

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**211675Orig1s000**

**OTHER REVIEW(S)**

## CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

<b>COA Tracking ID:</b>	C2019037
<b>NDA Number:</b>	211675
<b>Referenced IND for NDA/BLA:</b>	114717
<b>Applicant:</b>	AbbVie
<b>Established Name/Trade Name:</b>	Upadacitinib
<b>Indication:</b>	Rheumatoid arthritis
<b>Meeting Type/Deliverable:</b>	Advice Letter/Advice to Division
<b>Review Division:</b>	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
<b>Clinical Reviewer</b>	Keith Hull
<b>Clinical Team Leader (TL)</b>	Rachel Glaser
<b>Review Division Project Manager:</b>	Phuong Nina Ton
<b>COA Reviewer:</b>	Onyeka Illoh, OD, MPH
<b>COA TL:</b>	Wen-Hung Chen, PhD
<b>COA Associate Director:</b>	Elektra Papadopoulos, MD, MPH
<b>Date Consult Request Received:</b>	01/25/2019
<b>Date COA Review Completed:</b>	08/08/2019

*Please check all that apply:*

- Rare Disease/Orphan Designation  
 Pediatric

### A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) regarding NDA 211675 for upadacitinib. The Applicant is seeking an approval for upadacitinib for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to (b) (4)

The Applicant utilized the following patient-reported outcome (PRO) assessments in their randomized, double-blind, parallel group, placebo-controlled/active comparator-controlled, multi-center Phase 3 clinical trials (Studies M14-465, M13-542, M13-549, M13-545, and M15-555) in adult patients with moderately to severely active rheumatoid arthritis:

**Table 1.** PRO Instruments included in the Pivotal Phase 3 Clinical Trials

<b>COA Name (COA Type)</b>	<b>Concept(s)</b>	<b>Endpoint Position<sup>1</sup></b>
Disability Index of Health Assessment Questionnaire (HAQ-DI)	Physical Function	Secondary
36-Item Short Form, Version 2 (SF-36 v2)	General health status	Secondary
Functional Assessment of Chronic Illness Therapy-Fatigue Version 4 (FACIT-F)	Fatigue	Secondary
Morning Stiffness Measure	Morning stiffness duration	Secondary

The Applicant seeks COA-related labeling claim. The targeted COA-related labeling claims are listed in section C3.4 of this review.

This submission included an evidence dossier for the included PRO assessments. DPARP seeks COA Staff input on the adequacy of the PRO assessments, specifically the FACIT-F and (b) (4) to support labeling claims. As such, the subject of this review is restricted to the FACIT-F (b) (4)

The review concludes that the evidence submitted by the Applicant seems adequate to demonstrate that the FACIT-F is fit-for-purpose<sup>2</sup>, in the context of this drug development program, to measure and support labeling claims related to the concepts of fatigue associated with RA.



The participants from the patient interview study commented that Item 3 (I feel listless) and Item 10 (I am too tired to eat) were not as relevant to their fatigue symptoms. Therefore, we also recommend that a sensitivity analysis be conducted by removing Items 3 and 10 from FACIT-F to examine whether the results are consistent with those of the full FACIT-F.

<sup>1</sup> Please see Section C 1.3 of this COA review for the complete endpoint hierarchy.

<sup>2</sup> Fit-for-purpose: A conclusion that the level of validation associated with a tool is sufficient to support its context of use. (Source: BEST (Biomarkers, Endpoints and Other Tools) Resource; <https://www.ncbi.nlm.nih.gov/books/NBK338448/>)

## B. CLINICAL OUTCOME ASSESSMENT REVIEW

### 1 BACKGROUND AND MATERIALS REVIEWED

Upadacitinib is an oral JAK-1 inhibitor being developed for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA), either alone or in combination with methotrexate (MTX) or other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).

RA is a chronic systemic inflammatory autoimmune disease with an estimated prevalence of approximately 1%. RA is more frequent in women. The hallmark feature of RA is polyarticular joint swelling and tenderness caused by progressive inflammatory synovitis, which can result in severe, debilitating disease.

#### Materials reviewed:

- FACIT-F dossier
- (b) (4) dossier
- Clinical Overview in the NDA submission

### 2 FIT-FOR-PURPOSE SUMMARY

**Table 2.** Fit-for-purpose assessment (based on available evidence)

COA Name(s)	COA sufficient to support the context of use	Supported by:	Location of Supporting Materials
a) FACIT-F	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Potentially - insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input checked="" type="checkbox"/> Fit for regulatory purposes (i.e., COA can be linked to a clinical benefit attributable to the treatment) <input checked="" type="checkbox"/> Evidence of content validity <input checked="" type="checkbox"/> Face validity (concepts/items appear relevant, e.g., based on discussion with clinical reviewer, clinician input, etc.) <input checked="" type="checkbox"/> COA well-defined and concept is able to be accurately communicated <input checked="" type="checkbox"/> COA is sensitive to detect change <input checked="" type="checkbox"/> COA is culturally adapted and adequately translated, if appropriate	FACIT-F dossier

(b) (4)

COA Name(s)	COA sufficient to support the context of use	Supported by:	Location of Supporting Materials
(b) (4)			

### 3 CONTEXT OF USE

#### 3.1 Clinical Trial Population

The target population for Studies M14-465 (SELECT COMPARE), M13-542 (SELECT BEYOND), M13-549 (SELECT NEXT), M13-545 (SELECT EARLY), and M15-555 (SELECT MONO), the phase 3 studies, are adult female and male subjects who are at least 18 years of age with a diagnosis of RA for  $\geq 3$  months who fulfill the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA. Eligible study subjects must have  $\geq 6$  swollen joints (based on 66 joint counts) and  $\geq 6$  tender joints (based on 68 joint counts) at Screening and Baseline Visits, and high-sensitivity C-reactive protein (hsCRP)  $\geq 5$  mg/L (central lab, upper limit of normal [ULN] 2.87 mg/L) at Screening. The studies included subjects who were naïve to MTX, those who had an inadequate response to MTX and/or other csDMARDs, and those who were refractory or had intolerance to treatment with one or more biologic DMARDs (bDMARDs).

Details of the inclusion and exclusion criteria can be found in the full clinical study protocols in Appendix A of the (b) (4) dossier.

#### 3.2 Clinical Trial Design

Table 3 summarizes the clinical trial design of Studies M14-465, M13-542, M13-549, M13-545, and M15-555.

**Table 3.** Clinical Trial Design for Studies M14-465, M13-542, M13-549, M13-545, M15-555

Trial Phase	Trial Design	Trial Duration	Registration Intent
Phase 3	<input type="checkbox"/> Single arm <input type="checkbox"/> Open label <input checked="" type="checkbox"/> Double-blind <input checked="" type="checkbox"/> Randomized <input checked="" type="checkbox"/> Placebo-/Vehicle-controlled <input checked="" type="checkbox"/> Active comparator-controlled <input type="checkbox"/> Cross-over <input checked="" type="checkbox"/> Multinational <input type="checkbox"/> Non-inferiority	12 – 48 weeks	Yes

**Reviewer's comment(s):** Refer to the full clinical study protocols in Appendices A.1 – A.5 of the <sup>(b) (4)</sup> dossier for more details on the clinical trial design.

### 3.3 Endpoint Position, Definition, and Assessment Schedule

Table 4 describes the primary and ranked COA secondary endpoints included in the 5 pivotal phase 3 studies.

**Table 4.** Primary and ranked COA secondary endpoints included in the 5 pivotal phase 3 studies

Endpoint Position	Endpoint Definition (Assessment Schedule)				
	Study M13-545	Study M13-549	Study M14-465	Study M15-555	Study M13-542
Primary	ACR50 (Week 12)	ACR20 (Week 12)	ACR20 (Week 12)	ACR20 (Week 1)	ACR20 (Week 12)
Secondary (COA only) ☒ Ranked: 2	ΔHAQ-DI (Week 12)	ΔHAQ-DI (Week 12)	--	ΔHAQ-DI (Week 14)	--
Secondary (COA only) ☒ Ranked: 3	--	ΔSF-36 PCS (Week 12)	ΔHAQ-DI (Week 12)	ΔSF-36 PCS (Week 14)	ΔHAQ-DI (Week 12)
Secondary (COA only) ☒ Ranked: 5	--	--	ΔSF-36 PCS (Week 12)	--	--
Secondary (COA only) ☒ Ranked: 6	ΔSF-36 PCS (Week 12)	--	--	ΔMorning stiffness duration (Week 14)	ΔSF-36 PCS (Week 12)
Secondary (COA only) ☒ Ranked: 7	--	ΔMorning stiffness duration (Week 12)	--	--	--
Secondary (COA only) ☒ Ranked: 8	--	ΔFACIT-F (Week 12)	--	--	--
Secondary (COA only) ☒ Ranked: 9	--	--	ΔMorning stiffness duration (Week 12)	--	--
Secondary (COA only) ☒ Ranked: 10	--	--	ΔMorning stiffness duration (Week 12)	--	--

Δ=Change from baseline; ACR20/50=American College of Rheumatology 20/50 response; HAQ-DI=Disability Index of Health Assessment Questionnaire; SF-36 PCS=36-Item Short Form physical component score; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue

**Reviewer's comment(s):** Refer to the full clinical study protocols in Appendices A.1 – A.5 of the (b) (4) dossier for full details of the endpoints used in the studies.

### 3.4 Labeling or promotional claim(s) based on the COA

The Applicant seeks the following PRO-related labeling claim for the FACIT-F:



**Reviewer's comment(s):** The FACIT-F appears to be adequate to support labeling claims related to fatigue associated with RA as many items appear clinically relevant and meaningful to patients, and showed improvement. (b) (4)

See Section C.7 for additional details on the content validity of the FACIT-F (b) (4)

## 4 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

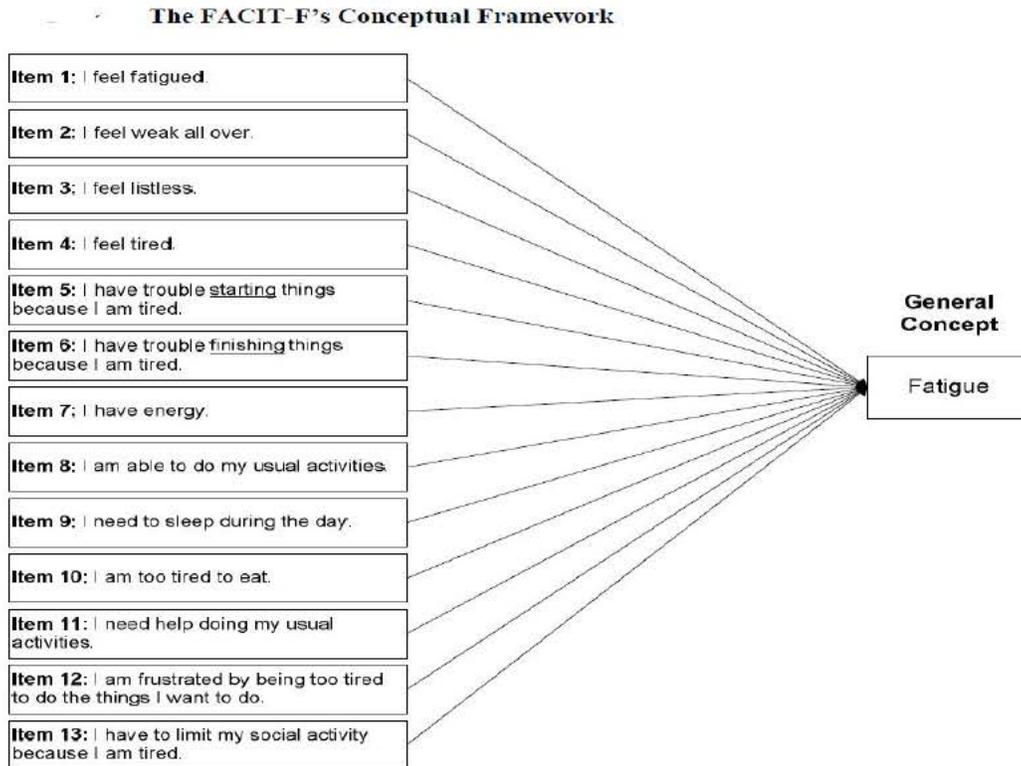
The concepts of interest for the FACIT-F (b) (4) are summarized in Table 5.

**Table 5.** Concepts of Interest for the FACIT-F (b) (4)

COA name	Concept(s)
Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F)	Fatigue

The conceptual framework(s) for the FACIT-F (b) (4) are shown in Figures 1 and 2 below respectively.

Figure 1: Conceptual Framework for FACIT-F



(b) (4)

## 5 CLINICAL OUTCOME ASSESSMENT(S)

### Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)

The FACIT-F is a 13-item measure designed to assess the impact of fatigue over the past 7 days (see Appendix 1). Items are rated on a 5-point Likert scale from 0 (not at all) to 4 (very much).

(b) (4)

*Reviewer's comment(s): Of note, the FACIT-F was initially developed as a cancer disease-specific instrument. It was developed as a subscale for the Functional Assessment of Cancer Therapy (FACT) Measurement System that was targeted to patient concerns associated with having anemia.*

## 6 SCORING ALGORITHM

### FACIT-F

The scoring guide identifies those items that must be reversed before being added to obtain subscale totals. Negatively stated items are reversed by subtracting the response from “4”. After reversing proper items, FACIT-F scale score is then calculated by adding up all item scores, multiplied by 13 and divided by the number of items answered. The scale score is ranged from 0 to 52 and the higher the score, the better the quality of life.

If there are missing items, the scale score can be prorated (as long as more than 50% of the items were answered). This is done by multiplying the sum of the item scores by the number of items in the subscale, then dividing by the number of items actually answered:

Prorated subscale score = [Sum of item scores]×[N of items in subscale]÷[N of items answered]

(b) (4)

## 7 CONTENT VALIDITY

To date, the following information has been submitted (check all that apply):

- Copy of instruments
- Literature review and/or publications
- Documentation of expert input
- Qualitative study protocols and interview guides for focus group or patient interviews
- Chronology of events for item generation, modification, and finalization (item tracking matrix)
- Synopsis of qualitative findings
- Qualitative summary report with evidence to support item relevance, item stems and response options, and recall period
- Quantitative summary report with evidence to support item retention and scoring
- Transcripts (if available)

Tables 6 and 7 document the adequacy of the content of the FACIT-F

(b) (4)

(b) (4)

**Table 6.** Review of Content Validity for FACIT-F

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Face validity	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	<input checked="" type="checkbox"/> Literature <input checked="" type="checkbox"/> Clinical input e.g. discussion with clinical reviewer	FACIT-F Dossier (Page 21 – 29)
Content validity	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Potentially – insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input checked="" type="checkbox"/> The item concepts are relevant/important to target patient population and appropriate to the study design and objectives <input checked="" type="checkbox"/> The instrument is comprehensive with respect to the concept (i.e., does not omit important content) <input checked="" type="checkbox"/> Target sample for qualitative research is appropriate. <input checked="" type="checkbox"/> Studied sample for qualitative research adequately represents the target patient population <input checked="" type="checkbox"/> Instructions, item stems, recall period, and response options well understood and appropriate for the study design and objectives <input checked="" type="checkbox"/> Response options appropriate for the item stems (measure the same dimensions, such as frequency or intensity) <input checked="" type="checkbox"/> COA is culturally adapted and adequately translated <input checked="" type="checkbox"/> Descriptive statistics (if available) support content relevance <input checked="" type="checkbox"/> Other (see Reviewer’s comments)	FACIT-F Dossier (Page 1745 – 1758)

**Table 7. Review of Content Validity** (b) (4)

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Face validity	(b) (4)		
Content validity			

Evidence of content validity of the FACIT-F (b) (4) was derived from:

- Literature review
- Clinical expert interviews; n = 3 rheumatologists
- Patient interviews; n = 22 patients (See Table 8 for patient demographics and characteristics). The first 6 interviews were strictly concept elicitation, while the remaining were combined concept elicitation and cognitive interviews.

Table 8 shows the demographics and characteristics of the patients from the qualitative study.

**Table 8.** Patient Demographics/Characteristics from AbbVie’s Qualitative Study

<b>Patient Demographics/Characteristics</b>	<b>N =22</b>
<b>Age</b> mean (range)	56.4 (39 – 71)
<b>Gender</b>	
Female	20 (90.9%)
Male	2 (9.1%)
<b>Race</b>	
White Caucasian	13 (59.0%)
Black/African	7 (31.8%)
Other	1 (4.5%)
Prefer not to answer	1 (4.5%)
<b>Ethnicity</b>	
Hispanic	1 (4.5%)
Not Hispanic	21 (95.5%)
<b>Education</b>	
High school diploma/GED	5 (22.7%)
Some college	11 (50.0%)
Associate’s degree	2 (9.1%)
Bachelor’s degree	3 (13.6%)
Graduate degree	1 (4.5%)
<b>Employment Status</b>	
Employed Full Time	13 (59.1%)
Employed Part Time	2 (9.1%)
Permanently unable to work (long-term sickness/disability)	3 (13.6%)
Retired	4 (18.2%)
<b>Years Living with RA</b> Mean (Range)	13.5 (2 mos – 33 yrs)
<b>Level of Disease Severity</b>	
Moderate	19 (86.4%)
High	3 (13.6%)

### **Concept Elicitation**

The results of the first six concept elicitation interviews showed that the most commonly reported symptoms mentioned by patients were stiffness (n=22), pain (22), fatigue (n=19), and swelling (n=18). Others included heat (n=9), sweating (n=2), and joint degeneration (n=1). Overall, 3 out of 22 participants stated they did not experience fatigue as part of their RA.

The remaining sixteen interviews included a shorter concept elicitation component that allowed patients to describe all their RA-related symptoms and impacts before being asked to focus on the morning stiffness and fatigue measures.

### **Cognitive Interviews**

During the cognitive interviewing section, patients were asked to evaluate the FACIT-F (b) (4)

(b) (4):

- **FACIT-F:** Results from the cognitive interviews conducted by Kaiser et al. highlighted two items that could potentially be dropped due to irrelevance (Item 3: “I feel listless (washed out)” and Item 10: “I feel too tired to eat”) in the RA patient population. The two specific items were then probed for clarity and relevance in AbbVie’s patient interviews

(n=22). It was revealed that half the participants stated that they would not use the words, “listless or washed out” to describe their experience while 17 participants did not report they “feel too tired to eat”.

Overall, all the participants had no issue comprehending and answering the questionnaire.



***Reviewer’s comment(s):*** Results from the concept elicitation interviews indicated that concept coverage was broad, but included symptoms and impacts that were highly relevant to patients with RA. Concept saturation was reached for all core RA symptoms and symptom impacts during the patient interviews.

Results from the cognitive interviews indicated that many items in the FACIT-F (b) (4) (b) (4) appear clinically relevant and meaningful to patients. However, two FACIT-F items (3 and 10) were found less relevant to RA fatigue. This review recommends that a sensitivity analysis be conducted by removing Items 3 and 10 from FACIT-F to examine whether the results are consistent with those of the full FACIT-F.



## 8 OTHER MEASUREMENT PROPERTIES

To date, the following information has been submitted (check all that apply):

- Literature review and/or publications
- Quantitative analysis synopsis
- Full quantitative analysis plan
- Quantitative summary report with evidence to support reliability, construct validity, ability to detect change and scoring

The quantitative analyses are adequate and are consistent with the following:

- Pre-specified hypothesized relationships among variables tested
- Pre-specified estimates for reliability
- Appropriate anchors (e.g., global scales) for evaluation of meaningful change.

Table 9 documents the adequacy of the other measurement properties of the FACIT-F.

**Table 9.** Review of Other Measurement Properties for FACIT-F

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Reliability	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Potentially – insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input checked="" type="checkbox"/> Internal consistency reliability estimates in acceptable range (e.g., Cronbach’s $\alpha > 0.70$ ) <input checked="" type="checkbox"/> Test-retest reliability (or intra-rater reliability) estimates in acceptable range (e.g., ICC $\geq 0.70$ ) <input checked="" type="checkbox"/> Other (see Reviewer’s comments)	FACIT-F Dossier (Page 30 – 44)
Construct validity	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Potentially – insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input checked="" type="checkbox"/> Relationship to other assessments with similar concepts is as expected <input checked="" type="checkbox"/> Relationship to other assessments with dissimilar concepts is as expected <input checked="" type="checkbox"/> COA differentiates between clinically distinct groups (i.e., known groups validity) <input checked="" type="checkbox"/> COA scores are related to a known gold standard assessment of the same concept <input checked="" type="checkbox"/> Other (see Reviewer’s comments)	
Ability to detect change	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Potentially – insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input checked="" type="checkbox"/> COA can identify differences in scores over time in individuals or groups who have changed with respect to the concept <input checked="" type="checkbox"/> Other (see Reviewer’s comments)	

## **FACIT-F**

Supportive data for the reliability (i.e. internal consistency), validity (i.e. convergent and known-groups validity), and ability to detect change for the FACIT-F in the RA patient population were derived from published literature. Supplemental analyses were also conducted on data from Study M13-537 to assess test-retest reliability and convergent/divergent validity. Results from the psychometric validation analyses showed:

- A high internal consistency at baseline, Week 12, and Week 24 (Cronbach's alpha = 0.86 to 0.87) <sup>3</sup>
- An acceptable test-retest reliability (between the Baseline and Week 4 scores) based on an Intraclass Correlation (ICC) of 0.78 using data from Study M13-537.
- A statistically significant strong correlations ( $r > 0.50$ ,  $p < 0.001$ ) between FACIT-F and all the hypothesized relevant measures thereby demonstrating excellent convergent validity for FACIT-F. From Study M13-537, divergent validity was supported by weaker correlations ( $r < 0.50$ ,  $p < 0.001$ ) between FACIT-F and EQ-5D-5L VAS, PtGA, and PhGA.
- Changes in the FACIT-F scores over 24 weeks successfully discriminated between groups defined by levels of the clinical endpoint, the ACR20, ACR50, and ACR70. Patients in ACR groups who reflected greater clinical improvement in RA also showed larger increases in their FACIT-F scores, indicating decreased levels of fatigue. <sup>4</sup>

(b) (4)

*Reviewer's comment(s): Overall, the FACIT-F* (b) (4) *demonstrated acceptable psychometric properties.* (b) (4)

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3 Cella D, Yount S, Sorensen M, et al. Validation of the functional assessment of chronic illness therapy fatigue scale relative to other instrumentation in patients with rheumatoid arthritis. *Journal of Rheumatology* 2005; 32(5):811-9.

## 9 INTERPRETATION OF SCORES

To date, the following information has been submitted (check all that apply):

- Anchor-based analyses
- Anchor-based empirical cumulative distribution function (eCDF) curves
- eCDF study arm curves (Treatment vs. Placebo/Active Comparator)
- Anchor-based probability density function (PDF) curves
- PDF study arm curves (Treatment vs. Placebo/Active Comparator)
- Qualitative support for meaningful change (e.g., patient input)

Table 10 documents the adequacy of the score interpretability of the FACIT-F.

**Table 10.** Review of Score Interpretability for the FACIT-F

COA Attribute	Attribute sufficiently established	Supported by:	Location of Supporting Materials
Score Interpretability	<input type="checkbox"/> Yes <input type="checkbox"/> Potentially – insufficient evidence available; additional information is needed <input checked="" type="checkbox"/> No	<input type="checkbox"/> Appropriate global anchor scales were included for anchor-based analyses <input type="checkbox"/> Threshold(s) for within-patient meaningful change identified (anchor-based methods) <input type="checkbox"/> Threshold(s) for within-patient meaningful change identified (eCDF/PDF curves) <input type="checkbox"/> Qualitative data supports meaningful change threshold(s) (e.g., cognitive interviews, exit surveys/interviews) <input checked="" type="checkbox"/> Other (see Reviewer’s comments)	FACIT-F Dossier (Page 45 – 58)

### **Estimates of Within-Patient Meaningful Change Scores for FACIT-F**

Analyses were performed on Study M13-549 data from baseline to week 12 to establish within-patient meaningful change scores for FACIT-F in the RA population using anchor-based methods (utilizing HAQ-DI and Patient’s Global Assessment of Disease Activity (PtGA) as anchors), distribution-based methods (estimates from SEM), Cumulative Distribution Functions (CDFs), and probability density functions (PDFs).

**Reviewer’s comment(s):** *The anchors used are not measuring similar concepts as FACIT-F (i.e. fatigue severity and impact). Because the anchors used are not appropriate, the results based on the anchor-based analyses is not acceptable.*

*For future studies, we recommend that anchor measures assessing fatigue are used for anchor-based analyses.*

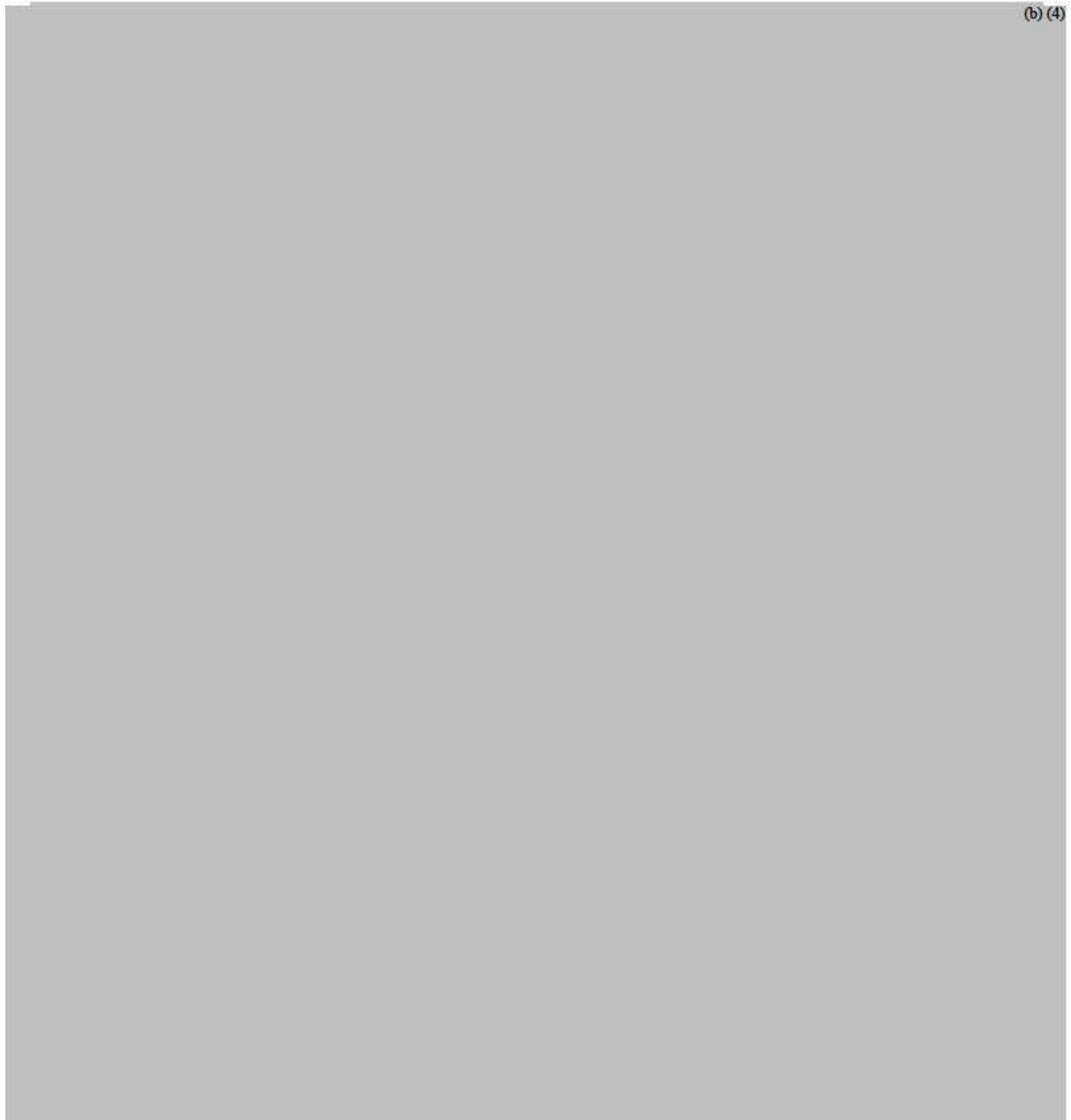
### **CDFs for FACIT-F Score Change by Treatment Arms**

The applicant submitted CDFs of the score changes for FACIT-F to evaluate the treatment differences across the three study arms in SELECT-NEXT (Study M13-549). The CDF plots show a clear differentiation between the curves for each of the two treatment groups and placebo.

*Reviewer's comment(s): Based on the CDFs, there is a clear separation between both treatment arms and placebo across the range of score changes. This result provides more confidence in the efficacy of the study treatment over placebo.*

## **D. APPENDICES**

### **Appendix 1: Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)**



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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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ONYEKACHUKWU A ILLOH

08/08/2019 11:12:35 AM

This review is the updated version of the review previously filed in DARRTS with a finalization date of 05/20/2019.

WEN-HUNG CHEN

08/08/2019 11:19:47 AM

Revised review to replace the May 2019 review.

ELEKTRA J PAPADOPOULOS

08/08/2019 11:36:15 AM

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MEMORANDUM  
REVIEW OF REVISED LABELS  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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Date of This Memorandum: August 6, 2019

Requesting Office or Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Application Type and Number: NDA 211675

Product Name and Strength: Rinvoq<sup>a</sup> (upadacitinib) extended-release oral tablets, 15mg

Applicant/Sponsor Name: AbbVie, Inc.

FDA Received Date: August 5, 2019

OSE RCM #: 2018-2751-2

DMEPA Safety Evaluator: Teresa McMillan, PharmD

DMEPA Team Leader: Lolita White, PharmD

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## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on August 5, 2019 for Rinvoq. Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the revised labels for Rinvoq (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>b</sup> In our review, we note that AbbVie accepted our recommendation to relocate the container labels “EXP/LOT” text next to the expiration date and lot number in the black space of the label. However, AbbVie proposed they retain the following expiration date format (DMMMYYYY).

## 2 CONCLUSION

We find AbbVie’s proposed container label acceptable and we have no additional recommendations at this time.

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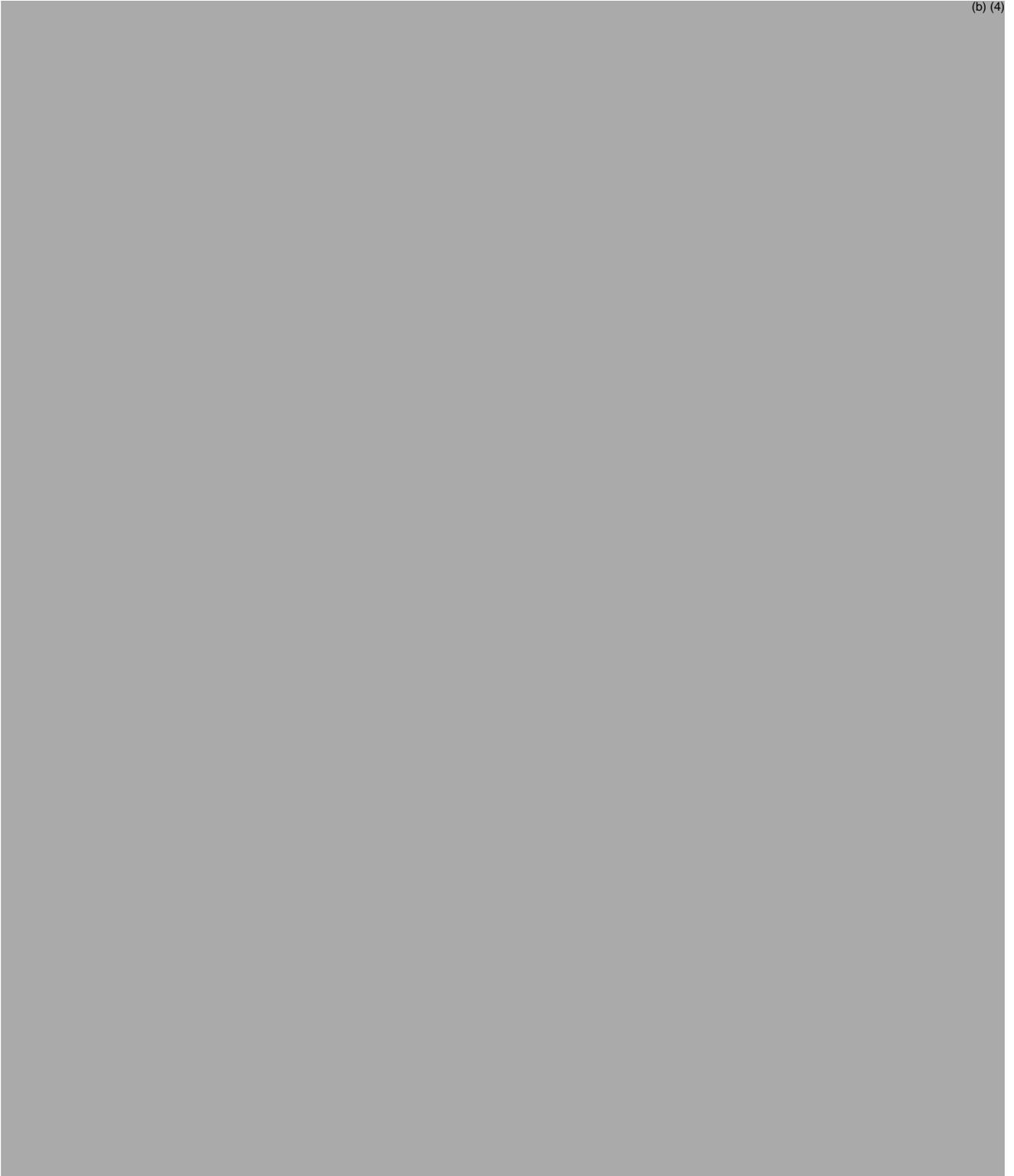
<sup>a</sup> The proposed proprietary name Rinvoq was found conditionally acceptable on March 5, 2019.

<sup>b</sup> McMillan T. Label and Labeling Review for Rinvoq (NDA 211675). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 23. RCM No.: 2018-2751-1.

APPEARS THIS WAY ON ORIGINAL

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON AUGUST 5, 2019

Container labels-(trade and professional sample) 14 count and 30 count



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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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TERESA S MCMILLAN  
08/06/2019 03:26:24 PM

LOLITA G WHITE  
08/06/2019 03:29:00 PM

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** July 31, 2019

**To:** Nina Ton, Pharm.D., Senior Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

**From:** Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Kathleen Klemm, Pharm.D., Team Leader, OPDP

**Subject:** OPDP Labeling Comments for Upadacitinib extended-release tablets, for oral use

**NDA:** 211675

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In response to DPARP's consult request dated January 7, 2019, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for Upadacitinib extended-release tablets, for oral use.

**PI and Medication Guide:** OPDP's comments on the proposed labeling are based on the draft PI and Medication Guide received by electronic mail from DPARP (Nina Ton) on July 17, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on July 25, 2019.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on July 19, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or [adewale.adeleye@fda.hhs.gov](mailto:adewale.adeleye@fda.hhs.gov).

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**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: July 25, 2019

To: Sally Seymour, MD  
Acting Director  
**Division of Pulmonary, Allergy, and Rheumatology  
Products (DPARP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Marcia Williams, PhD  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Maria Nguyen, MSHS, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Adewale Adeleye, Pharm.D., MBA  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): TRADENAME (upadacitinib)

Dosage Form and Route: extended-release tablets, for oral use

Application Type/Number: NDA 211675

Applicant: AbbVie Inc.

## 1 INTRODUCTION

On December 18, 2018, AbbVie Inc., submitted for the Agency's review, New Drug Application (NDA) 211675 TRADENAME (upadacitinib) extended-release tablets, for oral use. This NDA is under priority review with a proposed indication (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on January 7, 2019, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRADENAME (upadacitinib) extended-release tablets.

## 2 MATERIAL REVIEWED

- Draft TRADENAME (upadacitinib) MG extended-release tablets received on December 18, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 17, 2019.
- Draft TRADENAME (upadacitinib) extended-release tablets Prescribing Information (PI) received on December 18, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 17, 2019.
- Approved OLUMIANT (baricitinib) tablets, for oral use, comparator labeling dated May 31, 2018.
- Approved XELJANZ (tofacitinib) tablets, for oral use, comparator labeling dated October 18, 2018.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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DMPP-OPDP review of TRADENAME (upadacitinib) NDA 211675 MG

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MEMORANDUM  
REVIEW OF REVISED LABEL AND LABELING  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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Date of This Memorandum: July 23, 2019

Requesting Office or Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Application Type and Number: NDA 211675

Product Name and Strength: Rinvoq<sup>a</sup>(upadacitinib) extended-release oral tablets, 15 mg

Applicant/Sponsor Name: AbbVie, Inc

FDA Received Date: July 19, 2019

OSE RCM #: 2018-2751-1

DMEPA Safety Evaluator: Teresa McMillan, PharmD

DMEPA Team Leader: Lolita White, PharmD

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## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling and container labels received on July 19, 2019 for Rinvoq. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the revised labels and labeling for Rinvoq (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>b</sup>

## 2 CONCLUSION

The Applicant implemented our carton labeling and container label recommendation to relocate the net quantity statement away from the product strength. In regard to the other two recommendations, Abbvie has proposed to present the expiration date as the following on the carton labeling and container label: DMMMYYY and to maintain the "EXP/LOT" text on the container label due to lack of space. The revised container labels are unacceptable from a medication error perspective. We provide recommendations in Section 3 below.

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<sup>a</sup> The proposed proprietary name Rinvoq was found conditionally acceptable on March 5, 2019.

<sup>b</sup> Purcell J. Human Factors and Label and Labeling Review for Rinvoq (NDA 211675). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 12. RCM No.: 2018-2751 and 2018-2752.

### 3 RECOMMENDATIONS FOR ABBVIE, INC

We recommend the following be implemented prior to approval of this NDA supplement:

#### A. Container Label

The "EXP/LOT" text is not placed next to the expiration date and lot number. We are concerned the location of the "EXP/LOT" text as presented may pose risk of confusion and lead to degraded drug medication error. We recommend you relocate the "EXP/LOT" text next to the expiration date and lot number in the black space of the label. In addition, consider revising the expiration date format to the following:

EXP: YYYY-MMM

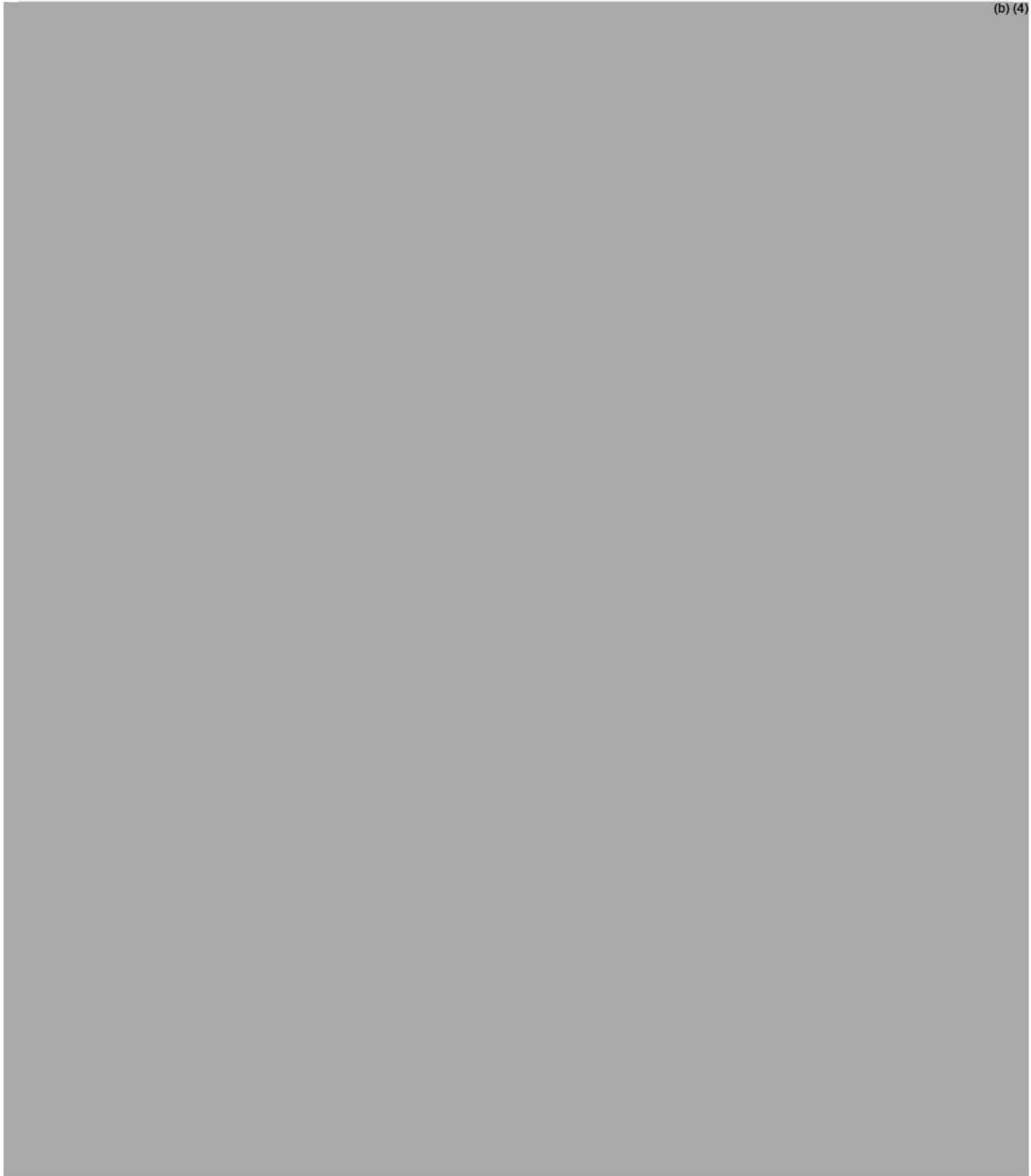
LOT:



**APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JULY 19, 2019**

**Container label (trade and professional sample) 14 count and 30 count**

**Sample container label provided in coverletter of submission to describe the expiration date and lot number location and format.**



(b) (4)

Carton labeling (trade and professional sample) 14 count and 30 count

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HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

\*\*\* This document contains proprietary information that cannot be released to the public\*\*\*

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Date of This Review:	July 12, 2019
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 211675
Product Type:	Single Ingredient Product
Drug Constituent Name and Strength	upadacitinib extended-release oral tablets, 15 mg
Rx or OTC:	Rx
Applicant/Sponsor Name:	AbbVie Inc.
Submission Date:	December 18, 2018 and June 10, 2019
OSE RCM #:	2018-2751 and 2018-2752
DMEPA Human Factors Evaluator:	Janine Purcell, MS
DMEPA Safety Evaluator(s):	Teresa McMillan, PharmD
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS

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## 1. REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under NDA 211675 for Rinvoq<sup>1</sup> (upadactinib) extended-release oral tablets, 15 mg. This is a single ingredient product with a (b) (4) cap which features a design element (b) (4). (b) (4) This product is intended to treat adults with moderately to severely active rheumatoid arthritis.

### 1.1. PRODUCT DESCRIPTION

Upadactinib is an orally administered medication for the treatment of Rheumatoid Arthritis. Upadactinib dosing consists of one 15 mg tablet once daily. The proposed packaging includes a carton and a high density polyethylene (HDPE) bottle cap (b) (4).

(b) (4) The bottle cap features a design element (b) (4). (b) (4)

(b) (4) The packaging is patient-centric having been specifically designed to improve the ease of opening the packaging for patients with impaired mobility of their hands, including patients with moderately to severely active rheumatoid arthritis. See Appendix A for more product information.

### 1.2. REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On December 18, 2018 AbbVie submitted a human factors validation study report, which is the subject of this review. The Agency has not received previous materials for human factors review for this product.

## 2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A

<sup>1</sup> The proposed proprietary name Rinvoq was found conditionally acceptable on March 5, 2019

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

### 3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provides a summary of the study design and one close call observed in the study (Table 2), and our analysis to determine if the results support the safe and effective use of the proposed product.

#### 3.1 SUMMARY OF STUDY DESIGN

The study design followed a simulated use methodology with the goal to ensure the intended users can safely and effectively use the proposed user interface (b) (4) in the intended home use environment. The study included 15 representative users who were patients with impaired mobility of their hands, including patients with moderately to severely active rheumatoid arthritis. The study evaluated two critical tasks: 1) (b) (4) and 2) Simulate taking a dose. For any observed errors for critical tasks, the moderator probed for root cause of the use error using open ended questions at the end of the session to determine root cause. We find the overall methodology acceptable.

### 3.2 RESULTS AND ANALYSES

Table 2 describes the study results, applicant's analyses of the results, and DMEPA's analyses and recommendations.

Table 2: Summary and Analyses of Study Results

Task	Number and Description of Close Call	Participant's Subjective Feedback	Applicant's Root Cause Analysis (RCA)	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
(b) (4)					



Task	Number and Description of Close Call	Participant's Subjective Feedback	Applicant's Root Cause Analysis (RCA)	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
					and we have no further recommendations at this time.

### 3.4. LABELS AND LABELING

Table 3 below includes the identified medication error issues with the submitted labels and labeling , our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 3: Identified Issues and Recommendations for AbbVie (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Container Labels and Carton Labeling			
1.	The net quantity is in close proximity to the product strength.	Product selection and dosing errors can occur due to the risk of numerical confusion between the net quantity and product strength.	Relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.
2.	The expiration date is not defined.	The expiration format is needed to help minimize confusion and reduce the risk for deteriorated drug medication errors.	We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
Container Labels			
1.	The lot number and expiration number are adjacent to one another.	As presented, the lot number and expiration date can be mistaken for one another.	Separate the expiration and lot number so they appear on separate lines. For example: EXP: LOT:

#### 4. CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study identified one close call with the task (b) (4) (b) (4). However, our evaluation indicates that the residual risk has been reduced to as low as practically reasonable.

Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to AbbVie so that recommendations are implemented prior to approval of this NDA.

##### 4.1 RECOMMENDATIONS FOR ABBVIE

Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 3. We recommend that you implement these recommendations prior to approval of this NDA.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Upadacitinib that AbbVie submitted on December 18, 2018.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Selective Janus kinase (JAK) 1 inhibitor
Active Ingredient (Drug or Biologic)	Upadacitinib
Indication	(b) (4)
Route of Administration	oral
Dosage Form	Extended-release tablets
Strength	15 mg
Dose and Frequency	15 mg once daily
How Supplied	30- count bottles
Storage	Store at 2°C to 25°C (36°F to 77°F)
Container Closure/Device Constituent	<p>The packaging features a bottle that is packaged into a reverse tuck carton that requires minimal force to open. The high density polyethylene (HDPE) bottle is (b) (4) (b) (4) closed with a (b) (4) cap. (b) (4)</p> <p>The cap (b) (4) features a design element (b) (4)</p> <p>The carton includes a panel on the front face of the carton which can be opened to view information about how to use the (b) (4) feature.</p>
Intended Users	Rheumatoid arthritis patients
Intended Use Environment	Home, clinic, and/or hospital use

## APPENDIX B. BACKGROUND INFORMATION

### B.1. PREVIOUS HF REVIEWS

#### B.1.1 Methods

On April 1, 2019, we searched the L:drive and AIMS using the terms, Upadactinib to identify reviews previously performed by DMEPA or CDRH.

#### B.1.2 Results

Our search identified no previous reviews.

## APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

### C.1. Description of intended product users, uses, use environments, and training for commercial product

- Intended users: patients diagnosed with moderately to severely active Rheumatoid Arthritis (RA).
- Intended uses: Patients taking Rheumatoid Arthritis medication are likely to administer this medication in their home environment, on their own. The carton containing the pill bottle and its contents of a 30 day supply of this medication are transportable and do not require special handling or storage situations, such as refrigeration.
- Training: The study did not include training for the participants.

### C.2 Graphical depiction and written description of product user interface

The packaging features a bottle that is packaged into a reverse tuck carton that requires

minimal force to open. The high density polyethylene (HDPE) bottle is (b) (4)

(b) (4) closed with a (b) (4) cap. (b) (4)

(b) (4)

(b) (4) The cap features a design element (b) (4)

(b) (4)

(b) (4)

(b) (4) The carton includes a panel on the front face of the carton which can be opened to view information about how to use the (b) (4)

feature.

Photos of the proposed commercial packaging are shown below.



### C.3 Known use problems with previous models of the package and with similar packages

This new cap design is currently not in use, so there are no known use problems with previous models of this package.

Regarding similar packages, Pharmaceutical packaging use-related errors tend to be attributable to one of the following key facets of the packaging: 1) Discernibility, 2) Comprehension of dose amount, and 3) Comprehension of dose frequency.

Common use errors related to packaging among drug products include:

- Failure to fully comply with treatment regimen
- Failure to fully read instructions about proper administration

- Failure to read detailed information provided (i.e., in the prescribing information (PI) or medication guide).
- Misinterpretations of labeling and pictures provided with respect to dosage
  - Incorrect interpretation of dose amount
  - Incorrect interpretation of dose frequency

(b) (4)

C.4 A summary of preliminary analyses and evaluations, including formative studies and key findings and any changes made to product or labeling, including how the findings were used to update the user interface and risk analysis

AbbVie conducted four studies to evaluate successive iterative designs to arrive at the intend-to market product.

The background information is accessible in EDR via:

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#### APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report is accessible in EDR via:

<\\cdsesub1\evsprod\nda211675\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\rheumatoid-arthritis\5354-other-stud-rep\hf-validation-report\human-factors-summative-val-rpt.pdf>

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW We issued an Information Request (IR) on March 15, 2019 with a clarifying question about the moderator's script. The applicant's response was acceptable.

The IR is accessible in EDR via:

[https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804e4763&\\_afRedirect=2376114690034893](https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804e4763&_afRedirect=2376114690034893)

## APPENDIX F. LABELS AND LABELING

### F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>2</sup> along with postmarket medication error data, we reviewed the following Upadacitinib labels and labeling submitted by AbbVie.

- Container label (trade and professional sample) received on June 10, 2019
- Carton labeling (trade and professional sample) received on June 10, 2019
- (b) (4) received on December 18, 2018
- Prescribing Information (Image not shown) received on December 18, 2018

### F.2 Label and Labeling Images

Container label (trade and professional sample) 14 count and 30 count



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<sup>2</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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## CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

<b>COA Tracking ID:</b>	C2019037
<b>NDA Number:</b>	211675
<b>Referenced IND for NDA/BLA:</b>	114717
<b>Applicant:</b>	AbbVie
<b>Established Name/Trade Name:</b>	Upadacitinib
<b>Indication:</b>	Rheumatoid arthritis
<b>Meeting Type/Deliverable:</b>	Advice Letter/Advice to Division
<b>Review Division:</b>	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
<b>Clinical Reviewer</b>	Keith Hull
<b>Clinical Team Leader (TL)</b>	Rachel Glaser
<b>Review Division Project Manager:</b>	Phuong Nina Ton
<b>COA Reviewer:</b>	Onyeka Illoh, OD, MPH
<b>COA TL:</b>	Wen-Hung Chen, PhD
<b>COA Associate Director:</b>	Elektra Papadopoulos, MD, MPH
<b>Date Consult Request Received:</b>	01/25/2019
<b>Date COA Review Completed:</b>	05/06/2019

*Please check all that apply:*

- Rare Disease/Orphan Designation  
 Pediatric

### A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) regarding NDA 211675 for upadacitinib. The Applicant is seeking an approval for upadacitinib for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance [REDACTED] (b) (4)

The Applicant utilized the following patient-reported outcome (PRO) assessments in their randomized, double-blind, parallel group, placebo-controlled/active comparator-controlled, multi-center Phase 3 clinical trials (Studies M14-465, M13-542, M13-549, M13-545, and M15-555) in adult patients with moderately to severely active rheumatoid arthritis:

**Table 1.** PRO Instruments included in the Pivotal Phase 3 Clinical Trials

<b>COA Name (COA Type)</b>	<b>Concept(s)</b>	<b>Endpoint Position<sup>1</sup></b>
Disability Index of Health Assessment Questionnaire (HAQ-DI)	Physical Function	Secondary
36-Item Short Form, Version 2 (SF-36 v2)	General health status	Secondary
Functional Assessment of Chronic Illness Therapy-Fatigue Version 4 (FACIT-F)	Fatigue	Secondary
Morning Stiffness Measure	Morning stiffness duration	Secondary

The Applicant seeks COA-related labeling claim. The targeted COA-related labeling claims are listed in section C3.4 of this review.

This submission included an evidence dossier for the included PRO assessments. DPARP seeks COA Staff input on the adequacy of the PRO assessments, specifically the FACIT-F and (b) (4) to support labeling claims. As such, the subject of this review is restricted to the FACIT-F (b) (4)

The review concludes that the evidence submitted by the Applicant seems adequate to demonstrate that the FACIT-F is fit-for-purpose<sup>2</sup>, in the context of this drug development program, to measure and support labeling claims related to the concepts of fatigue associated with RA.

(b) (4)

The participants from the patient interview study commented that Item 3 (I feel listless) and Item 10 (I am too tired to eat) were not as relevant to their fatigue symptoms. Therefore, we also recommend that a sensitivity analysis be conducted by removing Items 3 and 10 from FACIT-F to examine whether the results are consistent with those of the full FACIT-F.

<sup>1</sup> Please see Section C 1.3 of this COA review for the complete endpoint hierarchy.

<sup>2</sup> Fit-for-purpose: A conclusion that the level of validation associated with a tool is sufficient to support its context of use. (Source: BEST (Biomarkers, Endpoints and Other Tools) Resource; <https://www.ncbi.nlm.nih.gov/books/NBK338448/>)

## B. CLINICAL OUTCOME ASSESSMENT REVIEW

### 1 BACKGROUND AND MATERIALS REVIEWED

Upadacitinib is an oral JAK-1 inhibitor being developed for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA), either alone or in combination with methotrexate (MTX) or other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).

RA is a chronic systemic inflammatory autoimmune disease with an estimated prevalence of approximately 1%. RA is more frequent in women. The hallmark feature of RA is polyarticular joint swelling and tenderness caused by progressive inflammatory synovitis, which can result in severe, debilitating disease.

#### Materials reviewed:

- FACIT-F dossier
- (b) (4) dossier
- Clinical Overview in the NDA submission

### 2 FIT-FOR-PURPOSE SUMMARY

**Table 2.** Fit-for-purpose assessment (based on available evidence)

COA Name(s)	COA sufficient to support the context of use	Supported by:	Location of Supporting Materials
a) FACIT-F	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Potentially - insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input checked="" type="checkbox"/> Fit for regulatory purposes (i.e., COA can be linked to a clinical benefit attributable to the treatment) <input checked="" type="checkbox"/> Evidence of content validity <input checked="" type="checkbox"/> Face validity (concepts/items appear relevant, e.g., based on discussion with clinical reviewer, clinician input, etc.) <input checked="" type="checkbox"/> COA well-defined and concept is able to be accurately communicated <input checked="" type="checkbox"/> COA is sensitive to detect change <input checked="" type="checkbox"/> COA is culturally adapted and adequately translated, if appropriate	FACIT-F dossier

(b) (4)

COA Name(s)	COA sufficient to support the context of use	Supported by:	Location of Supporting Materials
(b) (4)			

### 3 CONTEXT OF USE

#### 3.1 Clinical Trial Population

The target population for Studies M14-465 (SELECT COMPARE), M13-542 (SELECT BEYOND), M13-549 (SELECT NEXT), M13-545 (SELECT EARLY), and M15-555 (SELECT MONO), the phase 3 studies, are adult female and male subjects who are at least 18 years of age with a diagnosis of RA for  $\geq 3$  months who fulfill the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA. Eligible study subjects must have  $\geq 6$  swollen joints (based on 66 joint counts) and  $\geq 6$  tender joints (based on 68 joint counts) at Screening and Baseline Visits, and high-sensitivity C-reactive protein (hsCRP)  $\geq 5$  mg/L (central lab, upper limit of normal [ULN] 2.87 mg/L) at Screening. The studies included subjects who were naïve to MTX, those who had an inadequate response to MTX and/or other csDMARDs, and those who were refractory or had intolerance to treatment with one or more biologic DMARDs (bDMARDs).

Details of the inclusion and exclusion criteria can be found in the full clinical study protocols in Appendix A of the (b) (4) dossier.

#### 3.2 Clinical Trial Design

Table 3 summarizes the clinical trial design of Studies M14-465, M13-542, M13-549, M13-545, and M15-555.

**Table 3.** Clinical Trial Design for Studies M14-465, M13-542, M13-549, M13-545, M15-555

Trial Phase	Trial Design	Trial Duration	Registration Intent
Phase 3	<input type="checkbox"/> Single arm <input type="checkbox"/> Open label <input checked="" type="checkbox"/> Double-blind <input checked="" type="checkbox"/> Randomized <input checked="" type="checkbox"/> Placebo-/Vehicle-controlled <input checked="" type="checkbox"/> Active comparator-controlled <input type="checkbox"/> Cross-over <input checked="" type="checkbox"/> Multinational <input type="checkbox"/> Non-inferiority	12 – 48 weeks	Yes

**Reviewer's comment(s):** Refer to the full clinical study protocols in Appendices A.1 – A.5 of the <sup>(b) (4)</sup> dossier for more details on the clinical trial design.

### 3.3 Endpoint Position, Definition, and Assessment Schedule

Table 4 describes the primary and ranked COA secondary endpoints included in the 5 pivotal phase 3 studies.

**Table 4.** Primary and ranked COA secondary endpoints included in the 5 pivotal phase 3 studies

Endpoint Position	Endpoint Definition (Assessment Schedule)				
	Study M13-545	Study M13-549	Study M14-465	Study M15-555	Study M13-542
Primary	ACR50 (Week 12)	ACR20 (Week 12)	ACR20 (Week 12)	ACR20 (Week 1)	ACR20 (Week 12)
Secondary (COA only) ☒ Ranked: 2	ΔHAQ-DI (Week 12)	ΔHAQ-DI (Week 12)	--	ΔHAQ-DI (Week 14)	--
Secondary (COA only) ☒ Ranked: 3	--	ΔSF-36 PCS (Week 12)	ΔHAQ-DI (Week 12)	ΔSF-36 PCS (Week 14)	ΔHAQ-DI (Week 12)
Secondary (COA only) ☒ Ranked: 5	--	--	ΔSF-36 PCS (Week 12)	--	--
Secondary (COA only) ☒ Ranked: 6	ΔSF-36 PCS (Week 12)	--	--	ΔMorning stiffness duration (Week 14)	ΔSF-36 PCS (Week 12)
Secondary (COA only) ☒ Ranked: 7	--	ΔMorning stiffness duration (Week 12)	--	--	--
Secondary (COA only) ☒ Ranked: 8	--	ΔFACIT-F (Week 12)	--	--	--
Secondary (COA only) ☒ Ranked: 9	--	--	ΔMorning stiffness duration (Week 12)	--	--
Secondary (COA only) ☒ Ranked: 10	--	--	ΔMorning stiffness duration (Week 12)	--	--

Δ=Change from baseline; ACR20/50=American College of Rheumatology 20/50 response; HAQ-DI=Disability Index of Health Assessment Questionnaire; SF-36 PCS=36-Item Short Form physical component score; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue

**Reviewer's comment(s):** Refer to the full clinical study protocols in Appendices A.1 – A.5 of the (b) (4) dossier for full details of the endpoints used in the studies.

### 3.4 Labeling or promotional claim(s) based on the COA

The Applicant seeks the following PRO-related labeling claim for the FACIT-F:

(b) (4)

**Reviewer's comment(s):** The FACIT-F appears to be adequate to support labeling claims related to fatigue associated with RA as many items appear clinically relevant and meaningful to patients, and showed improvement. (b) (4)

(b) (4) See Section C.7 for additional details on the content validity of the FACIT-F (b) (4)

## 4 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

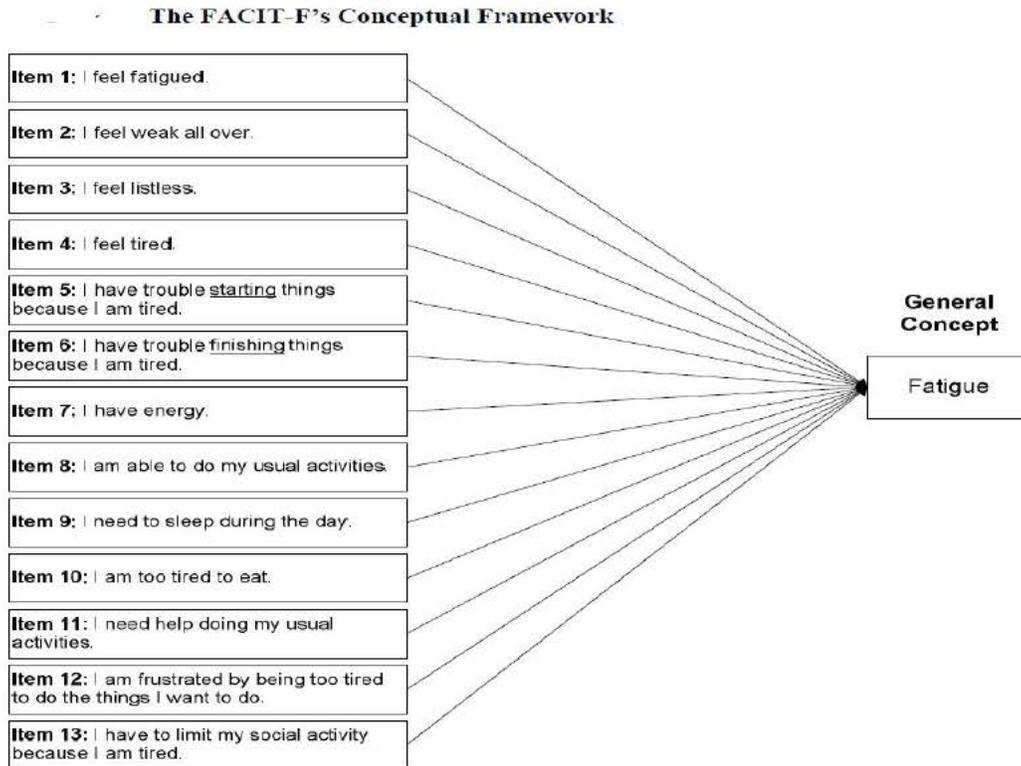
The concepts of interest for the FACIT-F (b) (4) are summarized in Table 5.

**Table 5.** Concepts of Interest for the FACIT-F (b) (4)

COA name	Concept(s)
Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F)	Fatigue
(b) (4)	

The conceptual framework(s) for the FACIT-F (b) (4) are shown in Figures 1 and 2 below respectively.

Figure 1: Conceptual Framework for FACIT-F



(b) (4)

## 5 CLINICAL OUTCOME ASSESSMENT(S)

### Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)

The FACIT-F is a 13-item measure designed to assess the impact of fatigue over the past 7 days (see Appendix 1). Items are rated on a 5-point Likert scale from 0 (not at all) to 4 (very much).

(b) (4)

*Reviewer's comment(s): Of note, the FACIT-F was initially developed as a cancer disease-specific instrument. It was developed as a subscale for the Functional Assessment of Cancer Therapy (FACT) Measurement System that was targeted to patient concerns associated with having anemia.*

## 6 SCORING ALGORITHM

### FACIT-F

The scoring guide identifies those items that must be reversed before being added to obtain subscale totals. Negatively stated items are reversed by subtracting the response from “4”. After reversing proper items, FACIT-F scale score is then calculated by adding up all item scores, multiplied by 13 and divided by the number of items answered. The scale score is ranged from 0 to 52 and the higher the score, the better the quality of life.

If there are missing items, the scale score can be prorated (as long as more than 50% of the items were answered). This is done by multiplying the sum of the item scores by the number of items in the subscale, then dividing by the number of items actually answered:

Prorated subscale score = [Sum of item scores]×[N of items in subscale]÷[N of items answered]

(b) (4)

## 7 CONTENT VALIDITY

To date, the following information has been submitted (check all that apply):

- Copy of instruments
- Literature review and/or publications
- Documentation of expert input
- Qualitative study protocols and interview guides for focus group or patient interviews
- Chronology of events for item generation, modification, and finalization (item tracking matrix)
- Synopsis of qualitative findings
- Qualitative summary report with evidence to support item relevance, item stems and response options, and recall period
- Quantitative summary report with evidence to support item retention and scoring
- Transcripts (if available)

Tables 6 and 7 document the adequacy of the content of the FACIT-F

(b) (4)

(b) (4)

**Table 6.** Review of Content Validity for FACIT-F

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Face validity	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	<input checked="" type="checkbox"/> Literature <input checked="" type="checkbox"/> Clinical input e.g. discussion with clinical reviewer	FACIT-F Dossier (Page 21 – 29)
Content validity	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Potentially – insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input checked="" type="checkbox"/> The item concepts are relevant/important to target patient population and appropriate to the study design and objectives <input checked="" type="checkbox"/> The instrument is comprehensive with respect to the concept (i.e., does not omit important content) <input checked="" type="checkbox"/> Target sample for qualitative research is appropriate. <input checked="" type="checkbox"/> Studied sample for qualitative research adequately represents the target patient population <input checked="" type="checkbox"/> Instructions, item stems, recall period, and response options well understood and appropriate for the study design and objectives <input checked="" type="checkbox"/> Response options appropriate for the item stems (measure the same dimensions, such as frequency or intensity) <input checked="" type="checkbox"/> COA is culturally adapted and adequately translated <input checked="" type="checkbox"/> Descriptive statistics (if available) support content relevance <input checked="" type="checkbox"/> Other (see Reviewer’s comments)	FACIT-F Dossier (Page 1745 – 1758)

**Table 7. Review of Content Validity** (b) (4)

<b>COA Attribute</b>	<b>Attribute sufficiently established</b>	<b>Supported by:</b>	<b>Location (i.e. page number) of Supporting Materials</b>
(b) (4)			

Evidence of content validity of the FACIT-F (b) (4) was derived from:

- Literature review
- Clinical expert interviews; n = 3 rheumatologists
- Patient interviews; n = 22 patients (See Table 8 for patient demographics and characteristics). The first 6 interviews were strictly concept elicitation, while the remaining were combined concept elicitation and cognitive interviews.

Table 8 shows the demographics and characteristics of the patients from the qualitative study.

**Table 8.** Patient Demographics/Characteristics from AbbVie’s Qualitative Study

<b>Patient Demographics/Characteristics</b>	<b>N =22</b>
<b>Age</b> mean (range)	56.4 (39 – 71)
<b>Gender</b>	
Female	20 (90.9%)
Male	2 (9.1%)
<b>Race</b>	
White Caucasian	13 (59.0%)
Black/African	7 (31.8%)
Other	1 (4.5%)
Prefer not to answer	1 (4.5%)
<b>Ethnicity</b>	
Hispanic	1 (4.5%)
Not Hispanic	21 (95.5%)
<b>Education</b>	
High school diploma/GED	5 (22.7%)
Some college	11 (50.0%)
Associate’s degree	2 (9.1%)
Bachelor’s degree	3 (13.6%)
Graduate degree	1 (4.5%)
<b>Employment Status</b>	
Employed Full Time	13 (59.1%)
Employed Part Time	2 (9.1%)
Permanently unable to work (long-term sickness/disability)	3 (13.6%)
Retired	4 (18.2%)
<b>Years Living with RA</b> Mean (Range)	13.5 (2 mos – 33 yrs)
<b>Level of Disease Severity</b>	
Moderate	19 (86.4%)
High	3 (13.6%)

### **Concept Elicitation**

The results of the first six concept elicitation interviews showed that the most commonly reported symptoms mentioned by patients were stiffness (n=22), pain (22), fatigue (n=19), and swelling (n=18). Others included heat (n=9), sweating (n=2), and joint degeneration (n=1). Overall, 3 out of 22 participants stated they did not experience fatigue as part of their RA.

The remaining sixteen interviews included a shorter concept elicitation component that allowed patients to describe all their RA-related symptoms and impacts before being asked to focus on the (b) (4) fatigue measures.

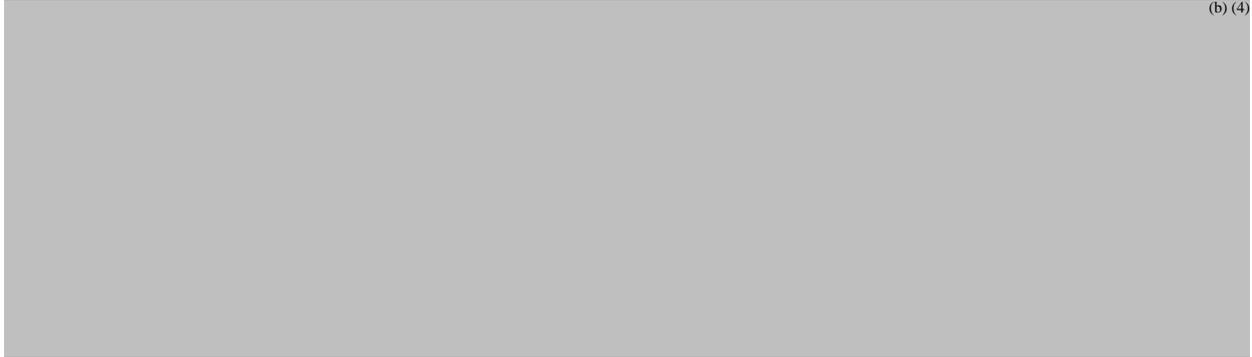
### **Cognitive Interviews**

During the cognitive interviewing section, patients were asked to evaluate the FACIT-F (b) (4) (b) (4):

- **FACIT-F:** Results from the cognitive interviews conducted by Kaiser et al. highlighted two items that could potentially be dropped due to irrelevance (Item 3: “I feel listless (washed out)” and Item 10: “I feel too tired to eat”) in the RA patient population. The two specific items were then probed for clarity and relevance in AbbVie’s patient interviews

(n=22). It was revealed that half the participants stated that they would not use the words, “listless or washed out” to describe their experience while 17 participants did not report they “feel too tired to eat”.

Overall, all the participants had no issue comprehending and answering the questionnaire.



***Reviewer’s comment(s):*** Results from the concept elicitation interviews indicated that concept coverage was broad, but included symptoms and impacts that were highly relevant to patients with RA. Concept saturation was reached for all core RA symptoms and symptom impacts during the patient interviews.

Results from the cognitive interviews indicated that many items in the FACIT-F  <sup>(b) (4)</sup>  appear clinically relevant and meaningful to patients. However, two FACIT-F items (3 and 10) were found less relevant to RA fatigue. This review recommends that a sensitivity analysis be conducted by removing Items 3 and 10 from FACIT-F to examine whether the results are consistent with those of the full FACIT-F.



## 8 OTHER MEASUREMENT PROPERTIES

To date, the following information has been submitted (check all that apply):

- Literature review and/or publications
- Quantitative analysis synopsis
- Full quantitative analysis plan
- Quantitative summary report with evidence to support reliability, construct validity, ability to detect change and scoring

The quantitative analyses are adequate and are consistent with the following:

- Pre-specified hypothesized relationships among variables tested
- Pre-specified estimates for reliability
- Appropriate anchors (e.g., global scales) for evaluation of meaningful change.

Table 9 documents the adequacy of the other measurement properties of the FACIT-F.

**Table 9.** Review of Other Measurement Properties for FACIT-F

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Reliability	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Potentially – insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input checked="" type="checkbox"/> Internal consistency reliability estimates in acceptable range (e.g., Cronbach’s $\alpha > 0.70$ ) <input checked="" type="checkbox"/> Test-retest reliability (or intra-rater reliability) estimates in acceptable range (e.g., ICC $\geq 0.70$ ) <input checked="" type="checkbox"/> Other (see Reviewer’s comments)	FACIT-F Dossier (Page 30 – 44)
Construct validity	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Potentially – insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input checked="" type="checkbox"/> Relationship to other assessments with similar concepts is as expected <input checked="" type="checkbox"/> Relationship to other assessments with dissimilar concepts is as expected <input checked="" type="checkbox"/> COA differentiates between clinically distinct groups (i.e., known groups validity) <input checked="" type="checkbox"/> COA scores are related to a known gold standard assessment of the same concept <input checked="" type="checkbox"/> Other (see Reviewer’s comments)	
Ability to detect change	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Potentially – insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input checked="" type="checkbox"/> COA can identify differences in scores over time in individuals or groups who have changed with respect to the concept <input checked="" type="checkbox"/> Other (see Reviewer’s comments)	

## **FACIT-F**

Supportive data for the reliability (i.e. internal consistency), validity (i.e. convergent and known-groups validity), and ability to detect change for the FACIT-F in the RA patient population were derived from published literature. Supplemental analyses were also conducted on data from Study M13-537 to assess test-retest reliability and convergent/divergent validity. Results from the psychometric validation analyses showed:

- A high internal consistency at baseline, Week 12, and Week 24 (Cronbach's alpha = 0.86 to 0.87) <sup>3</sup>
- An acceptable test-retest reliability (between the Baseline and Week 4 scores) based on an Intraclass Correlation (ICC) of 0.78 using data from Study M13-537.
- A statistically significant strong correlations ( $r > 0.50$ ,  $p < 0.001$ ) between FACIT-F and all the hypothesized relevant measures thereby demonstrating excellent convergent validity for FACIT-F. From Study M13-537, divergent validity was supported by weaker correlations ( $r < 0.50$ ,  $p < 0.001$ ) between FACIT-F and EQ-5D-5L VAS, PtGA, and PhGA.
- Changes in the FACIT-F scores over 24 weeks successfully discriminated between groups defined by levels of the clinical endpoint, the ACR20, ACR50, and ACR70. Patients in ACR groups who reflected greater clinical improvement in RA also showed larger increases in their FACIT-F scores, indicating decreased levels of fatigue. <sup>4</sup>

(b) (4)

*Reviewer's comment(s): Overall, the FACIT-F* (b) (4) *demonstrated acceptable psychometric properties.* (b) (4)

(b) (4)

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3 Cella D, Yount S, Sorensen M, et al. Validation of the functional assessment of chronic illness therapy fatigue scale relative to other instrumentation in patients with rheumatoid arthritis. *Journal of Rheumatology* 2005; 32(5):811-9.

## 9 INTERPRETATION OF SCORES

To date, the following information has been submitted (check all that apply):

- Anchor-based analyses
- Anchor-based empirical cumulative distribution function (eCDF) curves
- eCDF study arm curves (Treatment vs. Placebo/Active Comparator)
- Anchor-based probability density function (PDF) curves
- PDF study arm curves (Treatment vs. Placebo/Active Comparator)
- Qualitative support for meaningful change (e.g., patient input)

Table 10 documents the adequacy of the score interpretability of the FACIT-F.

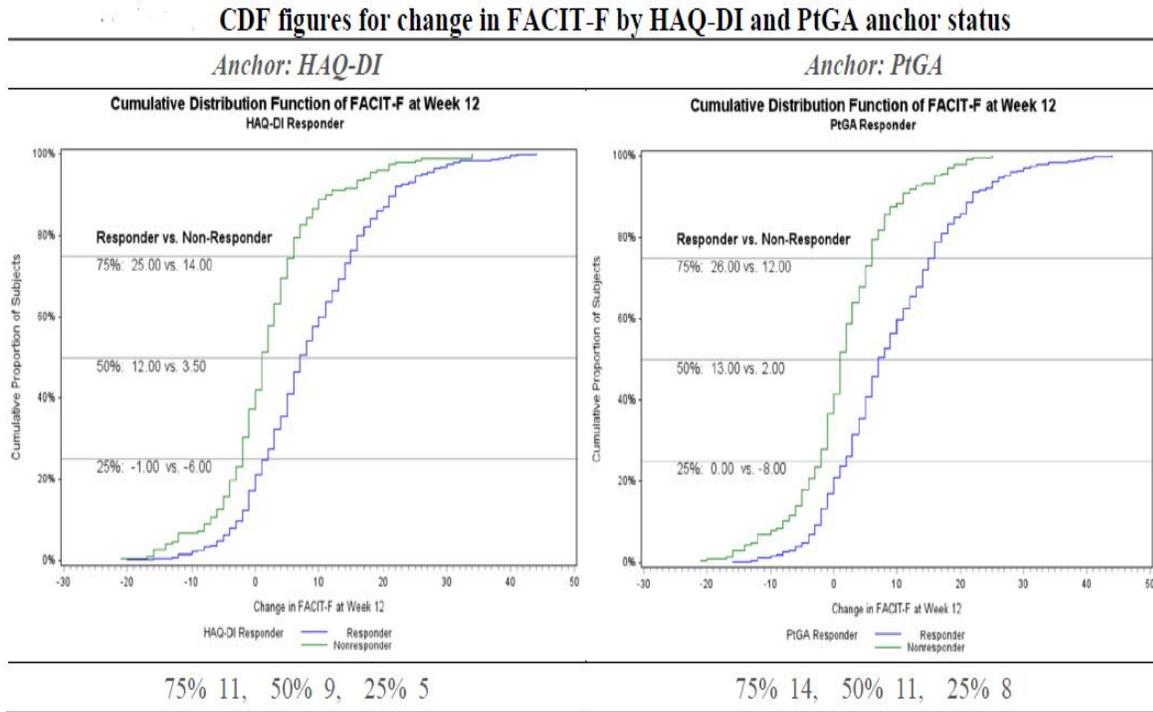
**Table 10.** Review of Score Interpretability for the FACIT-F

COA Attribute	Attribute sufficiently established	Supported by:	Location of Supporting Materials
Score Interpretability	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Potentially – insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input checked="" type="checkbox"/> Appropriate global anchor scales were included for anchor-based analyses <input checked="" type="checkbox"/> Threshold(s) for within-patient meaningful change identified (anchor-based methods) <input checked="" type="checkbox"/> Threshold(s) for within-patient meaningful change identified (eCDF/PDF curves) <input type="checkbox"/> Qualitative data supports meaningful change threshold(s) (e.g., cognitive interviews, exit surveys/interviews) <input checked="" type="checkbox"/> Other (see Reviewer’s comments)	FACIT-F Dossier (Page 45 – 58)

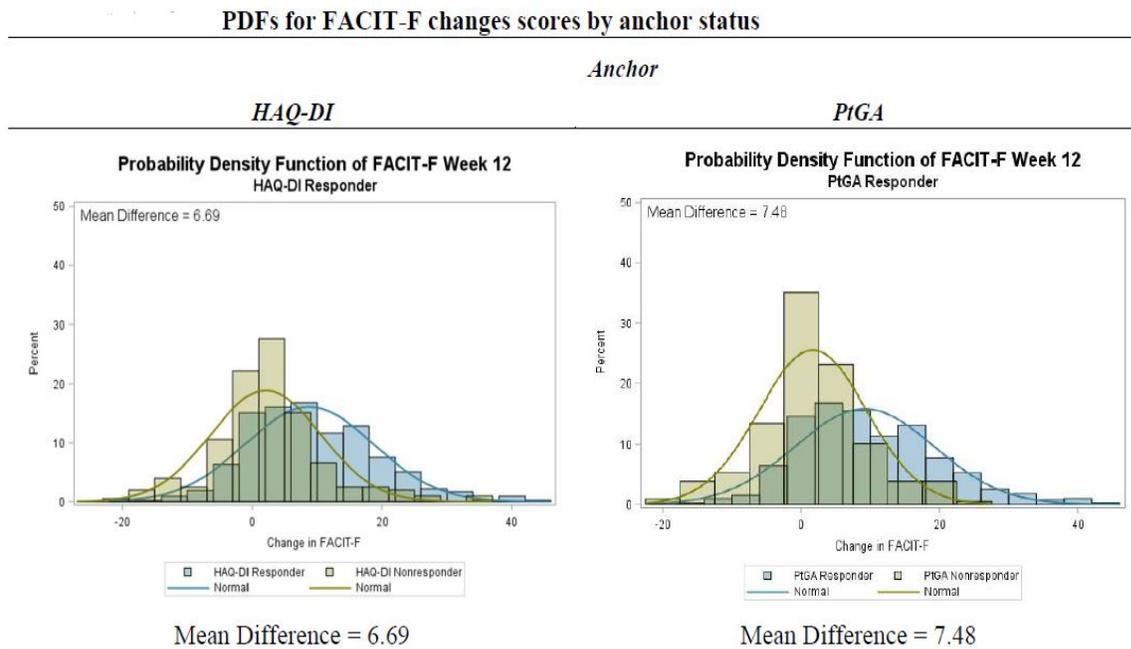
### **Estimates of Responder Definition for FACIT-F**

Analyses were performed on Study M13-549 data from baseline to week 12 to establish responder definitions for FACIT-F in the RA population using anchor-based and distribution-based methods. Anchor-based methods (using HAQ-DI and Patient’s Assessment of Pain (PtVAS) as anchors [ $r = -0.50$  and  $-0.47$ , respectively;  $p < 0.001$ ]), distribution-based methods (estimates from SEM), and Cumulative Distribution Functions (CDFs) [see Figure 3] supported by probability density functions (PDFs) [see Figure 4] resulted in a responder definition (individual-level threshold) of 9 for FACIT-F.

**Figure 3:**



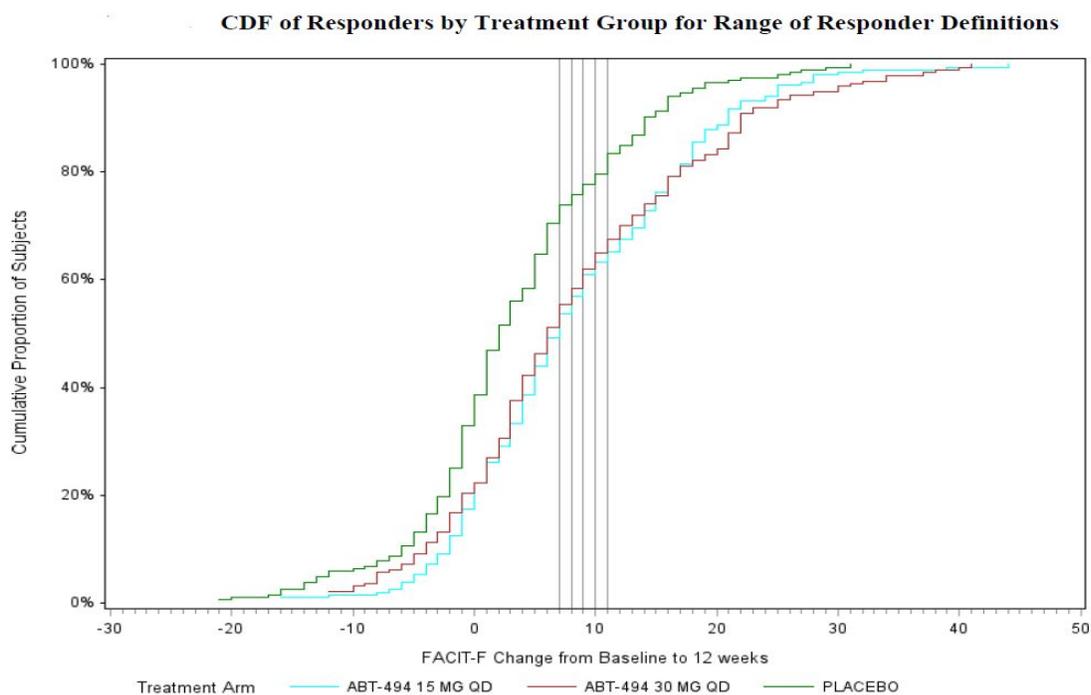
**Figure 4:**



## **Responder Analysis for FACIT-F**

A range of recommended responder definitions from anchor-based methods and CDFs was applied to the response in FACIT-F at the Week 12 assessment. The overall average responder definition estimate from triangulation (9 points) was kept at the center of the range, and two values above and below 9 points were tested, yielding a range of 7 to 11 points. Results were compared between the three treatment groups in SELECT-NEXT (Study M13-549) to estimate the number of responders and non-responders to treatment. Results from this responder analysis shows that for all responder definitions, both treatment groups include more responders than the placebo group. A CDF of responders by treatment group at each tested responder definition is shown in Figure 5 below.

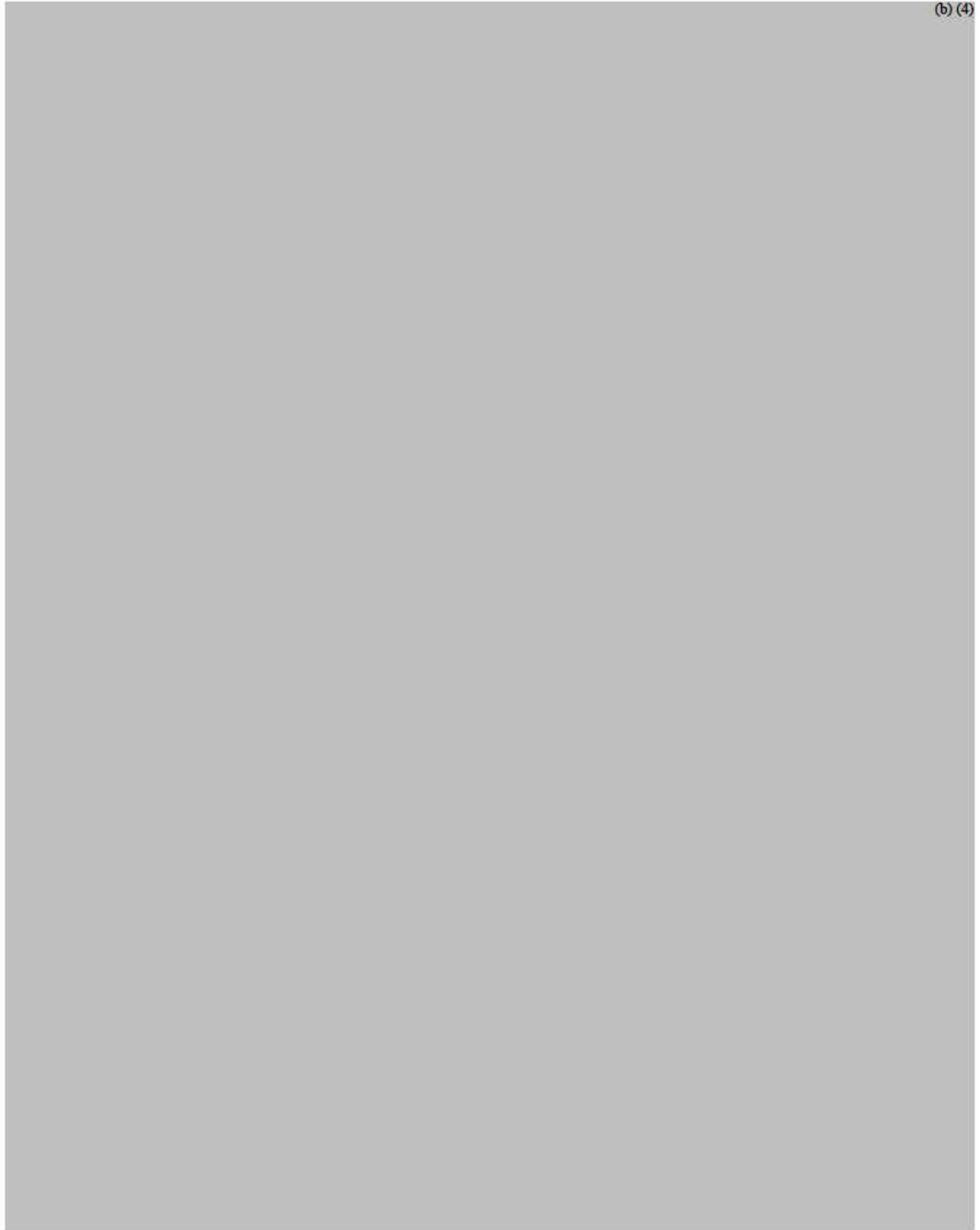
**Figure 5:**



**Reviewer's comment(s):** This reviewer finds the anchor-based analyses acceptable. The CDF plots show a clear differentiation between the curves for each of the treatment groups and placebo. The results indicate that 50% of patients treated with ABT-494 15mg and ABT-494 30 mg are achieving  $\geq 7$ -point improvement on the FACIT-F scale. The anchor-based eCDF curves suggests that the thresholds for meaningful change range from 5 – 14 points based on score-changes at 25%, 50%, and 75% percentiles in the HAQ-DI and PtGA anchor scales. The Applicant defined a clinically meaningful change as a 9-point improvement in the FACIT-F scale score. Based on the CDF there appears to be a clear separation between both treatment arms and placebo across the range of responder definitions. The Applicant did not provide any evidence of what PGI category the patients consider as meaningful.

## **D. APPENDICES**

### **Appendix 1: Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)**



(b) (4)

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ELEKTRA J PAPADOPOULOS  
05/20/2019 07:51:04 PM



# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 9, 2019

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.  
Clinical Analyst  
Division of Cardiovascular and Renal Products /CDER

To: Phuong Nina Ton, RPM  
DPARP

Subject: QT-IRT Consult to NDA 211675 (SDN 002)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 3/15/2019 regarding the sponsor's QT assessment. The QT-IRT reviewed the following materials:

- Previous QT-IRT reviews for IND 114717 dated 03/16/2016, 07/05/2016, and 10/12/2016 in DARRTS;
- [Summary of clinical pharmacology](#) (Submission 0002);
- Proposed [label](#) (Submission 0002); and
- Study report [RD71139](#) (Submission 0002).

## 1 QT-IRT Responses

Below are proposed edits to the label submitted to Submission 0002 from the QT-IRT. Our changes are highlighted ([addition](#), ~~deletion~~). Our edits are for suggestion only and we defer final labeling decisions to the Division.

### 12.2 Pharmacodynamics

#### Cardiac Electrophysiology

(b) (4)

At 6 times the mean maximum exposure of the 15 mg once daily dose, there were no clinically relevant effect on the QTc interval.

*We propose to use labeling language for this product consistent with the “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” guidance.*

## 2 BACKGROUND

Upadacitinib is a selective Janus kinase (JAK) 1 inhibitor (b) (4)

The recommended dose of upadacitinib extended-release tablet for oral use is 15 mg once daily.

Previously the QT-IRT reviewed a concentration-QTc report using PK/ECG data from the SAD (M13-401) and MAD (M13-845) studies. The two studies provided an approximately 3-fold exposure margin of highest therapeutic dose at the time of the review (314 ng/mL observed in the study vs. ~100 ng/mL expected at the 30 mg QD dose). The exposure margin is not adequate to waive the need of a separate positive control as the highest clinically relevant exposure scenario results in a 2-fold increase in C<sub>max</sub>. Based on the totality of evidence from the preclinical and clinical findings (including a bias report), the QT-IRT concluded that it is unlikely that upadacitinib would cause clinically relevant increases in the QTc interval at the expected therapeutic exposures following administration of 30 mg QD dose in RA patients.

In the current submission, the mean C<sub>max,ss</sub> in RA patients taking the extended-release tablet is 83.4 ng/mL at the 30 mg QD dose. This is similar to what was expected at the time of previous QT-IRT reviews. Therefore, we conclude a lack of clinically relevant effect on the QTc interval at the maximum exposure level observed in the QT assessment (314 ng/mL, approximately 6 times the mean maximum exposure of the 15 mg once daily dose).

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at [cdcrpqt@fda.hhs.gov](mailto:cdcrpqt@fda.hhs.gov)

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/s/  
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NAN ZHENG  
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CHRISTINE E GARNETT  
05/09/2019 09:47:41 AM

## CLINICAL INSPECTION SUMMARY

<b>Date</b>	April 25, 2019
<b>From</b>	Min Lu, M.D., M.P.H., Medical Officer Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
<b>To</b>	Keith Hull, M.D., Medical Officer Rachel Glaser, M.D., Clinical Team Leader Phuong Nina Ton, PharmD, RPM, Regulatory Project Manager Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
<b>NDA</b>	NDA 211675
<b>Applicant</b>	AbbVie, Inc.
<b>Drug</b>	Upadacitinib (ABT-494)
<b>NME</b>	Yes
<b>Therapeutic Classification</b>	JAK-1 inhibitor
<b>Proposed Indication</b>	Treatment of Rheumatoid Arthritis
<b>Consultation Request Date</b>	January 15, 2019
<b>Summary Goal Date</b>	May 3, 2019
<b>Action Goal Date</b>	August 16, 2019
<b>PDUFA Date</b>	August 18, 2019

### 1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

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

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

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

## 2. BACKGROUND

Upadacitinib (also known as ABT-494) is a novel oral selective and reversible JAK-1 inhibitor being developed for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA), either alone or in combination with methotrexate (MTX) or other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).

The sponsor's clinical development program for Upadacitinib in support of the proposed indication included five randomized, double-blind, Phase 3 studies. These studies enrolled a broad spectrum of patient populations with moderately to severely active RA, including those who were naïve to MTX (Study M13-545), those who had an inadequate response to MTX (Studies M14-465 and M15-555) and/or other csDMARDs (Study M13-549), and those who had an inadequate response to or were intolerant to treatment with one or more biologic disease-modifying anti-rheumatic drugs (bDMARDs) (Study M13-542).

### **Protocol M13-545**

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

This was a Phase 3 multicenter study that includes two periods and a Japan sub-study. Period 1 is a 48-week randomized, double-blind, active-controlled study and Period 2 is a long-term extension (up to 4 years) part of the study in subjects who have completed Period 1.

The study objectives of Period 1 of this study were to compare the safety and efficacy of upadacitinib 7.5 mg once daily (QD) (for subjects in Japan only), 15 mg QD, and 30 mg QD versus weekly MTX in MTX-naïve subjects with moderately to severely active RA. The study objective of Period 2 is to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 7.5 mg QD (for subjects in Japan only), 15 mg QD, and 30 mg QD in subjects with RA who have completed Period 1.

The primary efficacy endpoint was the proportion of subjects achieving American College of Rheumatology 50% (ACR50) response at Week 12. ACR50 response rate was determined based on 50% or greater improvement in tender joint count (TJC) and swollen joint count (SJC) and  $\geq 3$  of the 5 measures of Patient's Assessment of Pain, Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, Health Assessment Questionnaire – Disability Index (HAQ-DI), or high-sensitivity C-reactive protein (hsCRP).

The study main inclusion criteria included subjects at least 18 years of age with duration of symptoms consistent with RA for  $\geq 6$  weeks and fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA. Subjects must have been naïve to MTX or, if already on MTX, have received no more than 3 weekly MTX doses with requirement to complete a 4-week MTX washout before the first dose of study drug. Subjects with prior exposure to csDMARDs other than MTX may have been enrolled if completed the defined

washout period or washout should have been at least five times the mean terminal elimination half-life of a drug. Eligible study subjects must have had  $\geq 6$  swollen joints (based on 66 joint counts) and  $\geq 6$  tender joints (based on 68 joint counts) at screening and baseline visits; hsCRP  $\geq 5$  mg/L (central lab, ULN 2.87 mg/L) at screening; and  $\geq 1$  bone erosion on x-ray (by local reading) or in the absence of documented bone erosion, both positive rheumatoid factor (RF) and positive anti-cyclic citrullinated peptide (anti-CCP) autoantibodies at screening.

The study enrolled 1002 subjects from the 236 clinical sites in 43 countries. The study enrolled the first subject on February 23, 2016 and the last patient completed the last visit (Week 24) on March 15, 2018. The clinical study report presents results obtained through Week 24 in Period 1.

### **Protocol M14-465**

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

This was a Phase 3 multicenter study that includes two periods. Period 1 is a 48-week randomized, double-blind, placebo- and active-controlled, parallel group study to compare the safety and efficacy of upadacitinib 15 mg QD versus placebo, and versus adalimumab in subjects with moderately to severely active RA who are on a stable background of MTX and who have an inadequate response to MTX. Period 2 is a long-term extension to evaluate the safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with RA who had completed Period 1.

The primary efficacy endpoint was the proportion of subjects achieving ACR 20% (ACR20) response at Week 12.

The study main inclusion criteria included subjects at least 18 years of age with a diagnosis of RA for  $\geq 3$  months who also fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA who have had an inadequate response to MTX treatment. Eligible study subjects were to have had  $\geq 6$  swollen joints (based on 66 joint counts) and  $\geq 6$  tender joints (based on 68 joint counts) at Screening and Baseline Visits, and hs-CRP level  $\geq 5$  mg/L (central lab, upper limit of normal [ULN] 2.87 mg/L) at Screening. Subjects were also to have had the following at Screening:  $\geq 3$  bone erosions on x-ray; or  $\geq 1$  bone erosion and a positive rheumatoid factor; or  $\geq 1$  bone erosion and a positive anti-cyclic citrullinated peptide autoantibody.

The study enrolled 1629 subjects from the 286 clinical sites in 41 countries. The study enrolled the first subject on December 1, 2015 and the last patient completed the last visit (Week 26) on February 2, 2018. The clinical study report presents results obtained through Week 26 in Period 1.

### **Protocol M15-555**

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

This was a Phase 3 multicenter study that includes 2 periods. Period 1 was a 14-week, randomized, double-blind, parallel-group, controlled treatment period designed to compare the safety and efficacy of upadacitinib 30 mg QD alone and 15 mg QD alone versus continuing MTX alone for the treatment of signs and symptoms of RA in subjects with moderately to severely active RA despite stable doses of MTX (inadequate response to MTX). Period 2 is a blinded, long-term extension period to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 30 mg QD and 15 mg QD in subjects with RA who have completed Period 1.

The primary efficacy endpoint was the proportion of subjects achieving ACR 20% response (ACR20) at Week 14.

The study main inclusion criteria included subjects at least 18 years of age with a diagnosis of RA for  $\geq 3$  months who also fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA who have had an inadequate response to MTX treatment, but were able to tolerate  $\geq 15$  mg of weekly oral MTX or  $\geq 10$  mg/week in subjects who were intolerant of MTX at doses  $\geq 12.5$  mg/week. Local guidelines for MTX dosage may have applied. Eligible study subjects must have had  $\geq 6$  swollen joints (based on 66 joint counts) and  $\geq 6$  tender joints (based on 68 joint counts) at Screening and Baseline Visits, and hs-CRP level  $\geq 3$  mg/L (central lab) at Screening.

The study enrolled 648 subjects from the 138 clinical sites in 24 countries. The study enrolled the first subject on March 23, 2016 and the last patient completed the last visit (Period 1) on October 2, 2017. This clinical study report presents the results of Period 1 only.

### **Protocol M13-549**

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

This was a Phase 3 multicenter study that included two periods. Period 1 was a 12-week, randomized, double-blind, placebo-controlled study to compare the safety and efficacy of upadacitinib 30 mg QD and 15 mg QD versus placebo for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to csDMARDs. Period 2 is a blinded long-term extension period to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 30 mg QD and 15 mg QD in subjects with RA who had completed Period 1.

The primary efficacy endpoint was the proportion of subjects achieving ACR 20% response (ACR20) at Week 12.

The study main inclusion criteria included subjects at least 18 years of age with a diagnosis of RA for  $\geq 3$  months who also fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA who have had an inadequate response to

MTX treatment, but were able to tolerate  $\geq 15$  mg of weekly oral MTX or  $\geq 10$  mg/week in subjects who were intolerant of MTX at doses  $\geq 12.5$  mg/week. Local guidelines for MTX dosage may have applied. Eligible study subjects must have had  $\geq 6$  swollen joints (based on 66 joint counts) and  $\geq 6$  tender joints (based on 68 joint counts) at Screening and Baseline Visits, and hs-CRP level  $\geq 3$  mg/L (central lab) at Screening.

The study enrolled 661 subjects from the 150 clinical sites in 35 countries. The study enrolled the first subject on December 17, 2015 and the last patient completed the last visit (Period 1) on April 21, 2017. This clinical study report presents the results of Period 1 only.

### **Protocol M13-542**

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

This was a Phase 3 multicenter study that included two periods. Period 1 was a 12-week, randomized, double-blind, parallel-group, placebo-controlled period designed to compare the safety and efficacy of upadacitinib 30 mg QD and 15 mg QD versus placebo for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to csDMARDs. Period 2 is a blinded long-term extension period to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 30 mg QD and 15 mg QD in subjects with RA who had completed Period 1.

The primary efficacy endpoint was the proportion of subjects achieving ACR 20% response (ACR20) at Week 12.

The study main inclusion criteria Adult males and females enrolled in this study were at least 18 years old with a diagnosis of RA for  $\geq 3$  months and fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA. Eligible study subjects must have had  $\geq 6$  swollen joints (based on 66 joint counts) and  $\geq 6$  tender joints (based on 68 joint counts) at screening and baseline visits, and hs-CRP protein  $\geq 3$  mg/L (central lab) at screening. Subjects have been treated with bDMARD therapy for RA in the past and failed at least one bDMARD therapy prior to first dose of study drug as defined by either not showing an adequate response to at least one bDMARD after a treatment of  $\geq 3$  months or having had to discontinue at least one bDMARD due to intolerability or toxicity, irrespective of treatment duration. Subjects were to have been on csDMARD therapy  $\geq 3$  months and on a stable dose of csDMARD therapy (restricted to methotrexate, chloroquine, hydroxychloroquine, sulfasalazine, or leflunomide) for  $\geq 4$  weeks prior to the first dose of study drug.

The study enrolled 498 subjects from the 152 clinical sites in 26 countries. The study enrolled the first subject on March 15, 2016 and the last patient completed the last visit (Period 1) on June 27, 2017. This clinical study report presents the results of Period 1 only.

### Rationale for Site Selection

Three clinical sites were selected using risk ranking from clinical site selection tool for the five Phase 3 studies based on the high enrollment, better efficacy, involving multiple studies in this application, and financial disclosure.

### 3. RESULTS (by site):

Clinical Investigator Sites for inspection	Protocol #/ Site #/ # of Subjects	Inspection Date	Classification
Christine Coddling, M.D. 1211 North Shartel Ave, Suite 409 Oklahoma City, OK 73103	Protocol M13-542 Site# 18220 Subjects: 12  Protocol M15-555 Site# 18220 Subjects: 4  Protocol M13-549 Site# 18220 Subjects: 12	February 19-22, 2019	NAI
Roy Fleischmann, M.D. 8144 Walnut Hill Lane, Suite 810 Dallas, TX 75231	Protocol M13-542 Site# 3590 Subjects: 12  Protocol M13-549 Site# 3590 Subjects: 4  Protocol M14-465 Site# 3590 Subjects: 2	February 19-22, 25-26, 2019	NAI

<b>Clinical Investigator Sites for inspection</b>	<b>Protocol #/ Site #/ # of Subjects</b>	<b>Inspection Date</b>	<b>Classification</b>
Juan Ignacio Vargas, M.D. Dr. Otto Bader #810 Puerto Varas, NA 5550170 Chile	Protocol M14-465 Site# 52675 Subjects: 33  Protocol M15-555 Site# 52675 Subjects: 25  Protocol M13-545 Site# 52675 Subjects: 12	April 8-12, 15-18, 22-23, 2019	NAI*

#### Key to Compliance Classifications

NAI (No Action Indicated) = No deviation from regulations.

VAI (Voluntary Action Indicated) = Deviation(s) from regulations.

OAI (Official Action Indicated) = Significant deviations from regulations. Data unreliable.

\*Pending = Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

### Clinical Study Site Investigators

#### **1. Christine Coddington, M.D. (Site# 18220, Oklahoma City, OK)**

The site enrolled 28 subjects for three studies (Protocols M13-542, M15-555, and M13-549).

For Protocol M13-542, this site screened 15 subjects and enrolled 12 subjects. Among the 12 enrolled subjects, nine subjects completed the Period 1 and three subjects in the ABT-494 30 mg group discontinued from the study during the Period 1. Two subjects discontinued due to adverse events (Subject (b) (6): right herpes ophthalmicus; Subject (b) (6): worsening depression) and one subject withdrew the consent due to lack of efficacy (Subject (b) (6)). An audit was conducted for six of 12 enrolled subjects.

For Protocol M15-555, this site screened seven subjects and enrolled four subjects. Among the four subjects, three subjects completed the Period 1 and one subject (Subject (b) (6) [MTX group]) discontinued the study due to consent withdrawal. An audit was conducted for all four enrolled subjects.

For Protocol M13-549, the site screened 19 subjects and enrolled 12 subjects. Among the 19 subjects, 17 subjects completed the Period 1 and two subjects discontinued during the Period 1 (Subject (b) (6) [placebo group] was due to pneumonia and Subject (b) (6) [ABT-494 30 mg group] was lost to follow-up). An audit was conducted for one subject.

The inspection evaluated the following documents: source records, screening and enrollment logs, eligibility criteria, case report forms, study drug accountability logs, study monitoring visits, efficacy endpoints, adverse event reporting, and correspondence. Informed consent documents, IRB correspondence, and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events was noted.

The following issues were discussed at the end of inspection:

1. Several subjects in Study M13-542 were not re-consented for Informed Consent Form Version 3 at timely manner because the site was not notified for the new version of ICF posted to the IRB website.
2. One subject (Subject (b) (6)) was enrolled in Study M13-542 (in the ABT-494 30 mg group) after meeting the exclusion criteria for recurrent herpes zoster. The subject had three episodes of herpes zoster (scalp shingles) prior to enrollment and the site explained that they were only aware of one prior episode. The subject was hospitalized for right herpes ophthalmicus in the Period 1 and discontinued the study after hospital discharge. This was reported as protocol deviation in the study report and on the data listings.

In general, this clinical site appeared to be in compliance with Good Clinical Practices except the items described as above. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

## **2. Roy Fleischmann, M.D. (Site# 3590, Dallas, TX)**

The site enrolled 24 subjects for three studies (Protocols M13-542, M13-549, and M14-465).

For Protocol M13-542, this site screened 18 subjects and enrolled 10 subjects. All 10 enrolled subjects completed the Period 1. An audit was conducted for all 10 enrolled subjects.

For Protocol M13-549, the site screened 28 subjects and enrolled 12 subjects. Among the 12 subjects, 10 subjects completed the Period 1 and two subjects discontinued during the Period 1 (Subject (b) (6) due to increased liver enzymes/basil cell carcinoma and Subject (b) (6) due to consent withdrawal). An audit was conducted for all 12 enrolled subjects.

For Protocol M14-465, this site screened seven subjects and enrolled two subjects. Two enrolled subjects completed the Period 1. An audit was conducted for two enrolled subjects.

The inspection evaluated the following documents: informed consent, protocols, verification of endpoints, eligibility (subject selection and enrollment), laboratory reports, electrocardiograms, randomization and blinding, adverse events (AEs), protocol deviations, IRB correspondence and

study approvals, sponsor/monitor correspondence, source records, drug accountability records, and other regulatory documentation. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events was noted.

The following issue was discussed at the end of inspection at the site:

1. One subject (Subject (b) (6) in placebo group) in Study M13-542 failed to meet the inclusion criterion #5 for swollen joint count (4 joints) at baseline. However, the subject had 11 swollen joint count at screening. The deviation was reported to the IRB and sponsor. The sponsor approved the subject to remain in the study. This deviation was reported in the study report and on the data listings.

In general, this clinical site appeared to be in compliance with Good Clinical Practices except the item described as above. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

### **3. Juan Ignacio Vargas, M.D. (Puerto Varas, Chile)**

The site enrolled 70 subjects for three studies (Protocols M13-545, M14-465, and M15-555).

For Protocol M13-545, this site screened 26 subjects and enrolled 12 subjects. Among the 12 subjects, 11 subjects completed the Period 1 and one subject (Subject (b) (6) [ABT-494 15 mg group] lost to follow-up). An audit was conducted for all 11 enrolled subjects.

For Protocol M14-465, the site screened 57 subjects and enrolled 33 subjects. All 33 enrolled subjects completed the Period 1. An audit was conducted for all 33 enrolled subjects.

For Protocol M15-555, this site screened 35 subjects and enrolled 25 subjects. Among the 25 subjects, 23 subjects completed the Period 1 and two subjects discontinued during the Period 1 (Subject (b) (6) [ABT-494 15 mg group] died of hemorrhagic stroke, considered as unrelated by investigator and Subject (b) (6) [ABT-494 30 mg group] due to consent withdrawal). An audit was conducted for all 25 enrolled subjects.

The inspection evaluated the following documents: source records, screening and enrollment logs, eligibility criteria, case report forms, study drug accountability logs, study monitoring visits, efficacy endpoints, adverse event reporting, and correspondence. Informed consent documents, IRB correspondence, and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site for all three studies. No under-reporting of serious adverse events was noted.

The following non-serious adverse events were under-reporting noted during the inspection:

- One non-serious adverse event (Subject (b) (6) [adalimumab group] experienced bronchitis during (b) (6)) was found in chart notes but it was not in study database and on data listings for Study M14-465.
- Two adverse events (Subject (b) (6) [upadacitinib 30 mg group] experienced back pain in (b) (6) and tonsillitis in (b) (6)) was found in chart notes but they were not in study database. These events occurred after data cutoff date for the study report.

*OSI Reviewer Comment: Subject (b) (6) was randomized in the adalimumab active control group. Although this under-reporting non-serious adverse event is a protocol violation, this is less likely to affect the safety profile of upadacitinib. Subject (b) (6) was randomized in the upadacitinib 30 mg group. Two adverse events were occurred after data cutoff date for the study report in the NDA submission and were subsequently added to the study database by the investigator during the inspection. The studies are currently ongoing and those adverse events should be included in the full study report when the studies are completed.*

In general, this clinical site appeared to be in compliance with Good Clinical Practices except items described as above. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

*{See appended electronic signature page}*

Min Lu, M.D., M.P.H.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H.  
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**cc:**

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OSI/ GCP Program Analyst/Yolanda Patague

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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MIN LU  
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04/25/2019 11:43:47 AM



**Materials Reviewed:**

- Applicant's submitted background package for NDA 211675, dated December 18, 2018
- DPMH review of Xeljanz (tofacitinib) Tablet. Jane Liedtka, MD. March 20, 2018. DARRTS Reference ID 4236947.

**INTRODUCTION AND BACKGROUND**

On December 18, 2018, the applicant (AbbVie Inc) submitted a new NDA to DPARP. DPARP consulted DPMH on April 11, 2018, to advise regarding the following question.

A 505(b)(1) NDA submission for upadacitinib (UPA) is under priority review in DPARP (applicant redeemed a Priority Review Voucher). This is the third Janus Kinase (JAK) inhibitor indicated for rheumatoid arthritis (RA). The division is familiar with clinical and nonclinical data for additional JAK inhibitors approved for other indications and/or in late-stage clinical development.

JAK inhibitors reviewed by DPARP have been consistently teratogenic in rats and rabbits. These adverse embryo-fetal findings have been described in Section 8 of product labeling for Xeljanz (tofacitinib) NDA 203214 and Olumiant (baricitinib) NDA 207924, but not in Section 5 (Warnings and Precautions).

Results of embryo-fetal development studies with UPA in rats and rabbits show a clear potential risk for fetal harm. As shown in the table below, the NOAEL doses was associated with an AUC 5x lower than the clinical dose in rats and slightly above the clinical exposure in rabbits. Fetal malformations were observed at exposure roughly equal to the clinical dose in rats, and slightly higher in rabbits (see table below; note that two rat separate rat studies were conducted but are merged for presentation).

Species	Parameter	LD	MD	HD
Rat*	Dose (mg/kg/day)	1.5	4-5	≥25
	Multiple of clinical AUC	0.2	1.2-1.3	≥17
	Maternal toxicity	-	-	-
	Pregnancy outcomes	-	-	↑ Resorptions, ↓ live concepti ↓ Fetal body weight
	Skeletal malformations	-	Vertebral and sternum anomalies	
Rabbit	Dose (mg/kg/day)	2.5	10	25
	Multiple of clinical AUC	0.3	1.7	11
	Maternal toxicity	-	-	Abortions
	Pregnancy outcomes	-	-	↑ Early, total resorptions ↓ Fetal body weight
	Visceral malformations	-	-	Thoracic cavity
	Skeletal malformations	-	-	Sternum

<sup>1</sup>see below footnote

Compared to tofacitinib and baricitinib, the adverse embryofetal findings with UPA are similar in nature but occur at exposures with less safety margin compared to the proposed clinical dose. The table below shows exposure multiples for NOAELs and fetal malformations across the JAK inhibitor class (red shading denotes exposure level associated with fetal malformations).

<sup>1</sup> LD: low dose; MD: mid-dose; HD: high dose

Filgotinib, another JAK inhibitor and potent teratogen is included for context since this product is at the pre-NDA stage.

Drug / Reference	EFD Species	Doses expressed as multiples of clinical AUC		
		LD	MD	HD
Tofacitinib NDA 203214	Rat (A)	1	15	44
	Rat (B)	53	134	196 (no litters)
	Rabbit	3	12	58
Ruxolitinib NDA 202192	Rat	<0.1	0.3	2
	Rabbit	BLQ	<0.01	<0.1
Baricitinib NDA 207924	Rat	2	10	55
	Rabbit	2	6	42
(b) (4)	Rat	6	13	22
	Rabbit	3	7	39
Upadacitinib NDA 211675	Rat (A)	1.3	17	64
	Rat (B)			1.2
	Rabbit			11

DPARP views the embryofetal toxicity data with UPA (and filgotinib) as comparatively more concerning vs. tofacitinib and baricitinib based on exposure margins vs. approved / proposed clinical dose levels. The division feels that this risk should be included in the Warnings and Precautions section of the UPA label, particularly given the abundance of women of child bearing potential in the RA population. The applicant noted that the two approved JAK inhibitors do not carry a Warning for embryo-fetal toxicity, but the division feels that the determination should be product-specific based on the available nonclinical data.

**Question for DPMH**

1. Does the Maternal Health Team agree that the available data warrant the inclusion of embryo-fetal toxicity in Section 5 Warnings and Precautions of the upadacitinib product label?

## REVIEW

In the document *Guidance for Industry Reproductive and Developmental Toxicities-Integrating Study Results to Assess Concerns*, in section C entitled “Reproductive or Developmental Toxicity Endpoints with Positive Signal”, the authors state

The purpose of this relative exposure metric is to compare the dose causing reproductive or developmental toxicity in the test species to the therapeutic dose in humans, normalized to the doses causing a response common to both species.

In practice, this is done by taking the exposure at the NOEL for the adverse reproductive or developmental effect and dividing by the exposure at which the biomarker response is seen in the test species. This is compared to the human therapeutic exposure divided by the exposure at which the biomarker response is seen in the human. The ratio calculated for animals is then divided by the ratio calculated for humans. When this ratio of relative biomarker exposure (animal: human) is  $< 10$ , there is generally increased concern for human reproductive or developmental toxicity. When this ratio is  $> 25$ , there is generally less concern.

### *Reviewer's Comment*

*As noted in the text from the consult request from DPARP, for UPA this ratio (or multiple) in the rat is 1.2. Therefore, a higher level of concern regarding the animal findings for UPA is reasonable.*

Another factor to consider is precedent regarding labeling for other products in the class of small molecule kinase inhibitors. The applicant referenced tofacitinib and baricitinib, but these products have much higher ratios for relative exposure in their nonclinical studies. More relevant comparisons would be to other small molecule kinase inhibitors with oncologic indications. These products have ratios similar to what is seen with UPA and carry Warnings and Precautions for embryo-fetal toxicity. See Table 1 below for details.

Table 1: PLLR Converted Small Molecule Kinase Inhibitors

Name/NDA# /Date of most recent label	Type	Target	Indication	Animal data-multiples	W&P
Gilotrif (afatinib) 201292 Jan 2018	tyrosine kinase inhibitor (TKI)	epidermal growth factor receptor (EGFR)	metastatic non-small cell lung cancer (NSCLC)	Rats and rabbits-embryotoxicity at exposures up to two times the exposure at the recommended human dose	yes
Alecensa (alectinib) 208434 June 2018	TKI	anaplastic lymphoma kinase (ALK), rearranged during transfection" (RET) tyrosine kinase	anaplastic lymphoma kinase (ALK)-positive NSCLC	Rats and rabbits-embryo-fetal toxicity and abortion at maternally toxic doses with exposures approximately 2.7 times those observed in humans treated with alectinib at 600 mg twice daily	yes
Olumiant (baricitinib) 207924 May 2018	Janus Kinase (JAK) inhibitor	greater inhibitory potency at JAK1, JAK2 and TYK2 relative to JAK3	severely active rheumatoid arthritis (RA)	pregnant rats and rabbits at exposures equal to and greater than approximately 20 and 84 times the maximum recommended human dose (MRHD), respectively, resulted in reduced fetal body weights, increased embryolethality (rabbits only), and dose-related increases in skeletal malformations.	no
Zykadia (ceritinib) 205755 March 2019	TKI	ALK, insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and ROS1	anaplastic lymphoma kinase (ALK)-positive NSCLC	rats and rabbits during the period of organogenesis at maternal plasma exposures below the recommended human dose caused increases in skeletal anomalies	yes
Cotellic (cobimetinib) 206192 Jan 2018	inhibitor of mitogen-activated protein kinase (MAPK)	Reversible MAPK/ extracellular signal regulated kinase 1 (MEK1) and MEK2.	unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib	pregnant rats during organogenesis-teratogenic and embryotoxic at exposures (AUC) that were 0.9 to 1.4-times those observed in humans at the recommended human dose	Yes
Tarceva (erlotinib) 21743 Oct 2016	reversibly inhibits kinase activity of EGFR	EGFR exon 19 deletion or exon 21 (L858R) mutations	Metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine	embryo-fetal lethality and abortion in rabbits at exposures approximately 3 times the exposure at the recommended human daily dose of 150 mg	Yes
Lorbrena (lorlatinib) 210868 Nov 2018	kinase inhibitor	kinase inhibitor with in vitro activity against ALK and ROS1 as well as TYK1, FER, FPS, TRKA, TRKB, TRKC, FAK, FAK2, and ACK	ALK-positive NSCLC having failed crizotinib and at least one other ALK inhibitor for metastatic disease; or alectinib or ceritinib as the first ALK inhibitor therapy for metastatic disease	pregnant rats and rabbits by oral gavage during the period of organogenesis resulted in malformations, increased post-implantation loss, and abortion at maternal exposures that were equal to or less than the human exposure	Yes

Xeljanz (Tofacitinib) 203214	JAK inhibitor	inhibited the in vitro activities of JAK1/JAK2, JAK1/JAK3, and JAK2/JAK2 combinations with IC50 of 406, 56, and 1377 nM, respectively	<ul style="list-style-type: none"> <li>-moderately to severely active RA who have had an inadequate response or intolerance to methotrexate (MTX). It may be used as monotherapy or in combination with MTX or other nonbiologic disease-modifying antirheumatic drugs (DMARDs)</li> <li>-active psoriatic arthritis who have had an inadequate response or intolerance to MTX or other DMARDs</li> <li>-moderately to severely active ulcerative colitis</li> </ul>	In animal reproduction studies, fetocidal and teratogenic effects were noted when pregnant rats and rabbits received tofacitinib during the period of organogenesis at exposures multiples of 73-times and 6.3-times the maximum recommended dose of 10 mg twice daily, respectively.	no
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Source: Reviewer's Table

**DISCUSSION AND CONCLUSIONS**

Based on guidance and precedent set with other small molecule kinase inhibitors, DPMH agrees with DPARP that labeling for Upadacitinib should include a Warning and Precaution for embryofetal toxicity.

**LABELING RECOMMENDATIONS**

**DPMH Proposed Upadacitinib Pregnancy and Lactation Labeling**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**WARNINGS AND PRECAUTIONS**

• Embryo-Fetal Toxicity: TRADENAME may cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.X, 8.1, 8.3)

**FULL PRESCRIBING INFORMATION**

**5 WARNINGS AND PRECAUTIONS**

**5.X Embryo-Fetal Toxicity**

Based on findings in animal studies, TRADENAME may cause fetal harm when administered to a pregnant woman. (b)(4) administration of upadacitinib to rats during organogenesis

(b)(4) caused increases in (b)(4)

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TRADENAME and for \*\* following completion of therapy. [see Use in Specific Populations (8.1, 8.3)].

Commented [LJ1]: To be added by division PT team

Commented [LJ2]: To be added by division clin pharm team

APPEARS THIS WAY ON ORIGINAL

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JANE E LIEDTKA  
04/19/2019 02:41:36 PM

MIRIAM C DINATALE  
04/19/2019 03:49:26 PM

LYNNE P YAO  
04/24/2019 01:33:01 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: 4/3/2019

TO: Division of Pulmonary, Allergy and Rheumatology Products  
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 211675

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

**Rationale**

The Office of Regulatory Affairs (ORA) inspected the site in December 2017, which falls within the surveillance interval. The inspection was conducted under the following submissions: NDA

(b) (4)

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the outcome of the previous inspection and the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	AbbVie Clinical Pharmacology Research Unit	480 South US Highway 45, Grayslake, IL

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NICOLA M FENTY-STEWART  
04/03/2019 09:13:34 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: February 28, 2019

TO: Debra Birnkrant, M.D.  
Director  
Division of Antiviral Products (DAVP)  
Office of Antimicrobial Products (OAP)  
Office of New Drugs (OND)

Sally Seymour, M.D.  
Director (Acting)  
Division of Pulmonary, Allergy, and Rheumatology Products  
(DPARP)  
Office of Drug Evaluation II (ODE-II)  
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.  
Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.  
Deputy Director  
DNDBE  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection of AbbVie, Inc., North Chicago, IL

**Inspection Summary**

Per the requests of DAVP (**Attachment 1**) and DPARP (**Attachment 2**), the Office of Study Integrity and Surveillance (OSIS) inspected the analytical portion of Studies (b)(4) and M15-878 (NDA 211675, Upadacitinib) conducted at AbbVie, Inc., North Chicago, IL.

I did not observe objectionable conditions and did not issue Form FDA 483 at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

**Recommendation**

Based on my review of the inspectional findings, I conclude the concentration data from the audited studies are reliable to support a regulatory decision.

Concentration data from studies using similar methods (LC/MS) conducted between the previous inspection (February 2016) and the end of the current surveillance interval should be considered reliable without an inspection.

### **Inspected Studies**

(b) (4)

#### **NDA 211675**

**Study Number:** M15-878

**Study Title:** "A Phase 1 study to evaluate the bioavailability of upadacitinib (ABT-494) market-image formulation relative to the formulation utilized in upadacitinib Phase 3 rheumatoid arthritis trials and to assess the effect of high-fat meal on upadacitinib exposure from the market-image formulation"

**Sample Analysis Period:** 08/07/2017 - 11/29/2017

**Analytical Site:** AbbVie, Inc.

R46W (Department of Bioanalysis)  
1 North Waukegan Rd  
North Chicago, IL 60064

#### **Scope of Inspection**

OSIS scientist Yiyue Zhang, Ph.D., Staff Fellow audited the analytical portion of the above studies at AbbVie, Inc., North Chicago, IL from February 11 to 15, 2019.

The previous FDA inspection of AbbVie was conducted in February 2016 and was classified Voluntary Action Indicated (VAI). A Form FDA 483 was issued [REDACTED] (b) (4)

(b) (4)

AbbVie had implemented corrective and preventive actions and currently had no pending corrective actions.

The current inspection included a thorough examination of study records, facilities, laboratory equipment, method validation, and sample analysis, and interviews with the site's management and staff.

**Inspectional Findings**

At the conclusion of the inspection, I did not observe any objectionable conditions. I did not issue Form FDA 483 to AbbVie, Inc.

• **Specific concerns from OND/DAVP**

DAVP requested OSIS to evaluate possible reasons

(b) (4)

**Inspectional Findings**

(b) (4)

**OSIS Evaluation:**

(b) (4)

(b) (4)

(b) (4)

### **Conclusion**

After review of the inspectional findings, I conclude that the concentration data from the audited studies and **M15-878 (NDA 211675)** are reliable.

Additionally, concentration data from studies using similar methods (LC/MS) conducted at AbbVie between the previous inspection (February 2016) and the end of the current surveillance interval should be considered reliable without an inspection.

Yiyue Zhang, Ph.D.  
Staff Fellow

### **Final Classification**

#### **Analytical Site**

**NAI** - AbbVie, Inc., North Chicago, IL (FEI#: 3009751352)

#### **Attachments:**

**Attachment 1.** Consult from OND/DAVP

**Attachment 2.** Consult from OND/DPARP

**Attachment 3.** Additional results of Study

cc:

OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/[CDER-OSIS-BEQ@fda.hhs.gov](mailto:CDER-OSIS-BEQ@fda.hhs.gov)

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Zhang

OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au

Draft: YZ 02/26/2019

Edit: RCA 2/27/2019; AD 02/28/2019

ECMS: Cabinets/CDER OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL/AbbVie, North Chicago, IL, USA

OSIS File #: BE 8285 (NDA 209394/S006) and BE 8365 (NDA 211675)

**FACTS: 11896005**

# ATTACHMENT 1

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# **ATTACHMENT 2**

## OSIS Consult Request for Biopharmaceutical Inspections

Date	1/23/2019		
Subject	Request for Biopharmaceutical Inspections (BE)		
Addressed to	Project Management Staff Office of Study Integrity and Surveillance <a href="mailto:CDER-OSIS-BEQ@fda.hhs.gov">CDER-OSIS-BEQ@fda.hhs.gov</a>		
Consulting Office/Division	DPARP - Div of Pulmonary, Allergy and Rheumatology Prods		
Project Manager	Phuong Nina Ton		
PEPFAR?	<input type="checkbox"/>		
Application Type/Num /Sup Num	NDA	211675	Enter Sup Num
Priority Application?	<input checked="" type="checkbox"/>		
Drug Product	Upadacitinib		
Sponsor Name	Abbvie		
Sponsor Address	1 N. Waukegan Road, Dept. PA72/Bldg. AP30-4, North Chicago, Illinois 60064		
US Agent (if applicable)	Click here to enter text.		
US Agent Address	Click here to enter text.		
Electronic Submission	<input checked="" type="checkbox"/>		
GDUFA/PDUFA/BsUFA Goal	8/18/2019		
Action Goal Date	8/16/2019		
Requested Review Goal Date	4/30/2019		

Inspection Request Detail (Complete all applicable fields)	
<u>Study #1</u>	
Study Number	M15-878
Study Title	A Phase 1 study to evaluate the bioavailability of upadacitinib (ABT-494) market-image formulation relative to the formulation utilized in upadacitinib Phase 3 rheumatoid arthritis trials and to assess the effect of high-fat meal on upadacitinib exposure from the market-image formulation
Study Type	In Vivo BE
Other:	Click here to enter text.
Site #1 Type	Clinical
Site #1 Name	AbbVie Clinical Pharmacology Research Unit
Select one:	Routine Inspection
Street	480 South US Highway 45
City	Grayslake
State	IL 60030
Country	USA

tel	847-935-4421
fax	847-935-4402
Investigator	Kent Kamradt, MD
email	Kent.kamradt@abbvie.com
Site #2 Type	Analytical
Site #2 Name	AbbVie
Select one:	Routine Inspection
Street	1 North Waulegan Road
City	North Chicago
State	IL 60064
Country	USA
tel	Click here to enter text.
fax	Click here to enter text.
Investigator	Ogert Fisniku
email	
Site #3 Type	Choose an item.
Site #3 Name	Click here to enter text.
Select one:	Choose an item.
Street	Click here to enter text.
City	Click here to enter text.
State	Click here to enter text.
Country	Choose an item.
tel	Click here to enter text.
fax	Click here to enter text.
Investigator	Click here to enter text.
email	Click here to enter text.
Study Report: (location, eg., 5.3.1.2)	\\cdsesub1\evsprod\nda211675\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\m15-878\m15-878-report-body-1.pdf
Validation Report: (eg., 5.3.1.2)	\\cdsesub1\evsprod\nda211675\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\rd12654\c-da-rd12654-val-lcms-pla.pdf
Bioanalytical Report: (eg., 5.3.1.4)	\\cdsesub1\evsprod\nda211675\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\m15-878\m15878-analytical-plasma.pdf
<i>(please include specific review concerns or items to be addressed during the inspection in the appendix below)</i>	

<b>Inspection Request Detail (Complete all applicable fields)</b>
<b>Study #2</b>

Study Number	Click here to enter text.	
Study Title	Click here to enter text.	
Study Type	Choose an item.	
Other:	Click here to enter text.	
Site #1 Type	Choose an item.	
Site #1 Name	Click here to enter text.	
Select one:	Choose an item.	
Street	Click here to enter text.	
City	Click here to enter text.	
State	Click here to enter text.	
Country	Choose an item.	
tel	Click here to enter text.	
fax	Click here to enter text.	
Investigator	Click here to enter text.	
email	Click here to enter text.	
Site #2 Type	Choose an item.	
Site #2 Name	Click here to enter text.	
Select one:	Choose an item.	
Street	Click here to enter text.	
City	Click here to enter text.	
State	Click here to enter text.	
Country	Choose an item.	
tel	Click here to enter text.	
fax	Click here to enter text.	
Investigator	Click here to enter text.	
email	Click here to enter text.	
Site #3 Type	Choose an item.	
Site #3 Name	Click here to enter text.	
Select one:	Choose an item.	
Street	Click here to enter text.	
City	Click here to enter text.	
State	Click here to enter text.	
Country	Choose an item.	
tel	Click here to enter text.	
fax	Click here to enter text.	
Investigator	Click here to enter text.	
email	Click here to enter text.	
Study Report: (location, eg., 5.3.1.2)		Click here to add report link.
Validation Report: (eg., 5.3.1.2)		Click here to add report link.
Bioanalytical Report: (eg., 5.3.1.4)		Click here to add report link.
<i>(please include specific review concerns or items to be addressed during the inspection in the appendix below)</i>		

<b>Inspection Request Detail (Complete all applicable fields)</b>	
<b>Study #3</b>	
Study Number	Click here to enter text.
Study Title	
Study Type	Choose an item.
Other:	Click here to enter text.
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Site #1 Type	Choose an item.
Site #1 Name	Click here to enter text.
Select one:	Choose an item.
Street	Click here to enter text.
City	Click here to enter text.
State	Click here to enter text.
Country	Choose an item.
tel	Click here to enter text.
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Investigator	Click here to enter text.
email	Click here to enter text.
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Site #2 Type	Choose an item.
Site #2 Name	Click here to enter text.
Select one:	Choose an item.
Street	Click here to enter text.
City	Click here to enter text.
State	Click here to enter text.
Country	Choose an item.
tel	Click here to enter text.
fax	Click here to enter text.
Investigator	Click here to enter text.
email	Click here to enter text.
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Site #3 Type	Choose an item.
Site #3 Name	Click here to enter text.
Select one:	Choose an item.
Street	Click here to enter text.
City	Click here to enter text.
State	Click here to enter text.
Country	Choose an item.
tel	Click here to enter text.
fax	Click here to enter text.
Investigator	Click here to enter text.
email	Click here to enter text.
Study Report: (location, eg., 5.3.1.2)	Click here to add report link.
Validation Report: (eg., 5.3.1.2)	Click here to add report link.

Bioanalytical Report: (eg., 5.3.1.4)	<a href="#">Click here to add report link.</a>
<i>(please include specific review concerns or items to be addressed during the inspection in the appendix below)</i>	

## ***I. Appendix***

<b>Specific Items To be Addressed During the Inspection</b>
Clinical Site
a. General conduct of the study
b. Subject Disposition
c. Retain Samples
d. Bioanalytical sample prep work and storage
Analytical Site: Verify the validity of assay and the reported concentrations

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/s/  
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PHUONG N TON  
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# ATTACHMENT 3

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RUBEN C AYALA  
02/28/2019 11:24:06 AM

ARINDAM DASGUPTA  
02/28/2019 12:45:13 PM