY for each of the three treatment arms.

### Long-Term Period

In the long-term “Any Phase 3 UPA 15 mg” analysis set, EAER of AEs of lymphopenia was 2 E/100 PY and there were no SAEs related to lymphopenia. There was one subject treated with UPA 15 mg who discontinued study drug in Study 14-465 due to Grade 4 lymphopenia.

A similar pattern of mean changes from baseline in absolute lymphocyte count was observed for the UPA 15 mg group in the long-term analysis of the “Any Phase 3 UPA 15 mg and 30 mg” dataset. Subjects in the UPA 30 mg group also experienced a mean change increase in lymphocyte counts until Week 36 after which the mean changes dropped to slightly below baseline levels (data not shown). The percentages of subjects with Grade 3 and Grade 4 decreases in lymphocytes in the UPA 15 mg group were 17% and 1%, respectively compared to 21% and 2%, respectively, in the UPA 30 mg group.

The EAERs of AE of lymphopenia was greater in the UPA 30 mg arm compared to the UPA 15 mg arm, 3 E/100 PY vs. 2 E/100 PY, respectively. There were no SAEs of lymphopenia reported but one subject discontinued study drug due to lymphopenia.

Through the data cutoff for Study M13-545, the percentage of subjects with Grade 3 lymphopenia was higher in UPA 30 mg- and MTX-treated subjects compared to UPA 15 mg-treated subjects, 21%, 20% and 15%, respectively. Grade 4 lymphopenia was higher in the UPA 30 mg group (2%) compared to UPA 15 mg group (<1%).

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Similarly, through the data cutoff for Study M14-465, increased mean changes of absolute lymphocyte counts from baseline were observed in all groups except for subjects in the UPA 15 mg group who did not undergo treatment switching. Although there were mean increases in the absolute lymphocyte counts, some subjects experienced lymphocyte decreases during the study. The percentage of subjects with Grade 3 and Grade 4 decreases in lymphocytes was higher in the UPA 15 mg group (18% and 1%, respectively) compared to the ADA group (8% and <1%, respectively). In UPA 15 mg and ADA subjects who did not undergo treatment switching during Study 14-465, the EAER of lymphopenia was 3 E/100 PY and 1 E/100 PY, respectively. One UPA 15 mg-treated subject discontinued the study due to lymphopenia.

Analysis of the “Any RA UPA” dataset showed a small but detectable dose-dependent increase in cases of Grade 3 and Grade 4 lymphopenia (Table 113). There was no SAEs of lymphopenia in either UPA dosing group across all phase 2 and phase 3 RA studies; however, there was a single case in each dosing group that led to discontinuation of study drug. No clear evidence of an association between cases of lymphopenia and serious infections was found on subset analyses.

**Table 113. Number of Subjects Meeting Criteria for Potentially Clinically Significant Values for Lymphocytes (Any RA UPA Analysis Set)**

<b>Lymphocytes (10<sup>9</sup>/L)</b>	<b>UPA 6 mg BID/15 mg QD (N=2819) n/N OBS (%)</b>	<b>UPA 12mg BID/30 mg QD (N=1309) n/N OBS (%)</b>
Grade 3 (0.5 to <1)	469/2756 (17)	272/1297 (21)
Grade 4 (<0.5)	31/2756 (1)	30/1297 (2)

Adapted from Applicant’s ISS Table 2.5 6.1.1.1

Reviewer’s Comments:

Treatment with UPA was associated with a mean increase in absolute lymphocyte count over the initial 36 weeks of treatment, followed by small decreases thereafter. The percentages of subjects with Grade 3 and Grade 4 decreases in lymphocytes in the UPA 15 mg group was comparable with that observed with PBO through Week 12, lower than that observed with MTX, and higher than that observed with ADA with the long-term exposure. A higher frequency of lymphocyte count decreases was observed with UPA 30 mg treatment compared to UPA 15 mg. There were no SAEs of lymphopenia and few severe AEs of lymphopenia in the phase 2 and phase 3 studies. Although infections were observed in a few subjects with low lymphocyte counts, there was no clear association identified between low lymphocyte counts and the risk of infections including serious infections, opportunistic infections, and herpes zoster.

### 8.5.11. Adverse Events of Special Interest: CPK Elevations

#### Controlled Period

In the “PBO-controlled UPA 15 mg” analysis set, a greater mean increase in CPK levels from baseline to Week 12 was noted for subjects treated with UPA 15 mg compared with PBO, (60 U/L versus 2 U/L). The mean change in CPK from baseline peaked at two to four weeks in the UPA 15 mg group and remained stable until Week 12.

A greater proportion of subjects had Grade 2 and Grade 3 CPK increases in the UPA 15 mg group than in the PBO group (Table 114).

**Table 114. Number of Subjects Meeting Criteria for Potentially Clinically Significant Values for Creatine Kinase: PBO-Controlled UPA 15mg Analysis Set (PBO-Controlled UPA 15 mg and 30 mg Analysis Set)**

<b>Creatine kinase (U/L)</b>	<b>PBO (N=1042) n/N_OBS (%)</b>	<b>UPA 15 mg QD (N=1035) n/N_OBS (%)</b>
Grade 2 (>2.5 to 5 x ULN)	6/1037 (1)	29/1034 (3)
Grade 3 (>5 to 10 x ULN))	3/1037 (<1)	8/1034 (1)
Grade 4 (>10 x ULN)	0/1037	2/1034 (<0.1)

Adapted from Applicant’s ISS Table 2.5 1.2.1.2

Adverse events of CPK elevation were reported in 3% of subjects in the UPA 15 mg group compared to 1% in the PBO group. There were no SAEs or AEs leading to discontinuation of study drug in this analysis set.

In the “PBO-controlled UPA 15 mg and 30 mg” analysis set, the mean increases in CPK values from baseline to Week 12 were higher in the UPA 15 mg and 30 mg groups versus the PBO group, (61 U/L, 65 U/L and 11 U/L, respectively). While Grade 2 increases in CPK levels were greater in both UPA treatment arms compared to PBO, the number of Grade 3 and Grade 4 CPK increases were low and in similar proportions across all three treatment arms (data not shown).

In the “MTX-controlled” analysis set with exposure up to three months, the mean increase in CPK levels from baseline to Week 12 was greatest in the UPA 15 mg and 30 mg groups compared to the MTX group, 75 U/L, 114 U/L and 3 U/L, respectively. The number of Grade 3 or Grade 4 CPK elevations were few and similar across UPA treatment arms (data not shown). The percentage of subjects with AEs of CPK elevation appeared to be dose-dependent with the highest percentage in the UPA 15 mg and 30 mg groups compared to subjects in the MTX group, 2%, 5%, and <1%, respectively.

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Consistent with the results from the other phase 3 studies, mean increases in CPK levels were higher in UPA 15 mg-treated subjects (84 U/L) compared to ADA- (24 U/L) or PBO-treated subjects (1 U/L) from baseline to Week 26 of Study M14-465. Grade 3 and Grade 4 CPK increases were few and similar across treatment arms and not exceeding greater than 1% in any single treatment arm (data not shown). Through Week 26, EAERs of CPK elevation, with events censored at treatment switching, were higher in the UPA 15 mg group as compared to the ADA treatment group (9 E/100 PY vs. 1.5 E/100 PY, respectively). None of the AEs of CPK elevations were serious or led to study drug discontinuation.

### Long-Term Period

In the long-term “Any Phase 3 UPA 15 mg” analysis set, the mean increase from baseline to Week 84 in UPA 15 mg-treated subjects was 101 U/L. Grade 3 and Grade 4 elevations in CPK were 2% and <1%, respectively. There was 1 SAE of a Grade 2 CPK elevation and two nonserious CPK elevations that led to discontinuation of study drug.

The mean change from baseline in CPK level increased sharply by Week 4 then plateaued and remained relatively stable for the remainder of the study (data not shown).

Review of the long-term “Any Phase 3 UPA 15 mg and 30 mg” dataset showed dose-dependent elevations of CPK elevations from baseline to Week 84 in the UPA 15 mg and 30 mg groups, 102 U/L and 133 U/L, respectively. Similar trends were seen for Grade 3 and Grade 4 CPK elevations in UPA 15 mg (2% and <1%) and 30 mg groups (2% and 1%). There were two SAEs of CPK elevation, one in each of UPA 15 mg and 30 mg treatment arms, and five AEs that resulted in discontinuation of study drug: UPA 15 mg (n=2) and UPA 30 mg (n=3).

Analysis of the long-term exposure in Study M13-545, EAERs of CPK elevation were higher in the UPA 15 mg and UPA 30 mg groups compared to the MTX group, 2%, 5% and <1%, respectively.

UPA-associated CPK elevation was further noted in the long-term analysis of Study M14-465 that demonstrated higher EAER of CPK elevation in UPA-treated subjects compared to ADA-treated subjects, 5 E/100 PY vs. 2 E/100 PY, respectively.

In the “Any RA UPA” analysis set, five (0.1%) UPA-treated subjects in the global phase 2 and phase 3 RA studies discontinued study drug due to an AE of CPK elevation. The percentages of Grade 3 and Grade 4 elevations were similar between UPA 6 mg BID/15 mg QD and UPA 12 mg BID/30 mg QD groups (data not shown). One subject treated with UPA 30 mg reported an SAE of rhabdomyolysis, acute renal failure, influenza and pneumonia that resulted in study drug interruption and no recurrence of CPK elevation after restarting UPA 30 mg.

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Reviewer's Comments:

Elevation of CPK levels were higher dose-dependent in the UPA treatment groups compared to PBO, MTX, or ADA comparator arms. There were few study discontinuations due to CPK elevations. These findings are consistent other JAK inhibitors, which have also been demonstrated to increase CPK levels.

### 8.5.12. Adverse Events of Special Interest: Renal Dysfunction

#### Controlled Period

Analysis of the "PBO-controlled UPA 15 mg" dataset demonstrated greater mean increases in serum creatinine from baseline to Week 12 in subjects treated with UPA 15 mg (5 µmol/L) compared to PBO (1 µmol/L); however, these elevations were small and not clinically significant. Furthermore, Grade 2 increases of serum creatinine were low and similar between the two treatment arms (<1%) and only one UPA 15 mg subject reported a Grade 3 increase in serum creatinine.

In the "PBO-controlled UPA 15 mg and 30 mg" analysis set, small mean increases from baseline to Week 12 were observed in the UPA 15 mg and 30 mg groups (4 µmol/L and 5 µmol/L, respectively) which were higher than PBO (1 µmol/L) but not clinically significant. There were no Grade 3 or Grade 4 increases in serum creatinine. Two AEs of renal dysfunction were reported in the PBO treatment arm but none were reported in either UPA group.

Review of the "MTX-controlled" analysis set similarly demonstrated small mean increases in serum creatinine for subjects treated with UPA 15 mg and 30 mg (4 µmol/L and 5 µmol/L, respectively) compared to MTX subjects (1 µmol/L). There were no Grade 3 and Grade 4 increases of serum creatinine for any treatment arm. There was one AE of renal dysfunction in the UPA 30 mg group (SAE leading to discontinuation of study drug) but none reported in the UPA 15 mg or MTX treatment arms.

The mean change in serum creatinine was higher in the UPA 15 mg group (6 µmol/L) versus ADA (2 µmol/L) or PBO (1 µmol/L) through Week 26 of Study M14-465. There were no AEs of renal dysfunction in the PBO or UPA 15 mg groups and one AE in the ADA group.

#### Long-Term Period

In the long-term "Any Phase 3 UPA 15 mg" analysis set, the mean levels increased during the first four weeks of UPA therapy then plateaued between Week 8 and Week 36. By Week 84 the mean serum creatinine changed in UPA 15 mg-treated subjects was 5 µmol/L. One UPA 15 mg subject experienced a Grade 3 elevation in serum creatinine and two UPA-treated subjects experienced Grade 4 increases. The overall EAER of renal dysfunction AEs was 0.4 E/100 PY reported in 11 subjects and included three SAEs: acute kidney injury (n=2) and renal impairment (n=1).

Analysis of the long-term “Any Phase 3 UPA 15 mg and 30 mg” dataset was consistent with the data observed during the PBO-controlled period with small mean serum creatinine increases from baseline to Week 84 in the UPA 15 mg and UPA 30 mg groups, 5  $\mu\text{mol/L}$  and 7  $\mu\text{mol/L}$ , respectively. One UPA 15 mg subject developed a Grade 4 increase in serum creatinine and one UPA 30 mg subject developed a Grade 3 increase in serum creatinine. There were three SAEs of renal dysfunction in the UPA 15 mg group and six SAEs of renal dysfunction in the UPA 30 mg group. No AEs of renal dysfunction led to discontinuation of study drug in subjects treated with UPA 15 mg but the UPA 30 mg group experienced seven AEs of renal dysfunction that led to study drug discontinuation.

Through the study cutoff for Study M13-545, EAERs of renal dysfunction AEs in the UPA 15 mg and UPA 30 mg groups were 1 E/1100 PY and 2 E/100 PY, respectively compared with the MTX group, 0.3 E/100PY.

In the long-term analysis of Study M14-465, the EAERs of renal dysfunction were higher in subjects treated with ADA (1 E/100 PY) compared with UPA 15 mg (0.4 E/100 PY). Overall, AEs of renal dysfunction were infrequent and similar between treatment arms.

Review of the long-term data from “Any RA UPA” analysis set reported two Grade 3 and Grade 4 increases in serum creatinine concentrations among subjects treated with any dose of UPA. The EAER of AEs of renal dysfunction was 0.5 E/100 PY for the combined UPA group (data not shown). Nine subjects experienced an SAE of renal dysfunction and four subjects had an AE of renal dysfunction that led to discontinuation of study drug. Review of the SAEs revealed that all but one subject had a concomitant infection and other underlying risk factors for renal disease. There did not appear to be a temporal relationship between duration of UPA treatment and onset of renal dysfunction.

### 8.5.13. Adverse Events of Special Interest: MACE and Cardiovascular Events

Patients with RA have a greater risk of cardiovascular disease compared to the general population<sup>30,31</sup> and accounts for approximately one-third to half of all deaths in RA patients<sup>32,33</sup>. The chronic inflammation in RA patients may potentiate the overall risk of cardiovascular events in addition to the well-known risk factors of hypertension, hyperlipidemia, smoking and

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<sup>30</sup> Zegkos T et al. *Ther Adv Musculoskelet Dis* 2016 Jun;8(3):86-101

<sup>31</sup> Agca R et al *Ann Rheum Dis* 2017 Jan;76(10):17-28

<sup>32</sup> Pedersen JK et al *Scand J Rheumatol* 2018 Sep;47(5):371-377

<sup>33</sup> Avouac J et al *Semin Arthritis Rheum* 2017 Apr;46(5):537-543

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diabetes<sup>34</sup>. The unadjusted incident rate of MACE ranges from 0.3 E/100 PY to 0.7 E/100 PY in the RA population<sup>35</sup>. The relative risk of a myocardial infarction in the RA population compared to the general population was estimated at 1.52 (95% CI, 1.37-1.69) and the risk of cardiovascular mortality was approximately two-fold greater<sup>36</sup>.

Untreated, active RA is associated with decreased TC, HDL-C and LDL-C levels<sup>37</sup> and treatment of active RA may result in normalization of lipid parameters. Several approved therapies have also been noted to increase serum lipid levels including tocilizumab, and the JAK inhibitor, e.g., tofacitinib and baricitinib. Therefore, it is not unexpected that UPA has also been observed to increase serum lipid levels including TC, HDL-C and LDL-C (see Section 8.4.6.2).

An independent, externally-led, CAC was established during the phase 2 UPA development program to adjudicate all deaths and any suspected cardiovascular events in a blinded manner. All suspected cardiovascular events for adjudication were identified either by a programmed search of the clinical data for any events that fall under the set of specific SMQs per the charter, followed by the CAC chair review, or alternatively, by the investigative site as a potential cardiac, CNS, or thrombotic event.

A total of 41 fatal cases and 508 suspected nonfatal cardiovascular events from the phase 2 and phase 3 RA studies were reviewed and adjudicated by the committee. Of those, 130 cases were positively adjudicated per prespecified endpoints and definition as described in the CAC charter. All positively adjudicated cardiovascular events were categorized based on MACE (cardiovascular death, nonfatal MI, nonfatal CVA); undetermined/unknown causes of death; other adjudicated cardiovascular events (e.g., procedure, unstable angina requiring hospitalization); and thromboembolic events.

Subject demographics and the proportion of subjects with cardiovascular risk factors (e.g., diabetes, smoking, hypertension and hyperlipidemia) were similar between treatment arms and analysis sets at baseline (data not shown). Subjects were excluded from the phase 3 studies if within the previous six months they had a cardiovascular accident, MI, coronary stenting, uncontrolled hypertension, or any other condition that the investigator thought would put the subject at risk.

Table 115 and Table 116 shows the EAIRs of adjudicated MACE during the controlled periods and long-term periods across the global phase 3 RA studies, respectively.

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<sup>34</sup> McInnes I and Schett G N Engl J Med 2011; 365:2205-2219

<sup>35</sup> Lauper K et al Arthritis Care Res (Hoboken) 2018 Dec;70(12):1756-1763

<sup>36</sup> Solomon DH et al Circulation 2003 Mar 111;107(9):1303-7

<sup>37</sup> Choy E and Sattar N Ann RheumDis 2009 Apr;68(4):460-469

**Table 115. Adjudicated MACE EAIR Per 100 PY: Controlled Period Prior to Treatment Switching (Global Phase 3 Safety Analysis Set)**

	<b>PBO (N=1042) n/PY (n/100 PY)</b>	<b>MTX (N=530) n/PY (n/100 PY)</b>	<b>ADA (N=327) n/PY (n/100 PY)</b>	<b>UPA 15 mg QD (N=1569) n/PY (n/100 PY)</b>	<b>UPA 30 mg QD (N=913) n/PY (n/100 PY)</b>
Adjudicated MACE	3/257 (1.2)	1/122 (0.8)	1/86 (1.2)	3/386 (0.8)	4/211 (1.9)
<small>Adapted from Applicant s ISS Table 2.4_7.1.2</small>					

**Table 116. Adjudicated MACE EAIR Per 100 PY: Long-Term All Exposure (Global Phase 3 Safety Analysis Set)**

	<b>MTX (N=314) n/PY (n/100 PY)</b>	<b>ADA (N=579) n/PY (n/100 PY)</b>	<b>UPA 15 mg QD (N=2630) n/PY (n/100 PY)</b>	<b>UPA 30 mg QD (N=1204) n/PY (n/100 PY)</b>
Adjudicated MACE	2/314 (0.6)	2/468 (0.4)	16/2651 (0.6)	13/1362 (1)
<small>Adapted from Applicant s ISS Table 2.4_9.1.1.1.8, Table 2.4_11.1.1.2.2.1, Table 2.4_4.1.1.8.1, Table 2.4_5.1.1.8.1</small>				

The data from both the controlled and long-term periods demonstrate that UPA 15 mg-treated subjects have similar EAIRs as subjects treated with PBO, MTX and ADA. Conversely, the UPA 30 mg group appears to have an approximately two-fold greater EAIR compared to the UPA 15 mg group and is greater than the PBO and active control groups.

### Controlled Period

Overall, the number of MACE reported during the PBO- or active-controlled periods of the UPA phase 3 studies were small and definitive conclusions could not be drawn regarding the rates of adverse cardiovascular events during this short time period.

A total of four MACE were reported during the “PBO-controlled UPA 15 mg” dataset: three subjects in the PBO group (nonfatal MI, n=2; CV death, n=1) and one subject in the UPA 15 mg group (nonfatal CVA). One subject from each treatment arm discontinued study drug due to MACE.

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Similarly, few MACE were reported in the analysis of the PBO-controlled UPA 15 mg and 30 mg datasets with one UPA 15 mg-treated subject reporting a non-fatal CVA (previously mentioned), one UPA 30 mg-treated subject (nonfatal CVA) and no subjects in the PBO arm.

A total of six subjects reported a MACE through Week 12 of the “MTX-controlled” analysis dataset: MTX (n=1; CV death), UPA 15 mg (n=2; nonfatal MI, CV death) and UPA 30 mg (n=3, CV death, nonfatal MI, nonfatal CVA). In the “MTX-controlled” analysis set with exposure up to six month, the EAIRs of MACE for UPA 15 mg, UPA 30 mg and MTX groups were 1 n/100 PY, 2 n/100 PY and 1 n/100 PY, respectively, in subjects with no treatment switching.

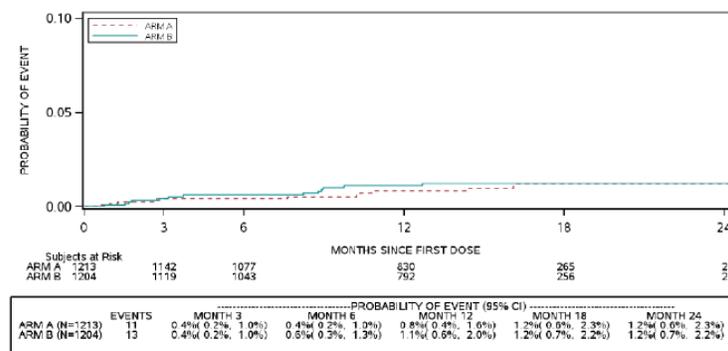
Through Week 24 of Study M14-465 there were a total of six MACE with three PBO-treated subjects (nonfatal MI, n=2; CV death, n=1, mentioned above), one subject from the ADA group (nonfatal CVA) and no events in the UPA 15 mg group.

### Long-Term Period

There was a total of 16 subjects with MACE in the long-term “Any Phase 3 UPA 15 mg” analysis set with an EAIR of 0.6 E/100 PY. All MACEs were reported as serious and five of the subjects discontinued study drug due to the event. There was no clear temporal relationship between duration of UPA 15 mg administration and onset of MACE (data not shown).

The UPA 15 mg and UPA 30 mg groups demonstrated similar EAIRs of adjudicated MACE (0.8 E/100 PY and 1 E/100 PY, respectively) in the “Any Phase 3 UPA 15 mg and 30 mg” analysis set. The Kaplan-Meier curve for MACE showed that the risk for a subject experiencing a MACE was similar between UPA 15 mg and UPA 30 mg groups over the 24-month treatment period (Figure 23).

**Figure 23. Kaplan-Meier Curve for Adjudicated MACE (Any Phase 3 UPA 15 mg and 30 mg Analysis Set)**



Adapted from Applicant's ISS Figure 2.4\_5.12.6.1

In the long-term “MTX-controlled” analysis set, the EAIR of MACE was similar between subjects treated with UPA 15 mg and MTX, 0.6 n/100 PY, and higher in the UPA 30 mg group (1.2 n/100

PY); however, the overall number events in each treatment arm was low with UPA 15 mg and MTX reporting two events each and UPA 30 mg reporting four events.

Through the data cutoff for Study M14-465, EAIRs of MACE were similar between UPA 15 mg and ADA groups, 0.4 n/100 PY. In subjects who did not undergo treatment switching, UPA 15 mg-treated subjects EAIR of MACE was 0.2 n/100 PY and ADA-treated subjects 1.1 n/100 PY.

The EAIR of MACE was 0.7 n/100 PY in the long-term “Any RA UPA” analysis set. There was a total of 12/4443 (0.3%) subjects across all doses of UPA who discontinued study drug due to a MACE.

As shown in Table 117, a total of 38 subjects treated with any dose of UPA reported 39 adjudicated MACE across all phase 2 and phase 3 RA studies: UPA 6 mg BID/15 mg QD, n=21; UPA 12 mg BID/30 mg QD, n=17. There was an additional nontreatment-emergent MACE (nonfatal MI) reported 56 days after the last dose of UPA 15mg. There were as a total of seven subjects with MACE events from PBO, MTX or ADA groups.

**Table 117. Number of subjects with Adjudicated MACE (Any RA UPA Analysis Set)**

	<b>PBO (N=1042)</b>	<b>MTX (N=314)</b>	<b>ADA (N=579)</b>	<b>UPA 6 mg BID/15 mg QD (N=3143)</b>	<b>UPA 12 mg BID/ 30 mg QD (N=1452)</b>	<b>Any UPA (n=4443)</b>
MACE	3	2	2	21	17	38
CV Death	1	1	1	7	6	13
Nonfatal MI	2	0	0	9	7	16
Nonfatal CVA	0	1	1	6	4	10

Adapted from Applicant's ISS Table 2.4\_1.3.1.21.1, Table 2.4\_11.2.14.1.1, Table 2.4\_9.2.13, Table 2.4\_6.6.3; Note: MACE events from Study M14-663 and from the placebo group in the Phase 2 studies are not included in this table.

Ages ranged between 42 to 83 years for the 38 UPA-treated subjects (female, n=23; male, n=15) who experienced an adjudicated MACE. A total of 63% of subjects were older than 60 years at the time of study entry and all subjects had at least one underlying cardiovascular risk factor in addition to the underlying RA. Subjects were on UPA treatment from 16 to 1181 days prior to onset of MACE and no clear temporal relationship was identified.

A total of 13 out of the 38 UPA-treated subjects experienced CV death: UPA 6 mg BID/15 mg QD, n=7; UPA 12 mg BID/30 mg QD, n=6. Eleven of the 13 deaths occurred during the study period and two subjects experienced a treatment-emergent MACE during the study but died subsequent to the end of the study at Days 84 and 167 after their last dose of UPA. Nine of the 11 subjects who died were 60 years-old or older and the remaining four subjects were 54 years-old or older.

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Treatment with UPA demonstrated a dose-dependent increase in all serum lipid concentrations but maintained atherogenic indices-based ratios of TC/HDL-C, LDL-C/HDL-C and apoB/apoA1 (see Clinical Laboratory Evaluation). There was no clear evidence to suggest an association between UPA-induced increased LDL-C concentrations and MACE (data not shown).

There were an additional 19 subjects who reported 20 other adjudicated cardiovascular AEs reported that included cardiovascular procedures, unstable angina requiring hospitalization, hospital-based treatment for heart failure and TIA in the global phase 2 and phase 3 RA studies. Seventeen of these events were in subjects treated with UPA 6 mg BID/15 mg QD and three events in subjects treated with UPA 12 mg BID/30 mg QD. Greater than 60% of the subjects were older than 60 years and all had underlying cardiovascular risk factors in addition to their underlying RA.

Reviewer's Comments:

During the controlled phases of the global Phase 3 studies, the EAIR of MACE in the UPA 15 mg group was similar to the PBO group. The risk of a cardiovascular event did not appear to increase over time with longer treatment of UPA. The EAIR of MACE in the UPA 15 mg group was comparable to the rates in the MTX and ADA groups. The overall EAIR in subjects receiving UPA 15 mg in the long-term global Phase 3 studies was 0.6 n/100 PY and was consistent across the various integrated analysis datasets. The EAIRs of MACE were generally comparable between the UPA 15 mg and 30 mg groups of the global Phase 3 studies, though some variations were noted in the individual analysis sets where the overall exposure was more limited. There was no association between elevated lipids and MACE observed.

#### **8.5.14. Adverse Events of Special Interest: Thrombotic Events**

In the general population, a higher risk of VTE has been associated with a history of VTE, increasing age, immobility, obesity, male sex, African American race, alcohol abuse, drug abuse, history of smoking, hypertension, COPD, infections and other chronic inflammatory conditions including inflammatory bowel disease. Elevated serum C-reactive protein (CRP) levels were also associated with an increased risk for VTE and cardiovascular events. A retrospective analysis of healthcare claims data in the US during a 5-year period of 2002 to 2006 showed the annual prevalence of VTE rose from 317 cases per 100,000 patients in 2002 to 422 cases per 100,000 patients in 2006, representing an overall increase of 33%.

Recent studies have reported that patients with RA are at increased risk of VTE, possibly due to hypercoagulability induced by active systemic inflammation and production of cytokines such as TNF-alpha and IL-1. Patients with RA have an approximate two-fold increased risk of VTE compared to the non-RA population in Western countries with an incidence rate ranging

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from 0.3 to 0.8 E/100 PY in the RA population and 0.1 to 0.4 E/100 PY among the non-RA population.

An increased risk of VTEs have been identified with use of the JAK inhibitors for treatment of inflammatory conditions. A dose-dependent increase in the number of VTEs was observed during the baricitinb clinical trials compared to PBO-treated subjects. Recently a safety signal of PE and increased mortality has emerged from a postmarketing study of tofacitinib in patients with RA. The signal was identified in RA patients taking tofacitinib 10 mg twice daily.

For the UPA clinical development program, an independent, externally led CAC was established during the UPA Phase 2 RA development program to adjudicate suspected cardiac and neurological events. Starting in November 2017, in addition to cardiology and neurology subcommittees, a thrombotic subcommittee was established within the CAC to adjudicate all suspected venous and arterial thrombotic events. The current CAC charter reflects this addition. All VTE that had been reported prior to the thrombotic subcommittee implementation were retrospectively adjudicated in a blinded manner and are presented in the tables as either venous or arterial thrombotic events per the external charter definitions.

Table 118 shows the pooled data across the controlled short-term periods of the Phase 3 studies assessing AEs of VTE in subjects prior to treatment switching. In general, UPA-treated subjects did not demonstrate a higher EAIR compared to PBO. Adalimumab-treated subjects reported the greatest incidence ratio (4 E/100 PY) compared to all other groups.

**Table 118. Treatment-Emergent Adjudicated VTE EAIR per 100 PY During the Controlled Short-Term Periods Prior to Treatment Switching (Global Phase 3 Safety Analysis Set)**

	<b>PBO (N=1042) n/PY (n/100 PY)</b>	<b>MTX<sup>a</sup> (N=530) n/PY (n/100 PY)</b>	<b>ADA (N=327) n/PY (n/100 PY)</b>	<b>UPA 15 mg (N=1569) n/PY (n/100 PY)</b>	<b>UPA 30 mg (N=913) n/PY (n/100 PY)</b>
VTE	1/257 (0.4)	0/122 (0)	3/86 (4)	3/386 (0.8)	1/212 (0.5)

Adapted from Applicant's ISS Table 2.4\_7.1.2; a. Includes both Studies M13-545 and M15-555

Table 119 demonstrates the pooled data across the controlled long-term periods of the Phase 3 studies assessing AEs of VTEs. The long-term data support the controlled-period results and demonstrate that UPA-treated subjects developed VTEs at a similar rate as MTX-active controlled subjects. Adalimumab-treated subjects reported a higher incident rate of VTE events compared to all other groups.

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**Table 119. Treatment-Emergent Adjudicated VTE EAIR per 100 PY During the Long-Term Periods (Global Phase 3 Safety Analysis Set)**

	<b>MTX<sup>a</sup></b> <b>(N=314)</b> <b>n/PY</b> <b>(n/100 PY)</b>	<b>ADA</b> <b>(N=579)</b> <b>n/PY</b> <b>(n/100 PY)</b>	<b>UPA 15 mg</b> <b>(N=2630)</b> <b>n/PY</b> <b>(n/100 PY)</b>	<b>UPA 30 mg</b> <b>(N=1204)</b> <b>n/PY</b> <b>(n/100 PY)</b>
VTE	2/314 (0.6)	5/468 (1.1)	16/2653 (0.6)	4/1362 (0.3)
<small>Adapted from Applicant's ISS Table 2.4_9.1.1.1.8, Table 2.4_11.1.1.2.2.1, Table 2.4_5.1.1.8.1, Table 2.4_4.1.1.8.1;  a. Includes M15-555 only which has long-term MTX exposure</small>				

### Controlled Period

Overall, the number of VTE-related AEs reported during the PBO- or active-controlled periods of the UPA phase 3 studies were small and definitive conclusions could not be drawn regarding the rates of events during this short time period.

In the PBO-controlled periods of Studies M13-542, M13-549 and M14-465, a total of two UPA 15 mg-treated subjects reported an adjudicated VTE (PE, n=1; DVT, n=1) and one PBO-treated subject (PE, n=1). There was only one reported adjudicated VTE event (PE) in the UPA 15 mg group during the “PBO-controlled UPA 15 mg and 30 mg” analysis set. No PBO or UPA 30 mg treated patients reported a VTE-related event. Similarly, in the “MTX-controlled” analysis set with exposure up to three months, adjudicated VTE were reported for one subject each in the UPA 15 mg group (PE) and 30 mg group (DVT) and no subjects in the MTX control group.

Through Week 14 of Study M14-465, there was one UPA 15 mg-treated subject (DVT), three ADA-treated subjects (PE, n=3), and one subject from the PBO arm (PE, n=1). Through Week 26 of the study, with events censored at treatment switching, the EAIR of adjudicated VTEs in the UPA 15mg and ADA groups were 0.7 n/100 PY and 2.2 n/100 PY, respectively.

### Long-Term Period

In the “Any Phase 3 UPA 15 mg” analysis set with one-year exposure, the EAIR of adjudicated VTE was 0.4 n/100 PY for UPA 15 mg-treated subjects. There was no clear pattern regarding the interval specific incident rate and no pattern regarding the time of onset of VTE (data not shown).

In the long-term analysis set of “Any Phase 3 UPA 15 mg and 30 mg”, the UPA 15 mg group reported an EAIR of adjudicated VTEs of 0.9 n/100 PY compared to 0.3 n/100 PY for the UPA 30 mg group. These data suggest that there is not a dose-dependent relationship regarding UPA and VTE AEs. There was no signal identified regarding the time of onset of VTE AEs.

Analysis of long-term data through the study cutoff for Study M13-545 demonstrated EAIRs of adjudicated VTE in the UPA 15 mg, UPA 30 mg and MTX control groups were 0 n/100 PY, 0.3 n/100 PY and 0.6 n/100 PY, respectively.

Through the data cutoff date for Study M14-465, the EAIRs of adjudicated VTEs were 0.3 n/100 PY in the UPA 15 mg and 1.1 n/100 PY in the ADA group. In subjects receiving either UPA or ADA with no treatment switching during the study, the EAIR of VTEs was 0 n/100 PY and 1.7 n/100 PY, respectively.

Review of the “Any RA UPA” analysis set did not suggest a higher EAIR of adjudicated VTEs for subjects continuously dosed with UPA 12 mg BID/30 mg QD (0.3 n/100 PY) compared to subjects continuously dosed with UPA 6 mg BID/15 mg QD (0.2 E/100 PY). A total of 13/4443 (0.3%) UPA-treated subjects in this dataset discontinued the study due to an AE of VTE.

Table 120 shows all adjudicated VTE AEs reported in the Applicant’s Phase 2 and Phase 3 RA studies.

**Table 120. Treatment-Emergent Adjudicated VTE (Any RA UPA)**

	<b>PBO (N=1042)</b>	<b>MTX (N=314)</b>	<b>ADA (N=579)</b>	<b>UPA 6 mg BID/15 mg QD (N=3143)</b>	<b>UPA 12 mg BID/ 30 mg QD (N=1452)</b>	<b>UPA Other Dose (N=315)</b>	<b>UPA Any Dose (n=4443)</b>
VTE	1	2	5	21	8	1	30
DVT	0	1	1	12	5	0	17
PE	1	2	4	13	4	1	18
DVT/PE	0	1	0	5	2	0	7

Adapted from Applicant's ISS Table 2.4\_1.3.1.21.2, Table 2.4\_11.2.14.2.1, Table 2.4\_9.2.14, Table 2.4\_6.6.4; Note: Subjects with concurrent DVT/PE are also counted under both DVT and PE rows. MACE events from Study M14-663 and from the placebo group in the Phase 2 studies are not included in this table.

Throughout the global UPA phase 2 and phase 3 RA studies, there were a total of 38 subjects that experienced an adjudicated VTE AE. Thirty subjects received UPA (UPA 6 mg BID/15 mg QD, n=21; UPA 12 mg BID/30 mg QD, n=8; UPA other dose, n=1; ADA, n=5; MTX, n=2; PBO, n=1). Two UPA-treated subjects with an adjudicated VTE died due to PE. There were two additional reports of nontreatment-emergent VTE in UPA-treated subjects, both of whom developed DVTs. All subjects had at least one risk factor for VTE, e.g., prior history of thrombotic event, obesity, hormonal therapy or recent surgery. The onset of VTE events ranged from 23 to 1127 days of UPA therapy and no definitive pattern of time of onset can be ascertained. No adjudicated VTE in UPA-treated subjects were associated with an increased platelet value >600 x 10<sup>9</sup>/L at the time of event; however, there was one subject with an elevated platelet count of 575 x 10<sup>9</sup>/L at the time of her VTE event.

There were three cases of UPA-treated subjects identified with noncardiac/non-neurologic arterial thromboembolic events as adjudicated by the CAC.

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- Subject (b) (6) (Study M13-538): 43-year-old female with history of PE/DVT being treated with rivaroxaban and receiving UPA 6 mg BID for 350 days when she developed a femoral arterial stenosis and femoral artery thrombosis.
- Subject (b) (6) (Study M13-545): 55-year-old male with history of femoral stents, bypass graft, hypertension, diabetes and former smoker developed a thrombosed stent in the common iliac artery after receiving UPA 30 mg for 92 days.
- Subject (b) (6) (Study M15-555): 54-year-old male with a history of smoking (37 pack years), obesity and peripheral vascular disease developed a left popliteal artery aneurysm and peripheral artery thrombosis after receiving UPA 30 mg for 281 days.

Reviewer's Comments:

Patients with RA may have an increased risk for VTE. In the UPA clinical development program, adjudicated VTEs were reported at comparable rates in UPA-treated subjects and subjects treated with PBO, MTX and ADA. No dose-dependent relationship in the rates of VTE, patterns in the time to onset of the events, or association with platelet count were observed. The long-term incidence rates for UPA 15 mg were within the range of VTE rates reported for the general RA population. However, the data are limited due to the majority of subjects only being exposed to UPA for one-year or less. It is unclear whether an increase of VTEs could occur with long-term (>1 year) treatment with UPA in light of safety signals from other drugs in the JAK inhibitor class.

## **8.6. Safety Analyses by Demographic Subgroups**

Subgroup analyses of the following intrinsic factors were examined: age, race, sex, and weight. In order to assess safety in these subgroups, the Applicant summarized AEs in the "PBO-Controlled UPA 15 mg", "PBO-Controlled 15 mg and 30 mg", "MTX-Controlled", "Any Phase 3 UPA 15 mg" and "Any Phase 3 UPA 15 mg and 30 mg" analysis sets.

### **8.6.1. Race**

The rates of AEs were higher for non-White subjects compared to White subjects across all analysis sets and treatment groups. The EAERs of SAEs, severe AEs and AEs leading to discontinuation of study drug were comparable between Whites and non-Whites. There were no notable differences in the types of AEs by race across the analysis sets.

### **8.6.2. Age**

In all controlled-period analysis sets, the percentages of subjects with AEs, SAEs, severe AEs, and AEs leading to discontinuation of study drug were similar across treatment arms. In the long-term analysis sets, the EAERs of these AEs were highest in subjects age  $\geq 75$  years and lowest in subjects  $< 65$  years of age. Subjects  $\geq 75$  years-old who were treated with UPA 30 mg experienced

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increased rates of overall infections compared to younger subjects. The rates of infections of subjects treated with UPA 15 mg was similar across all age groups.

### 8.6.3. Sex

The rates of AEs, SAEs, severe AEs and AEs leading to discontinuation of study drug were similar between males and females. In the long-term analysis sets, the rates of AEs and trended towards being greater in female subjects for both UPA doses.

### 8.6.4. Weight

In the controlled-period analysis sets, no clear pattern was observed regarding weight for AE categories. In the long-term analysis sets, AEs, SAEs, severe AEs and AEs leading to discontinuation of study drug were reported at a higher rate in the highest weight group ( $\geq 100$  kg) compared with other two weight groups.

There was no consistent pattern for the types of AEs by weight groups across the analysis sets, except in the long-term analysis set where a higher rate of neutropenia and herpes zoster was seen with UPA 30 mg among subjects in the  $< 60$  kg weight group.

## 8.7. Additional Safety Explorations

### 8.7.1. Human Reproduction and Pregnancy

Nonclinical embryofetal developmental studies have indicated that UPA is teratogenic in both rats and rabbits, including the to-be-marketed dose of 15 mg QD. Upadacitinib administration was associated with skeletal malformations in rats in the absence of maternal toxicity and with cardiac malformations in rabbits concurrent with maternal toxicity; however, UPA had no effect on maternal or reproductive parameters or on postnatal development of offspring in a study in rats.

For the UPA development program, pregnant and lactating women were excluded from the studies and all female subjects of childbearing potential were required to use protocol-specified pregnancy avoidance measures. Study drug was immediately discontinued in any female subject found to be pregnant during the clinical trials. Data on the pregnancy and fetal outcome were requested for all reported cases of pregnancy that occurred during the study.

As of August 2018, 19 pregnancies in female subjects were reported in the UPA clinical development program, of which 17 occurred in RA studies, one in a Crohn's disease study, and one in an ulcerative colitis study. Table 122 shows the pregnancy outcomes of the 16 subjects exposed to UPA during pregnancy. No congenital malformations were reported.

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**Table 121. Pregnancy Outcomes in the UPA Clinical Development Program (Maternal Exposure Pregnancies)**

Study Number Subject Number	Age	Indication	Treatment at Time of Pregnancy	Pregnancy Outcome	Comments
M13-538 (b) (6)	32	RA	UPA 6mg BID	Live birth without congenital abnormality	Full term infant without complications
M13-538 (b) (6)	37	RA	UPA 12mg BID	Live birth without congenital abnormality	Full term infant without complications
M13-538 (b) (6)	32	RA	UPA 12mg BID	Elective termination	Subject decision due to unknown teratogenic effects
M14-465 (b) (6)	25	RA	UPA 15 mg	Spontaneous abortion	Occurred at unknown gestational
M14-465 (b) (6)	29	RA	UPA 15 mg	Spontaneous abortion	Occurred first trimester
M14-465 (b) (6)	22	RA	UPA 15 mg	Ongoing pregnancy	-
M14-465 (b) (6)	29	RA	UPA 15 mg	Spontaneous abortion	Occurred at ~5 weeks gestation
M14-465 (b) (6)	27	RA	UPA 15 mg	Spontaneous abortion	Occurred at ~6 weeks gestation
M15-555 (b) (6)	36	RA	UPA 15 mg	Spontaneous abortion	Occurred at ~4 weeks gestation
M15-555 (b) (6)	38	RA	UPA 15 mg	Lost to follow-up	-
M15-555 (b) (6)	31	RA	UPA 15 mg	Ongoing pregnancy	-
M13-542 (b) (6)	37	RA	UPA 30 mg	Spontaneous abortion	Occurred ~2-weeks gestation
M13-549 (b) (6)	33	RA	UPA 30 mg	Elective termination	Reason for elective termination unknown
M15-555 (b) (6)	34	RA	UPA 30 mg	Live birth without congenital abnormality	28-week premature infant without complications
M13-740 (b) (6)	28	Crohn's disease	UPA 24 mg QD	Live birth without congenital abnormality	Full term infant without complications
M14-234 (b) (6)	23	Ulcerative colitis	UPA 15 mg QD	Ongoing pregnancy	-

Source: Applicant's Summary of Clinical Safety, Table 130

Three additional subjects who became pregnant in the RA clinical trials were not on UPA at the time of pregnancy. In Study M15-555, two subjects were randomized to MTX and one had a live birth without congenital anomaly and the other had an elective termination. The third subject was enrolled in Study M14-465 and was initially on UPA but became pregnant after rescue

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treatment with adalimumab (last menstrual period was reported as occurring 17 days after switching from upadacitinib to adalimumab). Her pregnancy resulted in an elective termination.

A total of 6/16 (38%) of the maternal exposures to UPA resulted in spontaneous abortions. All six subjects were either taking MTX concomitantly or used MTX within one month prior to conception. Of the subjects who had a spontaneous abortion, five were receiving UPA 15 mg and one was receiving UPA 30 mg.

In the general population, approximately 14 to 27% of pregnancies in the US end in spontaneous abortion, with the highest percentage occurring in women older than 35 year of age<sup>38</sup>. In patients with RA treated with TNF inhibitors and MTX or leflunomide, the rate of spontaneous abortion is 33%, while the rate in those treated with TNF inhibitors without MTX or leflunomide was 24%<sup>39</sup>.

Four paternal exposure pregnancies were reported in the partners of male subjects in the UPA clinical development program (one in a RA study and three in a Crohn's disease study). All male subjects were exposed to UPA when the female partners became pregnant. Outcomes of the four partner's pregnancies resulted in a live birth without congenital anomaly, an ongoing pregnancy, a spontaneous abortion and one subject lost to follow-up. Studies conducted by the Applicant has demonstrated that UPA is not genotoxic, therefore the male-mediated developmental risk involving effects on the germ cell is considered to be low.

Given the available pharmacodynamic and toxicological data in animals that have shown excretion of UPA in milk, it is likely that UPA is also secreted in human milk as well. However, there are no direct data on the presence of UPA or its metabolites in human milk at this time.

The available clinical trial data are inadequate to draw conclusions regarding use of UPA during pregnancy in humans. However, given the embryo-fetal toxicity observed in animals at the to-be-marketed dose, the Agency recommends labeling for UPA should include a Warning and Precaution statement regarding potential teratogenicity.

### 8.7.2. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

In the "Any UPA RA" analysis set, the rate of overdose was rare (< 0.1%). There were two subjects (UPA 6 mg BID/15 mg QD, n=1; UPA 12 mg BID/30 mg QD, n=1) in the Phase 2 open-label extension of Study M13-538 who accidentally took the wrong dose of UPA. One subject was up titrated from 6 mg BID to 12 mg BID but accidentally took 24 mg BID for 47 days; the other subject was titrated to 12 mg BID but took 48 mg daily for 29 days. For both subjects there were no AEs reported and the AEs of overdose were considered mild in severity and study drug was continued. No dose-limiting toxicity was observed during clinical studies.

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<sup>38</sup> Ventura SJ et al Nat Vital Stat Report 2011 Jun;60(7): 1-21

<sup>39</sup> Vestappen SM et al Ann Rheum Dis 2011 May;70(5):823-6

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The highest dose administered in humans was 48 mg as a single dose using the immediate-release formulation in the Phase 1 Study M13-401. Upadacitinib was well-tolerated without any reported SAEs or AEs leading to discontinuation.

There were no reports of drug abuse or dependence or other information relevant for drug abuse in these studies. A comprehensive analysis was performed by the Applicant on the UPA clinical studies across all indications and with doses/dosages at or bracketing the to-be-marketed dose of UPA (15 mg QD), leveraging an Abuse Liability CMQ search designed to identify events related to potential abuse liability. Results of the analysis demonstrated that UPA treatment was not associated with abuse potential. There is no evidence for and no anticipation of drug abuse with UPA treatment.

There were no reports of withdrawal or rebound effects in any of the studies in the UPA RA program.

## **8.8. Safety in the Postmarket Setting**

### **8.8.1. Human Reproduction and Pregnancy**

The available clinical trial data are inadequate to draw conclusions regarding use of UPA during pregnancy in humans. However, given the embryo-fetal toxicity observed in animals at the to-be-marketed dose, the Agency recommends labeling for UPA should include a Warning and Precaution statement regarding potential teratogenicity.

### **8.8.2. Safety Concerns Identified Through Postmarket Experience**

Upadacitinib is not approved for use for any indication anywhere in the world. Consequently, there is no postmarketing experience with UPA.

## **8.9. Integrated Assessment of Safety**

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A total of 4443 subjects were exposed to UPA in the combined periods of the phase 2 and phase 3 RA trials and formed the primary source of evidence for the safety review. Of these subjects, 2972 (67%) were exposed to UPA for at least 48 weeks which provides sufficient data to allow for the initial determination of the overall risk-benefit assessment of UPA for the treatment of patients with moderately to severely active RA; however, caution is required when interpreting the data as certain types of AEs may be more frequently observed with longer durations of exposure to UPA, e.g., malignancies, VTEs and MACE. Additionally, it is worth noting that the safety analyses included comparisons of AEs between the UPA 15 mg and 30 mg doses but only the UPA 15 mg dose is being sought for approval by the Applicant. Thus, while many of the AEs appear to be dose-dependent, the relative risk-benefit assessment will be performed using the UPA 15 mg dose.

The overall EAER of deaths of UPA 15 mg, the proposed to-be-marketed dose, was similar to PBO during the controlled periods and the MTX control group during the long-term periods of the phase 3 program. There was a two-fold higher EAER of deaths in subjects treated with UPA 30 mg compared to UPA 15 mg during the long-term periods of the phase 3 studies; however, the rate of deaths in the UPA 30 mg was comparable to that of ADA-treated subjects during the same period and the overall numbers of deaths were small, making it difficult to draw firm conclusions. The most common cause of death in subjects treated with UPA were cardiovascular related, which is consistent with the overall RA population. The overall mortality rate of the UPA-treated subjects was consistent with rates in the general population when matched by country, age and gender. There were no specific safety signals identified regarding causes of death and no temporal relationship was identified between duration of UPA treatment and time of death.

There was a greater percentage of subjects experiencing an AE or SAE in subjects treated with UPA 15 mg compared to PBO-treated subjects. This greater percentage of AEs and SAEs was dose-dependent and observed during both the controlled and long-term periods of the phase 3 studies. The types of AEs and SAEs were similar between treatment arms and were consistent with events reported in other RA studies of immunosuppressants and JAK inhibitors. Review of the data did not identify a relationship between the duration of UPA treatment and the onset of AEs or SAEs.

Review of safety data from other JAK inhibitor development programs, e.g., tofacitinib and baricitinib, has demonstrated several potential class-related risks of AEs: malignancy, serious infections, opportunistic infections, VTE, gastrointestinal perforations, viral reactivation and laboratory changes including lymphopenia, neutropenia, anemia, hyperlipidemia, liver enzyme and CPK elevations. Consequently, the UPA safety database was specifically analyzed for these AEs of special interest.

Malignancies were reported across all treatment arms in the short-term PBO-controlled, MTX-controlled and ADA-controlled datasets; however, the small number of events limits any

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comparison of malignancy rates during these periods. The long-term MTX-controlled and ADA-controlled datasets do not indicate an increased risk of malignancies other than NMSC with UPA treatment compared to treatment with either MTX or ADA. The types of malignancies reported in the UPA studies are consistent with that anticipated in a RA study population.

Rates for malignancies were generally similar between the UPA 30 mg and 15 mg groups except for the rates of NMSC, which were higher in the upadacitinib 30 mg group. Analysis of the long-term periods demonstrated that the incidence rate of malignancies other than NMSC in subjects receiving UPA 15 mg did not appear to increase over time. Across all UPA groups, the incidence rates of malignancies, excluding NMSC, for patients receiving UPA 15 mg were within the range expected for a population of patients with RA. The age-gender adjusted SIR for malignancies other than NMSC indicates that the malignancy risk with UPA 15 mg was within the expected range for the general population.

While these data suggest that there is no increased risk of malignancy with UPA, excluding NMSC, it should be noted that the data are limited due to the majority of subjects being exposed to UPA for one year or less. Prolonged immunosuppression is associated with an increased risk of malignancy, thus, there is the potential for an increased risk of malignancies with long-term (>1 year) UPA treatment consistent with safety signals from other immunosuppressant drugs and drugs from the JAK inhibitor class.

A higher rate of serious infections was observed in a dose-dependent manner of UPA-treated subjects compared to control subjects across all analysis sets. Overall, there was a greater percentage of subjects experiencing a serious infection when treated with UPA 15 mg compared to PBO-treated subjects. This greater percentage of serious infections was dose-dependent with higher proportions of UPA 30 mg-treated subjects reporting serious infections compared to subjects treated with UPA 15 mg, PBO or MTX. The dose-dependent increase of serious infections was also demonstrated in the long-term period analysis with higher EAERs of serious infection in UPA 30 mg-treated subjects. The types of serious infections were similar between treatment arms and no clear temporal relationship between the duration of UPA treatment and onset of serious infection was identified.

During the controlled periods of the phase 3 studies, the percentage of subjects with opportunistic infections was similar between subjects treated with UPA 15 mg and subjects who received PBO or MTX in the control groups. A greater percentage of subjects reported opportunistic infections in the UPA 30 mg treatment group compared to UPA 15 mg treatment group over the same time periods. In the long-term analysis of Studies M14-465 and M13-545, the rates of opportunistic infections were similar between the UPA 15 mg, ADA and MTX groups. The most common opportunistic infections were nonserious mucosal candidiasis infections.

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In the UPA clinical development program, adjudicated VTEs were reported at comparable rates in UPA-treated subjects and subjects treated with PBO, MTX and ADA. No dose-dependent relationship in the rates of VTE, patterns in the time to onset of the events, or association with platelet count were observed. The long-term incidence rates for UPA 15 mg were within the range of VTE rates reported for the general RA population. As stated with the malignancy analysis, these data need to be interpreted with caution due to the majority of subjects having been exposed for one-year or less. It is unclear whether an increase of VTEs may occur with longer term (>1 year) treatment with UPA in light of safety signals from other drugs in the JAK inhibitor class.

An increased frequency of gastrointestinal perforations has been reported with tofacitinib and baricitinib. A total of six plausible UPA-related cases of gastrointestinal perforations were reported in the phase 3 studies compared to no cases in subjects treated with PBO, MTX or ADA. In the context of the data from other JAK inhibitors, the data suggest that subjects treated with UPA are at an increased risk of developing gastrointestinal perforations.

Viral reactivation, e.g. herpes zoster, has been reported in patients treated with potent immunosuppressants including members of the JAK inhibitor family of drugs. The rates of herpes zoster infection were higher in subjects treated with UPA compared to subjects in the PBO, MTX and ADA groups. There was a dose-dependent effect observed with higher rates of herpes zoster infections in subjects treated with UPA 30 mg compared to UPA 15 mg subjects. The majority of herpes zoster cases involved a single dermatome although cases of ophthalmic zoster and disseminated cutaneous zoster were also reported in both UPA groups. In addition, HBV reactivation was observed with two definitive cases reported in UPA-treated subjects during the phase 2 and phase 3 program.

As noted with other drugs of its class, UPA-treated subjects reported a greater frequency of Grade 2 and Grade 3 neutropenia compared to subjects treated with PBO. Neutrophil decreases occurred to a greater extent in the UPA 30 mg group compared to the 15 mg group with neutrophil counts decreasing over the first eight weeks of UPA treatment without further decreases over longer-term treatment. Adverse events of neutropenia were observed at similar rates in the UPA 15 mg group compared to the ADA and MTX treatment groups. No clear evidence of an association of serious infections, opportunistic infections or herpes zoster with a low neutrophil count was observed.

Subjects treated with UPA demonstrated a dose-dependent decrease in hemoglobin concentrations compared to PBO, MTX and ADA during the controlled periods of the phase 3 studies; however, the magnitude of the decreases in hemoglobin were not clinically meaningful. In contrast, the UPA 30 mg group demonstrated larger decreases in hemoglobin and higher frequencies of AE of anemia compared to the UPA 15 mg group. During the long-term periods, a dose-dependent increase in the number of AE and SAEs in subjects treated with UPA was

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observed. While SAEs of anemia were associated with UPA 15 mg-treated subjects, the overall number was small.

Treatment with UPA was associated with a mean increase in absolute lymphocyte count over the initial 36 weeks of starting treatment, followed by small decreases thereafter. The percentages of subjects with Grade 3 and Grade 4 decreases in lymphocytes in the UPA 15 mg group was comparable with that observed with PBO through Week 12, lower than that observed with MTX, and higher than that observed with ADA with the long-term exposure. A higher frequency of lymphocyte count decreases was observed with UPA 30 mg treatment compared to UPA 15 mg. There were no SAEs of lymphopenia and few severe AEs of lymphopenia in the phase 2 and phase 3 studies. Although infections were observed in a few subjects with low lymphocyte counts, there was no clear association identified between low lymphocyte counts and the risk of infections including serious infections, opportunistic infections, and herpes zoster.

Upadacitinib treatment resulted in a greater percentage of transaminase level elevations and AEs of hepatic disorders compared to PBO-treated subjects, and similar to those reported in MTX-treated subjects. Transaminase elevations and EAERs of hepatic disorders were similar between the UPA 15 mg and UPA 30 groups. Most of the transaminase elevations did not result in study drug discontinuation and resolved after discontinuation of UPA. No cases of drug-induced liver injury were identified.

Similar to lipid elevations observed with other JAK inhibitors, UPA treatment was associated with a dose-dependent increase in all lipid parameters including TC, LDL-C and HDL-C; however, the increased lipid concentrations did not affect the overall atherogenic indices as evidenced by ratios of TC/HDL-C and LDL-C/HDL-C. The observed lipid elevations were responsive to statin therapy and there was no relationship identified between subjects with elevated lipids and MACE in the phase 3 studies.

Elevation of CPK levels were higher in the UPA treatment groups compared to PBO, MTX, or ADA comparator arms. While there was a dose-dependent increase in CPK elevations, the majority of elevations were asymptomatic; however, there were several cases of CPK elevation that led to study discontinuations but no cases of UPA-associated rhabdomyolysis. These findings are consistent with other JAK inhibitors, which have also been demonstrated to increase CPK levels.

In summary, review of the UPA safety database demonstrate that UPA treatment was associated with increased frequencies of SAEs, AEs, serious infections, opportunistic infections, gastrointestinal perforations, viral reactivations, neutropenia, lymphopenia, anemia, and elevated liver transaminase, lipid elevations and CPK concentrations. These findings are consistent with what has been observed with other JAK inhibitors. Consequently, similar labeling language should be included in the prescribing information for the UPA 15 mg.

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In contrast to what has been identified with other JAK inhibitors, the data from the UPA program did not demonstrate an increased rate of malignancies (other than NMSC) or VTE. However, these results need to be interpreted cautiously since the majority of subjects had been exposed to UPA treatment for one-year or less. Given UPA's mechanism of action and the degree of immunosuppression, it is unclear whether an increased frequency of malignancies or VTEs may occur with longer duration of treatment. The Agency has recently determined that class labeling of JAK inhibitors for malignancies and VTEs will be included all JAK inhibitor drugs including UPA 15 mg.

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## **9. Advisory Committee Meeting and Other External Consultations**

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An Advisory Committee Meeting was not conducted for this application.

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## **10. Labeling Recommendations**

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### **Prescription Drug Labeling**

Key product labeling recommendations will include limiting the indication for use in subjects with moderately to severely active RA who have failed first-line therapy with MTX. Safety language should be added detailing UPA-related AEs including serious/opportunistic infections, reactivation of herpes zoster and hepatitis B virus, gastrointestinal perforations, anemia, neutropenia, elevated CPK, elevated lipids and potential embryo-fetal toxicity. Additionally, the Agency has recently determined that class labeling of JAK inhibitors for malignancies and VTEs will be included all JAK inhibitor drugs including UPA 15 mg. Consequently, RINVOQ will receive a BLACK BOX Warning for serious infections, TB, malignancies, and risk of VTE.

## **11. Risk Evaluation and Mitigation Strategies (REMS)**

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After review of the safety data, the Agency concludes that a Risk Evaluation and Mitigation Strategy is not required at this time and that the safety issues associated with UPA 15 mg can be adequately managed through labeling and that additional requirements are not necessary to maintain a favorable benefit-risk balance at this time.

Specifically, safety signals known to be associated with potent immunosuppression and JAK inhibitors were observed at similar frequencies consistent with bDMARDs and other members of UPA's drug class and are clinically monitorable and typically treatable, e.g., serious infections, laboratory abnormalities, and gastrointestinal perforations. Potentially concerning is the developing recognition of possible JAK inhibitor-associated adverse events that include increased frequencies of malignancy and VTE, both of which have been observed in the clinical development programs of tofacitinib and baricitinib. However, no increase in the frequency of malignancies or VTEs was observed in the safety analyses of UPA. Nevertheless, these data need to be interpreted with caution as the data are limited as the majority of subjects were exposed to UPA for 48 weeks or less. To address the potential for later occurring AEs with long-term UPA exposure, the Applicant's is collecting data from the phase 3 studies which are designed to follow subjects for five years with interval reporting.

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## **12. Postmarketing Requirements and Commitments**

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The Applicant will perform two PMR/PMCs concerning pediatric studies in accordance with the Pediatric Research Equity Act (PREA):

- A multiple-dose pharmacokinetic study in children from 2 to less than 18 years of age with juvenile idiopathic arthritis (JIA)
- A randomized withdrawal, double-blind, placebo-controlled study to evaluate the efficacy and safety of upadacitinib in children from 2 to less than 18 years of age with polyarticular-course JIA.

After review of the safety data, the Agency concludes that Postmarketing Requirements or Commitments are not required at this time due to the overall safety profile of UPA 15 mg regarding JAK inhibitor-related AEs (e.g., malignancy and VTE) and the relative safety compared to other immunosuppressants (e.g., MTX and TNF inhibitors) frequently used for the treatment of RA. Based on the current data, the Agency believes safety issues associated with UPA 15 mg can be adequately managed through labeling and that additional requirements are not necessary to maintain a favorable benefit-risk balance at this time.

## 13. Appendices

### 13.1. Financial Disclosure

#### 13.1.1. Studies M13-542, M13-549, M14-465, M13-545, M15-555

A financial disclosure review was conducted for all five phase 3 studies. Because many investigators participated in more than one study, a combined review of the financial disclosures will be presented Table 122.

**Table 122. All Five Phase 3 Studies: Financial Disclosure Review Template**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>4650</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>41</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: <u>4</u></p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

A total of 41 investigators had disclosable financial interests/arrangements. Each investigator's financial disclosure documentation was reviewed. For these investigators with disclosable financial interests/arrangements: none received compensation for conducting the study where the value could be influenced by the outcome of the study; no investigators received significant

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payments of other sorts; no investigators had proprietary interest in the product being tested held by the investigator; no investigator had significant equity interest in the Sponsor covered study.

These financial disclosures do not raise concerns regarding the integrity of the phase 3 studies as the Applicant took steps to minimize potential bias of clinical investigators with financial interests and arrangements by using proper study design and operations. The clinical studies were blinded to the study site personnel and the participating subjects through the primary endpoint collection for the studies. Each active dose of investigational drug product was identical in appearance to its matched PBO and each subject was randomly assigned to their treatment arm independent of the investigator and the study site. Additionally, the number of subjects enrolled at the individual investigator sites were small compared to the total number of subjects enrolled in the overall study.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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KEITH M HULL  
12/04/2019 12:41:34 PM  
Amended Clinical Review

RACHEL GLASER  
12/04/2019 12:46:03 PM