CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211675Orig1s000

SUMMARY REVIEW
<table>
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<th>Date</th>
<th>July 11, 2019</th>
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| From       | Rachel Glaser, MD, Clinical Team Leader, DPARP  
|            | Sally Seymour, MD, Director, DPARP  
|            | Mary Thanh Hai, MD, Acting Director, ODEII |
| Subject    | Cross-Discipline Team Leader Review  
|            | Division Director Summary  
|            | Office Director Summary |
| NDA/BLA # and Supplement# | 211675 |
| Applicant  | AbbVie Inc |
| Date of Submission | December 18, 2018 |
| PDUFA Goal Date   | August 18, 2019 |
| Proprietary Name | RINVOQ |
| Established or Proper Name | Upadacitinib |
| Dosage Form(s)  | 15 mg extended release tablets |
| Applicant Proposed Indication(s)/Population(s) | 15 mg orally administered once daily |
| Applicant Proposed Dosing Regimen(s) | 15 mg orally administered once daily |
| Recommendation on Regulatory Action | Approval |
| Recommended Indication(s)/Population(s) (if applicable) | Treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate |
| Recommended Dosing Regimen(s) (if applicable) | 15 mg orally administered once daily |
1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Rheumatoid arthritis (RA) is a serious medical condition that affects over 1.3 million Americans. RA is a chronic progressive disease that primarily affects the joints, but can involve other organs. Disease progression impacts quality of life and is associated with morbidity and increased mortality. There are a large number of therapeutic options for treatment of RA. However, despite the number of available therapies, there is still a need for additional therapies for those patients who do not have an adequate response to current therapies.

AbbVie submitted new drug application (NDA) 211675 on December 18, 2018, for the new molecular entity (NME) upadacitinib, an oral small molecule inhibitor of the Janus associated kinases (JAK) being proposed for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA). The proposed dose of upadacitinib is a 15 mg tablet for oral administration once daily. Upadacitinib is not currently marketed in the US or any other country. There are two other JAK inhibitors approved in the US for the treatment of RA, tofacitinib and baricitinib. JAK inhibitors are potent immunosuppressants and there are a number of well-known safety issues associated with use of this class of medications, including serious infections, malignancy and lymphoproliferative disorders, gastrointestinal perforations, lymphopenia, neutropenia, anemia, and lipid elevations. Based upon accumulating data regarding the risk of thrombosis with JAK inhibitors, thrombosis is now also considered a class safety issue with JAK inhibitors.

The upadacitinib clinical development program included 5 adequate and well-controlled phase 3 studies in patients with moderately to severely active RA. Two doses of upadacitinib were studied in the phase 3 program – 15 mg QD and 30 mg QD. Primary efficacy endpoints were based upon American College of Rheumatology (ACR) composite measures of response that are validated and well-established. Key secondary efficacy variables were also validated and well-established.

Efficacy results from the clinical development program demonstrated substantial evidence of efficacy of both doses (15 mg QD and 30 mg QD) of upadacitinib. Results from the program show that treatment with upadacitinib improves clinical response, physical function, and fatigue. Treatment with upadacitinib also inhibited radiographic progression. While both doses of upadacitinib are effective, there is only a small incremental benefit of the 30 mg dose of upadacitinib over the 15 mg dose of upadacitinib.

The clinical development program conducted by the Applicant provided sufficient data to evaluate the safety profile of upadacitinib in patients with RA. Results from the upadacitinib clinical program showed that the safety profile of upadacitinib is generally consistent with other JAK inhibitors. Serious infections, gastrointestinal perforation and laboratory abnormalities were associated with use of upadacitinib. Some of the safety findings were dose-related, particularly laboratory abnormalities.
The benefit-risk profile of the upadacitinib 15 mg dose is more favorable than the 30 mg dose. The small incremental benefit of the 30 mg dose does not outweigh the dose-related safety findings with the 30 mg dose of upadacitinib. We agree with the Applicant's proposal to market the 15 mg dose of upadacitinib, which has a more favorable benefit-risk profile.

Risks of serious infections, malignancies, and thrombosis are considered class effects. The class labeling and results from the upadacitinib program will be included in the Boxed Warning section of the product label. Gastrointestinal perforations and laboratory abnormalities (neutropenia, anemia, elevated lipid profile) are also class effects and results from the upadacitinib program will be included in the Warnings/Precaution section of the product label. Animal studies with other JAK inhibitors have shown a signal of teratogenicity, which is described in the Pregnancy section of the tofacitinib and baricitinib product label. Animal studies with upadacitinib showed teratogenicity findings (skeletal malformations and death), but these findings were more concerning compared to other JAK inhibitors because teratogenicity was noted at lower exposure margins considered clinically relevant exposures. Therefore, the upadacitinib label will include a Warning/Precaution regarding teratogenicity.

Given that the safety profile of upadacitinib is generally consistent with other immunosuppressants and JAK inhibitors approved for RA patients, the risks can be adequately described in product labeling and a Risk Evaluation and Mitigation Strategy (REMS) is not necessary. No post-marketing safety trials will be required, but pediatric studies will be required under PREA.

### Benefit-Risk Dimensions

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| **Analysis of Condition** | - Rheumatoid arthritis is a chronic systemic inflammatory disease that primarily affects the 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 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.  
- As the disease progresses patients develop joint deformities caused by bone erosions and tendon/ligament damage that limit physical function resulting in deformity, early disability, and even death. | Rheumatoid arthritis is a serious medical condition that affects over 1.3 million Americans. RA is a chronic progressive disease that primarily affects the joints, but can involve other organs. Disease progression impacts quality of life and is associated with morbidity and increased mortality. |
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<td>Current Treatment Options</td>
<td>- The goal of treatment is early and aggressive use of medications to try to prevent functional impairment and irreversible joint damage.</td>
<td>There are a large number of therapeutic options for treatment of RA. However, despite the number of available therapies, there is still a need for additional therapies for those patients who do not have an adequate response to current therapies.</td>
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|                   | - Current treatment options for RA include NSAIDs, corticosteroids, conventional DMARDs (csDMARDs), biologic DMARDs (bDMARDs), and JAK inhibitors.  
  - 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.  
  - Use of cDMARDs as monotherapy or combination therapy is the current standard of care in newly diagnosed patients. In general, cDMARDs are effective for patients with mild to moderately active disease and who are at low risk to develop erosions.  
  - Based on current treatment guidelines, RA patients who are inadequate responders to cDMARDs are treated with bDMARDs or JAK inhibitors as monotherapy or in combination with cDMARDs. These drugs are typically more effective than cDMARDs in treating the signs and symptoms of RA as well as inhibiting the radiographic progression. They are generally well-tolerated; however, they pose a greater safety risk compared to cDMARDs alone.  
  - Biologic DMARDs and JAK inhibitors are potent immunosuppressants associated with increased risks of serious infections, opportunistic infections, malignancy and hematologic changes. Additionally, clinical studies of the JAK inhibitors, tofacitinib and baricitinib, have suggested potential class-related adverse effects, most notably increased rates of malignancy and thromboembolic events.                                                                 |                                                                                                                                                                                                                      |
<p>| Benefit           | - The upadacitinib clinical development program included 5 adequate and well-controlled phase 3 studies in patients with moderately to severely active RA. Two doses of upadacitinib were studied in the phase 3 program - 15 mg QD and 30 mg QD. Primary efficacy endpoints were based upon American College of Rheumatology (ACR) composite measures of response that are validated and well-established. The ACR response composite includes an assessment of tender and swollen joints, patient and physician symptom assessment, and patient global assessment.  | The clinical development program conducted by the Applicant demonstrated substantial evidence of efficacy of both doses (15mg QD and 30mg QD) of upadacitinib. Results from the program show that treatment with upadacitinib improves clinical response, physical function, and patient-reported outcomes. |</p>
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<td>global assessment, patient assessment of pain, Health Assessment Questionnaire-Disability Index (HAQ-DI), and acute phase reactant. Key secondary efficacy variables were also validated and well-established.</td>
<td>function, and fatigue. Treatment with upadacitinib also inhibited radiographic progression. While both doses of upadacitinib are effective, the incremental benefit of the 30mg dose of upadacitinib does not outweigh the increased risk with the higher dose. The Applicant has proposed to market only the 15mg dose of upadacitinib, which has a more favorable benefit-risk profile.</td>
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<td>Results of all 5 studies showed that both doses of upadacitinib were effective compared to placebo or control with respect to the prespecified ACR response, which is an assessment of the clinical response of the signs and symptoms of RA.</td>
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<td>Key secondary efficacy variables were supportive of the benefit of upadacitinib in patients with RA.</td>
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<td>Disease activity as measured by DAS28 showed a greater improvement in patients treated with upadacitinib compared to placebo or control.</td>
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<td>Physical function as measured by the HAQ-DI showed a greater improvement in patients treated with upadacitinib compared to placebo or control.</td>
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<td>Structural joint damage assessed by radiographic progression using the modified total Sharp Score (mTSS) showed greater inhibition in patients treated with upadacitinib compared to placebo or control.</td>
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<td>Fatigue as measured by the FACIT-F score showed a greater improvement in patients treated with upadacitinib compared to placebo or control.</td>
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<td>There were numerical differences in treatment response between the two doses of upadacitinib generally favoring the 30mg dose; however, the benefit of the 30 mg dose over the 15mg dose is small. Given the increased safety concerns with the higher dose (e.g. anemia, neutropenia), the incremental benefit of the 30 mg dose does not outweigh the increased risk.</td>
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<td>Risk and Risk Management</td>
<td>The size of the upadacitinib safety database and duration of exposure provide sufficient data to evaluate the safety profile of upadacitinib. A total of 4443 subjects were exposed to upadacitinib in the combined phase 2 and 3 RA trials.</td>
<td>JAK inhibitors are potent immunosuppressants and there are a number of well-known safety issues associated with use of this class of medications, including serious infections, malignancy and lymphoproliferative disorders, gastrointestinal perforations, lymphopenia, neutropenia, anemia,</td>
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CDER Cross Discipline Team Leader Review Template

Version date: October 10, 2017 for all NDAs and BLAs
**Evidence and Uncertainties**

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<td>perforations, lymphopenia, neutropenia, anemia, and lipid elevations. Many of the known safety issues are dose-related (i.e. higher rate with higher dose compared to lower dose). Some safety issues (e.g. malignancy) may require longer duration of exposure to characterize.</td>
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<td>Risk of thrombosis was identified in the baricitinib development program and the baricitinib label includes a Boxed Warning regarding this safety issue. At the time of approval of baricitinib, thrombosis was not known to be a class safety issue with JAK inhibitors. Since approval of baricitinib, interim results from a large, ongoing safety trial with tofacitinib have also identified an increased risk of pulmonary embolism and mortality with the 10mg dose of tofacitinib. Note that tofacitinib 5mg is approved for the treatment of RA in the US and the 10mg dose of tofacitinib is not approved for RA in the US. Based on the interim results from this ongoing trial, a Boxed Warning was recently added to the tofacitinib product label describing the available data regarding thrombosis and mortality. Given that two JAK inhibitor programs have identified thrombosis as a safety signal, thrombosis is now considered a class safety issue.</td>
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<td>Review of the safety data from the upadacitinib program showed that there was a higher percentage of AEs and SAEs in patients treated with upadacitinib compared to placebo. AEs and SAEs were generally dose dependent. The types of AEs and SAEs were consistent with events reported in other RA studies of immunosuppressants and JAK inhibitors.</td>
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<td>A higher rate of serious infections was observed in a dose-dependent manner in upadacitinib treated patients compared to placebo. This finding is consistent with other RA programs of immunosuppressants and JAK inhibitors. The product labeling will include a Boxed Warning regarding the risk of serious infection similar to other immunosuppressants and JAK inhibitors approved for RA.</td>
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**Conclusions and Reasons**

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<td>and lipid elevations. Based upon accumulating data regarding the risk of thrombosis with JAK inhibitors, thrombosis is now also considered a class safety issue with JAK inhibitors.</td>
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<td>The clinical development program conducted by the Applicant provided sufficient data to evaluate the safety profile of upadacitinib in patients with RA.</td>
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<td>Results from the upadacitinib clinical program showed that the safety profile of upadacitinib is generally consistent with other JAK inhibitors. Serious infections, gastrointestinal perforation and laboratory abnormalities were associated with use of upadacitinib. Some of the safety findings were dose-related, meaning that there was a higher rate of events with the upadacitinib 30mg dose compared to the upadacitinib 15mg dose.</td>
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<td>The benefit-risk profile of the upadacitinib 15mg dose is more favorable than the 30mg dose. The small incremental benefit of the 30mg dose does not outweigh the dose-related safety findings with the 30mg dose of upadacitinib. The Applicant has proposed to market the 15mg dose of upadacitinib, which has a more favorable benefit-risk profile.</td>
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Evidence and Uncertainties

- RA patients have a higher occurrence of certain malignancies (e.g., lymphoma) compared to the general population.\(^2\)\(^,\)\(^3\) Assessment of the risk of malignancy in the upadacitinib program is limited because of the short placebo-controlled period with few number of events. Review of the long term safety data provides some comparison between the two doses of upadacitinib and exposure adjusted incidence rates were compared to expected ranges for the general population and RA patients. The types of malignancies in the upadacitinib program were consistent with the patient population and exposure adjusted incidence rates were within the expected ranges. Because of the limitations with the malignancy data in the upadacitinib program, the available data are not adequate to conclude that there is not a risk of malignancy with upadacitinib. Therefore, the product label will include the class Boxed Warning for malignancy and describe the available data from the upadacitinib program.

- VTE rates were comparable across treatment groups in the upadacitinib program. No dose-dependent relationship was noted; however, differences in study designs limit the interpretation of dose-related effects. In addition, the short placebo-controlled period with few number of events limits definitive conclusions about the risk of thrombosis with upadacitinib. The product labeling will include a Boxed Warning regarding the risk of thrombosis associated with JAK inhibitors.

- Gastrointestinal perforations were reported more frequently with upadacitinib than placebo or control in the phase 3 studies, which is consistent with the known risk of JAK inhibitors. The product label will include a Warning/Precaution regarding this class effect.

- Dose related neutropenia, anemia, and lipid elevation were noted in the upadacitinib program. These are expected events consistent with other JAK inhibitors. No clear evidence of an association of serious infections, opportunistic infections or herpes zoster with a low neutrophil count was observed. There was no relationship identified between patients with elevated lipids and MACE in the

Conclusions and Reasons

Risks of serious infections, malignancies, and thrombosis are considered class effects. The class labeling and results from the upadacitinib program will be included in the Boxed Warning section of the product label. Gastrointestinal perforations and laboratory abnormalities (neutropenia, anemia, elevated lipid profile) are also class effects and results from the upadacitinib program will be included in the Warnings/Precaution section of the product label.

Animal studies with other JAK inhibitors have shown a signal of teratogenicity, which is described in the Pregnancy section of the tofacitinib and baricitinib product labels. Animal studies with upadacitinib showed teratogenicity findings (skeletal malformations and death), but these findings were more concerning compared to other JAK inhibitors because teratogenicity was noted at lower exposure margins considered clinically relevant exposures. Therefore, the upadacitinib label will include a Warning/Precaution regarding teratogenicity.

Given that the safety profile of upadacitinib is generally consistent with other immunosuppressants and JAK inhibitors approved for RA patients, the risks can be adequately

\(^3\) Smitten Al et al. Arthritis Res Ther 2008;10(2):R45
### Evidence and Uncertainties

- 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 patients treated with upadacitinib compared to placebo or control. This finding was dose-dependent, i.e. higher rates of herpes zoster infections in patients treated with upadacitinib 30 mg compared to patients treated with upadacitinib 15 mg. There were two definitive cases of HBV reactivation reported in upadacitinib treated patients in the phase 2 and phase 3 program. The product label will include information regarding viral reactivation in the Warning/Precaution for Serious Infections.

- Nonclinical studies with the JAK inhibitors baricitinib and tofacitinib have shown a signal of teratogenicity. Nonclinical reproductive and developmental toxicity studies with upadacitinib showed a signal of teratogenicity (skeletal malformations and death) at clinically relevant exposures. The embryo-fetal toxicity finding with upadacitinib is more concerning compared to tofacitinib and baricitinib because of the relatively low exposure margins. While nonclinical teratogenicity findings are described in the Pregnancy section of the tofacitinib and baricitinib product labels, the upadacitinib label will include a Warning/Precaution because the teratogenicity finding is at lower exposure margins that are clinically relevant.

### Conclusions and Reasons

described in product labeling and a Risk Evaluation and Mitigation Strategy (REMS) is not necessary. No post-marketing safety trials will be required.
2. Background

AbbVie submitted new drug application (NDA) 211675 on December 18, 2018, for the new molecular entity (NME) upadacitinib, an oral small molecule inhibitor of the Janus associated kinases (JAK) being proposed for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA). The product is a 15mg tablet for oral administration once daily. Upadacitinib is not currently marketed in the US or any other country.

Upadacitinib would be the third JAK inhibitor for RA in the United States, with tofacitinib (Xeljanz, NDA 20321, approved November 6, 2012) and baricitinib (Olumiant, NDA 207924, approved May 31, 2018) being the other two JAK inhibitors available in the US for RA patients. Another JAK inhibitor, ruxolitinib (Jakafi, NDA 202192), has been approved since November 2011 for myelofibrosis.

The RA indication proposed by AbbVie is broader than the indications for the other two JAK inhibitors approved for RA. Tofacitinib is approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. Baricitinib is approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies. The proposed indication for upadacitinib would be consistent with a first line therapy, whereas the indication for tofacitinib is consistent with second line therapy, and baricitinib is consistent with third line therapy. The indication for baricitinib is more limited because of concerns related to a safety signal of thrombosis events identified with the 4 mg dose in the clinical program and a limited safety database with the approved 2 mg dose. The indication for upadacitinib will be discussed further in the labeling section of this memo.

RA is a chronic, symmetric inflammatory polyarthritis that primarily involves synovial joints. In RA, synovial tissues become inflamed and proliferate, forming pannus that invades bone, cartilage, and ligament and leads to joint damage and deformities. Destruction of synovial joints can lead to severe disability and premature mortality.4,5

RA affects approximately 1% of the adult population in North America and Northern Europe.6 The disease is three times more frequent in women than men. Prevalence rises with age and is highest in woman older than 65 years. While there is heterogeneity in the natural history of RA, it is generally a chronic, progressive disease. Patients can develop joint destruction, severe

physical disability and multiple comorbidities. In contrast to clinical symptoms, structural damage is irreversible and cumulative.7

Patients diagnosed with RA are generally treated with disease-modifying antirheumatic drugs (DMARDs). A variety of non-biologic DMARDs are approved for RA, including corticosteroids, various nonsteroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, hydroxychloroquine, auranofin, methotrexate (MTX), azathioprine, penicillamine, cyclosporine, and leflunomide.

Non-biologic DMARDs, such as MTX, are the first line of therapy for RA.8 Treatment with a tumor necrosis factor-alpha (TNF-α) antagonist is generally the next line of treatment for patients with ongoing disease activity. Currently approved TNF-α antagonists include etanercept (ENBREL), infliximab (REMICADE), adalimumab (HUMIRA), golimumab (SIMPONI), certolizumab pegol (CIMZIA), golimumab IV (SIMPONI ARIA), infliximab-dyyb (INFLECTRA), etanercept-szxs (ERELZI), adalimumab-atto (AMJEVITA), infliximab-abda (RENFLERIS), adalimumab-adbm (CYLTEZO), infliximab-qbtx (IXIFI), adalimumab-adaz (HYRIMOZ), etanercept-ykro (ETICVO), and adalimumab-bwwd (HADLIMA). Between 30% and 40% of patients fail to respond or become intolerant to anti-TNF-α therapy.9 For patients with ongoing disease activity, the therapeutic strategy usually involves trying another TNF-α antagonist or switching to a medication with a different mechanism of action. Approved alternative therapies include orally bioavailable Janus kinase (JAK) inhibitors (tofacitinib/XELJANZ OR XELJANZ XR and baricitinib/OLUMIANT), and biological DMARDs targeting the B-cell antigen CD-20 (rituximab/RITUXAN), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4; abatacept/ORENCIA), and the pro-inflammatory cytokines IL-1 (anakinra/KINERET) and IL-6 (tocilizumab/ACTEMRA).

The long-term goal of treatment is prevention of irreversible joint destruction and functional impairment given the significant impact on patients and public health. The short-term goal of treatment is improvement in signs, symptoms, and functional status.

Key Regulatory Interactions

RA development programs are well-established so the interactions between AbbVie and FDA regarding the upadacitinib program were standard with respect to major milestone meetings held between FDA and Applicants. A pre-IND meeting (April 2012) was held where discussion focused on design of the phase 1 studies and the nonclinical support for the proposed dosing. IND 114717 was opened in July 2012 for upadacitinib. The following is a high-level summary of key regulatory interactions.

An End-of-Phase 2 meeting was held in October 2015. The following were the main discussion points:

- The two doses proposed by AbbVie were reasonable for further development depending on the results of the phase 1 comparability study between the capsule formulation used for BID dosing in the phase 2 studies and the tablet formulation to be used for QD dosing in the phase 3 studies.
- The Agency noted that the proposed monotherapy study (Study M15-555) was not necessary, if this population (MTX inadequate responders) was included elsewhere in the development program. In addition, the proposed enrollment was insufficient.
- The Agency raised concerns about whether a single study (M14-465) would be sufficient to support a claim of inhibition of radiographic progression. Use of linear extrapolation for non-responders was discouraged.
- The overall RA development program was reasonable, including the estimated size of the safety database.
- Patients should be maintained on the dose of study drug as originally randomized during the long-term extension studies to best interpret safety events. Patients with active disease should be escaped to standard of care and not dose-escalate to a higher dose of study drug. Patients should not cross-over between study treatments to avoid confounding long-term safety and efficacy comparisons between the randomized group.
- The Agency agreed that inclusion of adalimumab as an active comparator had utility but was not required for approval.

A pre-NDA meeting was held in May 2018, during which primarily general content and format of the NDA submission were discussed. The NDA was submitted to the Agency on December 18, 2018. The Applicant requested a Priority Review and used Rare Pediatric Disease Priority Review Voucher No. PRV BLA 125516 to support their request.

### 3. Product Quality

**Drug Substance Reviewer:** Sam Bain, Ph.D.; **Supervisor:** Donna Christner, Ph.D.
**Drug Product Reviewer:** Valerie Anspacher; **Supervisor:** Craig M. Bertha
**Process/Microbiology/Facility Reviewer:** Pratibha Bhat; **Supervisor:** Joanne Wang
**Biopharmaceutics Reviewer:** Rajesh Savkur; **Supervisor:** Haritha Mandula/Sandra Suarez

- **General product quality considerations**

The drug substance, upadacitinib, is proposed by the Applicant to be a novel, oral, selective, reversible JAK-1 inhibitor. It is a white to light brown crystalline powder that is manufactured via (b) Cl. The drug substance is not hygroscopic. The Pharmacology/Toxicology team evaluated 35 impurities and concluded these did not present any safety concern. The drug substance is packaged in
The drug substance is manufactured (b) (d) The proposed retest period (b) (d) was determined to be satisfactory by the drug substance reviewer.

The drug product is formulated as an extended-release, (b) (d) tablet. The Applicant developed the 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 formulation is composed of excipients. The excipients are compendial (b) (d) The drug product is packaged in 3 oz bottles (b) (d) The drug product is manufactured at AbbVie Ireland in Sligo, Ireland and packaged at AbbVie Inc in Chicago, IL. The stability data supports the proposed 24 month shelf life/expiry for the drug product.

The phase 3 clinical trial formulation differs from the proposed commercial formulation. The Applicant has bridged the two formulations via an in vitro dissolution comparison and an in vivo bioequivalence study. The biopharmaceutics team has determined based on the submitted information that bridging of the two formulations has been adequately established and the two formulations are similar to each other.

- Facilities review/inspection

The drug product and drug substance facilities are approved based on the firm’s inspection history and manufacturing experience. There are no major GMP issues raised based on the review of the submitted site-specific stability/qualification batches.

- Other notable issues (resolved or outstanding)

From a Chemistry, Manufacturing, and Controls (CMC) perspective, the application is recommended for approval. No CMC Phase 4 commitments are recommended.

4. Nonclinical Pharmacology/Toxicology

Pharm-Tox Reviewer: Brett Jones, Ph.D.; Supervisor/TL: Andrew Goodwin, Ph.D.

- General nonclinical pharmacology/toxicology considerations
Abbvie conducted a complete and adequate program of nonclinical pharmacology, pharmacokinetics, and toxicology studies with upadacitinib. General toxicology studies via oral route of administration were conducted in rats and dogs. The target organs of toxicity in rats included: kidneys (tubular degeneration/regeneration), thymus (lymphoid depletion), spleen (lymphoid depletion), and lymph nodes (lymphoid depletion). The toxicities in beagle dogs included skin (interdigital cysts and multifocal cell inflammation in the interdigital skin), popliteal lymph node (mixed cell inflammation), precapsular lymph node (mixed cell inflammation), spleen (lymphoid depletion), and thymus (lymphoid depletion). These findings were attributed to the immunosuppressive effects of upadacitinib.

The proposed human doses were covered by the NOAELs (no observed adverse effect levels) from animal studies. Dose limiting findings of renal tubular degeneration/regeneration in the kidney were observed in rats at higher doses. Treatment-related reversible findings of decreased lymphocytes in lymphoid tissues and decreases in RBC mass observed in toxicology studies in rats and dogs. The limiting toxicities were thought to be monitorable in a clinical setting.

- **Carcinogenicity**

Upadacitinib was not mutagenic or genotoxic based on in vitro and in vivo tests for gene mutations, chromosomal damage, and DNA damage. Carcinogenicity of upadacitinib was evaluated in a six-month study in CBByB6F1-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.

- **Reproductive toxicity**

The reproductive and developmental toxicity of upadacitinib was evaluated in: (1) an oral developmental toxicity study in rats (2 studies), (2) an oral developmental toxicity study in rabbits, and (3) an oral pre-/postnatal developmental (PPND) toxicity study in rats. Upadacitinib was embryolethal in rabbits, and associated with fetal skeletal malformations and variations in rats and rabbits. The finding of teratogenicity in rats and rabbits at clinically relevant exposures indicates a serious risk for human fetal toxicity. The nonclinical reviewer considered the embryo-fetal toxicity data with upadacitinib 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. The Division of Pediatric and Maternal Health (DPMH) was consulted and concluded that a higher level of concern regarding the animal findings was reasonable based on the lower exposure margins to the 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 upadacitinib 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 upadacitinib should include a Warning and Precaution for embryo-fetal toxicity. The Pharmacology/Toxicology review team agreed with the recommendation to include a
Warning for embryo-fetal toxicity (Highlights and Section 5), as well as a risk summary and detailed animal data (Section 8.1) and recommendations for pregnancy testing and contraception use for females of reproductive potential (Section 8.3). We agree with this recommendation.

- **Other notable issues (resolved or outstanding)**

From the Pharmacology/Toxicology perspective, the information in this application is adequate to support approval of upadacitinib at the proposed 15 mg daily dose. There were no unresolved toxicology issues and the application was deemed approvable from a nonclinical perspective.

### 5. Clinical Pharmacology

*Clinical pharmacology reviewer: Lei He, Ph.D.; Team Leaders: Anshu Marathe, Ph.D.; Jianmeng Chen, M.D., Ph.D.*  
*Pharmacometrics reviewer: Jing Niu, M.D.; Manuela Grimstein, Ph.D.; Team Leaders: Jingyu Yu, Ph.D.; Xinyuan Zhang, Ph.D.*  
*Pharmacogenomics reviewers: Robert Schuck, Ph.D.; Team Leaders: Christian Grimstein, Ph.D.*  
*Division Director: Chandrasah Sahajwalla, Ph.D.*

- **General clinical pharmacology considerations, including absorption, food effects, bioavailability, etc.**

Following a single dose administration of upadacitinib, the median Tmax was 2-3 hours. High-fat and high-caloric meal increased upadacitinib Cmax and AUC0-inf by 40% and 30%, respectively, suggesting no clinically relevant food-drug interactions. Following QD dosing, steady state was achieved within 4 days with minimal accumulation. Upadacitinib Cmax and AUC were approximately dose-proportional over evaluated dose ranges.

Upadacitinib is approximately 52% bound to human plasma proteins. For a typical patient with RA with body weight of 74 kg, steady-state volume of distribution for upadacitinib is estimated to be 224 L following administration of extended release (ER) formulation.

- **Pathway of elimination, including metabolism, half-life, and excretion.**

Upadacitinib 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. Approximately 53% (38% as unchanged parent drug) and 43% (24% as unchanged parent drug) of the administered dose was excreted in feces and urine, respectively. Upadacitinib mean terminal elimination t1/2 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.
Briefly comment on each of the critical intrinsic factors potentially affecting elimination: age, gender, hepatic impairment, and renal impairment.

No alternative dosing regimen and management strategy is required for subpopulations based on intrinsic factors. No dose adjustment is needed for patients with mild, moderate, or severe renal impairment, and mild or moderate hepatic impairment. Upadacitinib has not been evaluated in patients with severe hepatic impairment. The clinical pharmacology team does not recommend upadacitinib treatment for these patients. We agree with this recommendation.

**Drug-drug interactions**

Upadacitinib coadministration with a strong CYP3A inhibitor, ketoconazole, increased upadacitinib exposure by 75% for AUC0-inf and 70% for Cmax. Coadministration with a strong CYP3A4 inducer, rifampin, resulted in decrease in upadacitinib exposure by 61% for AUC0-inf and 51% for Cmax. Coadministration with methotrexate did not result in clinically meaningful difference in upadacitinib PK. The clinical pharmacology review team recommends upadacitinib should be used with caution if patients receive chronic treatment with strong CYP3A4 inhibitors. Coadministration with strong CYP3A4 inducers are not recommended because that may result in ineffective concentrations of upadacitinib. We agree with these recommendations.

**Demographic interactions/specific populations**

Population PK analysis showed that body weight, gender, race, ethnicity, and age did not have a clinically meaningful effect on upadacitinib exposure. However, population PK analysis in RA patients showed a 25% lower apparent total clearance (leading to a 33% higher estimated AUC) in RA patients compared to healthy subjects.

**Whether there is sufficient bridging between the formulation(s) tested in clinical studies and the to-be-marketed formulation**

Two phase 2 dose-ranging studies were conducted using immediate release formulation in RA patients. To enhance patient compliance, an ER tablet formulation was developed. The Applicant conducted a bioequivalence study that demonstrated comparable systemic exposures at steady state following administration of upadacitinib 15 mg QD and 30 mg QD (ER formulation) to 6 mg BID and 12 mg BID (IR formulation), respectively.

The Applicant also conducted a bioequivalence study in healthy subjects to demonstrate the bioequivalence between the to-be-marketed formulation and the phase 3 study formulation under fasted condition. The Office of Study Integrity and Surveillance (OSIS) conducted an analytical inspection and concluded that the concentration data from the audited studies are reliable. The clinical pharmacology team has determined, and we agree, that the to-be-marketed formulation is bioequivalent to the clinical study tablet.
• **Thorough QT study or other QT assessment**

Christine Garnett, Pharm.D. of the CDER DCRP QT Interdisciplinary Review Team assessed the effect of upadacitinib 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).

• **Other notable issues (resolved or outstanding)**

AbbVie submitted a complete and adequate clinical pharmacology program for upadacitinib. The Office of Clinical Pharmacology has determined the information in NDA 211675 is acceptable. No outstanding issues have been identified. No postmarketing commitments or requirements have been recommended.

6. **Clinical Microbiology**

There are no outstanding clinical microbiology issues.

7. **Clinical/Statistical- Efficacy**

*Clinical Primary Reviewer: Keith Hull, M.D., Ph.D.; Clinical Team Leader: Rachel Glaser, M.D.*

*Statistical Reviewer: William Koh, Ph.D.; Statistical Team Leader/Supervisor: Peiling Yang, Ph.D.*

**Overview of the Clinical Program**

Five randomized placebo- or methotrexate-controlled phase 3 trials have been submitted as the primary evidence of efficacy and safety of upadacitinib at the proposed dose of 15 mg once daily, as summarized in Table 1 below. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section. All studies were conducted in accordance with Good Clinical Practice guidelines and relevant regulatory requirements.

**Table 1: Summary of the Phase 3 Studies in RA**

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td>DB, MC, PG 12-week PC study</td>
<td>DB, MC, PG 24-weeks (12-week PC → 12-week CO to UPA)</td>
<td>DB, MC, DD, PG 48-week PC (CO at Week 26)</td>
<td>DB, MC, PG 48-week AC (CO to UPA at Week 26)</td>
<td>DB, MC, PG 14-week AC (CO to UPA at Week 12)</td>
</tr>
<tr>
<td><strong>Controlled Period</strong></td>
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</tbody>
</table>
All five phase 3 studies were randomized, multicenter, double-blinded, placebo (M13-542, M13-549, M14-465) or methotrexate controlled (M13-545, M15-555) studies conducted in patients 18 years of age and older with moderate to severe active RA and met the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria. The phase 3 studies evaluated upadacitinib treatment in a broad population of patients with rheumatoid arthritis including patients who were naïve to MTX, those with an intolerant or had inadequate response to MTX and/or other conventional DMARDs (cDMARDs), and those who were intolerant or had an inadequate response to biologic DMARDs (bDMARDs), as shown in Table 1. Stable doses of non-steroidal anti-inflammatory drug, acetaminophen, and oral corticosteroids (equivalent to prednisone ≤ 10 mg/day) were allowed. The primary efficacy variables in the studies are listed in Table 1. Each study included provisions for rescue therapy based on clinical response. Safety assessment in all studies included recording of adverse events, vital signs, physical examination, and clinical laboratory measures.

Each study had its own long-term extension period. During the long-term extension, each patient remained on the same dose of upadacitinib (UPA) as they received during the randomized controlled period. Patients who received placebo or methotrexate during the controlled periods were treated with upadacitinib without subsequent dose increase. In M14-465, patients randomized to adalimumab (ADA) continued to receive adalimumab through the long-term extension.
Brief Description of Efficacy Endpoints

The efficacy variables relevant to this submission were American College of Rheumatology (ACR) response criteria, the Health Assessment Questionnaire-Disability Index (HAQ-DI), Disease Activity Score 28 (DAS-28), and van der Heijde modified total Sharp Score (mTSS). These are described below. An understanding of these endpoints will help interpret the study and results described in subsequent sections.

The American College of Rheumatology (ACR) response criteria is a composite endpoint with seven components that calculates proportion of patients achieving a target percentage of improvement from baseline. The ACR criteria have been used extensively in clinical trials in RA as a measure of efficacy of a therapeutic agent. The ACR20 response is calculated as at least 20% reduction in tender joint count of 68 joints, and 20% reduction in swollen joint count of 66 joints, and at least a 20% reduction in at least 3 of the 5 measures: patient global assessment of arthritis on a visual analog scale, physician global assessment of arthritis on a visual analog scale, patient assessment of pain on a visual analog scale, patient assessment of physical functioning (e.g., health assessment questionnaire), and acute phase reactant (ESR or CRP). The ACR50 and ACR70 are similarly calculated using the higher 50% and 70% levels of improvement, respectively. The Agency has accepted ACR20 response as an acceptable demonstration of efficacy of a therapeutic agent supporting a “clinical response” claim, and ACR70 response lasting for 6 months as supportive of a claim of a “major clinical response.”

Health assessment Questionnaire-Disability Index (HAQ-DI) assesses a patient’s level of functional ability and includes questions regarding fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning intended to represent a comprehensive set of functional activities, including dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. Patients are asked to grade their status on a scale from 0 (no difficulty) to 3 (unable to do) for each question. The 8 category scores are averaged into an overall HAQ-DI score on a scale from 0 (no disability) to 3 (completely disabled). The HAQ-DI has been validated for use in RA, with a minimal clinically important difference (MCID) of 0.25 units (for a given patient) or 0.22 units (based on group means). The Agency has accepted a “physical function response” claim based on HAQ-DI.

Disease Activity Score 28 (DAS28) is a composite index of RA disease activity which incorporates the number of tender and swollen joints (out of 28 possible), a patient global assessment of disease activity (0-100 mm visual analog scale), and ESR. An alternative equation is available for use with CRP. These variables are summed and weighted mathematically into a single numerical value ranging from 0 to 10. The ACR and DAS28 are


Reference ID: 4478224
conceptually similar, but differ with in number of joints counted (e.g. DAS28 does not include the joints of the feet), and physician global assessment, patient pain, and HAQ score, which are incorporated into the ACR response criteria but not in DAS28. Another difference is that the DAS28 measures disease activity at a given time point, whereas the ACR response criteria are calculated as improvement in the variables over a set period of time. A DAS28 score >5.1 is indicative of high disease activity, and <3.2 of low disease activity. A score of <2.6 has been used to describe an even lower threshold of disease activity.

The van del Heijde-modified total Sharp-Genant score (mTSS) is an accepted radiographic scoring system for RA\textsuperscript{13} based on the presence of erosions in the joints of the hands and feet, and the presence of joint space narrowing (JSN) in the hands, wrists, and feet. The scores for each feature for the individual joints are summed. Erosions are assessed at 16 locations in each hand and wrists and 12 locations in each foot, using a 6-point scale from 0 to 5. Scores are derived based on the number and size of discrete erosions in each location, but are summed to a maximum of 5. Thus the maximum erosion score for the hands/wrists is 160, and the maximum erosion score for the feet is 120, for a maximum total erosion score of 280. JSN scores are based on 15 locations in each hand and wrist and 6 locations in each foot, scored using a 5-point scale from 0 to 4: 0 = normal; 1 = focal or minimal and generalized narrowing; 2 = generalized narrowing <50%; 3 = generalized narrowing >50% or subluxation; and 4 = ankylosis or complete dislocation. The maximum total JSN for the hands/wrists is 120, and the maximum total JSN for the feet is 48, for a maximum total JSN score of 168. Therefore the theoretical maximum modified total Sharp Score (mTSS) is 448, although the actual clinical range in RA drug development trials is typically much lower because a given individual typically only has a fraction of his or her joints affected by radiographically evident damage. The smallest detectable difference on a per-individual basis has been identified for the van der Heijde modification of the Sharp-Genant score as approximately 5 units.\textsuperscript{14} The Agency has accepted a “radiographic response” claim based on mTSS.

Short Form Health Survey (SF-36) is an instrument used to measure health-related quality of life or general health status. It consists of eight subscales that are scored individually: physical functioning (10 items), role-physical (four items), bodily pain (two items), general health (five items), vitality (four items), social functioning (two items), role-emotional (three items), and mental health (five items). Two summary scores, the physical component summary (PCS) (based on physical functioning, role-physical, bodily pain, and general health) and the mental component summary (MCS) (based on vitality, social functioning, role-emotional, and mental health), are computed. The eight domains are age and gender adjusted, and scored 0 (severe impairment)-100 (no impairment). The PCS and MCS are reported based on normative-based scoring.

Functional assessment of chronic illness therapy-fatigue (FACIT-F) is a 13-item questionnaire that measures an individual’s level of fatigue over the past week on a four-point Likert scale.

\textsuperscript{14} K Bruynesteyn et al., Arthritis & Rheum  2002; 46:913-920.
The range of the score is from 0 to 52 and the higher scores, the better the quality of life. The scores are added together and pro-rated according to the number of items answered. The response values of all 13 items are added with equal weight to obtain the total score. If less than 7 items are answered, the score will not be computed. The interpretation of FACIT-F scores is such that a higher score indicates less fatigue, with a range of possible scores of 0-52, with 0 being the worst possible score and 52 the best. To obtain the 0-52 score, 11 of the 13 items require recoding such that the response value of 0 represents greatest fatigue and the response value of 4 represents no fatigue.

The reader is referred to Dr. Koh’s review for additional description of the efficacy endpoints.

**Dose Selection**

The phase 2 studies were designed as proof-of-concept and dose-ranging trials in patients with RA. Study M13-537 assessed the upadacitinib immediate-release (IR) formulation at doses of 3 mg, 6 mg, 12 mg, 18 mg BID and 24 mg QD in MTX-IR patients. Study M13-550 evaluated the upadacitinib IR formulation at doses of 3 mg, 6 mg, 12 mg and 18 mg in TNF-IR patients. Results from the phase 2 studies using the IR formulation showed efficacy at 6 mg and 12 mg BID dose levels, with a slight increase in efficacy at the 12 mg BID dose, and no additional increase in efficacy observed for doses higher than 12 mg BID (Table 2). Therefore, upadacitinib 6 mg and 12 mg BID dosing regimens using the IR formulation were selected as the target exposure for doses in the phase 3 studies. 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 upadacitinib 15 mg and 30 mg QD dosing for the phase 3 studies.

**Table 2: Summary of the primary efficacy results from phase 2 dose-ranging studies**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Patient Population</th>
<th>Formulation</th>
<th>ACR Response Rate at Week 12*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>placebo</td>
</tr>
<tr>
<td>M13-537</td>
<td>RA with inadequate resp. to MTX</td>
<td>IR</td>
<td>50%     (23/46)</td>
</tr>
<tr>
<td></td>
<td>(n=299)</td>
<td></td>
<td>(n.s.)</td>
</tr>
<tr>
<td>M13-550</td>
<td>RA on MTX, inadequate resp. to anti-TNF biologics (n=276)</td>
<td>IR</td>
<td>35.2% (19/54)</td>
</tr>
</tbody>
</table>

* listed as response rate (%) calculated by response patient number/total patient number; p value is the comparison of ACR 20 between treatment group and placebo.

Source: FDA Clinical Pharmacology reviewer
Study Conduct

Treatment groups in the studies were generally balanced with respect to demographics and baseline characteristics. Baseline disease characteristics were balanced, except for mean duration of RA which was shortest in Study M13-545 (MTX-naïve population) and longest in Study M13-542 (bDMARD-IR population). This is consistent with the intended population of each study. Overall completion rates were in the 85 to 95% range for active and control groups. Drop outs due to lack of efficacy was low across treatment groups (0-3.2%), and higher in the placebo and active comparator groups.

In each study, the dataset used for the primary statistical analysis was based on the full analysis set, which includes all randomized patients who received at least one dose of study treatment. The primary analysis timepoint for non-radiographic endpoints for all studies (except M15-555) is at Week 12. In Study M15-555, the primary analysis timepoint for non-radiographic endpoints is Week 14. In each study, the primary efficacy endpoint, the proportion of ACR20 responders (or ACR50 responders for study M13-545), and key secondary responder type endpoints, were analyzed using the difference in binomial proportions by comparing each dose of upadacitinib arm with the reference arm.

The presence of missing data can affect the interpretation of the study results. In general, the amount of missing data, i.e., due to lost-to-follow-up, withdrawal of informed consent to continue further participation, in the study was small and balanced across arms within each study.

Efficacy findings

The submitted data show efficacy for upadacitinib for clinical response or reducing signs and symptoms and improvement in physical function at the proposed dose of 15 mg daily.

ACR Response Rates

The primary endpoint was the ACR20 at Week 12 for the placebo controlled studies (M13-549, M13-542, and M14-465), while the MTX-controlled studies evaluated the ACR20 at Week 14 (M15-555), and ACR50 at Week 12 (M13-545). In all studies, there was a statistically significantly higher proportion of ACR20 (ACR50 for M13-545) responders comparing upadacitinib (UPA) 15 mg QD with the reference arm at the primary efficacy time point (Table 3). In 3 of the 4 studies evaluating both doses of upadacitinib, the probability of ACR20 (ACR50 for M13-545) response rates were similar between the dose levels, while in Study M13-542, the ACR20 response rate at Week 12 for UPA 30 mg was numerically lower than UPA 15 mg. The individual components of ACR were statistically significant and were consistent with primary findings of ACR20 for all studies. The tipping point analysis for the primary efficacy endpoints for the proposed 15 mg dose in each study were robust to missing data assumptions.
Table 3: Summary of Primary Efficacy Endpoint Results in Phase 3 Studies

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>N</th>
<th>Count(%)</th>
<th>Diff (%) 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>MTX Add-on Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M13-542</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>169</td>
<td>48 (28%)</td>
<td>36.2% (26.2% - 46.2%); &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>164</td>
<td>106 (65%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPA 30 mg QD</td>
<td>165</td>
<td>93 (56%)</td>
<td>28.0% (17.8% - 38.1%); &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>M13-549</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>221</td>
<td>79 (36%)</td>
<td>28.1% (19.1% - 37.0%); &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>221</td>
<td>141 (64%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPA 30 mg QD</td>
<td>219</td>
<td>145 (66%)</td>
<td>30.5% (21.6% - 39.4%); &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>M14-465</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>651</td>
<td>237 (36%)</td>
<td>34.1% (29.0% - 39.2%); &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>651</td>
<td>459 (71%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADA 40 mg EOW</td>
<td>327</td>
<td>206 (63%)</td>
<td>26.6% (20.2% - 33.0%); &lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>MTX Monotherapy Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>M15-555</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>216</td>
<td>89 (41%)</td>
<td>26.5% (17.5% - 35.6%); &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>217</td>
<td>147 (68%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPA 30 mg QD</td>
<td>215</td>
<td>153 (71%)</td>
<td>30.0% (21.0% - 38.9%); &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>M13-545 (ACR50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>314</td>
<td>89 (28%)</td>
<td>23.7% (16.3% - 31.1%); &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>317</td>
<td>165 (52%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPA 30 mg QD</td>
<td>314</td>
<td>177 (56%)</td>
<td>28.0% (20.6% - 35.4%); &lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

NRI was used to impute patients who had discontinued the study treatment prior to primary efficacy timepoint, were lost to follow-up, or had withdrawn from the study.
1: Counts and percentages relative to N in parenthesis are reported for the probability of ACR20 response (ACR50 for M13-545).
2: Difference in the probability of ACR response, respective 95% CI using normal approximation to difference in binomial proportions, p-values from the Cochran Mantel Haenszel test were reported.
3: The primary time-point in Study M15-555 is Week 14 while other studies are evaluated at Week 12.

Abbreviations: ACR=American College of Rheumatology; MTX=methotrexate; UPA=upadacitinib; QD=once daily; CI=confidence intervals; EOW=every other week; ADA=adalimumab; Diff=difference
Source: FDA Statistical Reviewer

Consistent with the primary endpoint results, the proportions of patients with ACR50 and ACR70 responses were higher in the UPA groups compared to the placebo or MTX control groups, with the exception of ACR70 in Study M13-542 where the difference between the UPA 15 mg group and the placebo group at Week 12 was not statistically significant. Patients treated with UPA 30 mg consistently had a numerically higher proportion of patients with greater ACR50 and ACR70 responses compared to the UPA 15 mg group; however, given the relatively small increase in benefit, the degree of clinical meaningfulness is uncertain.
All phase 3 trials also assessed the treatment effect of upadacitinib on HAQ-DI. Table 4 presents the change from baseline in HAQ-DI at the primary timepoint of assessment (Week 14 for M13-555, Week 12 for other studies). Upadacitinib treatment was associated with a statistically significant improvement (greater decrease) in the mean change from baseline in HAQ-DI at the primary efficacy timepoint. The improvement of physical function as measured using the change from baseline in HAQ-DI in the MTX add-on studies and monotherapy studies were on average between 0.2 to 0.3 and 0.3 to 0.4, respectively, comparing upadacitinib 15 mg QD with reference arm. In all 5 studies, a greater proportion of patients treated with UPA 15 mg achieved a clinically significant improvement in HAQ score (≥ 0.22 u) from baseline compared to the respective comparator groups. In studies evaluating both doses of upadacitinib, improvements from baseline were similar between the dose groups.

Table 4: Summary of Change from Baseline in HAQ-DI in Phase 3 Studies

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>N</th>
<th>Baseline Mean (SD)</th>
<th>n</th>
<th>Visit 1 Mean (SD)</th>
<th>Adj Diff (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MTX add-on studies</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M13-542</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>166</td>
<td>1.6 (0.6)</td>
<td>150</td>
<td>1.3 (0.7)</td>
<td>-0.2 (-0.3, -0.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>163</td>
<td>1.7 (0.6)</td>
<td>160</td>
<td>1.2 (0.8)</td>
<td>-0.2 (-0.3, -0.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 30 mg QD</td>
<td>161</td>
<td>1.6 (0.6)</td>
<td>154</td>
<td>1.2 (0.7)</td>
<td>-0.2 (-0.3, -0.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>M13-549</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>221</td>
<td>1.4 (0.6)</td>
<td>206</td>
<td>1.1 (0.7)</td>
<td>-0.3 (-0.4, -0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>216</td>
<td>1.5 (0.6)</td>
<td>210</td>
<td>0.9 (0.7)</td>
<td>-0.3 (-0.4, -0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 30 mg QD</td>
<td>219</td>
<td>1.5 (0.6)</td>
<td>200</td>
<td>0.9 (0.7)</td>
<td>-0.3 (-0.4, -0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>M14-465</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>650</td>
<td>1.6 (0.6)</td>
<td>617</td>
<td>1.3 (0.7)</td>
<td>-0.3 (-0.4, -0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>645</td>
<td>1.6 (0.6)</td>
<td>617</td>
<td>1.0 (0.7)</td>
<td>-0.3 (-0.4, -0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADA 40 mg EOW</td>
<td>325</td>
<td>1.6 (0.6)</td>
<td>309</td>
<td>1.1 (0.7)</td>
<td>-0.2 (-0.3, -0.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Monotherapy studies</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>M15-555</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>216</td>
<td>1.5 (0.7)</td>
<td>195</td>
<td>1.2 (0.7)</td>
<td>-0.3 (-0.5, -0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>216</td>
<td>1.5 (0.7)</td>
<td>199</td>
<td>0.8 (0.7)</td>
<td>-0.4 (-0.5, -0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 30 mg QD</td>
<td>215</td>
<td>1.5 (0.7)</td>
<td>201</td>
<td>0.8 (0.7)</td>
<td>-0.4 (-0.5, -0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>M13-545</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>314</td>
<td>1.6 (0.7)</td>
<td>278</td>
<td>1.1 (0.7)</td>
<td>-0.3 (-0.4, -0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>317</td>
<td>1.6 (0.7)</td>
<td>302</td>
<td>0.8 (0.7)</td>
<td>-0.3 (-0.4, -0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 30 mg QD</td>
<td>311</td>
<td>1.5 (0.7)</td>
<td>298</td>
<td>0.7 (0.7)</td>
<td>-0.3 (-0.4, -0.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

1: The primary time-point in Study M15-555 is Week 14 while other studies are evaluated at Week 12.
Results of DAS28 were generally consistent with the results of ACR responses and supported the efficacy of upadacitinib as a potential treatment for RA. Patients receiving UPA 15 mg and 30 mg had a greater adjusted mean decrease from baseline in DAS28(CRP), indicating improvement in signs and symptoms, as compared to the comparator groups in the phase 3 studies, and including adalimumab in Study M14-465. The mean adjusted change from baseline in DAS28(CRP) compared to reference were similar between the UPA 15 mg and 30 mg QD groups, except in Study M15-555 where UPA 30 mg monotherapy had greater improvement as compared to UPA 15 mg.

Table 5: Summary of Change from Baseline in DAS28(CRP) in Phase 3 Studies

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>N</th>
<th>Baseline Mean (SD)</th>
<th>n</th>
<th>Visit1 Mean (SD)</th>
<th>Adj Diff2 (95% CI)</th>
<th>P-value2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>MTX Add-on Studies</td>
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</tr>
<tr>
<td>M13-542</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>166</td>
<td>5.8 (1.0)</td>
<td>147</td>
<td>4.7 (1.4)</td>
<td>-1.2 (-1.5, -0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>163</td>
<td>5.9 (0.9)</td>
<td>157</td>
<td>3.5 (1.3)</td>
<td>-1.2 (-1.5, -0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 30 mg QD</td>
<td>163</td>
<td>5.8 (0.9)</td>
<td>149</td>
<td>3.5 (1.5)</td>
<td>-1.1 (-1.4, -0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>M13-549</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>221</td>
<td>5.6 (0.8)</td>
<td>206</td>
<td>4.5 (1.5)</td>
<td>-1.2 (-1.4, -0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>217</td>
<td>5.7 (1.0)</td>
<td>206</td>
<td>3.4 (1.4)</td>
<td>-1.2 (-1.4, -0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 30 mg QD</td>
<td>219</td>
<td>5.7 (0.9)</td>
<td>200</td>
<td>3.3 (1.2)</td>
<td>-1.3 (-1.6, -1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>M14-465</td>
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</tr>
<tr>
<td>Placebo</td>
<td>649</td>
<td>5.8 (0.9)</td>
<td>595</td>
<td>4.7 (1.4)</td>
<td>-1.3 (-1.5, -1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>647</td>
<td>5.8 (1.0)</td>
<td>586</td>
<td>3.3 (1.3)</td>
<td>-1.3 (-1.5, -1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADA 40 mg EOW</td>
<td>324</td>
<td>5.9 (1.0)</td>
<td>295</td>
<td>3.8 (1.4)</td>
<td>-0.9 (-1.0, -0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Monotherapy Studies</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>M15-555</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>216</td>
<td>5.6 (1.0)</td>
<td>194</td>
<td>4.4 (1.4)</td>
<td>-1.1 (-1.3, -0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>216</td>
<td>5.6 (0.9)</td>
<td>195</td>
<td>3.3 (1.4)</td>
<td>-1.1 (-1.3, -0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 30 mg QD</td>
<td>215</td>
<td>5.6 (1.1)</td>
<td>198</td>
<td>3.0 (1.3)</td>
<td>-1.4 (-1.7, -1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>M13-545</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>315</td>
<td>5.9 (1.0)</td>
<td>290</td>
<td>4.0 (1.4)</td>
<td>-0.9 (-1.1, -0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>317</td>
<td>5.9 (1.0)</td>
<td>303</td>
<td>3.2 (1.4)</td>
<td>-0.9 (-1.1, -0.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
DAS28(CRP) < 2.6 was assessed as a measure of clinical remission in all phase 3 studies. Of note, the DAS28 based criteria for remission does not meet the Agency’s definition of remission since patients 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. However, DAS28(CRP) is one measure of low disease activity. As shown in Table 6, a greater proportion of patients treated with UPA 15 mg QD achieved a DAS28(CRP) < 2.6 compared to their respective controls at the primary endpoint assessment timepoint. The proportion of patients with a DAS28(CRP) < 2.6 at the primary efficacy timepoint was numerically higher on the UPA 15 mg than the 30 mg QD groups in the placebo-controlled studies that included both doses. In MTX-controlled studies, the proportion of patients with DAS28(CRP) < 2.6 were higher in the UPA 30 mg QD group as compared to the UPA 15 mg QD group.

Table 6: Proportion of Randomized Patients with DAS28(CRP) < 2.6 and Remained on Randomized Treatment through Primary Timepoint for Phase 3 Studies

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Total</th>
<th>DAS28(CRP) &lt; 2.6</th>
<th>DAS28(CRP) &lt; 3.3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Counts (%)</td>
<td>Diff (%) [95 % CI]</td>
</tr>
<tr>
<td><strong>MTX Add-on Studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M13-542</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>169</td>
<td>16 (9%)</td>
<td>19.2% (11.0%, 27.4%)</td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>164</td>
<td>47 (29%)</td>
<td>14.2% (6.3%, 22.0%)</td>
</tr>
<tr>
<td>UPA 30 mg QD</td>
<td>165</td>
<td>39 (24%)</td>
<td>6.2% (11.2%, 25.5%)</td>
</tr>
<tr>
<td>M13-549</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>221</td>
<td>22 (10%)</td>
<td>20.8% (13.6%, 28.1%)</td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>221</td>
<td>68 (31%)</td>
<td>18.4% (11.2%, 25.5%)</td>
</tr>
<tr>
<td>UPA 30 mg QD</td>
<td>219</td>
<td>62 (28%)</td>
<td>30.8% (22.5%, 39.0%)</td>
</tr>
<tr>
<td>M14-465</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>651</td>
<td>40 (6%)</td>
<td>11.9% (7.3%, 16.5%)</td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>651</td>
<td>187 (29%)</td>
<td>22.6% (18.6%, 26.5%)</td>
</tr>
<tr>
<td>ADA 40 mg EOW</td>
<td>327</td>
<td>59 (18%)</td>
<td>22.6% (18.6%, 26.5%)</td>
</tr>
</tbody>
</table>
Monotherapy Studies

<table>
<thead>
<tr>
<th></th>
<th>M15-555</th>
<th>M13-545</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MTX 216</td>
<td>MTX 314</td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>217</td>
<td>42 (8%)</td>
</tr>
<tr>
<td>UPA 30 mg QD</td>
<td>215</td>
<td>61 (28%)</td>
</tr>
<tr>
<td></td>
<td>87 (40%)</td>
<td>32.1% (24.6%, 39.7%)</td>
</tr>
<tr>
<td>UPA 30 mg QD</td>
<td>314</td>
<td>113 (36%)</td>
</tr>
<tr>
<td></td>
<td>128 (41%)</td>
<td>27.4% (20.8%, 34.0%)</td>
</tr>
</tbody>
</table>

NRI was used to impute patients who had discontinued the study treatment prior to primary efficacy timepoint, were lost to follow-up, or had withdrawn from the study.

Counts (%): Counts and percentages relative to N in parenthesis are reported for the probability of response.

Diff (95% CI); p-value: Difference in the probability of response, respective 95% CI using normal approximation to difference in binomial proportions.

Abbreviations: UPA=upadacitinib; QD=once daily; MTX=methotrexate; ADA=adalimumab; EOW=every other week; Adj=adjusted

Source: FDA Statistical Reviewer

- Radiographic Outcomes: Van der Heijde Modified Total Sharp Score

Studies M14-465 and M13-545 assessed the ability of upadacitinib to inhibit radiographic progression using the mTSS. The primary analysis timepoint for radiographic endpoints was Week 26 in Study M14-465 and Week 24 in Study M13-545.

In Study M14-465, linear extrapolation was used to impute missing radiographic data and radiographic data after discontinuation of originally randomized study drug at or after Week 14 and at or before Week 18. A straight line was fit using the baseline and Week 14 x-ray to extrapolate the Week 26 mTSS outcome.

In Study 13-545, linear extrapolation was used to impute patients who discontinued randomized treatment at or after Week 12 and prior to Week 16. X-rays collected from patients who discontinued randomized treatment after Week 16 were treated as missing. For these patients, if an earlier x-ray was collected between Week 12 and Week 16, then the x-ray was used to extrapolate Week 24 results.

In presubmission communications, the Agency advised against the use of linear extrapolation as a single imputation approach to impute radiographic scores in patients who escape or withdraw from the study early. The linear extrapolation approach assumes that placebo patients’ scores would, in the absence of crossover to another treatment, continue to change at the same linear rate as was observed through the time of escape. This assumption is strong and unverifiable, and may in some situations tend to overstate true progression on placebo.

Further, the linear extrapolation approach is a single-imputation method that, even if the overall progression is truly linear on average, does not appropriately consider the statistical uncertainty of the imputation process. This leads to underestimates of the variability and overestimates of the degree of evidence of a treatment effect. Instead, the Agency emphasized
that an analysis evaluating the intention-to-treat or de facto estimand based on all Week 24 data in all randomized patients regardless of adherence or use of ancillary therapies would be critical from a regulatory perspective. During the review, the statistical reviewer included an analysis based on a random coefficient model to more appropriately account for the statistical uncertainty with the linear extrapolation assumption.

In study M14-465, based on the statistical reviewer’s analysis, there was a statistically significant delay in the estimated rate of mTSS progression at Week 26 comparing randomized patients randomized to UPA 15 mg vs placebo patients, in the absence of escape and assuming linear rate of progression (Table 7). The results for the components of mTSS were consistent with findings with mTSS. The proportions of patients with no radiographic progression as measured by change from baseline ≤ 0 at Week 26, in the absence of escape, was statistically significantly greater in the UPA 15 mg treatment group as compared to the placebo group, and was consistent with the overall findings. Analyses targeting the treatment policy estimand, i.e., the difference in the mean change from baseline at week 26 regardless of escape or adherence to randomized treatment, were statistically significant. Tipping point analyses to address missing data and analysis based on the proportion of patients with no radiographic progression based on all data collected regardless of escape or study drug discontinuation were also supportive of the benefit of UPA 15 mg in delaying radiograph progression over 26 weeks.

In study M13-545, in the absence of rescue, there was a statistically significant delay in radiographic progression as evaluated using the difference in the adjusted mean change from baseline in mTSS at Week 24 comparing UPA 15 mg and 30 mg monotherapy arms relative to MTX monotherapy (Table 7, UPA 30 mg data not shown). Statistically significant findings were also observed in the components of mTSS. These findings were consistent with the supportive analysis that included all radiographs collected following discontinuation of randomized treatment. The proportions of patients with no radiographic progression as measured by an observed change from baseline ≤ 0 at Week 24 was statistically significantly greater in the UPA treatment groups as compared to the MTX control group, and similar between UPA dose groups. Analyses were consistent when including and excluding the data collected after rescue. Tipping point analyses and additional sensitivity analyses were also supportive of the benefit of UPA 15 mg and 30 mg in delaying radiograph progression over 24 weeks.

Table 7: Radiographic Evaluation for mTSS, Study M14-465 and Study M13-545

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>UPA 15 mg QD</th>
<th>Estimated Diff (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Mean (SD)</td>
<td>35.9 (52)</td>
<td>34.0 (50.1)</td>
<td>-0.63 (-0.92, -0.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Week 26 Rate (SE)</td>
<td>0.78 (0.14)</td>
<td>0.15 (0.06)</td>
<td>-0.63 (-0.92, -0.34)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MTX Monotherapy</th>
<th>UPA 15 mg QD Monotherapy</th>
<th>Estimated Diff (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Mean (SD)</td>
<td>13.3 (31)</td>
<td>18.1 (38.2)</td>
<td>-4.8 (-8.3, -1.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Week 24 Mean (SD) | 0.6 (2.8) | 0.1 (1.4) | -0.52 (-0.8, -0.2) | <0.001

1: Random coefficient model fit to the mTSS value adjusting for time, treatment group, prior bDMARDs use, treatment group-by-time interaction with random slopes and random intercept. Covariance structure allowed for heterogeneity between treatment groups.
2: Observed mean change from baseline at Week 24 and standard deviation based on patients remaining on randomized treatment.
3: Estimated difference in the adjusted mean change from baseline compared to MDC, respective 95% CI, and p-values were based on a linear regression fit to the change from baseline in mTSS component adjusting for treatment, baseline mTSS component, key stratification factor. There was no linear extrapolation used in this analysis.

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; N=total number of patients at baseline with measurement; n=total number of patients with observed x-ray

Source: Adapted from FDA statistical reviewer

The data submitted from Study M14-465 and M13-545 provide convincing evidence of a statistically significant benefit on radiographic progression, as assessed by mTSS, for upadacitinib relative to placebo and upadacitinib relative to methotrexate monotherapy.

Additional sensitivity and tipping point analyses conducted by the statistical reviewer support the primary analysis.

- **Patient Reported Outcomes**

SF-36 was assessed as a measure of general health status. In all studies except M13-542, there were statistically significant improvements in physical component score, mental component score, and all 8 domains comparing upadacitinib 15 mg to reference arm at Week 12/14. In Study M13-542, patients receiving UPA 15 mg had greater improvement from baseline in PCS score and its components. There was not significant improvement in overall MCS score and numerical improvements were observed in some components based on the statistical reviewer’s analysis. These findings are consistent with several other RA programs, in which patients tend to have less improvement on the mental component score than the physical component score, and thus it is more difficult to demonstrate efficacy on these domains. See the statistical review for the numerical results.

FACIT-F was studied in the upadacitinib confirmatory clinical program and was proposed for labeling as a measure of fatigue. We note that FACIT-F has not previously been included in labeling for drugs for rheumatoid arthritis. However, fatigue has been increasingly recognized by patients and the academic community as the most commonly reported troublesome symptom in RA\textsuperscript{15} which appears to reflect an additional aspect of the disease, not captured by endpoints traditionally used in the labeling of products for the treatment of RA.\textsuperscript{16} Further, the Clinical Outcomes Assessment (COA) team determined that the FACIT-F, as an instrument, was adequate to support labeling claims related to fatigue associated with RA as many items appear clinically relevant and meaningful to patients, and showed improvement. Studies M13-542, M14-465 and M13-545 assessed the FACIT-F. In each of the studies, UPA-treated


\textsuperscript{16} Guidance for Industry Rheumatoid Arthritis: Developing Drug Products for Treatment
patients achieved statistically significant improvement in fatigue as measured by an increase in FACIT-F scores (Table 8). There was lack of numerical trends towards greater mean change from baseline in FACIT-F at Week 12 for patients treated with the higher dose of UPA for studies M13-542 and M13-545.

Table 8: Change from Baseline in FACIT-F at Week 12 in Studies M13-542, M14-465, and M13-545

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>N</th>
<th>Baseline Mean (SD)</th>
<th>n</th>
<th>Visit1 Mean (SD)</th>
<th>Adj Mean Diff2 (95% CI)</th>
<th>P-value2</th>
</tr>
</thead>
<tbody>
<tr>
<td>M13-542</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>221</td>
<td>28.3 (11.5)</td>
<td>207</td>
<td>31.6 (11.8)</td>
<td>4.8 (3.2, 6.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>216</td>
<td>28.1 (11.1)</td>
<td>211</td>
<td>36.0 (10.4)</td>
<td>8.0 (5.5, 10.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 30 mg QD</td>
<td>217</td>
<td>27.5 (12.6)</td>
<td>199</td>
<td>36.4 (11.4)</td>
<td>9.7 (6.5, 13.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>M14-465</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>644</td>
<td>27.0 (11.1)</td>
<td>632</td>
<td>31.5 (11.6)</td>
<td>4.5 (3.0, 6.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>646</td>
<td>26.9 (11.1)</td>
<td>632</td>
<td>35.3 (10.5)</td>
<td>8.7 (5.5, 10.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADA 40 mg EOW</td>
<td>325</td>
<td>26.2 (11.4)</td>
<td>322</td>
<td>33.8 (11.3)</td>
<td>7.7 (5.5, 9.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>M13-545</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>314</td>
<td>26.6 (11.7)</td>
<td>300</td>
<td>33.6 (11.3)</td>
<td>7.0 (5.5, 8.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 15 mg QD</td>
<td>316</td>
<td>26.4 (11.9)</td>
<td>308</td>
<td>37.0 (10.8)</td>
<td>10.6 (8.5, 12.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPA 30 mg QD</td>
<td>310</td>
<td>27.8 (11.1)</td>
<td>306</td>
<td>37.4 (10.7)</td>
<td>9.6 (7.5, 11.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mean(SD): Mean and standard deviation in parenthesis of the observed data were reported.
1: The primary time-point in Study M15-555 is Week 14 while other studies are evaluated at Week 12.
2: Estimated difference in the adjusted mean change from baseline compared to reference (placebo or MTX), respective 95% CI were reported based on a linear regression fit to the change from baseline in FACIT-F adjusting for treatment groups, baseline FACIT-F, and key stratification factor listed in Table 4 of statistical review. Wald-based p-values were reported from the same regression model.

Abbreviations: UPA=upadacitinib; SD=standard deviation; CI=confidence interval; N=total randomized; QD=once daily; n=number of patients with observed data; MTX= methotrexate; ADA=adalimumab; EOW= every other week; FACIT-F= functional assessment of chronic illness-fatigue

Source: FDA Statistical Reviewer

Morning stiffness was assessed in all 5 phase 3 studies. In Study M13-549 and M15-555, there was a statistically significantly reduction in the estimated mean adjusted change from baseline in duration of morning stiffness at the primary timepoint comparing randomized patients on UPA 15 mg QD arm relative to the reference arm (placebo and methotrexate, respectively). These results were also consistent in the remaining studies where the endpoint was not included in the multiplicity hierarchy. There was nominally statistically significant reduction in mean adjusted change from baseline in the severity of morning stiffness comparing patients treated with UPA 15 mg QD relative to the reference arm. COA staff reviewed the Morning Stiffness Measure.

- Discussion of statistical and clinical efficacy reviews with explanation for CDTL’s conclusions and ways that any disagreements were addressed.
The clinical and statistical review teams are in agreement that upadacitinib at both 15 and 30 mg doses is efficacious for signs and symptoms (ACR Responses, DAS28), physical function (HAQ-DI), and structural outcomes (mTSS). Although in some circumstances (depending on study and efficacy outcome) the 30 mg dose was observed to have a numerical benefit in some efficacy outcomes over the 15 mg dose, this was not a consistent finding across all studies and endpoints.

- Includes discussion of notable efficacy issues both resolved and outstanding

The submitted data shows efficacy of upadacitinib as a monotherapy and as a combination therapy in patients with active rheumatoid arthritis for clinical response or reductions in signs and symptoms as measured by ACR criteria and DAS28, and for improvement in physical function as measured by HAQ-DI. Efficacy of upadacitinib as a monotherapy (such as in patients who cannot tolerate non-biologic DMARDs such as methotrexate) for reducing signs and symptoms and improvement in physical function is supported by data from Studies M13-545 and M15-555. Efficacy of upadacitinib as a combination therapy (such as a combination with methotrexate or other cDMARDs) for reducing signs and symptoms and improvement in physical function is supported by data from Studies M13-542, M13-549, and M14-465. Results of Study M14-465 show that in patients receiving background methotrexate, efficacy of upadacitinib for reducing signs and symptoms and improvement in physical function was numerically better than adalimumab. Study M14-465 and M13-545 provide support for the benefit on radiographic progression, as assessed by mTSS, for upadacitinib relative to placebo and upadacitinib relative to methotrexate monotherapy, respectively.

While both doses of upadacitinib are effective, comparisons between the two dosing regimens did not suggest a consistent trend in favor of a particular dose. Given these results, the Applicant is only requesting approval of the upadacitinib 15 mg QD dose. We agree with the Applicant’s proposal.

As originally submitted, the Applicant proposed

Upadacitinib has not been approved in other rheumatologic disease populations. The results from study M14-465 based on the efficacy endpoint ACR50, as well as other thresholds, at Week 12 provide evidence of an effect comparing upadacitinib 15 mg relative to adalimumab. However, it is unclear whether the risk:benefit can be robustly assessed from Study M14-465.
due to potential design limitations after patients could potentially crossover after Week 14.

There are no unresolved efficacy issues.

8. Safety

Studies contributing to integrated safety analyses, and AbbVie’s pooling and attribution strategies

The assessment of the safety of upadacitinib is primarily derived from the five phase 3 studies which were designed to assess the safety profile of once daily upadacitinib 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 upadacitinib (15 mg and 30 mg) compared to PBO, MTX and adalimumab. The studies enrolled a broad population of patients with moderately to severely active RA who were either naïve to MTX, had an inadequate response (IR) or intolerance to MTX or cDMARDs, or had an IR or were intolerant to biologic DMARDs. Additional supportive safety data when assessing the all patient exposure to upadacitinib is provided by three phase 2 studies, including two dose-ranging studies of the immediate-release upadacitinib formulation using the twice daily dosing regimen in RA patients with an inadequate response to MTX (Study M13-537) or TNF-inhibitors (Study M13-550), and one bioavailability study (Study M13-538) 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.

For each individual study, an independent external Data Monitoring Committee (DMC) reviewed unblinded safety data at regular intervals. In addition, an independent external Cardiovascular Adjudication Committee (CAC) reviewed and adjudicated all potential cardiovascular (CV) events, including VTEs, as well as deaths.

Treatment emergent adverse events (TEAEs) were defined as AEs on or after the first dose of study drug, and no more than 30 days (70 days for adalimumab) after the last dose of study drug. In the event of treatment switching between upadacitinib and adalimumab:

CDER Cross Discipline Team Leader Review Template
Version date: October 10, 2017 for all NDAs and BLAs
For patients who switching from UPA to ADA, an AE was counted as a TEAE under UPA if the event occurred within 30 days after the last dose of UPA and before the first dose of ADA

For patients who switched from ADA to UPA, an AE was counted as TEAE under UPA if the event occurred on or after the first dose of UPA and within 30 days after the last dose of UPA

Safety analyses included all patients enrolled in the upadacitinib 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 upadacitinib dose and comparator during the controlled periods and long-term extension periods of the phase 3 studies. These six analysis sets, proposed by the Applicant, 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 patients 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 patients 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 patients.
  - The “MTX-Controlled” analysis set included data from Studies M13-545 and M15-555. These studies randomized patients 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 patients. Pooling of these two studies was deemed acceptable despite having Study M13-545 enrolled MTX-naïve patients and Study M15-555 enrolled MTX-IR patients.

- 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 patients 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, M13-549, M13-545 and M15-555. These studies followed patients 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 patients enrolled in the
  phase 2 and phase 3 studies. For this analysis set, the Applicant pooled
  patients 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
patients was deemed acceptable for the safety analyses.

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.
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 patients treated with ADA and
PBO in the controlled period. However, the study design allowed multiple potential
crossovers between active control, placebo control, and upadacitinib that further limited an
adequate comparison of long-term safety.

Review of the long-term period primarily utilized the “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.

There are limitations to interpretation for the long-term safety based on the available data. The
“Any Phase 3 UPA 15 mg and 30 mg” analysis set provides long-term information with respect
to dose. The “Any RA UPA” provides additional characterization of rare adverse events.
Interpretation of “Any Phase 3 UPA 15 mg” had no concurrent control to provide context. For
example, patients from M14-465 on the 15 mg dose were excluded from “Any Phase 3 UPA 15
mg and 30 mg” set because the 30 mg dose was not evaluated, and naïvely pooling studies with
different doses can potentially introduce confounding due to Simpson’s paradox.

Exposure adjusted event rates (EAERs) were provided to summarize long-term AEs, while
exposure adjusted incidence rates (EAIRs) were summarized for AEs which typically occur as
single instances or for composite endpoints of interrelated events (i.e., deaths, malignancies,
MACE, and VTE). EAIRs were preferred for presentation in the prescribing information to
account for the different follow-up of patients between treatment groups in the integrated
studies. While the EAERs and EAIRs vary for outcomes other than death, the overall
conclusions about the safety of the doses of UPA relative to the control groups and comparative
safety are unchanged. The EAIRs are described in the statistical review.
Adequacy of the database, major findings/signals, special studies

A total of 4443 patients received at least one dose of UPA in the phase 2 or phase 3 studies, of which 3833 patients were in the phase 3 program. Of all Phase 2 or 3 studies, 2972 (67%) were exposed to UPA for at least 48 weeks. A total of 2630 patients 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.

In all studies excluding M14-465, 1213 patients received at least 1 dose of upadacitinib 15 mg, of which 986 patients were exposed for at least one year, and 1203 patients received at least 1 dose of upadacitinib 30 mg, of which 946 were exposed for at least one year. The size and scope of the safety database were reasonable and consistent with the safety database of other biologic and JAK inhibitor products approved for RA.

Table 9: Number and Percentage of Patients Exposed to Study Drug by Duration Intervals ("Any Ph 3 UPA 15 mg and 30 mg" Analysis Set)

<table>
<thead>
<tr>
<th>Duration</th>
<th>UPA 15 mg QD (N=1213)</th>
<th>UPA 30 mg QD (N=1203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥4 weeks (28 days)</td>
<td>1191 (98)</td>
<td>1181 (98)</td>
</tr>
<tr>
<td>≥12 weeks (84 days)</td>
<td>1152 (95)</td>
<td>1130 (94)</td>
</tr>
<tr>
<td>≥24 weeks (168 days)</td>
<td>1101 (91)</td>
<td>1057 (88)</td>
</tr>
<tr>
<td>≥36 weeks (252 days)</td>
<td>1061 (88)</td>
<td>1024 (85)</td>
</tr>
<tr>
<td>≥52 weeks (336 days)</td>
<td>986 (81)</td>
<td>946 (79)</td>
</tr>
<tr>
<td>≥72 weeks (504 days)</td>
<td>810 (67)</td>
<td>768 (64)</td>
</tr>
<tr>
<td>≥96 weeks (672 days)</td>
<td>435 (36)</td>
<td>427 (36)</td>
</tr>
</tbody>
</table>

Adapted from Applicant’s Response to Labeling Comments dated August 12, 2019

General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests

Deaths

A total of 40 deaths were reported in the phase 2 and phase 3 RA studies. Thirty-three (25 treatment-emergent) deaths occurred in the UPA treatment arms: UPA 15 mg (n=14); UPA 30 mg (n=14), UPA 6 mg BID (n=4) and UPA 12 mg BID (n=1). Additionally, there were deaths in the ADA (n=4), PBO (n=2), and MTX (n=1) arms.

Based on the short-term PBO- and MTX-controlled studies, the EAERs of death in patients treated with UPA 15 mg were similar to the control group. However, the number of deaths are too few to draw definitive conclusions.
Table 10 shows the pooled data across the long-term periods of the Phase 3 studies for death. The long-term data for death rates in MTX, adalimumab, and all upadacitinib patients in the phase 3 program has limitations because the studies were pooled without considering differences in study designs and doses being evaluated. Given these limitations, comparison of UPA 15 mg and 30 mg is the primary focus. As shown in the table below, there was a numerical increase in EAIR for death in the UPA 30 mg group compared to the UPA 15 mg group; however, the number of events was small.

Table 10: Death EAIR Per 100 PY: Long-Term Period All Exposure (Global Phase 3 Safety Analysis Set)

<table>
<thead>
<tr>
<th></th>
<th>MTX(^a) (N=314) n/PY (n/100 PY)</th>
<th>ADA(^b) (N=579) n/PY (n/100 PY)</th>
<th>All UPA 15 mg QD(^c) (N=2630) n/PY (n/100 PY)</th>
<th>UPA 15 mg QD(^d) (N=1213) n/PY (n/100 PY)</th>
<th>UPA 30 mg QD(^d) (N=1204) n/PY (n/100 PY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>1/314 (0.3)</td>
<td>4/468 (0.9)</td>
<td>14/2925 (0.5)</td>
<td>9/1451.9 (0.6)</td>
<td>14/1410.3 (1.0)</td>
</tr>
</tbody>
</table>

\(^a\) Includes Studies M13-545 and M15-555
\(^b\) Include patients on adalimumab arm from Study M14-465
\(^c\) Includes Studies M13-542, M13-549, M14-465, M13-545, and M15-555
\(^d\) Includes Studies M13-542, M13-549, M13-545, and M15-555
\(^e\) Includes nontreatment-emergent deaths
\(^f\) EAIR are naively pooled without accounting for differences in study design.
\(^g\) EAIR rates were stratified by study using MH weights based on the total exposure within each study. Comparison of EAIR is limited to the two doses in the bold box and cannot be directly compared to the other groups.

Adapted from Applicant’s SCS Table 29 and ISS Table 2.4 5.1.1.5

All deaths in the UPA development program were adjudicated by a Cardiovascular Adjudication Committee (CAC) to assess for a cardiovascular (CV) or non-cardiovascular cause of death. Of the 25 treatment-emergent deaths in patients receiving upadacitinib, 11 (44%) were adjudicated as CV; all adjudicated CV deaths occurred in patients with cardiac risk factors. Refer to Dr. Hull’s review for a listing of all causes of death. The causes of death in upadacitinib-treated patients were consistent with the profile of an immunosuppressant and also with the underlying patient population, with infections, malignancy and cardiovascular disorders being most common.

Review of the data regarding deaths in the upadacitinib program do not raise a concern regarding the Applicant’s proposal for the 15 mg dose of UPA.

**Nonfatal Serious Adverse Events (SAEs)**

Overall, increased SAEs were observed in patients treated with UPA as compared to PBO and MTX control groups, but less than observed with adalimumab. Increases in SAEs were dose dependent with increased EAERs with UPA 30 mg compared to UPA 15 mg. 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 patients. The types of SAEs were similar between treatment arms and the majority of events were reported in single patients within an individual study and with no SAE occurring in more than three patients. In addition, the types of SAEs are consistent with the known safety profile of potent immunosuppressant and other JAK inhibitors.

**Discontinuations due to AEs**

The percentages of AEs leading to discontinuation of study drug were similar between patients in the UPA 15 mg groups and PBO and MTX groups during the controlled periods of the five phase 3 studies. However, patients 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. In the long-term period, patients treated with UPA 30 mg had a higher EAER of AEs leading to discontinuation than patients treated with UPA 15 mg. The most common AE leading to discontinuation of study drug was pneumonia (UPA 15 mg: 0.5 E/100 PY, UPA 30 mg 0.9 E/100 PY). Overall, the types of AEs leading to discontinuation are consistent with the known safety profile of potent immunosuppressant and other JAK inhibitors.

**Common AEs**

Common adverse events seen were typical of studies conducted with a DMARD in rheumatoid arthritis. The most frequent AEs by PT that were reported in ≥4% of UPA 15 mg treated patients and more frequent than PBO-treated patients were upper respiratory tract infection (UPA 5%, PBO 4%), nasopharyngitis (UPA 4%, PBO 3%), urinary tract infection (UPA 4%, PBO 3%), and nausea (UPA 4%, PBO 2%). With long-term exposure, the types of AEs were similar to those observed during the controlled period. Overall, the types of AEs are consistent with the known safety profile of potent immunosuppressant and other JAK inhibitors.

**Laboratory Tests**

Upadacitinib treatment was associated with changes in certain hematologic, hepatobiliary, serum chemistry (creatine phosphokinase), and lipid parameters. Similar laboratory changes have been observed for other JAK inhibitors and other DMARDs.

**Hematologic Abnormalities**

**Neutropenia**

Grade 2 and Grade 3 neutropenia were observed more frequently in the UPA 15 mg and 30 mg groups compared to patients treated with PBO. Grade 4 neutrophil decreases were uncommon across the UPA groups. Decreases in neutrophils were greater in the UPA groups compared to MTX. 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.

In the “PBO-Controlled UPA 15 mg” analysis set, mean neutrophil counts decreased -0.9 x 10^9/L and 1 x 10^9/L in the UPA 15 mg compared to -0.003 x 10^9/L with the PBO group. Grade
2, 3, and 4 neutropenia was observed in a greater proportion of patients on UPA 15 mg (4.0%, 0.6%, 0.5%, respectively), as compared to PBO (0.6%, < 0.1%, and 0). There was a dose-dependent increase in Grade 2 and 3 neutropenia with UPA treatment based on analysis of the “PBO-controlled periods of UPA 15 mg and 30 mg” dataset (Grade 2: 6.8%, 4.4%, 0.3%; Grade 3: 2.4%, 0.8%, 0.3%; Grade 4: 0, 0.5%, 0 for UPA 30 mg, UPA 15 mg, and PBO, respectively). The mean decrease in neutrophil counts was also greater in the UPA 15 mg and 30 mg groups (-1.3 x 10⁹/L and -1.2 x 10⁹/L, respectively) than in the MTX group (-0.6 x 10⁹/L) in analysis of the three-month “MTX-controlled” set.

In the long-term period, mean decreases in neutrophils remained greater in the UPA 30 mg relative to UPA 15 mg, and greater proportions of patients had Grade 3 decreases in UPA 30 mg (“Any Ph 3 UPA 15 and 30 mg” set).

Adverse events of neutropenia were lower in the UPA 15 mg group compared with the 30 mg group for both short-term (11.5 E/100 PY and 16.5 E/100 PY) and long-term (4.2 E/100 PY and 7.3 E/100 PY) exposure periods (“PBO-controlled UPA 15 mg and 30 mg” and “Any Ph 3 UPA 15 and 30 mg” sets). Similarly, the “MTX-controlled” analysis set, and the data available through the data cut-off for Study M13-545, showed dose-dependent increase in EAERs of TEAEs of neutropenia with UPA 30 mg and UPA 15 mg over MTX. In the any RA UPA analysis, there were 13 patients with Grade 4 neutrophil counts, 3 had associated infections (nonserious tooth abscess (UPA 15 mg), urosepsis (UPA 15 mg), pneumonia/sepsis (UPA 30 mg)) with onset within 30 days of the Grade 4 neutropenia. Subgroup analyses to evaluate a relationship between neutropenia and infectious events did not find clear evidence of an association of serious infections, opportunistic infections, or herpes zoster with a low neutrophil count.

**Lymphopenia**

Treatment with UPA was associated with a mean increase in absolute lymphocyte count (ALC) over the initial 36 weeks of treatment, followed by small decreases thereafter. While the mean ALC increased, some patients experienced decreases in ALC. The percentages of patients with Grade 3 and Grade 4 decreases in lymphocytes in the UPA 15 mg group was comparable with that observed with PBO (Grade 3: 13.5% vs. 11.5%; Grade 4: 0.9% vs. 0.7%, respectively) through Week 12. A higher frequency of lymphocyte count decreases was observed with UPA 30 mg treatment compared to UPA 15 mg. In the “PBO-Controlled UPA 15 mg and 30 mg” analysis set, Grade 3 and 4 decreases were more frequently reported in the UPA 30 mg (13.9%, 2.4%) than the UPA 15 mg (12.5%, 0.5%), and the PBO (10.1%, 0.5%) groups. Similar trends were noted in the MTX-controlled analysis set, and in the long-term period analysis sets.

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 few patients 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.

**Platelets**

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Version date: October 10, 2017 for all NDAs and BLAs
There was a larger decrease in mean platelet counts at Week 4 in the UPA 15 mg group compared to the PBO group, -27 x 10^9/L versus -0.5 x 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. Mean platelet decreases to Week 4 were generally slightly greater in the UPA 30 mg dose groups as compared to the UPA 15 mg dose groups, and greater compared to the PBO group in the “PBO-controlled UPA 15 mg and 30 mg” and “MTX-controlled” sets. In the long-term “Any Ph 3 UPA 15 mg” analysis set, mean platelet values returned to baseline up to Week 60. Very few patients experienced an AE related to thrombocytopenia 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.

**Chemistry Abnormalities**

**Hepatic Enzymes**

In the “PBO-controlled UPA 15mg,” ALT and AST ≥3x the upper limit of normal (ULN) were observed more frequently in patients receiving UPA 15 mg (2.1% and 1.5%) than PBO (1.5% and 0.7%, respectively) from baseline to Week 12. In patients treated with UPA 15 mg, ALT and AST levels increased during the initial four weeks of therapy and plateaued between Week 8 and 12. In the “PBO-controlled UPA 15 mg and 30 mg” analysis set, the proportions of patients with ALT and AST ≥3x ULN were similar across the treatment groups (PBO: 1.3%, 1.0%; UPA 15 mg: 0.8%, 1.0%; UPA 30 mg: 1.0%, 0). In the MTX-controlled studies, ALT and AST ≥3x ULN occurred more frequently with MTX treatment (1.9%, 0.9%, respectively) and UPA 30 mg (1.7%, 1.3%) as compared to UPA 15 mg (0.8%, 0.4%).

In the long-term period, a greater proportion of patients had ALT ≥3x ULN in the UPA 30 mg group (3.8%) compared to the UPA 15 mg (3.0%), while AST ≥3x ULN was similar between groups (“Any Ph 3 UPA 15 mg and 30 mg” analysis set).

TEAEs of hepatic disorders were more frequent in the UPA 15 mg arm (4.4%) than the PBO arm (3.6%). One patient (UPA 15 mg) had serious hepatitis requiring study drug interruption; 3 patients discontinued UPA 15 mg during the placebo-controlled period due to a hepatic disorder TEAE. In the “PBO-controlled UPA 15 mg and 30 mg” analysis set, TEAEs of hepatic disorder were similar across the PBO (2.3%), UPA 15 mg (1.3%), and UPA 30 mg (2.3%) treatment groups. There were no SAEs of hepatic disorder. TEAEs of hepatic disorder leading to discontinuation only occurred in the upadacitinib groups and were similar in each arm (UPA 15 mg: 0.5%, UPA 30 mg: 0.3%). In the long-term “Any Ph 3 UPA 15 and 30 mg” set, EAERs of TEAEs of hepatic disorder were 11.5 E/100 PY and 12.7 E/100 PY for UPA 15 mg and 30 mg, respectively. The EAERs for any serious hepatic disorder and hepatic disorder leading to discontinuation for UPA 15 mg were 0.2 E/100 PY and 0.7 E/100 PY respectively, compared to 0.1 E/100 PY and 1.1 E/100 PY for UPA 30 mg.

In the “Any RA UPA” set, 4 patients (2 UPA 6 mg BID/15 mg QD, 2 UPA 12 mg BID/UPA 30 mg QD) met biochemical criteria for Hy’s Law (ALT and or AST ≥3x ULN and total bilirubin ≥2x ULN). Other confounding factors including concomitant MTX, INH, hepatitis B, and malignant melanoma metastatic to the liver. None of the cases were consistent with probable drug induced liver injury related to upadacitinib. One patient (UPA 15 mg) had an
AE of hepatic enzyme increased with fatal outcome. The patient had a complicated clinical course with bronchitis/pneumonia, high-output heart failure, and dyspnea; the Applicant judged the cause of death possibly overwhelming sepsis and/or cardiac failure and/or arrhythmia with possible hypoperfusion of the liver causing the hepatic enzyme abnormalities.

Upadacitinib treatment resulted in a greater percentage of transaminase elevations compared to PBO-treated patients. Transaminase elevations were similar between UPA 30 mg and MTX, but lower in the UPA 15 mg arm in the MTX-controlled short-term period. Transaminase elevations were similar, but numerically higher, in the UPA 30 mg group as compared to the UPA 15 mg group in the PBO-controlled and long-term periods. TEAEs of hepatic disorders were reported more frequently with UPA 30 mg than UPA 15 mg in the short-term and long-term periods, although differences between groups were small. No cases of probable drug-induced liver injury were identified.

**Lipid Elevations**
Upadacitinib treatment was associated with dose-dependent increases in total cholesterol (TC), LDL cholesterol, HDL cholesterol, and triglycerides. Increases generally peaked by Week 8 and then generally plateaued. In the PBO-controlled Ph 3 UPA 15 mg analysis set, mean changes from baseline to Week 12 were higher in the UPA 15 mg compared to the PBO group (TC: 0.66 vs. -0.04 mmol/L, HDL: 0.21 vs. 0.02 mmol/L, LDL 0.38 vs. -0.03 mmol/L, TG: 0.15 vs. -0.05 mmol/L, respectively). In the PBO-controlled UPA 15 mg and 30 mg analysis set and the MTX-controlled set, there were small numerical mean increases in the UPA 30 mg over the UPA 15 mg group; both UPA arms had greater mean increases than PBO. The overall LDL/HDL ratios and TC/HDL did not appear to change. There was no clear association between LDL and occurrence of MACE in the phase 3 studies. The Applicant has proposed labeling to advise prescribers to assess lipid parameters 12 weeks after initiation of treatment and manage patients according to applicable clinical guidelines for hyperlipidemia.

**Creatine Kinase (CK)**
Upadacitinib treatment was associated with limited dose-dependent increases in CK of approximately 60 U/L to 115 U/L during the controlled periods of the phase 3 studies. In the long-term “Any Ph 3 UPA 15 mg” analysis, including all five phase 3 studies, the mean change from baseline in CK remained relatively stable after Week 12 of treatment. There was 1 SAE of CK elevation and 2 nonserious TEAEs of CK elevations leading to discontinuation of study drug. In the “PBO-Controlled UPA 15 mg and 30 mg” analysis set, CK elevations > 5x ULN occurred in 1.6% and 0.3% of patients in the UPA 15 mg and placebo groups, and in no patients in the UPA 30 mg group. In the long-term “Any Ph 3 UPA 15 mg and 30 mg” data analysis, mean changes in CK were higher in the UPA 30 mg group compared to the 15 mg group, however the percentages of patients with Grade 3 and Grade 4 increases in CK levels were similar between UPA arms. There was one case of rhabdomyolysis (UPA 30 mg) assessed as not related to study drug by the investigator in a patient with concurrent influenza.

**Immunogenicity**
As an orally administered small molecule, upadacitinib is not expected to be associated with immunogenicity.

**Special safety concerns**

Adverse Events of Special Interest (AESI) were identified based on safety concerns reported for other JAK inhibitors, as well as upadacitinib data from earlier phase studies and regulatory concerns for novel small molecule drugs. AESI in the upadacitinib phase 3 studies include serious infection, opportunistic infection, herpes zoster, active/latent tuberculosis, major adverse cardiovascular events (MACE), thromboembolic events, malignancy, hepatic disorders, gastrointestinal perforation, anemia, neutropenia, lymphopenia, renal dysfunction, and CPK elevation.

**Serious Infections**

In the placebo-controlled periods of the phase 3 studies, serious infections were more frequently reported by patients in the UPA 15 mg treatment group. In the “PBO-controlled UPA 15 mg” analysis set, the proportion of patients with serious infections was higher in the UPA 15 mg group (1.2%, 5.8 E/100 PY) vs. the PBO group (0.6%, 3.1 E/100 PY). Serious infections reported in ≥ 2 patients treated with UPA 15 mg were appendicitis, gastroenteritis and viral infection.

In the “PBO-controlled UPA 15 mg and 30 mg” analysis set, the EAER of serious infection was higher in the UPA 30 mg group (8.2 E/100 PY), than the UPA 15 mg (2.3 E/100 PY) and PBO groups (1.2 E/100 PY). The only serious infection reported in ≥ 2 patients in a group was pneumonia in the UPA 30 mg treatment arm.

In the “MTX-controlled” analysis set, EAERs for serious infections up to 24 weeks 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 patients who did not switch treatment arms.

In Study M14-465 through Week 26, the EAERs of serious infections in the UPA 15 mg (5.2 E/100 PY) and ADA groups (4.4 E/100 PY) were similar, and greater than PBO (2.8 E/100 PY).

In the long-term “Any Ph 3 UPA 15 and 30 mg” analysis set, EAERs of serious infections were lower in the UPA 15 mg group (3.6 E/100 PY) as compared to UPA 30 mg QD (6.2 E/100 PY). The most common serious infections in UPA 15 mg-treated patients were pneumonia, bronchitis, and cellulitis. The most common serious infections in patients treated with UPA 30 mg were pneumonia, sepsis, herpes zoster, bronchitis, and influenza. Three patients treated with UPA 30 mg died due to serious infection (meningitis, peritonitis, and sepsis/pneumonia).

In summary, during the placebo or MTX-controlled periods, a higher rate of serious infections was observed in a dose-dependent manner of UPA-treated patients compared to control.
patients. Similarly, in the long-term period, there was a dose-dependent increase in serious infections infection in UPA 30 mg-treated patients compared to UPA 15 mg treated patients.

**Opportunistic Infections and Tuberculosis**

During the controlled periods of the phase 3 studies, the proportion of patients with opportunistic infections was similar between patients treated with UPA 15 mg and patients who received PBO or MTX in the control groups. Opportunistic infections occurred more frequently in the UPA 30 mg-treated patients compared to UPA 15 mg-treated patients over the same time periods (2.1 E/100 PY vs. 0.8 E/100 PY, respectively based on “PBO-controlled UPA 15 mg and 30 mg” set).

In the “Any Ph 3 UPA 15 mg and 30 mg” analysis of the long-term period, EAERs of opportunistic infections were higher in the UPA 30 mg (1.8 E/100 PY) as compared to the UPA 15 mg (0.6 E/100 PY) groups.

In the phase 3 studies, the most common opportunistic infections were nonserious mucosal candidiasis infections in the controlled and long-term periods. Serious opportunistic infections occurred in 3 patients receiving UPA 15 mg (herpes zoster disseminated, bronchopulmonary aspergillosis, and pneumonia cryptococcal), 1 UPA 30 mg-treated patient (serious primary varicella infection and non-serious varicella zoster pneumonia), and 2 placebo-treated patients (pneumocystis jirovecii pneumonia).

In the “Any RA UPA” analysis set, the EAER of active-latent TB for UPA 6 mg BID/15 mg QD and UPA 12 mg BID/30 mg QD was 2.1 E/100 PY and 1.5 E/100 PY, respectively. The Applicant’s review of the data identified six cases of active TB: five patients receiving UPA (<0.1 E/100 PY) and one patient receiving ADA. Of the five patients receiving UPA, three were treated with UPA 15 mg (one in Study M14-465) and two with UPA 30 mg at the time of their event. Extra-pulmonary TB occurred in 2 of the UPA-treated patients and none of the ADA-treated patients.

**Herpes Zoster**

The rates of herpes zoster infection were higher in the UPA groups compared to PBO, MTX and ADA groups. Based on the “PBO-Controlled UPA 15 mg” analysis set, 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.

There was a dose-dependent effect observed with higher rates of herpes zoster infections in patients treated with UPA 30 mg compared to UPA 15 mg patients in the controlled and long-term periods. In the “PBO-Controlled UPA 15 mg and 30 mg” EAERs for the UPA 15 mg and 30 mg groups were 2.3 E/100 PY and 8.2 E/100 PY, respectively, and in the “Any Ph 3 UPA 15 and 30 mg” set for the long-term period, EAERs were 3.8 E/100 PY and 9.2 E/100 PY, respectively. In the controlled and long-term periods of the MTX-controlled studies, the EAER of herpes zoster was higher in the UPA 30 and UPA 15 mg groups as compared to MTX.
Through Week 26 of Study M14-465, the EAER of herpes zoster was higher in the UPA 15 mg group (1.7 E/100 PY) compared to the ADA (0.7 E/100 PY) and PBO (1.2 E/100 PY) groups, prior to patients switching treatment. This trend continued through the study cutoff day (after patients 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).

In the “Any RA UPA” analysis set, the EAER for herpes zoster in the UPA 6 mg BID/15 mg QD and UPA 12 mg BID/30 mg QD groups were 3.6/100 PY and 7.0 E/100 PY, respectively. The majority of the zoster cases involved a single dermatome, however there were 13 patients with disseminated cutaneous only zoster, 8 patients with ophthalmic herpes zoster involvement, and 2 patients with herpes zoster oticus.

**Malignancy**

Malignancies were reported across all treatment arms in the short-term PBO-controlled, MTX-controlled, and ADA-controlled datasets. In the “PBO-controlled UPA 15 mg” dataset, there were 3 patients with malignancies, 2 on PBO (basal cell carcinoma, cervical carcinoma) and 1 on UPA 15 mg (malignant melanoma in situ). In the “PBO-controlled UPA 15 mg and 30 mg” analysis set, malignancies other than non-melanoma skin cancer (NMSC) were reported in 1 patient in the UPA 15 mg (malignancy melanoma in situ, as discussed) and 3 patients in the UPA 30 mg group (2 prostate cancer, 1 B-cell small lymphocytic lymphoma/chronic lymphocytic leukemia). In addition, NMSC were reported in 2 patients in the UPA 30 mg group. In the MTX-controlled analysis set, malignancies other than NMSC were reported in 3 patients in the UPA 15 mg group, 1 patient on MTX, and 0 patients on UPA 30 mg. NMSC was reported in 1 patient in the MTX group.

Overall, the 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. In the “Any Ph 3 UPA 15 mg and 30 mg” analysis set, the EAIRs of malignancy other than NMSC were similar for UPA 15 mg and 30 mg (1.2 n/100 PY and 1.3 n/100 PY, respectively). Different types of malignancies with EAIRs ≤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) and squamous cell skin cancer (UPA 30 mg, 0.6 E/100 PY).

**GI Perforations**

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 (2 on UPA 15 mg, 4 on UPA 30 mg) were reported in the phase 3 studies compared to no cases in patients treated with PBO, MTX or ADA. In addition, 1 UPA 15 mg-treated patient in phase 2 study M14-663 had an AE of intestinal perforation.
Major adverse cardiac events (MACE) were defined as CV death, non-fatal myocardial infarction, and non-fatal stroke. Patients were excluded from the global phase 3 studies if they had a history of recent (within 6 months) CV accident, myocardial infarction, coronary stentin, or uncontrolled hypertension, or other condition which in opinion of investigator would put the patient at risk. Baseline cardiovascular risk factors were similar between treatment arms at baseline.

A Cardiovascular Adjudication Committee (CAC) adjudicated all potential CV events, including deaths to assess for MACE. In the analysis of the short-term integrated datasets, the number of MACE events are too few to draw conclusions. In the long-term “Any Ph 3 UPA 15 and 30 mg” analysis set, similar EAIRs for MACE were observed in the UPA 15 mg (0.8 n/100 PY) and UPA 30 mg (1.0 n/100 PY) groups (Table 11).

Overall, the rates of MACE events in the long-term period were similar between the doses evaluated in absence of controlled comparisons. The long-term data for rates for MACE in MTX, adalimumab and all upadacitinib patients in the phase 3 program has limited interpretation because the studies were pooled without considering differences in study designs and doses being evaluated, however the rates are generally consistent across treatment arms.

### Table 11: Adjudicated MACE EAIR Per 100 PY: Long-Term All Exposure (Global Ph 3 Safety Analysis Set)

<table>
<thead>
<tr>
<th></th>
<th>MTXa (N=314) n/PY (n/100 PY)</th>
<th>ADAb (N=579) n/PY (n/100 PY)</th>
<th>UPA 15 mg QDc (N=2630) n/PY (n/100 PY)</th>
<th>UPA 15 mg QDd (N=1213) n/PY (n/100 PY)</th>
<th>UPA 30 mg QDd (N=1204) n/PY (n/100 PY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjudicated MACEc</td>
<td>2/314 (0.6)</td>
<td>2/468 (0.4)</td>
<td>16/2651 (0.6)</td>
<td>11/1407.8 (0.8)</td>
<td>13/1361.5 (1.0)</td>
</tr>
</tbody>
</table>

*Includes Studies M13-545 and M15-555

*b Include patients on adalimumab arm from Study M14-465

*c Includes Studies M13-542, M13-549, M14-465, M13-545, and M15-555


*MACE: major adverse cardiovascular events, defined as CV death, non-fatal MI and non-fatal stroke

*a,bc EAIR are naïvely pooled without accounting for differences in study design.

d EAIR rates were stratified by study using MH weights based on the total exposure within each study. Comparison of EAIR is limited to the two doses in the bold box and cannot be directly compared to the other groups.

Adapted from Applicant’s SCS Table 107, and 109

In the global phase 2 and phase 3 studies, 38 patients on upadacitinib experienced treatment-emergent MACE: 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 seven patients with MACE events from PBO, MTX or ADA groups. All patients had at least one additional CV risk factor other than RA. A total of 13 out of the 38 UPA-treated patients experienced CV death: UPA 6 mg BID/15 mg QD, n=7; UPA
12 mg BID/30 mg QD, n=6. Sixteen UPA-treated patients had MACE events of non-fatal MI and 10 had non-fatal stroke. There was no clear evidence to suggest an association between UPA-induced increased LDL concentrations and MACE, although conclusions are limited by the relatively small number of MACE events.

**Thrombosis**

Increased risks of thrombosis were observed in the baricitinib clinical development program and the baricitinib label includes a Boxed Warning regarding this safety issue. More recently, an interim analysis of an ongoing post-marketing long-term safety study of tofacitinib has also identified an increased risk of pulmonary embolism and mortality with the 10 mg dose of tofacitinib. Note that tofacitinib 5mg is approved for the treatment of RA in the US and the 10mg dose of tofacitinib is not approved for RA in the US. Based on the interim results from this ongoing trial, a Boxed Warning was recently added to the tofacitinib product label describing the available data regarding thrombosis and mortality. Given that two JAK inhibitor programs have identified thrombosis as a safety signal, thrombosis is now considered a class safety issue.

In the short-term controlled studies, UPA-treated patients did not demonstrate a higher EAIR of venous thrombotic events (VTE) compared to PBO, MTX, or ADA, however the number of VTE are too few to draw definitive conclusions.

Table 12 shows the pooled data across the controlled long-term periods of the Phase 3 studies assessing AEs of VTEs. The long-term data for VTEs in MTX, adalimumab, and all upadacitinib patients in the phase 3 program has limitations because the studies were pooled without considering differences in study designs and doses being evaluated. However, the EAIR for VTE was numerically higher in the UPA 15 mg group compared to the UPA 30 mg group.
Table 12: Treatment-Emergent Adjudicated VTE EAIR per 100 PY During the Long-Term Periods (Global Ph 3 Safety Analysis Set)

<table>
<thead>
<tr>
<th></th>
<th>MTX^a</th>
<th>ADA^b</th>
<th>All UPA 15 mg^c</th>
<th>Any UPA 15 mg^d</th>
<th>Any UPA 30 mg^d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=314)</td>
<td>(N=579)</td>
<td>(N=2630)</td>
<td>(N=1213)</td>
<td>(N=1204)</td>
</tr>
<tr>
<td></td>
<td>n/PY</td>
<td>n/PY</td>
<td>n/PY</td>
<td>n/PY</td>
<td>n/PY</td>
</tr>
<tr>
<td>VTE</td>
<td>2/314</td>
<td>5/468</td>
<td>16/2653</td>
<td>12/1409</td>
<td>5/1362</td>
</tr>
<tr>
<td></td>
<td>(0.6)</td>
<td>(1.1)</td>
<td>(0.6)</td>
<td>(0.9)</td>
<td>(0.3)</td>
</tr>
</tbody>
</table>

^a Includes Studies M13-545 and M15-555
^b Include patients on adalimumab arm from Study M14-465
^c Includes Studies M13-542, M13-549, M14-465, M13-545, and M15-555

EAIR are naïvely pooled without accounting for differences in study design.
EAIR rates were stratified by study using MH weights based on the total exposure within each study. Comparison of EAIR is limited to the two doses in the bold box and cannot be directly compared to the other groups.

Adapted from Applicant’s ISS Table 2.4 9.1.1.1.8, Table 2.4 11.1.2.2.1, Table 2.4 5.1.1.8.1, Table 2.4 4.1.1.8.1;

Throughout the global UPA phase 2 and phase 3 RA studies, there were a total of 38 patients that experienced an adjudicated VTE AE. Thirty patients 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), 5 patients received ADA, 2 patients received MTX, and 1 patient received PBO. Two UPA-treated patients with an adjudicated VTE died due to PE. All patients with VTE had 1 or more risk factors for VTE. Review of the “Any RA UPA” analysis set did not suggest a higher EAIR of adjudicated VTEs for patients continuously dosed with UPA 12 mg BID/30 mg QD (0.3 n/100 PY) compared to patients continuously dosed with UPA 6 mg BID/15 mg QD (0.2 n/100 PY).

In the overall clinical program, there were 3 UPA-treated patients with adjudicated noncardiac and non-neurologic arterial thromboembolic events. These included events of femoral artery thrombosis in a patient with a history of PE/DVT on anticoagulation (UPA 6 mg BID), stent thrombosis of the common iliac artery in a patient with multiple CV risk factors (UPA 30 mg), and peripheral artery thrombosis complicating resection of popliteal artery aneurysm resection and graft implantation (UPA 30 mg).

Given that two JAK inhibitor programs have identified thrombosis as a safety signal, thrombosis is now considered a class safety issue and the upadacitinib product label will include a Boxed Warning regarding VTE.

Discussion of primary reviewer’s comments and conclusions

We are in agreement with Dr. Hull that the currently submitted safety data and analyses are adequate to inform the decision regarding the benefit-risk profile of upadacitinib. The safety data submitted for upadacitinib suggests it is associated with significant immunosuppression, as manifested by increased risks of SAEs, AEs, serious infections, opportunistic infections, GI perforations, viral reactivations, neutropenia, lymphopenia, anemia, elevated liver...
transaminases, lipid elevations and CK concentrations. Some of these risks appeared to have a dose- and/or exposure- dependent increase, such as serious infections, opportunistic infections, herpes zoster, NMSC, and laboratory abnormalities such as neutropenia, lipid elevations, and CK elevations. Increased risks of malignancies were noted in clinical development programs for other JAK inhibitors. In the upadacitinib studies, the available long-term data do not indicate an increased risk of malignancies excluding NMSC with UPA treatment compared to treatment with either MTX or ADA. Thrombosis has also been observed with treatment with baricitinib, and recently determined to be a class related AE based on the interim analysis of the tofacitinib post-marketing required safety study. In the upadacitinib development program, adjudicated VTEs were reported at similar rates in UPA-treated patients and patients treated with PBO, MTX and ADA in the short-term period. Risk of VTEs were not dose-dependent with long-term exposure. Overall, the safety profile of upadacitinib is consistent with what has been observed with other JAK inhibitors, and other immunosuppressive agents used to treat rheumatoid arthritis, and are therefore not issues that necessarily preclude approval.

9. Advisory Committee Meeting

An advisory committee meeting was not held for this application. No issues were identified warranting advisory committee input. The efficacy of upadacitinib in rheumatoid arthritis was clear and substantial, with an acceptable safety profile, consistent with the safety profile of approved JAK inhibitors.

10. Pediatrics

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Polyarticular juvenile idiopathic arthritis (PJIA) has been considered the juvenile equivalent of adult rheumatoid arthritis, and thus a study in PJIA patients would be required by the Pediatric Research Equity Act (PREA) if this NDA in RA patients is approved. With this NDA, AbbVie submitted a pediatric assessment consistent with the agreed initial Pediatric Study Plan. The pediatric assessment included a request for a partial waiver for children under 2 years of age, because studies in this age group are impossible or highly impracticable due to the rarity of PJIA in children under 2 years of age. A deferral was requested for children ages 2 to < 18 years of age until the results of the juvenile rat studies and safety data from the adult development program are available. The proposed pediatric assessment includes the following studies:

- A multiple dose pharmacokinetic study in children from 2 to less than 18 years of age with active PJIA to determine the appropriate dosing regimen comparable to optimal efficacious and safe dose in adults
- 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 active PJIA
In addition, the Applicant plans to conduct a randomized withdrawal, double-blind, placebo-controlled study in patients with active systemic juvenile idiopathic arthritis in children 1 to <18 years of age. This study does not address a PREA requirement.

The upadacitinib pediatric program was reviewed by the Pediatric Review Committee (PeRC) meeting on July 10, 2019. The PeRC agreed with the requested waiver and deferrals.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**

Review of the application did not raise concerns of any wrongful acts that raise significant questions regarding data reliability.

- **Exclusivity or patent issues of concern**

There are no exclusivity and patent issues of concern with this application.

- **Financial disclosures**

The Applicant submitted acceptable financial disclosure statements. Forty-one investigators had disclosable financial interests/arrangements, however, none received compensation for conducting the study where the value could be influenced by the outcome of the study, received significant payments of other sorts, had proprietary interest in the product being tested, nor had significant equity interest in the sponsor covered study. The number of patients enrolled at the individual investigator sites were small compared to the total number of patients enrolled in the overall study. Furthermore, the multi-center and blinded nature of the studies make it unlikely that the financial interest could have influenced or biased the results of these studies.

- **Other Good Clinical Practice (GCP) issues**

There are no GCP issues with this application. All studies were conducted in accordance with accepted ethical standards.

- **Office of Scientific Investigations (OSI) audits**

OSI audited 3 clinical sites selected based on high enrollment, better efficacy, participating in multiple studies used to support this application, and financial disclosure. Final reports of the
DSI inspections revealed adherence to Good Clinical Practices. Minor deficiencies were noted, but these were isolated and deemed unlikely to impact data integrity and patient safety. During review of the submission no irregularities were found that would raise concerns regarding data integrity.

- Any other outstanding regulatory issues

None

12. Labeling

- Proprietary name

The proposed proprietary name for upadacitinib is Rinvoq. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and by the Office of Prescription Drug Promotion (OPDP) and found to be acceptable.

- Physician Labeling

The label was reviewed by various disciplines of this Division, OPDP, and DMPP. Various changes to different sections of the label were done to reflect the data accurately and better communicate the findings to health care providers. Major issues with the originally-proposed labeling (version submitted December 18, 2018) are as follows:

- INDICATIONS AND USAGE:
  Proposed indication

The proposed indication statement suggests

Therefore, the indication statement was revised to “TRADENAME is a Janus kinase (JAK) inhibitor for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response to or intolerance to methotrexate.”

- DOSAGE AND ADMINISTRATION: “The recommended dose of TRADENAME is 15 mg once daily.”
  - The Applicant-proposed dosage regimen is appropriate based on the efficacy and safety findings in the clinical studies.
Consistent with the recommendations of the clinical pharmacology review team, the PI includes statements that treatment is not recommended for use in patients with severe hepatic impairment (Section 2.2), and exposure is decreased when co-administered with strong CYP3A inducers (such as rifampin) which may lead to reduced therapeutic effect (7.2). The Applicant has proposed a statement however, this language was strengthened based on the 61% decrease in upadacitinib AUC which may result in inefficacious concentrations.

- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS:
  - BOXED WARNING
    - Based on risks of thrombosis observed with approved JAK inhibitors, a class boxed warning regarding the risk of thrombosis will be added.
    - In the upadacitinib program, there was a dose dependent increase in risk of malignancy for NMSC, and there is a potential for an increased risk of malignancy based on the mechanism of action of upadacitinib. Therefore, consistent with the labeling of other JAK inhibitors, the risk of malignancy will be included in the Boxed Warning section.
  - WARNINGS AND PRECAUTIONS
    - The risk of embryo-fetal toxicity was added to the Warnings and Precautions based on the results of the nonclinical embryo-fetal toxicity studies and the relatively small clinical exposure margins. Language was added to advise females of reproductive potential to use effective contraception.
    - Based on the safety data observed in the upadacitinib program and the labeling of other JAK inhibitors, the risks of hepatitis B reactivation and GI perforations will be included.
    - The Laboratory Parameters subsection was revised to include recommended monitoring and management for laboratory abnormalities.

- ADVERSE REACTIONS
  - In Section 6.1 Clinical Trials Experience, safety data should be presented for placebo controlled periods and methotrexate controlled periods comparing upadacitinib 15 mg, upadacitinib 30 mg, and placebo/methotrexate. Since there is no long term placebo or methotrexate controlled data, exposure adjusted incidence or event rates should be presented for upadacitinib 15 mg and upadacitinib 30 mg through 12 months. The 12 month exposure will be derived from the “Any Ph 3 UPA 15 mg and 30 mg” integrated analysis set. Note, Study M14-465 is not included in this analysis set as this study did not include an UPA 30 mg arm.

- CLINICAL STUDIES
In M14-465, ACR20 response over time to be presented only up to Week 14, prior to escape, to provide the most appropriate interpretation for comparison between upadacitinib with placebo.

Additional considerations on specific claims:
- Inclusion of the FACIT-F as a measure of fatigue, as discussed in the Efficacy Findings section above. The Clinical Outcomes Assessment (COA) team determined that the FACIT-F is fit-for-purpose, in the context of this drug development program, to measure and support labeling claims related to the concepts of fatigue associated with RA. This is of note because FACIT-F, and other patient reported outcomes to assess fatigue, have not previously been included in labeling for drugs for rheumatoid arthritis.

Other Labeling
- Patient labeling (i.e., Medication Guide, Patient Information, Instructions for Use)

Revisions to the Medication Guide were made for consistency with the Prescribing Information. Minor edits and formatting revisions were incorporated based on the patient labeling review team recommendations.

- Carton and container labeling

These were reviewed by various disciplines of this Division, and DMEPA, and found to be acceptable after agreement to relocate the container labels “EXP/LOT” text next to the expiration date and lot number in the black space of the label.
13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

A REMS is not recommended based on the submitted data. The information necessary to use upadacitinib safely and effectively will be provided through prescribing information and patient labeling.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

JAK inhibitors currently approved for rheumatoid arthritis were approved with post-marketing required safety studies to further evaluate safety signals with this new therapeutic class that were not adequately quantified in the pre-marketing studies. Specifically, as described below, post-marketing studies were required for additional assessment of dose- and exposure-related increased safety risks to further characterize the safety of higher doses proposed for marketing for which the benefit-risk has been a specific concern.

Tofacitinib was the first JAK inhibitor approved in the US for RA. Because of dose related safety concerns noted in the tofacitinib program (5 mg and 10 mg), e.g. herpes zoster, malignancies, and laboratories abnormalities, including an increase in lipid parameters, the 5 mg dose was approved in the US. Given the safety issues identified in the clinical program and concern regarding adverse CV outcomes with the increase in lipid parameters, a postmarketing safety trial was required to evaluate the risk of MACE, serious infections, including opportunistic infections, and malignancies with treatment of tofacitinib.

Baricitinib was the second JAK inhibitor approved in the US for RA. For baricitinib, there were 2 doses evaluated in the phase 3 program – 2 mg and 4 mg. Because of a signal of VTE (and other dose related safety concerns) with the 4 mg dose of baricitinib, the 2 mg dose of baricitinib was approved for RA. However, given the limited size of the safety database with the 2 mg dose, there was uncertainty about the VTE risk and other serious adverse events of special interest. Thus, a post marketing safety trial was required to evaluate the risk of VTE, as well as MACE, opportunistic infections, and malignancy with treatment of baricitinib.

In terms of the upadacitinib program and the determination of whether a PMR is warranted, we note that the use of upadacitinib was associated with lipid elevations, but not associated with an increase in MACE. As noted above, in the past we have required dedicated CVOT for lipid elevations with the approved JAK inhibitors and other products. However, more recently, based on concerns regarding feasibility of conducting the large trials necessary to answer the question of whether the increase in cholesterol was associated with an effect on MACE, and due to concerns about interpretation of a CVOT given that patients may receive treatment for elevated lipids during the course of the study, post-marketing CVOTs were not required. Respectively, a dedicated CVOT to assess the risk of MACE from the upadacitinib-induced lipid elevations is not warranted.
While dose-dependent toxicities were also seen in the upadacitinib clinical program, as described in this memorandum above, there were no new or unique safety signals identified in the upadacitinib development program that were not already described in the product labeling of the currently approved JAK inhibitors for RA. The risk of thrombosis is now considered a class safety issue as described in Section 8 Special safety concerns above. The potential risks of thrombosis and malignancy are included as boxed warnings in the prescribing information, consistent with class labeling. Further, the Applicant has proposed only the lower 15 mg dose, which had a more favorable benefit-risk assessment, for marketing. Therefore, no additional post-marketing safety study is warranted for upadacitinib.

As discussed in Section 10, there will be clinical post-marketing requirement (PMR) studies to address PREA, as follows:

1. A multiple-dose pharmacokinetic study in children 2 to less than 18 years of age with juvenile idiopathic arthritis
2. 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

14. **Recommended Comments to the Applicant**

The regulatory action will be Approval. There are no comments for AbbVie.
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.

/s/

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