

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211675Orig1s000

NON-CLINICAL REVIEW(S)

Tertiary Pharmacology/Toxicology Review

Date: July 5, 2019
From: Timothy J. McGovern, PhD, ODE Associate Director for
Pharmacology and Toxicology, OND IO
NDA: 211675
Agency receipt date: December 18, 2018
Drug: Upadacitinib
Sponsor: AbbVie, Inc.

Indication: Treatment of moderately to severely active rheumatoid arthritis in adults 18 years of age or older

Reviewing Division: Division of Pulmonary, Allergy, and Rheumatology Products

The primary pharmacology/toxicology reviewer and supervisor concluded that the nonclinical data for upadacitinib support approval for the indication listed above. The proposed clinical dose is 15 mg per day as an extended release tablet.

Upadacitinib is a Janus kinase (JAK) inhibitor. The molecule showed selectivity for JAK1 relative to JAK2 and JAK3 in in vitro assays but the relationship between inhibition of specific JAK isoforms and clinical effectiveness is unknown. The Established Pharmacologic Class (EPC) for upadacitinib was determined to be “Janus kinase (JAK) inhibitor”. This EPC is consistent with the EPCs for the previously approved JAK inhibitors tofacitinib and baricitinib.

Pivotal nonclinical toxicology studies of upadacitinib were conducted in rats and dogs. In studies up to 6 months duration in rats and 9 months duration in dogs, the most common treatment-related findings in both species included immunosuppressant effects. In rats, liver and kidney toxicity were observed. The nonclinical studies provided safety margins compared to the maximum recommended human dose (MRHD, 15 mg/day) of 22 (rats) and 2 (dogs).

Upadacitinib tested negatively in a battery of genotoxicity assays and was negative in a 2-year carcinogenicity study in rats and a 26-week study in Tg.rasH2 mice. The carcinogenicity findings were evaluated by CDER’s Executive Carcinogenicity Assessment Committee.

Developmental and reproductive studies were conducted with upadacitinib in rats and rabbits. Fertility (increased postimplantation loss and reduced live fetuses per litter) was affected in rats. In embryofetal development studies, upadacitinib was teratogenic with skeletal malformations observed in rats and rabbits; other findings and decreased fetal body weights and increased postimplantation loss in rabbits. NOAELs related to developmental toxicity of 1.5 and 10 mg/kg/day in rats and rabbits, respectively, were identified; the NOAELs provided an approximate 0.3- to 2.2-fold exposure margin based on anticipated human exposure at the MRHD. While the observed findings are consistent with those observed with other JAK inhibitors, the findings with upadacitinib occurred at

very low clinical exposure margins. The review team concluded that the Warnings and Precautions section of the product label should discuss the embryo-fetal toxicity associated with upadacitinib and that pregnancy testing should be recommended for women of reproductive potential prior to starting treatment. Upadacitinib was observed in the milk of lactating rats at levels ~ 30-fold greater than that in plasma.

Conclusion: I agree with the Division pharmacology/toxicology conclusion that this NDA can be approved from the pharmacology/toxicology perspective. The EPC for upadacitinib is appropriate. I have discussed and agree with labeling revisions currently proposed by the Division.

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/s/

TIMOTHY J MCGOVERN
07/05/2019 11:57:07 AM

Pharmacology and Toxicology Secondary Review for NDA 211675

Date:

June 7, 2019

To:

NDA 211675

Upadacitinib (UPA) extended release tablets

Abbvie

From:

Andrew Goodwin, PhD

Pharmacology-Toxicology Supervisor

Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Abbvie submitted this 505(b)(1) NDA seeking approval of upadacitinib (UPA) for the treatment of rheumatoid arthritis (RA) in adults ≥ 18 years of age. Upadacitinib is administered orally at a dose of 15 mg once daily.

The applicant conducted a broad program of nonclinical pharmacology and toxicology studies to characterize UPA. These studies have been reviewed in detail under IND 114717 and NDA 211675. Refer to the IND nonclinical reviews as well as the primary nonclinical review by Dr. Brett Jones dated May 21, 2019.

Upadacitinib is formulated as 15 mg extended-release tablets. There are no nonclinical safety concerns with the levels of excipients in the product. Nonclinical safety assessment was conducted on a range of observed and potential impurities and degradants. At this time, there are no outstanding issues and the applicant has provided adequate data and/or justification to support safety from the nonclinical perspective.

Abbvie conducted a variety of in vitro and in vivo studies to assess the pharmacological activity of UPA against the related kinases JAK1, JAK2, JAK3, and TYK2. In a cell-free enzyme assay, UPA inhibited JAK1 ($IC_{50} = 43$ nM) and JAK2 (120 nM) with greater potency than JAK3 (2.3 μ M) and TYK2 (4.7 μ M). In human cell-based assays of inhibition of STAT phosphorylation, UPA more potently inhibited JAK1/JAK1 ($EC_{50} = 9$ nM) and JAK1/JAK3 (13 nM) mediated signaling compared to JAK2/JAK2-mediated signaling (628 nM). While UPA does display some degree of selectivity towards JAK1 based on in vitro assays, the relationship between inhibition of specific JAK isoforms and clinical effectiveness is unknown. Therefore, the applicant's proposal to describe UPA as a "selective JAK1 inhibitor" was not considered justified based on being unduly

promotional and not clinically meaningful.¹ The review team concluded that the Established Pharmacologic Class (EPC) for UPA is “Janus Kinase (JAK) inhibitor” – consistent with prior approved therapies in this class for RA (i.e., tofacitinib and baricitinib).

The general toxicology program with UPA was conducted in rats and dogs. In rats, high doses of UPA resulted in mortality as well as liver (necrosis) and kidney (tubular epithelial degeneration / regeneration) toxicities. Additional findings were related to the pharmacological activity of the drug (i.e., decreased red blood cell mass, decreased white blood cell counts, and lymphoid depletion). No adverse findings were noted in a chronic rat study at a dose level resulting in exposures 13 times higher than the proposed clinical dose. In a chronic dog study, no adverse findings were noted at a dose level resulting in exposures 2 times higher than the proposed clinical dose. Key findings in the dog study were considered related to immunosuppression (i.e., skin infection, inflammation and cysts as well as lymphoid depletion).

The developmental and reproductive toxicity of UPA was evaluated in fertility, embryo-fetal development (EFD), and pre/post-natal development (PPND) studies. Adverse effects attributed to UPA were observed in the rat fertility (increased postimplantation loss and reduced live fetuses per litter), rat EFD (skeletal malformations), and rabbit EFD (skeletal malformations, postimplantation loss, decreased fetal body weights) studies. No adverse findings were noted in the PPND study.

Upadacitinib is a potent teratogen in rats and rabbits, with NOAELs in these studies associated with exposures similar to or less than the proposed clinical dose. While other approved JAK inhibitors are also teratogenic, the review team expressed concern regarding the lack of exposure margins between the embryo-fetal toxicity and the proposed clinical dose level. Based on discussion among the nonclinical review team, clinical review team (Dr. Keith Hull and Dr. Rachel Glaser), DPARP management, ODE2 Pharmacology-Toxicology Associate Director Dr. Timothy McGovern, and the Division of Pediatric and Maternal Health, a consensus was reached that the UPA label should include a Warning for embryo-fetal toxicity based on nonclinical data.

Upadacitinib was considered negative for genotoxic potential based on a standard battery of in vitro and in vivo assays. Carcinogenic potential was evaluated in a two-year study in rats and a six-month study in transgenic mice. The CDER Executive

¹ Refer to *Guidance for Industry and Review Staff Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information* (October 2009)

Carcinogenicity Assessment Committee (ECAC) concluded that there were no drug-related neoplasms in either study.

Dr. Jones reviewed the nonclinical sections of the UPA product labeling and provided comments in a labeling review dated June 3, 2019. I concur with the recommended labeling edits for the EPC, Section 5, Section 8, Section 12, and Section 13.

There are no outstanding nonclinical issues. I concur with Dr. Jones's conclusion that NDA 211675 is recommended for approval from the pharmacology-toxicology perspective.

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

/s/

ANDREW C GOODWIN
06/07/2019 10:53:47 AM

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

PHARMACOLOGY/TOXICOLOGY NDA LABELING REVIEW AND EVALUATION

Application number: NDA 211675
Supporting document/s: SDN 002
Applicant's letter date: December 18, 2018
CDER stamp date: December 18, 2018
Product: Upadacitinib (ABT-494, A-1293543)
Indication: Rheumatoid arthritis
Applicant: AbbVie Inc.
Review Division: Division of Pulmonary, Allergy, and
Rheumatology Products
Reviewer: Brett Jones, PhD
Supervisor/Team Leader: Andrew Goodwin, PhD
Division Director: Sally Seymour, MD
Project Manager: Nina Ton, PharmD

Template Version: September 1, 2010

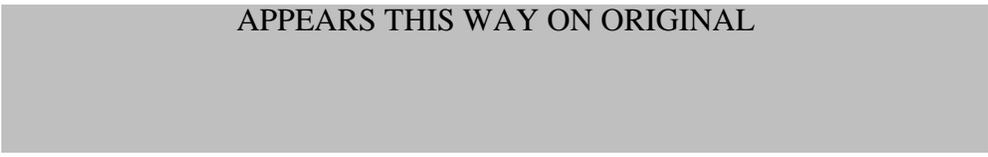
Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 211675 are owned by Abbvie or are data for which Abbvie has obtained a written right of reference. Any information or data necessary for approval of NDA 211675 that Abbvie does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 211675.

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APPEARS THIS WAY ON ORIGINAL



1 Executive Summary

1.1 Introduction

AbbVie Inc. submitted an original 505(b)(1) New Drug Application (NDA) 211675 on December 18, 2018, for upadacitinib. This is a review of the nonclinical sections of the Sponsor's proposed labeling submitted on December 18, 2018. This review evaluated the Sponsor's proposed prescribing information for Indications and Usage and Warnings and Precautions (both under Highlights of Prescribing Information), Section 5.X (Embryo-Fetal Toxicity), Section 8.1 (Pregnancy), Section 8.2 (Lactation), Section 8.3 (Females and Males of Reproductive Potential), Section 12.1 (Mechanism of Action), and Section 13 (Nonclinical Toxicology). An integrated review and evaluation of the nonclinical pharmacology and toxicology studies to support the safety of upadacitinib for approval was completed on May 21, 2019.

1.3 Recommendations

1.3.3 Labeling

Provided below are the recommended nonclinical changes to the sections of the Sponsor's proposed prescribing information mentioned in the Introduction.

The underlined text is recommended for insertion and the ~~striketrough~~ text is recommended for deletion.

HIGHLIGHTS OF PRESCRIBING INFORMATION INDICATIONS AND USAGE

TRADENAME is a ^{(b) (4)} Janus kinase (JAK) 4 inhibitor

(b) (4)

(b) (4)

WARNINGS AND PRECAUTIONS

- Serious Infections: Avoid use of TRADENAME in patients with active, serious infection, including localized infections. (5.1)
- Vaccinations: Avoid use of TRADENAME with live vaccines. (5.2)
- Malignancy: Consider the risks and benefits of TRADENAME treatment prior to initiating therapy in patients with a known malignancy. (5.3)
- Laboratory Monitoring: Recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids. (5.4)
- 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. (5.5, 8.1, 8.3)

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 and rabbits during organogenesis (b) (4) caused increases (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 4 weeks following completion of therapy [see Use in Specific Populations (8.1, 8.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited human data on use of (b) (4) TRADENAME in pregnant women are not sufficient to evaluate (b) (4) a drug-associated risk for major birth defects or (b) (4) miscarriage. Based on animal studies, upadacitinib has the potential to adversely affect a developing fetus.

In animal embryo-fetal development studies, oral upadacitinib administration to pregnant rats and rabbits at exposures equal to or greater than approximately 1.6 and 15 times the maximum recommended human dose (MRHD), respectively, resulted in dose-related increases in skeletal malformations, increased post-implantation loss (rabbits only), and decreased fetal body weights (rabbits only). No developmental toxicity was observed in pregnant rats and rabbits (b) (4)

In a pre- and post-natal development study in pregnant female rats, oral upadacitinib administration at exposures approximately 3 times the MRHD resulted in no maternal or developmental toxicity [see Animal Data]. (b) (4)

The estimated background risks of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. (b) (4) In the U.S. general population, the estimated background risk of major birth defects and miscarriages (b) (4) are 2–4% and 15–20% (b) (4) respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo/Fetal Risk

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data

Animal Data

(b) (4)

In an oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 5, 25, and 75 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that consisted of misshapen humerus and bent scapula) at exposures equal to or greater than approximately 1.7 times the MRHD (on an AUC basis at maternal oral doses of 5 mg/kg/day and higher). Additional skeletal malformations ((b) (4) bent forelimbs/hindlimbs) and decreased fetal body weights were observed in the absence of maternal toxicity at an exposure approximately 84 times the MRHD (on an AUC basis at a maternal oral dose of 75 mg/kg/day).

(b) (4)

In a second oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 1.5 and 4 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that (b) (4) bent humerus, (b) (4)) at exposures (b) (4) (b) (4) approximately 1.6 times the MRHD (on an AUC basis at maternal oral doses of 4 mg/kg/day and higher). No developmental toxicity was observed in rats at an exposure approximately 0.3 times the MRHD (on an AUC basis at a maternal oral dose of 1.5 mg/kg/day).

In an oral embryo-fetal developmental study, pregnant rabbits received upadacitinib at doses of 2.5, 10, and 25 mg/kg/day during the period of organogenesis from gestation day 7 to 19. Embryo lethality, decreased fetal body weights, and (b) (4) malformations (b) (4) were observed in the presence of maternal toxicity at an exposure approximately 15 times the MRHD (on an AUC basis at a maternal oral dose of 25 mg/kg/day). Embryo lethality consisted of increased post-implantation loss that was due to elevated incidences of both total and early resorptions. No developmental toxicity was observed in rabbits at an exposure approximately 2 times the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

(b) (4)

In an oral pre- and post-natal development study, pregnant female rats received upadacitinib at doses of 2.5, 5, and 10 mg/kg/day from gestation day 6 through lactation day 20. No maternal or developmental toxicity was observed in either mothers or offspring, respectively, at an exposure approximately 3 times the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

(b) (4)

8.2 Lactation

Risk Summary

There are no data on the presence of upadacitinib in human milk, the effects of the drug on the breastfed infant, or the effects

(b) (4)

on milk production.

(b) (4)

Available

pharmacodynamic/toxicological data in animals have shown excretion of upadacitinib in milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with upadacitinib, and for

(b) (4)

after the last dose.

(b) (4)

Data

Animal Data

A single oral dose of 10 mg/kg radiolabeled upadacitinib was administered to lactating female Sprague-Dawley rats on post-partum days 7-8. Drug exposure was approximately 30-fold greater in milk than in maternal plasma based on AUC_{0-t} values.

(b) (4)

-Approximately 97% of drug-related material in milk was parent drug.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

(b) (4)

Contraception

Females

(b) (4)

Based on animal studies, upadacitinib can cause embryo-fetal harm when administered to pregnant women [see *Use in Specific Populations (8.1)*]. Advise female (b) (4) patients of reproductive potential to use (b) (4) effective contraception (b) (4) during treatment with TRADENAME and for 4 weeks after (b) (4) the final dose (b) (4)

(b) (4)

(b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Upadacitinib is a Janus kinase (JAK) inhibitor. (b) (4) (JAKs) are (b) (4) intracellular enzymes which (b) (4) transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence (b) (4) cellular processes of (b) (4) hematopoiesis and immune cell function (b) (4). Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Upadacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs. (b) (4)

(b) (4)

(b) (4) JAK enzymes transmit cytokine signaling through their pairing (e.g., JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, JAK2/JAK2, JAK2/TYK2). In a cell-free isolated enzyme assay, upadacitinib had greater inhibitory potency at JAK1 and JAK2 relative to JAK3 and TYK2 (b) (4)

In human leukocyte cellular assays, upadacitinib inhibited cytokine-induced STAT phosphorylation mediated by JAK1/JAK1 and

JAK1/JAK3 more potently than JAK2/JAK2 mediated STAT phosphorylation (b) (4)

However, the relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of upadacitinib was evaluated in Sprague-Dawley rats and Tg.rasH2 mice. No evidence of tumorigenicity was observed in male or female rats that received upadacitinib for up to 101 weeks at oral doses up to 15 or 20 mg/kg/day, respectively (approximately 4 and 10 times the MRHD (b) (4) on an AUC basis (b) (4) respectively). No evidence of tumorigenicity was observed in male or female Tg.rasH2 mice that received upadacitinib for 26 weeks at oral doses up to 20 mg/kg/day (b) (4)

Mutagenesis

Upadacitinib tested negatively in the following genotoxicity assays: the *in vitro* bacterial mutagenicity assay (Ames assay), *in vitro* chromosome aberration assay in human peripheral blood lymphocytes, and *in vivo* rat bone marrow micronucleus assay (b) (4)

Impairment of Fertility

Upadacitinib had no effect on fertility in male or female rats at oral doses up to 50 mg/kg/day in males and 75 mg/kg/day in females (approximately (b) (4) and 84 times the MRHD in males and females, respectively, on an AUC basis) (b) (4)

However, maintenance of pregnancy was adversely affected at oral doses of 25 mg/kg/day and 75 mg/kg/day based upon dose-related findings of increased post-implantation losses (increased resorptions) and decreased numbers of mean viable embryos per litter (approximately 22 and 84 times the MRHD on an AUC basis, respectively). The number of viable embryos was unaffected in female rats that received upadacitinib at an oral dose of 5 mg/kg/day and were mated to males that received the same dose (approximately 2 times the MRHD on an AUC basis). (b) (4)

(b) (4)

11 Integrated Summary and Safety Evaluation

Presented below is the Sponsor's proposed wording for the upadacitinib product insert. The Sponsor's proposed text is from their draft prescribing information dated December 18, 2018. Also presented below are the nonclinical revisions to the Sponsor's proposed labeling and a rationale for the proposed changes. The underlined text is recommended for insertion and the ~~strike through~~ text is recommended for deletion from the Sponsor's proposed text.

The approved label for OLUMIANT (baracitinib) was used for reference as it is a recently approved JAK inhibitor, which is the same FDA established pharmacologic class (EPC) as upadacitinib.

Sponsor's Proposed Labeling for Indications and Usage and Warnings and Precautions in the Highlights of Prescribing Information Section:

HIGHLIGHTS OF PRESCRIBING INFORMATION INDICATIONS AND USAGE

TRADENAME is a ^{(b) (4)} Janus kinase (JAK) 1 inhibitor

(b) (4)

(b) (4)

WARNINGS AND PRECAUTIONS

- Serious Infections: Avoid use of TRADENAME in patients with active, serious infection, including localized infections. (5.1)
- Vaccinations: Avoid use of TRADENAME with live vaccines. (5.2)
- Malignancy: Consider the risks and benefits of TRADENAME treatment prior to initiating therapy in patients with a known malignancy. (5.3)
- Laboratory Monitoring: Recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids. (5.4)

DPARP's Proposed Nonclinical Labeling for Indications and Usage and Warnings and Precautions in the Highlights of Prescribing Information:

HIGHLIGHTS OF PRESCRIBING INFORMATION INDICATIONS AND USAGE

TRADENAME is a ^{(b) (4)} Janus kinase (JAK) 4 inhibitor

(b) (4)

(b) (4)

WARNINGS AND PRECAUTIONS

- Serious Infections: Avoid use of TRADENAME in patients with active, serious infection, including localized infections. (5.1)
- Vaccinations: Avoid use of TRADENAME with live vaccines. (5.2)
- Malignancy: Consider the risks and benefits of TRADENAME treatment prior to initiating therapy in patients with a known malignancy. (5.3)
- Laboratory Monitoring: Recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids. (5.4)
- 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. (5.5, 8.1, 8.3)

Rationale for Changes in Indications and Usage and Warnings and Precautions in the Highlights of Prescribing Information Section:

Nonclinical reviewed the EPC class for upadacitinib (b) (4) (b) (4) JAK inhibitor is recognized as an FDA EPC. The pharmacology studies conducted with upadacitinib support the classification of upadacitinib as a JAK inhibitor.

An additional bullet statement regarding the potential for embryo-fetal toxicity with upadacitinib was added to the Warnings and Precautions based on a consultation with DPMH and discussions with the Clinical Team. Upadacitinib is teratogenic in rats and rabbits and is associated with skeletal malformations in rats at doses of ≥ 4 mg/kg/day in the absence of maternal toxicity and cardiac malformations in rabbits concurrent with maternal toxicity. The finding of teratogenicity in rats and rabbits at clinically relevant exposures indicated a serious risk for human fetal toxicity. In the DPMH consult review, the reviewer stated that a higher level of concern regarding the animal's findings for upadacitinib was reasonable based upon the lower exposure margins to proposed clinical dose levels. Based on the Guidance and precedent established with other approved small molecule kinase inhibitor products, DPMH stated that labeling for upadacitinib should include a Warning and Precaution for embryo-fetal toxicity.

DPARP's Proposed Nonclinical Labeling for Section 5.X:

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 and rabbits during organogenesis (b) (4) caused increases (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 4 weeks following completion of therapy [see Use in Specific Populations (8.1, 8.3)].

Rationale for Changes in Section 5.X:

DPMH proposed additional language for Section 5.X to highlight the potential for embryo-fetal toxicity with upadacitinib at clinically relevant maternal plasma exposures. See above for further details.

Sponsor's Proposed Labeling for Sections 8.1, 8.2, and 8.3:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited human data (b) (4) TRADENAME in pregnant women are not sufficient to (b) (4) drug-associated risk for major birth defects and miscarriage.

(b) (4)

In animal embryofetal development studies, (b) (4)

(b) (4)

The estimated background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. (b) (4) in the U.S. general population of major birth defects and miscarriages are 2–4% and 15–20% of clinically recognized pregnancies, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data

Animal Data

(b) (4)

(b) (4)

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Infertility

Based on findings in rats, treatment with upadacitinib does not reduce fertility in males or females of reproductive potential [see *Nonclinical Toxicology (13.1)*].

DPARP's Proposed Nonclinical Labeling for Sections 8.1, 8.2, and 8.3:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited human data on use of (b) (4) TRADENAME in pregnant women are not sufficient to evaluate (b) (4) a drug-associated risk for major birth defects or and miscarriage. Based on animal studies, upadacitinib has the potential to adversely affect a developing fetus.

In animal embryo-fetal development studies, oral upadacitinib administration to pregnant rats and rabbits at exposures equal to or greater than approximately 1.6 and 15 times the maximum recommended human dose (MRHD), respectively, resulted in dose-related increases in skeletal malformations, increased post-implantation loss (rabbits only), and decreased fetal body weights (rabbits only). No developmental toxicity was observed in pregnant rats and rabbits (b) (4)

In a pre- and post-natal development study in pregnant female rats, oral upadacitinib administration at exposures approximately 3 times the MRHD resulted in no maternal or developmental toxicity [see *Animal Data*]. (b) (4)

The estimated background risks of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. (b) (4) In the U.S. general population, the estimated background risk of major birth defects and miscarriages (b) (4) (b) (4) 2–4% and 15–20% (b) (4) respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo/Fetal Risk

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

DataAnimal Data

(b) (4)

In an oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 5, 25, and 75 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that consisted of misshapen humerus and bent scapula) at exposures equal to or greater than approximately 1.7 times the MRHD (on an AUC basis at maternal oral doses of 5 mg/kg/day and higher). Additional skeletal malformations ((b) (4) bent forelimbs/hindlimbs) and decreased fetal body weights were observed in the absence of maternal toxicity at an exposure approximately 84 times the MRHD (on an AUC basis at a maternal oral dose of 75 mg/kg/day)

(b) (4)

In a second oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 1.5 and 4 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that (b) (4) bent humerus, (b) (4)) at exposures (b) (4) (b) (4) approximately 1.6 times the MRHD (on an AUC basis at maternal oral doses of 4 mg/kg/day and higher). No developmental toxicity was observed in rats at an exposure approximately 0.3 times the MRHD (on an AUC basis at a maternal oral dose of 1.5 mg/kg/day).

In an oral embryo-fetal developmental study, pregnant rabbits received upadacitinib at doses of 2.5, 10, and 25 mg/kg/day during the period of organogenesis from gestation day 7 to 19. Embryo lethality, decreased fetal body weights, and (b) (4) malformations (b) (4) were observed in the presence of maternal toxicity at an exposure approximately 15 times the MRHD (on an AUC basis at a maternal oral dose of 25 mg/kg/day). Embryo lethality consisted of increased post-implantation loss that was due to elevated incidences of both total and early resorptions. No developmental toxicity was observed in rabbits at an exposure approximately 2 times the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

(b) (4)

(b) (4)

In an oral pre- and post-natal development study, pregnant female rats received upadacitinib at doses of 2.5, 5, and 10 mg/kg/day from gestation day 6 through lactation day 20. No maternal or developmental toxicity was observed in either mothers or offspring, respectively, at an exposure approximately 3 times the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

(b) (4)

8.2 Lactation

Risk Summary

There are no data on the presence of upadacitinib in human milk, the effects of the drug on the breastfed infant, or the effects

(b) (4)

on milk production.

(b) (4)

Available

pharmacodynamic/toxicological data in animals have shown excretion of upadacitinib in milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with upadacitinib, and for

(b) (4)

after the last dose.

(b) (4)

Data

Animal Data

A single oral dose of 10 mg/kg radiolabeled upadacitinib was administered to lactating female Sprague-Dawley rats on post-partum days 7-8. Drug exposure was approximately 30-fold greater in milk than in maternal plasma based on AUC_{0-t} values.

(b) (4)

-Approximately 97% of drug-related material in milk was parent drug.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

(b) (4)

Contraception

Females

(b) (4)

Based on animal studies, upadacitinib can cause embryo-fetal harm when administered to pregnant women [see Use in Specific Populations (8.1)]. Advise females patients of reproductive potential to use (b) (4) effective contraception (b) (4) during treatment with TRADENAME and for 4 weeks after (b) (4) the final dose of (b) (4)

(b) (4)

Rationale for Changes to Sections 8.1, 8.2, and 8.3:

General edits were made to Sections 8.1, 8.2, and 8.3 to remove unnecessary subheadings and text. Sections 8.1, 8.2, and 8.3 of the upadacitinib product label were modified to be consistent with the OLUMIANT product label.

Additional language is proposed for the Risk Summary and Animal Data in Section 8.1 to provide specific details on the routes of administration, dose levels, and observed toxicity findings of the embryo-fetal development studies conducted with upadacitinib. For the animal data, the consistent inclusion of AUC ratios was also added. These changes were made to maintain consistency with division labeling practices for comparable products and are based on the recommendations in the *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* guidance document (June 2015).

An additional subheading (i.e., Pregnancy Testing) and text is proposed for Section 8.3 to highlight the potential for upadacitinib to cause fetal harm and to advise females of reproductive potential to have a pregnancy test prior to treatment.

Sponsor's Proposed Labeling for Section 12.1:

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4)

(b) (4)

(b) (4)

DPARP's Proposed Nonclinical Labeling for Section 12.1:

12 CLINICAL PHARMACOLOGY**12.1 Mechanism of Action**

Upadacitinib is a Janus kinase (JAK) inhibitor. (b) (4) (JAKs) are (b) (4) intracellular enzymes which (b) (4) transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence (b) (4) hematopoiesis and immune cell function (b) (4). Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Upadacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs. (b) (4)

(b) (4) JAK enzymes transmit cytokine signaling through their pairing (e.g., JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, JAK2/JAK2, JAK2/TYK2). In a cell-free isolated enzyme assay, upadacitinib had greater inhibitory potency at JAK1 and JAK2 relative to JAK3 and TYK2. (b) (4)

In human leukocyte cellular assays, upadacitinib inhibited cytokine-induced STAT phosphorylation mediated by JAK1/JAK1 and JAK1/JAK3 more potently than JAK2/JAK2 mediated STAT phosphorylation (b) (4)

However, the relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known.

Rationale for Changes to Section 12.1:

Revisions to Section 12.1 were made to be consistent with the OLUMIANT label, as both upadacitinib and OLUMIANT are JAK inhibitors with a similar mechanism of action. Also, any potential promotional language was removed.

The second paragraph of 12.1 was also revised to include additional data on *in vitro* pharmacology studies conducted with upadacitinib.

Sponsor's Proposed Labeling for Sections 13.1 and 13.2:

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[Redacted] (b) (4)

Carcinogenesis

The carcinogenic potential of upadacitinib was evaluated in Sprague-Dawley rats and Tg.rasH2 mice. No evidence of tumorigenicity was observed in male or female rats that received upadacitinib for up to 101 weeks at oral doses up to 15 or 20 mg/kg/day, respectively (approximately 4 and 10 times the [Redacted] (b) (4) on an AUC basis [Redacted] (b) (4), respectively). No evidence of tumorigenicity was observed in Tg.rasH2 mice that received upadacitinib for 26 weeks at oral doses up to 20 mg/kg/day [Redacted] (b) (4)

Mutagenesis

[Redacted] (b) (4)

Impairment of Fertility

Upadacitinib had no effect on fertility in male or female rats at doses up to 50 mg/kg/day in males and 75 mg/kg/day in females [Redacted] (b) (4)

[Redacted] (b) (4)

DPARP's Proposed Nonclinical Labeling for Sections 13.1 and 13.2:

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[Redacted] (b) (4)

Carcinogenesis

The carcinogenic potential of upadacitinib was evaluated in Sprague-Dawley rats and Tg.rasH2 mice. No evidence of tumorigenicity was observed in male or female rats that received upadacitinib for up to 101 weeks at oral doses up to 15 or 20 mg/kg/day, respectively (approximately 4 and 10 times the MRHD (b) (4) on an AUC basis (b) (4) respectively). No evidence of tumorigenicity was observed in male or female Tg.rasH2 mice that received upadacitinib for 26 weeks at oral doses up to 20 mg/kg/day ~~in male or female mice~~.

Mutagenesis

Upadacitinib tested negatively in the following genotoxicity assays: the *in vitro* bacterial mutagenicity assay (Ames assay), *in vitro* chromosome aberration assay in human peripheral blood lymphocytes, and *in vivo* rat bone marrow micronucleus assay (b) (4)

Impairment of Fertility

Upadacitinib had no effect on fertility in male or female rats at oral doses up to 50 mg/kg/day in males and 75 mg/kg/day in females (approximately (b) (4) and 84 times the MRHD in males and females, respectively, on an AUC basis) (b) (4)

However, maintenance of pregnancy was adversely affected at oral doses of 25 mg/kg/day and 75 mg/kg/day based upon dose-related findings of increased post-implantation losses (increased resorptions) and decreased numbers of mean viable embryos per litter (approximately 22 and 84 times the MRHD on an AUC basis, respectively). The number of viable embryos was unaffected in female rats that received upadacitinib at an oral dose of 5 mg/kg/day and were mated to males that received the same dose (approximately 2 times the MRHD on an AUC basis). (b) (4)

Rationale for Changes in Sections 13.1 and 13.2:

General edits were made to Sections 13.1 to remove unnecessary text.

The second paragraph of Section 13.1 was revised to include specific information on the individual assay types.

The paragraph in Section 13.1 regarding fertility was revised to include information on the route of administration of the fertility study in rats (i.e., oral). Additional text was also proposed to provide a description of observed toxicity findings and systemic dose ratios compared to the proposed clinical dose.

[Redacted text block]

(b) (4)

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/s/

BRETT R JONES
06/03/2019 12:33:40 PM

ANDREW C GOODWIN
06/03/2019 03:45:39 PM
I concur

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 211675
Supporting document/s: SDN 0002
Applicant's letter date: December 18, 2018
CDER stamp date: December 18, 2018
Product: Upadacitinib (A-1293543, ABT-494)
Indication: Rheumatoid Arthritis
Applicant: AbbVie Inc.
Review Division: Division of Pulmonary, Allergy, and
Rheumatology Products (DPARP)
Reviewer: Brett Jones, PhD
Supervisor/Team Leader: Andrew Goodwin, PhD
Division Director: Sally Seymour, MD
Project Manager: Nina Ton, PharmD

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 211675 are owned by AbbVie Inc. or are data for which AbbVie Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 211675 that AbbVie Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 211675.

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1 Executive Summary

1.1 Introduction

AbbVie Inc. submitted an original 505(b)(1) New Drug Application (NDA) on December 18, 2018, for upadacitinib as an extended-release tablet for oral use. Upadacitinib is a Janus kinase (JAK) inhibitor proposed for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) at a dose of 15 mg per day. Upadacitinib is proposed as monotherapy or in combination with methotrexate or other conventional synthetic disease-modifying antirheumatic drugs (DMARDs). This review provides brief summaries of the nonclinical pharmacology and toxicology studies to support the safety of upadacitinib for approval. Refer to the relevant Pharmacology and Toxicology Reviews for further information. Upadacitinib was previously referred to by the code names ABT-494 or A-1293543 in certain nonclinical study reports; however, the test article is consistently referred to as upadacitinib (UPA) throughout this review for clarity.

1.2 Brief Discussion of Nonclinical Findings

The Applicant conducted a complete program of nonclinical pharmacology, pharmacokinetics, and toxicology studies with UPA.

In a cell-free isolated enzyme assay, the *in vitro* potency of upadacitinib towards JAK1, JAK2, and JAK3 at 0.1 mM ATP was 0.043 μ M, 0.12 μ M, and 2.3 μ M, respectively. In human leukocytes, UPA inhibited cytokine induced STAT phosphorylation mediated by JAK1/JAK3 and JAK1/JAK1 with comparable potencies. In a concanavalin-induced IFN γ *in vivo* rat model assessing the effects on IL-2 signaling, upadacitinib inhibited IFN γ induction with an ED₅₀ of 0.4 mg/kg. In an Adjuvant-Induced Arthritis (AIA) *in vivo* rat model, oral treatment with UPA resulted in a dose-dependent inhibition of paw swelling, with >90% inhibition observed at 10 mg/kg.

Oral bioavailability was moderate in rats (31%) and higher in both monkeys (59%) and dogs (77%). The mean $t_{1/2}$ of UPA ranged from 1-3 hrs in rats, dogs, and monkeys following IV dosing. Upadacitinib exhibited moderate to high plasma clearance and high volumes of distribution. In repeat dose studies of upadacitinib in mice, rats, rabbits, and dogs, UPA exposure (C_{max} and AUC) increased in greater than a dose-proportional manner across a range of doses. No UPA accumulation was observed following repeat dosing. No sex differences in UPA exposure were observed in mice and dogs; however, in rats AUC values were higher in females than males.

Upadacitinib exhibited low plasma protein binding in all nonclinical species examined.

Unchanged UPA was the primary component in circulation in all species (i.e., >79% plasma radioactivity in humans). The glucuronide metabolite M4 (i.e., 13%) was the major metabolite in human plasma. It was not considered a safety concern. All human metabolites were observed in nonclinical species. Upadacitinib was primarily cleared via

the biliary or renal routes of excretion. Upadacitinib was a weak inducer of CYP3A4 at clinically relevant doses.

General toxicology studies were conducted via the oral route of administration in rats and dogs. The GLP-compliant studies included 4-week studies in rats and dogs (each with a 4-week recovery period) followed by chronic toxicity studies in rats (26-weeks duration) and dogs (39-weeks duration). A GLP-compliant, 4-week, repeat-dose oral toxicity study in CByB6F1-Tg(HRAS)2Jic wild-type mice was conducted to enable dose selection for a 26-week carcinogenicity study in CByB6F1-Tg(HRAS)2Jic hemizygous mice.

In a 26-week toxicology study, rats were administered UPA at doses of 0, 5, 20, or 50 mg/kg/day. The target organs of toxicity for UPA were identified as the kidneys, thymus, spleen, and lymph nodes (mandibular, medial iliac, mediastinal, and mesenteric). Minimal to moderate tubular degeneration/regeneration in the kidneys was observed for males and females in the 50 mg/kg/day treatment groups. This finding was considered adverse and dose-limiting. Lymphoid depletion observed in the thymus, spleen, and lymph nodes correlated with reductions of lymphocyte counts and was considered monitorable in a clinical setting. A No Observed Adverse Effect Level (NOAEL) of 20 mg/kg/day was established for this study based upon observed histopathological findings in the kidneys at 50 mg/kg/day. Mean AUC values for male and female rats at the NOAEL of 20 mg/kg/day on Day 178 were 3.83 and 6.84 $\mu\text{g}\cdot\text{hr}/\text{mL}$, respectively, or 5.32 $\mu\text{g}\cdot\text{hr}/\text{mL}$ for males and females combined (i.e., 13-fold exposure margin to the proposed 15 mg clinical dose; see table 7).

Upadacitinib was administered to beagle dogs at oral doses of 0, 0.1, 0.5, and 1.5 mg/kg/day for up to 39 weeks. The skin was identified as a target organ of toxicity. Increased incidences of interdigital cysts were observed in the skin of males in the 0.5 and 1.5 mg/kg/day treatment groups and in females administered 0.5 mg/kg/day. A dose-dependent increase in severity of mixed, multifocal cell inflammation in the interdigital skin was observed for males in all UPA treatment groups. One male animal (#4005) in the 1.5 mg/kg/day group had dosing suspended on Day 219 due to observed significant skin lesions that included cutaneous inflammation and demodicosis. These findings were attributed to the immunosuppressive effects of UPA and were considered monitorable in a clinical setting. Other target organs of toxicity were identified as the popliteal lymph node (LN), precapsular LN, spleen, and thymus. An increased incidence and severity of mixed cell inflammation was observed in the precapsular and popliteal lymph nodes of males and/or females at ≥ 0.5 mg/kg/day. A decrease in lymphocytes in the spleen and thymus were observed for males at ≥ 0.5 mg/kg/day. These findings were also attributed to the immunosuppressive effects of UPA and were considered monitorable in a clinical setting. A NOAEL of 1.5 mg/kg/day was established for this study. Mean AUC exposure at the NOAEL of 1.5 mg/kg/day on Day 272 was 888 $\text{ng}\cdot\text{hr}/\text{mL}$ (i.e., 2-fold exposure margin to the proposed 15 mg clinical dose; see table 7).

Upadacitinib was non-mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay and was negative in an *in vitro* chromosomal aberration assay for structural

chromosomal aberrations. A significant increase in polyploidy was observed under conditions without metabolic activation (4 or 20 hr exposures); however, upadacitinib was negative in a subsequent *in vivo* rat micronucleus assay.

In a 26-week oral carcinogenicity study, male and female CB6F1-Tg(HRAS)^{2Jic} hemizygous ("TgRas") mice received UPA at doses of 0, 5, 10, and 20 mg/kg/day. No statistically significant test article-related tumor findings in male or female mice were observed. Mean AUC exposure of UPA after oral administration of high dose UPA was 844 ng*hr/mL and 1440 ng*hr/mL, for males and females, respectively. The CDER Executive Carcinogenicity Assessment Committee (ECAC) concurred that the study was adequate and that there were no drug-related neoplasms in males or females in the study.

In a 104-week oral carcinogenicity study, male and female SD rats received UPA at doses of 0, 4, 7.5, and 15 mg/kg/day (males) and 0, 3, 7.5, and 20 mg/kg/day (females). There were no test article-related effects on mortality. No statistically significant test article-related tumor findings in male and female rats were observed. Mean AUC exposure of UPA following oral administration of high dose UPA was 1.67 µg*hr/mL (15 mg/kg/day) and 4.17 µg*hr/mL (20 mg/kg/day), for males and females, respectively. The ECAC concurred that the study was adequate and that there were no drug-related neoplasms in males or females in the study.

The reproductive and developmental toxicity of upadacitinib was evaluated in: (1) an oral developmental toxicity study in rats (2 studies), 2) an oral developmental toxicity study in rabbits, and 3) an oral pre-/postnatal developmental (PPND) toxicity study in rats. An oral male and female fertility study in rats was also conducted.

In an initial oral embryo-fetal development (EFD) study in rats at doses of 0, 5, 25, and 75 mg/kg/day UPA, no maternal toxicity was observed. However, UPA was associated with fetal skeletal malformations and variations at all doses. Due to the observed fetal malformations at all treatment doses, the NOAEL for developmental toxicity in this study was unable to be established.

In a second low dosage oral EFD study in rats at doses of 0, 1.5, and 4 mg/kg/day UPA, one single fetus (#12) from a 4 mg/kg/day female (Animal #3519) exhibited skeletal malformations of bent humerus, bent radius, bent ulna, misshapen tympanic ring, misshapen neural arches (thoracic vertebra) and fused neural arches (cervical vertebra). These findings were considered treatment-related and adverse based on consistency with the findings at ≥5 mg/kg/day in the prior study. The NOAEL for maternal toxicity was 4 mg/kg/day. The NOAEL for developmental toxicity was 1.5 mg/kg/day. Mean AUC exposure at the NOAEL for developmental toxicity was 115 ng*hr/mL (i.e., 0.3-fold exposure margin at the proposed 15 mg clinical dose; see table 7).

In the oral EFD study in rabbits, UPA was administered at doses of 0, 2.5, 10, and 25 mg/kg/day. Embryoletality observed at 25 mg/kg/day was considered adverse and test

article related. In addition, UPA at 25 mg/kg/day was associated with increased post-implantation loss and total/early resorptions and decreased fetal body weight and gravid uterine weight. Fetal visceral malformations (i.e., thoracic cavity) and skeletal variations and malformations (i.e., sternum) were observed in offspring at 25 mg/kg/day. The NOAEL for maternal and developmental toxicity was determined to be 10 mg/kg/day. Mean AUC exposure at the NOAEL for maternal and developmental toxicity was 881 ng*hr/mL (i.e., 2-fold exposure margin at the proposed 15 mg clinical dose; see table 7).

In the oral PPND study with pregnant rats, UPA at doses up to 10 mg/kg/day produced no evidence of maternal toxicity, embryofetal toxicity, or postnatal toxicity. The NOAEL for both maternal and peri/postnatal toxicity was the high dose (10 mg/kg/day). Mean AUC exposure at the NOAEL for maternal and peri-postnatal toxicity was 1090 ng*hr/mL (i.e., ~3-fold exposure margin at the proposed 15 mg clinical dose; see table 7).

In an oral fertility study in rats at doses of 0, 5, 25, 50 (M), and 75 (F) mg/kg/day UPA, no test article-related effects on male or female mating and fertility indices were observed; therefore, 50 mg/kg/day and 75 mg/kg/day UPA were considered as the NOAELs for male and female fertility, respectively. Doses of 25 mg/kg/day UPA or greater were associated with increased post-implantation loss, an increased number of resorptions, and decreased mean number of live concepti per litter. These effects were considered adverse and the NOAEL for early embryonic development was considered as 5 mg/kg/day UPA. Mean AUC exposure at the NOAEL for early embryonic development was estimated at 680 ng*hr/mL (i.e., ~2-fold exposure margin at the proposed 15 mg clinical dose).

Upadacitinib was embryo-lethal in rabbits and teratogenic in rats and rabbits and is associated with skeletal malformations in rats at doses of ≥ 4 mg/kg/day in the absence of maternal toxicity and cardiac and skeletal malformations in rabbits concurrent with maternal toxicity. The finding of teratogenicity in rats and rabbits at clinically relevant exposures indicates a serious risk for human fetal toxicity. This was not an unexpected finding due to the pharmacological activity of upadacitinib and similar findings reported for other JAK inhibitors. However, the nonclinical reviewer considered the embryo-fetal toxicity data with upadacitinib as comparatively more concerning than previously approved JAK inhibitor products (e.g., tofacitinib, baricitinib) based on the observed lower exposure margins to proposed clinical dose levels. A consult request was submitted to the Division of Pediatric and Maternal Health (DPMH) to review the embryo-fetal toxicity issue for possible inclusion into the Warnings and Precautions section of the proposed product label. Based on the guidance and precedent established with other approved small molecule kinase inhibitor products, DPMH recommended that labeling for upadacitinib should include a Warning and Precaution for embryo-fetal toxicity. After discussion with the DPARP clinical review team, the pharmacology-toxicology review team agrees and recommends labeling edits to communicate this risk based on nonclinical data. Specifically, the labeling recommendations include a Warning for Embryo-Fetal toxicity (Highlights and Section

5), risk summary and detailed animal data (Section 8.1), as well as pregnancy testing and contraception use for females of reproductive potential (Section 8.3).

Treatment-related reversible findings of decreased lymphocytes in lymphoid tissues and decreases in RBC mass were observed in toxicology studies in rats and dogs. Following chronic dosing in dogs, nonclinical findings of immunosuppression were also observed (i.e., ~2-fold exposure margin to clinical dose on AUC basis). Dose-limiting findings of renal tubular degeneration/regeneration in the kidney were observed in rats at higher doses (i.e., 43-fold exposure margin to clinical dose on AUC basis). No evidence of genotoxicity, phototoxicity, or carcinogenicity of upadacitinib was observed. The Applicant has adequately characterized the pharmacology and toxicology of UPA and the totality of the data support approval for chronic use in RA at the proposed 15 mg daily dose.

1.3 Recommendations

- **1.3.1 Approvability**

From the nonclinical perspective, NDA 211,675 is recommended for approval.

- **1.3.2 Additional Non Clinical Recommendations**

None.

- **1.3.3 Labeling**

Nonclinical sections of the product label will be evaluated in a separate review.

2 Drug Information

2.1 Drug

CAS Registry Number

1310726-60-3

Generic Name

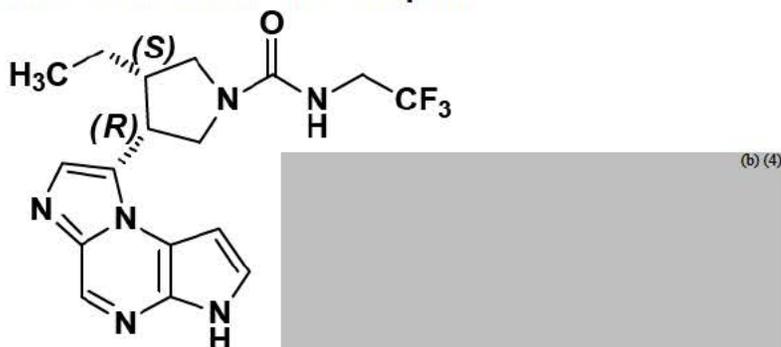
Upadacitinib

Code Name

ABT-494, A-1293543

Chemical Name

(3S,4R)-3-Ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazine-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrate (2:1)

Molecular Formula/Molecular WeightC₁₇H₁₉F₃N₆O · (b) (4)**Structure or Biochemical Description****Pharmacologic Class**

Janus kinase (JAK) inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 114717:

2.3 Drug Formulation

The drug product is provided as an extended-release, (b) (4) tablet containing 15 mg of upadacitinib.

(Excerpt from Sponsor's submission)

Table 1. Qualitative composition of 15 mg upadacitinib tablets

Component	Quality Standard	Function	Amount (mg)/Tablet
(b) (4)			

(Excerpt from Sponsor's submission)

Table 2. Composition

(b) (4)	
(b) (4)	

2.4 Comments on Novel Excipients

There are no safety concerns with the proposed excipients.

2.5 Comments on Impurities/Degradants of Concern

None. Refer to the Pharmacology and Toxicology Reviews of IND 114,717 by Dr. Jessica Bonzo and Dr. Brett Jones dated January 11, 2019 and April 22, 2019, respectively, for nonclinical safety evaluations of identified impurities in the drug product. There are no safety concerns related to UPA impurities for the proposed dose, duration, and patient population.

2.6 Proposed Clinical Population and Dosing Regimen

Upadacitinib is proposed for use in adult patients with moderately to severely active RA as monotherapy or in combination with methotrexate or other conventional synthetic DMARDs. The planned dose of upadacitinib is 15 mg once daily taken orally.

2.7 Regulatory Background

Provided below is a brief summary of the regulatory background related to the nonclinical development program for upadacitinib.

- The initial submission for IND 114,717 by Abbott Laboratories was received on June 1, 2012. The proposed first in human (FIH) phase 1 clinical study was deemed safe to proceed at a maximum clinical single dose of 24 mg UPA based on the 30-day safety review.
- A Special Protocol Assessment (SPA) agreement letter was issued for the two-year rat carcinogenicity assay on April 30, 2015.
- The End of Phase 2 (EOP2) meeting with AbbVie Inc. to discuss the planned phase 3 clinical and nonclinical programs occurred on October 26, 2015 (see meeting minutes dated November 16, 2015).
- An SPA agreement letter was issued for the six-month transgenic mouse carcinogenicity assay on July 27, 2016.
- A pre-NDA meeting occurred on May 1, 2018 with AbbVie Inc to discuss specific clinical, nonclinical, clinical pharmacology, statistics, and regulatory questions related to the NDA submission for upadacitinib (see meeting minutes dated May 31, 2018). It was agreed upon at the meeting that the upadacitinib nonclinical program was sufficient to support submission and review of an NDA. It was also agreed upon that the Division considers RA a chronic condition and the Division's safety assessment at the time of NDA review will be based on an acceptable daily intake of (b)(4) µg per day for mutagenic or potentially mutagenic impurities.
- Additional communication between the Division and AbbVie in 2018 related to the assessment and qualification of potentially genotoxic impurities in the UPA drug substance.

- The NDA for upadacitinib (15 mg tablet) was submitted on December 18, 2018, and the application was filed on February 8, 2019. Abbvie redeemed a Priority Review Voucher; therefore, the application was granted priority review with a PDUFA goal date of August 18, 2019.

3 Studies Submitted

3.1 Studies Reviewed

3.2 Studies Not Reviewed

3.3 Previous Reviews Referenced

Pharmacology and Toxicology Review of IND 114717 (Impurities) by Dr. Jessica Bonzo dated January 11, 2019

Pharmacology and Toxicology Review of IND 114717 (Impurities) by Dr. Brett Jones dated April 22, 2019

Pharmacology and Toxicology Review of IND 114717 (Carcinogenicity) by Dr. Brett Jones dated March 26, 2019

Pharmacology and Toxicology Review of IND 114717 (39-Week Dog Study, PK/ADME, Reproductive Toxicology) by Dr. Brett Jones dated January 24, 2019

Pharmacology and Toxicology Review of IND 114717 (26-Week Rat, 39-Week Dog (Prelim)) by Dr. Timothy Robison dated October 22, 2013

Pharmacology and Toxicology Review of IND 114717 (Pharmacology, 28-Day Rat and Dog Studies, Genetic Toxicology) by Dr. Asoke Mukherjee dated December 3, 2013

Division of Pediatric and Maternal Health Consult Review of NDA 211675 by Dr. Jane Liedtke dated April 19, 2019

4 Pharmacology

A number of pharmacology studies were submitted and reviewed under IND 114,717; a brief synopsis of these studies is included below (see Pharmacology and Toxicology Review of IND 114,717 by Dr. Asoke Mukherjee dated December 3, 2013 for further information). Also provided below is a more detailed review of pharmacology studies that were not previously reviewed under IND 114,717 or that were submitted to NDA 211675.

4.1 Primary Pharmacology

Study title: Enzyme Potency, Selectivity, and Mechanism of Inhibition (Study No. R&D/12/424; non-GLP)

The potency, selectivity, competitiveness with respect to ATP, and association/disassociation kinetics of UPA was characterized in various cell-free biochemical kinase assays that utilize either Homogenous time resolved fluorescence (HTRF) activity assays or Time-resolved fluorescence resonance energy transfer (TR-FRET) direct binding detection. Upadacitinib inhibited JAK1 with an IC_{50} of 0.043 μ M when tested at 0.1 mM ATP. It also inhibited JAK2 (IC_{50} of 0.12 μ M) and JAK3 (IC_{50} of 2.3 μ M) at weaker potencies. However, JAK1 and JAK2 were both inhibited at < 0.0032 μ M (lower limit of detection) at 0.001 mM ATP. Of the 70+ kinases tested in the panel, six non-JAK kinases exhibited an IC_{50} below 5 μ M, but only two non-JAK kinases had IC_{50} s equal to or below 1 μ M (i.e., Rock1 and Rock 2). The assays also determined that UPA inhibits JAK1 via a reversible, ATP competitive mechanism and displays rapid association and disassociation kinetics. Under the conditions of this cell-free assay at 0.1 mM ATP, UPA displayed 2.8-fold selectivity for JAK1 vs. JAK2 and 53-fold selectivity for JAK1 vs. JAK3.

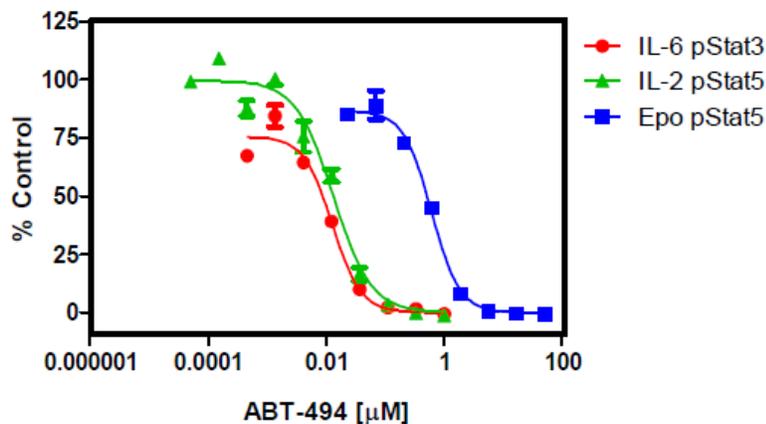
Table 3. Upadacitinib kinome selectivity (Sponsor's Table)

Kinase	Assay	[ATP] (mM)	Average IC ₅₀ (μM)
Jak1	HTRF Activity	0.1, 0.001	0.043, <0.0032
Jak2	HTRF Activity	0.1, 0.001	0.12, <0.0032
Jak2	TR-FRET Binding	-	0.008
Jak3	HTRF Activity	0.1, 0.001	2.3, 0.054
Jak3	TR-FRET Binding	-	0.068
Tyk2	HTRF Activity	0.1, 0.001	4.7, 0.055
ABL	TR-FRET Binding	-	>10
ACVR1	TR-FRET Binding	-	>10
Akt1	TR-FRET Binding	-	>10
ALK	TR-FRET Binding	-	>7.8
AMPK	TR-FRET Binding	-	>7.2
Aurora 1	TR-FRET Binding	-	>7.7
Aurora 2	TR-FRET Binding	-	4.6
BRAF	TR-FRET Binding	-	>10
BTK	TR-FRET Binding	-	>10
CAMK1D	TR-FRET Binding	-	2.5
CAMK2A	TR-FRET Binding	-	>10
CAMKK2	TR-FRET Binding	-	>10
CDK11	TR-FRET Binding	-	>10
CDK2	TR-FRET Binding	-	>10
CDK7/Cyclin H/Mat1	TR-FRET Binding	-	>10
CDK8/Cyclin C	TR-FRET Binding	-	>10
CDK9/Cyclin K	TR-FRET Binding	-	>10
CLK2	TR-FRET Binding	-	>10
Cklalpha1	TR-FRET Binding	-	>10
cMET	TR-FRET Binding	-	>10
CSF1R	TR-FRET Binding	-	>10
DDR1	TR-FRET Binding	-	>10
DYRK1A	TR-FRET Binding	-	>10
DYRK1B	TR-FRET Binding	-	>10
EGFR	TR-FRET Binding	-	>10
Erk2	TR-FRET Binding	-	>10
Kinase	Assay	[ATP] (mM)	Average IC ₅₀ (μM)
p38 alpha	TR-FRET Binding	-	>10
RET	TR-FRET Binding	-	2.5
Rock1	TR-FRET Binding	-	1.0
Rock2	TR-FRET Binding	-	0.42
Rsk2	TR-FRET Binding	-	>9.8
SGK1	TR-FRET Binding	-	>10
Src	TR-FRET Binding	-	>10
STK16	TR-FRET Binding	-	9.7
STK33	TR-FRET Binding	-	>10
Syk	TR-FRET Binding	-	>10
TAOK2	TR-FRET Binding	-	>10
TBK1	TR-FRET Binding	-	>10
TNK2	TR-FRET Binding	-	5.1
TrkA	TR-FRET Binding	-	>10
TrkB	TR-FRET Binding	-	>10
TrkC	TR-FRET Binding	-	>10
TTK	TR-FRET Binding	-	>10
TYRO3	TR-FRET Binding	-	>10
Wee1	TR-FRET Binding	-	>10
Zipk	TR-FRET Binding	-	>10

Study title: ABT-494: Potency in Janus Kinase-Dependent Cellular Assays (Study No. R&D/12/445; non-GLP)

The potency of UPA in inhibiting selected JAK-dependent cellular assays was assessed. IL-2 is considered to signal via a receptor complex that requires the kinase activity of both JAK1 and JAK3. To investigate the effects of UPA on JAK1/JAK3 signaling, the inhibition of IL-2 induced phosphorylation of STAT5 in T-blasts by UPA was assessed by AlphaScreen readout. The EC₅₀ for UPA was 13 nM, with complete inhibition of STAT5 phosphorylation. IL-6 is considered to signal via a receptor complex that requires the kinase activity of two JAK1 molecules. To evaluate the effects of UPA on JAK1 signaling, the inhibition of IL-6 induced phosphorylation of STAT3 in TF-1 cells by UPA was assessed by AlphaScreen readout. The EC₅₀ for UPA was 9 nM, with complete inhibition of STAT3 phosphorylation. Erythropoietin (EPO) is considered to signal via a receptor complex that requires the kinase activity of two JAK2 molecules. To evaluate the effects of UPA on JAK2 inhibition, the inhibition of EPO induced phosphorylation of STAT5 in U-7 cells by UPA was assessed by AlphaScreen readout. The EC₅₀ for UPA was 628 nM, with complete inhibition of STAT5 phosphorylation. In summary, UPA displayed more potency in inhibiting JAK1-mediated and IL-2-induced and IL-6-induced STAT phosphorylation (9-13 nM) compared to JAK2-mediated and EPO-induced STAT phosphorylation (628 nM).

Figure 1. Representative data for Upadacitinib in Jak-dependent cellular assays (Sponsor's Figure)



Study title: Efficacy of a JAK1 Inhibitor, ABT-494, in Concanavalin A-induced Cytokine and Adjuvant-Induced Arthritis Models in Rat (Study No. R&D/12/444; non-GLP)

Methods: A concanavalin A (Con A)-induced cytokine production model in rats was used to determine the effects of UPA on IFN- γ production. Rats were dosed orally with UPA (0.1-10 mg/kg; 0 minutes) then injected intravenously with 10 mg/kg Concanavalin A (30 minutes). An Adjuvant-induced arthritis (AIA) model in rats was also used to determine the efficacy of UPA on the development of paw swelling inhibition, bone erosion, and ankle histology. On Day 0, rats were intradermally administered 0.1 mL (200 μ g/rat) Mycobacterium tuberculosis suspension in the right footpad. On Day 7, rats

were dosed orally twice a day for 10 days post-immunization with either vehicle or UPA (0.1, 0.3, 1, 3, and 10 mg/kg/day, Days 7-17).

Results: Upadacitinib administered orally at 0.1-10 mg/kg in male rats 30 minutes prior to Con A challenge dose-dependently inhibited IFN- γ production relative to control animals at 4 hrs post Con A challenge. No significant effect on IL-2 levels was observed. In the AIA rat model, oral treatment with UPA resulted in a dose-dependent inhibition of paw swelling, with >90% inhibition observed at 10 mg/kg. A histological examination of the left paws and ankles from rats revealed that UPA at ≥ 3 mg/kg/day significantly improved joint morphology (i.e., synovial hypertrophy/inflammation, cartilage damage, and bone erosion). Finally, analysis of ankles by micro-computed tomography (μ CT) showed that UPA oral treatment at ≥ 3 mg/kg/day resulted in \sim 90% inhibition of bone erosion relative to non-arthritic control animals.

Figure 2. Effect of Upadacitinib on paw swelling in AIA (Sponsor's Figure)

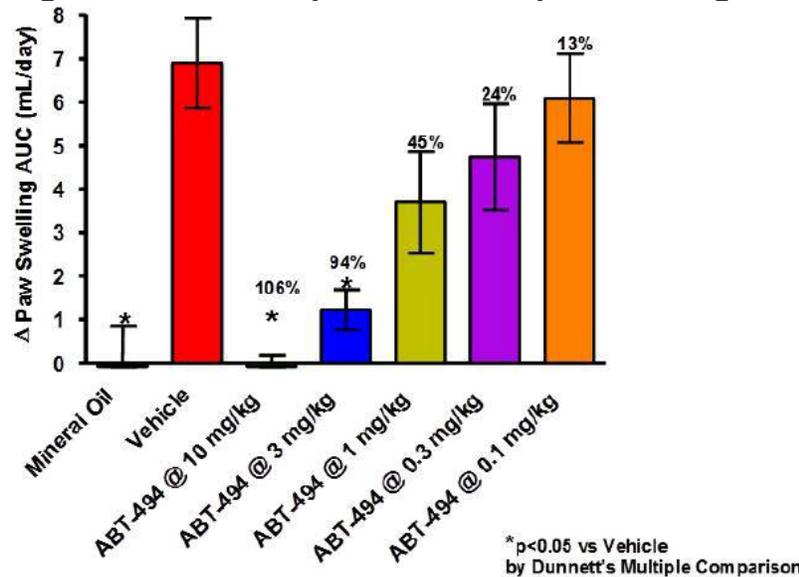
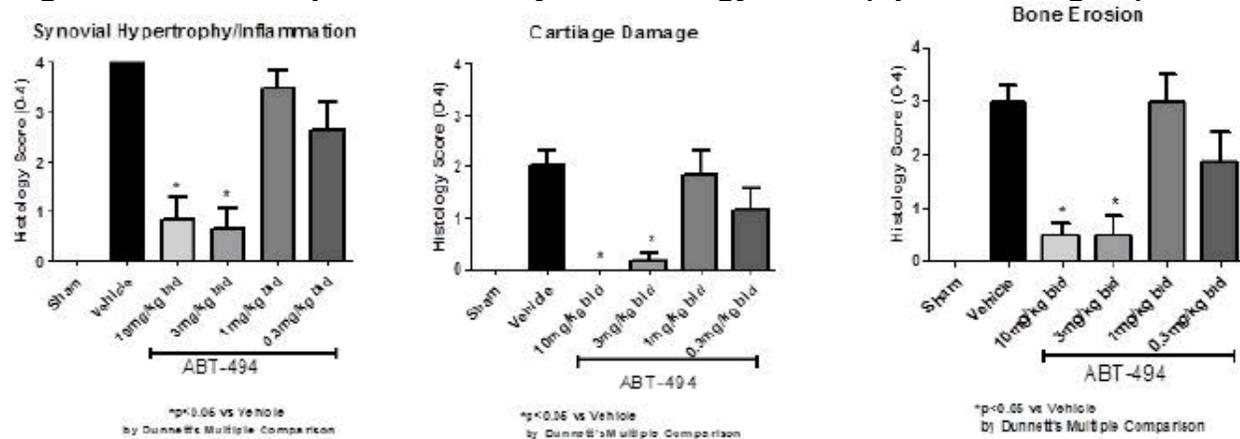


Figure 3. Effect of Upadacitinib on joint histology in AIA (Sponsor's Figure)



Study title: Effect of ABT-494 on IL-7 Induced pSTAT5 Ex Vivo and Circulating NK Cell Counts in Healthy Rats (Study No. R&D/12/446; non-GLP)

In this study, the level of JAK inhibition in vivo and in blood samples ex vivo were determined. The inhibition of JAK1 kinase by UPA has previously been shown to also inhibit the proliferation of NK cells and STAT phosphorylation. The in vivo effect of UPA treatment in healthy rats on the ex vivo IL-7 induced STAT5 phosphorylation and peripheral blood NK cells was determined as a probe to JAK1 and JAK3 mediated processes. Healthy rats were orally administered UPA at doses of 0, 0.3, 1, 3, 10, and 30 mg/kg/day for 14 days. Following treatment with UPA, peripheral NK cell counts and IL-7-induced pSTAT5 formation ex vivo were both inhibited.

4.2 Secondary Pharmacology**Study title: Study of A-1293543.0: Abbott High-Throughput Profile (Study No. 8604526_4; non-GLP)**

The effects of UPA in various *in vitro* receptor binding assays was investigated. A panel of 80 receptors was screened with UPA (10 μ M). Upadacitinib exhibited 46%, 52%, and 48% inhibition of specific ligand binding for AT₁, CGRP, and A₃ receptors, respectively.

4.3 Safety Pharmacology

A number of safety pharmacology studies were conducted with upadacitinib (ABT-494, A-1293543). These studies were reviewed under IND 114,717 and brief summaries are provided below. Refer to the Pharmacology and Toxicology Review of IND 114,717 by Dr. Asoke Mukherjee dated December 3, 2013 for further information.

Study title: A Neurobehavioral Safety Evaluation of Orally Administered A-1293543 (ABT-494) in Rats (Study No. TA11-247)**Key Study Findings**

- Female conscious SD rats (8/group) were administered UPA at doses of 0, 10, 50, and 100 mg/kg in a GLP-compliant study. Functional Observational Battery evaluations were taken at predose, 1 and 3 hr postdose.
- No mortality or treatment-related clinical signs were observed.
- A significant decrease (55%) in rearing behavior was observed for rats in the 100 mg/kg treatment group at 1 hr postdose relative to control animals. This effect was not observed at 3 hr postdose.

Study title: Effects of Spontaneous Locomotor Activity in the Rat (P.O Administration) (Study No. R&D/11/1263)**Key Study Findings**

- Male Wistar rats (10/group) were administered UPA at oral doses of 0, 2, 6, 20, 60, and 200 mg/kg in a non-GLP study. Vehicle control and distilled water control groups were included.
- A 55%, 42%, 33%, and 42% significant increase in rearing behavior (i.e., vertical locomotor activity) was observed for rats at 2, 6, 20, and 60 mg/kg UPA, respectively.
- No significant effects on rearing behavior were observed at 200 mg/kg UPA.
- No significant effects on horizontal activity (i.e., crossings) were observed at any dose level from 20-40 minutes.

Study title: Evaluation of the Effects of A-1293543 (ABT-494) on Cloned HERG Channels Expressed in Human Embryonic Kidney (HEK293) Cells (Study No. TX15-272)**Key Study Findings**

- UPA was evaluated at concentrations of 6.7, 20, and 60 µg/mL in a GLP-compliant study.
- A dose-dependent increase in inhibition of mean hERG-mediated potassium currents ranging from approximately 15 to 59% was observed in the study.
- An IC₅₀ of 39.5 µg/mL was estimated.

Study title: A Cardiovascular Safety Evaluation of Orally Administered A-1293543 (ABT-494) in Beagle Dogs (Study No. TB11-249)**Key Study Findings**

- Conscious telemetric male beagle dogs (6) were administered UPA at oral doses of 0, 0.5, 1.5, and 5 mg/kg in a Latin square design in a GLP-compliant study. A 3- or 4-day washout period was between each treatment.
- Cardiovascular parameters were monitored continuously in conscious animals from at least 3.5 hrs prior to dosing until at least 24 hrs postdose.
- No mortality or treatment-related clinical signs were observed.
- A transient decrease in mean arterial blood pressure was observed at 1.5 and 5 mg/kg UPA
- An increase in heart rate, with reflective decreases in the RR, PR, and uncorrected QT intervals, was observed at 5 mg/kg UPA.
- No treatment-related effects on the QRS duration or QTc interval were observed.

Study title: A Respiratory Safety Evaluation of Orally Administered A-1293543 (ABT-494) in Rats (Study No. TA11-248)**Key Study Findings**

- Male conscious SD rats (8/group) were administered UPA at oral doses of 0, 10, 50, and 100 mg/kg in a GLP-compliant study.
- Respiratory function was monitored for at least 1 hr prior to dosing and for at least 4 hrs postdose.
- No treatment-related effects on mortality or respiratory parameters (i.e., respirator rate, tidal volume, or minute volume) were observed.

5 Pharmacokinetics/ADME/Toxicokinetics

A number of *in vitro* and *in vivo* ADME studies were conducted with upadacitinib. These studies were reviewed under IND 114,717 and brief summaries of selected assays are provided below. Refer to the Pharmacology and Toxicology Review of IND 114,717 by Dr. Asoke Mukherjee dated December 3, 2013 and the Pharmacology and Toxicology Review of IND 114,717 by Dr. Brett Jones dated January 24, 2019 for further information.

5.1 PK/ADME

Absorption

Study title: A-1293543 Toxicokinetics following Multiple Oral Dosing in CByB6F1-Tg(HRAS)2Jic Wild Type Mice, Sprague-Dawley Rats, New Zealand White Rabbits, and Beagle Dogs (Study No. R&D/17/0323)

The studies used to profile UPA toxicokinetics utilized three separate formulations. Studies in mice administered a suspension of the free base in 0.2% HPMC. Studies in pregnant rabbits dosed a solution/suspension of the (b) (4) in 0.2% HPMC. In dogs, initial studies administered a solution of the free base in acidified PEG-400: Tween 20, while later studies administered solutions of the (b) (4). All three formulations were utilized in rat studies.

Mice: Three studies profiled the UPA toxicokinetics following daily oral dosing in CByB6F1-Tg(HRAS)2Jic wild-type mice or CByB6F1-Tg(HRAS)2Jic wild-type (non-transgenic littermates) mice at dosing durations ranging from 7-91 days. Within the three studies, the increase in AUC was slightly greater than proportional to the increase in dose, with AUC values following multiple dosing slightly higher than calculated on Day 1. No consistent sex differences in AUC were observed.

Rats: Three different formulations were utilized in the studies which profiled the UPA pharmacokinetics following multiple oral dosing in Sprague-Dawley rats (i.e., 4-week, 26-week, 104-week). Upadacitinib was rapidly absorbed in rats, with peak concentrations observed within the first hour after oral dosing. AUC exposures after

repeated dosing were generally comparable to those observed on the first day of the study. AUC values in female rats were higher than that observed with males at all dose levels. The increase in UPA AUC values was greater than proportional to the administered dose over the 7.5-100 mg/kg/day dose range. Upadacitinib AUC values in pregnant rats were slightly lower than those observed in non-pregnant animals.

Rabbits: Two embryo-fetal developmental toxicity studies were conducted with UPA in pregnant New Zealand white rabbits. In both studies, the increase in AUC was greater than proportional to the dose. Upadacitinib AUCs on GD18 were higher than observed on the first day of dosing (GD7) in all treatment groups.

Dogs: Three studies profiled the UPA pharmacokinetics over 4- and 39-weeks of daily oral dosing in male and female beagle dogs. Within the studies, the increase in UPA peak plasma concentrations (C_{max}) and AUC was greater than proportional to the increase in dose. There were no sex differences in either C_{max} or AUC.

Study title: Absorption, Distribution, Metabolism, and Excretion of [14 C]A-1293543 in Male Sprague-Dawley Rats (Study No. R&D/12/255)

The absorption, distribution, metabolism, and excretion of [14 C]A-1293543 was evaluated in male Sprague-Dawley rats following single oral or IV dose administration of 3 mg/kg [14 C]A-1293543 followed by the serial collection of bile, urine, and feces up to 48 hrs postdose. For IV dosed rats, radiolabeled A-1293543 was eliminated mainly through biliary excretion, with 49.7% recovered in bile and 29.7% of the dose recovered in urine. Similarly, in orally dosed rats the mean total recoveries of radiolabeled A-1293543 in bile, urine, and feces were 52.6%, 11.1%, and 22.5%, respectively. Approximately 64% of the dose was orally absorbed. Following IV dosing, radioactivity maximally distributed into the kidneys, liver, skin, and muscle at 1 hr postdose. Nine metabolites (i.e., all <10% dose) were detected in excreta. In plasma, unchanged parent was the major component (~85% of total radioactivity).

Study title: Absorption, Distribution, Metabolism, and Excretion Study of [14 C]ABT-494 in Healthy Male Subjects Following Single Oral Dose Administration (Study No. R&D/15/0191)

An absorption, distribution, metabolism, and excretion (ADME) study of [14 C]UPA has been conducted in healthy male subjects following a single oral dose administration of 30 mg [14 C]UPA (Study no. R&D/15/0191). Following the single oral dose of 30 mg [14 C]UPA, 96% of the radioactivity was recovered in urine and feces within 216 hrs of dosing. Of the total administered radioactive dose, approximately 53% was recovered in feces and 43% was recovered in urine. Unchanged UPA accounted for 79% of the total radioactivity in plasma while metabolites M4 (product of monooxidation followed by glucuronidation) and M11 (product of monooxidation followed by ring-opening) accounted for 13.4% and 7.1% of the total plasma radioactivity, respectively. Approximately 61% of the administered radioactive dose was excreted in urine and feces as parent UPA and 34% was excreted as metabolites. Approximately 24% of the administered dose was recovered as unchanged parent drug in urine and 9.6% and

3.6% of the dose were recovered as M4 and M10 (product of monooxidation), respectively. In feces, approximately 38% of the total radioactive dose was recovered as parent drug and 6.3% was recovered as M11 metabolite. QSAR analyses of the metabolites were not conducted. The major metabolite of UPA in human plasma (i.e., M4, 13%) following a single oral dose is not covered by equivalent amounts detected in either dog (i.e., M4, 0.9%) or rat (i.e., M4, not detected) ADME studies. However, as the M4 human metabolite is a product of monooxidation followed by glucuronidation it was not considered a safety concern, consistent with ICH M3(R) Questions & Answers (June 2011). The conclusion that no additional safety testing of the glucuronide metabolite M4 was warranted was documented in the ECAC meeting minutes dated April 30, 2015.

Distribution

Study title: Determination of the Unbound Fraction of A-1293543 in Plasma and Microsomal Protein and Blood-to-Plasma Concentration Ratios (Study No. R&D/17/0325)

Methods

The aim of this non-GLP study was to determine the unbound fraction of UPA in human and animal plasma and to assess blood-to-plasma ratios across species (e.g., mouse, rat, dog, monkey, and human whole blood). Plasma protein binding was evaluated at concentrations of UPA ranging from 0.1-100 μM in a single experiment.

Results

The binding of UPA to plasma protein was low and independent of concentration from 0.1 to 100 μM in any species. The mean unbound fraction of UPA (at 1 μM) was 0.28, 0.41, 0.69, 0.47, and 0.48 for mouse, rat, dog, monkey, and human plasma, respectively. Upadacitinib exhibited blood-to-plasma ratios of 0.99, 1.28, 1.18, 1.31, and 1.00 in mouse, rat, dog, monkey, and human, respectively.

Study title: Quantitative Whole Body Autoradiography of Pigmented Rats following Oral Administration of ^{14}C -ABT-494 (Study No. 8300751)

Methods: The aim of this study was to assess the extent of tissue distribution of ^{14}C -UPA by quantitative whole-body autoradiography (QWBA) in male Long Evans rats following a single oral administration. The volume of radiolabeled dose formulation (Group 1) or nonradiolabeled dose formulation (Group 2) to be administered to each animal was calculated based on the body weight taken on the day of dose administration. Group 1 animals received a mean oral dose of 5.16 mg/kg and Group 2 animals received an oral dose of 7.21 mg/kg. One animal per time-point (Group 1) was prepared for QWBA at 0.5, 1, 2, 4, 8, 24, 48, 96, 168, and 192 hr postdose. One animal (Group 2) was prepared for QWBA at 24 hr postdose.

Results: The distribution of ^{14}C -UPA into tissues was greatest between 0.5 and 4 hr postdose. Most tissue C_{max} values occurred at 0.5 hr postdose with a few exceptions (e.g., skin, testes, and vitreous humor [C_{max} at 1 hr] and eye and uveal tract [C_{max} at 4

hr]). At 0.5 to 4 hr postdose, highest radioactivity concentrations were observed in the adrenal gland, kidneys, liver, eye uveal tract, bile, arterial wall, and intervertebral discs. Lowest concentrations were present in the brain, spinal cord, and lens of the eye. Generally, radioactivity concentrations were highest in most tissues at 0.5 hr postdose. An observed distribution of UPA to the eye uveal tract that persisted through 192 hr postdose could indicate an affinity for ocular melanin. At 8 hr postdose, radioactivity concentrations in the majority of tissues had significantly declined from those observed at 1 hr. At 24 hr postdose, radioactivity concentrations in most tissues was either not detected or below the limit of quantitation (i.e., <51.9 ng equivalents/g).

Study title: Placental Transfer, Lactal Excretion, and Tissue Distribution of Radioactivity in Pregnant and Lactating Female Sprague-Dawley Rats after Oral Administration of ^{14}C -ABT-494 (Study No. R&D/16/1391, GLP)

Methods: Lactal excretion, placental transfer, and tissue distribution of total radioactivity were assessed in Sprague-Dawley rats following oral administration of ^{14}C -UPA. At 0.5 hrs postdose, blood and milk were collected from one lactating group (Group 1) given an oral dose of the dose solution vehicle to determine background levels for milk, blood, and plasma. Lactating (Group 2) and pregnant (Group 3) rats were administered a single oral dose of ^{14}C -UPA at target dose levels of 10 mg/kg and 200 $\mu\text{Ci}/\text{kg}$ in a dose volume of 1 mL/kg. Milk and blood were collected from three lactating rats/time point at select times through 72 hrs postdose to assess lactal excretion of ^{14}C -UPA-derived radioactivity (Group 2). Blood, milk, and plasma were analyzed for total radioactivity by liquid scintillation counting. One pregnant rat/time point dosed on Gestation Day 18 was euthanized at select times through 72 hrs postdose to assess placental transfer of the dosed radioactivity by whole-body autoradiography (Group 3). Pharmacokinetic parameters were calculated for milk, blood, and plasma.

Results:

Lactal Excretion: The mean C_{max} of ^{14}C -UPA-derived radioactivity in milk from lactating rats occurred at 1 hr postdose (Group 2). Blood and plasma radioactivity C_{max} occurred at 0.5 hrs postdose. Radioactivity was measurable in milk for at least 24 hrs following an oral dose of ^{14}C -UPA. Radioactivity concentrations in milk and plasma declined below measurable levels by 48 hrs postdose. Radioactivity was measurable in blood through the last sampling time of 72 hrs postdose. Radioactivity was not detected in blood, milk, or plasma obtained from control lactating rat (Group 1).

Placental Transfer: Following an oral dose of ^{14}C -UPA to pregnant rats, radioactivity was present in fetal blood and all evaluated tissues at 0.5 hrs postdose. Except for the brain and spinal cord, all other fetal tissues and fetal blood had measurable radioactivity concentrations through 4 hrs postdose. From 8 through 72 hrs postdose, fetal blood and all fetal tissues were devoid of radioactivity. Radioactivity was present in most maternal tissues from 0.5 through 4 hrs postdose. Radioactivity C_{max} for all maternal tissues occurred at 0.5 hrs postdose. Except for the first time point, amniotic fluid, maternal non-circumventricular central nervous system tissues, bone, eye lens, and white adipose were devoid of radioactivity throughout the time course of the study. The

placenta, uterus, amniotic sac and ovary, and mammary gland had measurable radioactivity concentrations through 4, 12, 24, and 48 hrs postdose, respectively. Except for the maternal kidney and liver, radioactivity was eliminated from all other maternal tissues by the last collection time of 72 hrs postdose.

In summary, ¹⁴C-UPA-derived radioactivity was present in milk for 24 hrs postdose.. Accumulation of radioactivity was not observed in any maternal or fetal tissue and was eliminated from most maternal tissues by 72 hrs postdose and from all fetal tissues by 8 hrs postdose. Tissue distribution data showed that ¹⁴C-UPA-derived radioactivity distributed into the amniotic sac and placenta, and distributed into fetal tissues for a limited time after an oral dose of ¹⁴C-UPA.

Metabolism

Study title: Metabolic Stability Memo No. 06: Assessment of A-1293543 Stability in Hepatic Enzyme Systems (Study No. Memo 06)

Methods

The aim of this non-GLP *in vitro* study was to evaluate the metabolic stability of UPA in hepatocytes across species (e.g., mouse, rat, cynomolgus monkey, beagle dog, human) at a single 1 μM concentration.

Cryopreserved mouse, rat, monkey, dog, and human hepatocytes were incubated at a substrate concentration of 1 μM and 500,000 cells/mL. Each incubation was run in duplicate.

Results

The scaled intrinsic clearance of UPA was 25.6, 4.07, 0.413, 0.415, and 0.366 L/h/kg in mouse, rat, monkey, dog, and human hepatocytes, respectively.

Study title: Drug Metabolism Report No. 04: In Vitro Biotransformation of [¹⁴C]A-1293543 (Study No. R&D/12/256)

Methods

The aim of this non-GLP study was to investigate the *in vitro* metabolism of [¹⁴C]UPA using liver cytosol and hepatocytes from mouse, rat, dog, monkey, and human, as well as recombinant human CYP enzymes (2D6, 3A4, and 3A5). Using liver cytosol, incubations of [¹⁴C]UPA were conducted in duplicate for 60 min at 10 μM for metabolite identification. To identify the metabolites of [¹⁴C]UPA in hepatocytes, incubations were conducted at 10 μM concentrations in a 24-well plate containing 500,000 cells/mL at 37°C for 0 and 4 hrs.

Results

A total of 9 metabolites were characterized in *in vitro* hepatic systems, including products of mono-oxidation, di-oxidation, oxidation followed by glucuronidation, loss of the trifluoromethyl moiety and oxidation followed by ring opening. No metabolism of

[¹⁴C]UPA was observed in liver cytosol incubations. In hepatocytes, a total of 5 minor metabolites were characterized, with 4 found in human, 3 in monkey, dog, mouse and rat. Seven metabolites were observed in incubations of [¹⁴C]UPA with recombinant human CYP2D6, 3A4, or 3A5. CYP2D6, 3A4, and 3A5 primarily metabolized UPA to form the major metabolite M11 via oxidation at the pyrrolopyrazine moiety, followed by ring opening.

Table 4. Composite metabolite table for Upadacitinib in vitro metabolism (Sponsor's Table)

ID	Mouse	Rat	Dog	Monkey	Human	CYP2D6	CYP3A4	CYP3A5
M1	-	-	√	√	√	-	√	√
M2	√	√	√	√	√	-	√	√
M3	√	√	-	-	√	-	-	-
M4		√	√	√	√	-	-	-
M6	-	-	-	-	-	√	√	√
M7	-	-	-	-	-	-	√	-
M8	-	-	-	-	-	√	√	√
M10	√	-	-	-	-	-	√	√
M11	-	-	-	-	-	√	√	√

√ Detected in hepatocyte or rh CYP incubations; - Not detected

Study title: Metabolism and Disposition of [¹⁴C]A-1293543 (ABT-494) after a Single 5 mg/kg Oral Dose in Male Dogs (Study No. R&D/15/0801)

Methods

The aim of this non-GLP study was to investigate the metabolism and disposition of UPA in male beagle dogs following a single oral dose of 5 mg/kg (200 µCi/dog).

Single oral doses of [¹⁴C]UPA (5 mg/kg) were administered to male dogs (n = 3) via oral gavage. Blood was collected via serial sampling at 0.5, 1, 2, 3, 6, 8, 24, 48, and 72 hr post-dose into EDTA tubes. Urine and feces were collected at 0-24 hr, 24-48 hr, and 48-72 hr intervals. Dog plasma samples were pooled equally by time-point. Pooled dog plasma sample analytes were separated by HPLC and the HPLC eluent was split to a mass spectrometer for structural elucidation and to a 96-well fraction collector for determination of radioactivity of [¹⁴C]UPA and metabolites.

Results

Elimination

The overall mean recovery of radioactivity was 105.7% (± 8.7%) over the 72 hr collection period. A mean of 54.6% (± 11.5%) of the administered 5 mg/kg single oral dose was recovered in feces and 46.9% (± 6.1%) was recovered in urine through the last collection interval (72 hr post dose).

Metabolism

Unchanged parent drug (UPA) was the major component in plasma, representing 87.7% of total radioactivity in time-point weighted pooled plasma (0-24 hr). Minor metabolites including M1, M2, M4, M11, and M21 were identified in plasma, representing 1.5, 5.3, 0.9, 3.4, and 1.2% of total plasma radioactivity, respectively (see table below)

Table 5. Distribution of parent drug and metabolites in AUC_{0-24hr} pooled plasma following a single 5 mg/kg oral dose of [¹⁴C]A-1293543 to male beagle dogs (Sponsor's Table)

Compound	% Total Radioactivity
A-1293543	87.7
M1	1.5
M2	5.3
M4	0.9
M11	3.4
M21	1.2

In feces, 20.6% of the administered dose was recovered as the intact parent drug; 33.3% of the dose was excreted as metabolites. The most abundant metabolite in feces was M2, representing 9.5% of the administered dose. Other minor metabolites detected in feces included M1, M3, M11, M17, M20, M21, Unk1, Unk2, and Unk3 each representing ≤7% of the administered dose (see table below).

In dog urine, 36.2% of the administered single dose was recovered as the intact parent drug; 8.8% was excreted as metabolites. The most abundant metabolite in urine was M2, representing 4.2% of the administered dose. Additional minor metabolites detected in urine included M1, M3, M4, M11, M19, M20, and M21 each representing <2% of the administered dose (see table below).

The most significant metabolite in urine, feces, and plasma was M2, representing 4.2, 9.5%, and 5.3% of the administered dose, respectively.

Table 6. Distribution of parent drug and metabolites in feces and urine following a single 5 mg/kg oral dose of [¹⁴C]A-1293543 to male beagle dogs (Sponsor's Table)

Compound	% of the Administered Dose		
	Feces (0-48 h)	Urine (0-24h)	Total
A-1293543	20.6	36.2	56.8
M1	2.6	1.5	4.1
M2	9.5	4.2	13.7
M3	1.6	0.5	2.1
M4	ND	MS	0.0
M11	2.9	1.1	4.0
M17	0.8	ND	0.8
M19	ND	0.5	0.5
M20	2.5	0.8	3.3
M21	1.6	0.2	1.8
Unk1	4.8	ND	4.8
Unk2	6.0	ND	6.0
Unk3	1.0	ND	1.0

ND - not detected; MS – Detected by MS only

Study title: Drug Metabolism Memo No. 09: Assessment of the Enzymes involved in the Metabolism of [¹⁴C]A-1293543 using Recombinant Enzymes (Study No. Memo 09)

Methods

The aim of this non-GLP *in vitro* study was to evaluate the potential for [¹⁴C]UPA to be metabolized by cytochrome P450 enzymes (CYPs) and flavin monooxygenases (FMOs) using recombinant systems. A total of 12 commercially available enzymes were incubated with radiolabeled [¹⁴C]UPA for up to 60 minutes and loss of parent compound was monitored. The recombinant enzymes included human CYP isoforms 1A2, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2J2, 3A4, 3A5, and FMO isoforms FMO1 and FMO3.

Results

The enzymes identified to potentially contribute to the metabolism of [¹⁴C]UPA based on percent parent remaining after a fixed incubation were CYP3A4 (36.0% remaining), CYP2D6 (73.4%), and CYP3A5 (80.6%). The percent parent remaining for other enzymes was greater than 98%. Using Michaelis-Menten enzyme kinetics, the apparent K_m and V_{max} for CYP3A4 were estimated to be 8.32 μ M and 0.71 pmol/min/pmol CYP, respectively.

6 General Toxicology

6.1 Single-Dose Toxicity

No single-dose toxicity studies were conducted. In the 28-day repeat-dose oral toxicology study in rats, mortality occurred following a single dose of upadacitinib at 100 mg/kg (one male) and 200 mg/kg.

6.2 Repeat-Dose Toxicity

GLP-compliant oral repeat-dose toxicology studies were conducted with upadacitinib in Sprague-Dawley rats for durations of 28-days and 26-weeks and in Beagle dogs for durations of 28-days and 39-weeks. These repeat-dose toxicology studies were reviewed under IND 114,717 and brief summaries are provided below. Refer to the Pharmacology and Toxicology Review of IND 114,717 by Dr. Asoke Mukherjee dated December 3, 2013 and the Pharmacology and Toxicology Review of IND 114,717 by Dr. Brett Jones dated January 24, 2019 for further information. Also, refer to the Pharmacology and Toxicology Review of IND 114,717 by Dr. Timothy Robison dated October 22, 2013 for further information.

Rat

Study title: 4-Week Oral Toxicity of A-1293543 in Sprague-Dawley Rats with a 4-Week Recovery Period (Study No. TA11-224, GLP)

Key Study Findings

- In a 28-day oral toxicology study, rats (10/sex/group) were administered UPA at doses of 0, 10, 50, 100, and 200 mg/kg/day. Additional animals (5/sex/group) were included in the control, 50 mg/kg/day, and 100 mg/kg/day groups for a 4-week recovery period.
- Treatment-related mortality was observed at doses of 100 and 200 mg/kg/day. On Day 1, several rats at 200 mg/kg/day (4 males and 6 females) were found dead or sacrificed due to extreme toxicity. Remaining rats at 200 mg/kg/day were sacrificed on Day 2 or 3 and discarded without examination. Mortality was also observed for male rats (5/15) in the 100 mg/kg/day group; these deaths were attributed to lymphoid suppression, degenerative and atrophic changes in the kidney tubules, and moderate to marked multifocal, midzonal, or diffuse liver necrosis in three of the five males.
- One male animal in the 50 mg/kg/day group was sacrificed on Day 26 due to findings of severe skin ulceration. Skin lesions were not observed for rats in the 100 mg/kg/day groups. A potential role of the immunosuppressive properties of the drug leading to the skin ulceration cannot be excluded; however, no deaths were observed with a dose of 50 mg/kg/day in the subsequent 26-week toxicology study in rats. The death was judged by the reviewer to be unrelated to the test article.
- The target organs of toxicity for UPA were identified as the bone marrow, spleen, thymus, kidney, and liver.

- Hypocellularity in the bone marrow was observed for males and females in the 100 mg/kg/day treatment groups. This finding was reversible.
- A decrease in lymphocytes (i.e., in marginal zone) in the spleen was observed for males in the 100 mg/kg/day treatment group. This finding was reversible.
- A decrease in lymphocytes (i.e., cortex and medulla) in the thymus was observed for males and females in the 50 and 100 mg/kg/day treatment groups. This finding was reversible.
- A decrease in lymphocyte counts appeared to correlate with observed histopathological findings in the bone marrow, spleen, and thymus. These findings were attributed to the immunosuppressive properties of the drug and were considered monitorable in a clinical setting.
- Tubular degeneration in the kidneys was observed for males and females in the 100 mg/kg/day treatment groups. The kidney toxicity was associated with increases in urinary protein, bilirubin, blood and urobilinogen in rats at 10, 50, and 100 mg/kg/day UPA. These findings were reversible.
- Adverse liver findings were observed in males (3/5) in the 100 mg/kg/day treatment group with early mortality. Findings consisted of moderate to marked multifocal, midzonal, or diffuse liver necrosis. These findings were not observed in animals administered UPA that survived to the scheduled terminal sacrifice or end of the recovery period.
- Systemic exposure to UPA increased in a greater than dose-proportional manner in the 10 and 50 mg/kg/day treatment groups on Day 29; however, an approximate dose-proportional increase in exposure was observed for males and females in the 50 and 100 mg/kg/day groups on Day 29.
- A NOAEL of 50 mg/kg/day was established for this study. The male death at 50 mg/kg/day was judged to be unrelated to treatment given the absence of similar findings (i.e., skin ulceration) for other animals in the 50 mg/kg/day treatment group or at a higher dose of 100 mg/kg/day. Also, no deaths were observed with a dose of 50 mg/kg/day in the 26-week toxicology study in rats.

Study title: 26-Week Oral Dose Toxicity with A-1293543 (b) (4) in Sprague-Dawley Rats (Study No. TA12-067, GLP)

Key Study Findings

- In a 26-week oral toxicity study, rats (20/sex/group) were administered UPA at oral doses of 0, 5, 20, or 50 mg/kg/day.
- The target organs of toxicity for UPA were identified as the kidneys, thymus, spleen, lymph nodes (mandibular, medial iliac, mediastinal, and mesenteric), and liver.
- Minimal to moderate tubular degeneration/regeneration in the kidneys was observed for males and females in the 50 mg/kg/day treatment groups. This finding was considered adverse and dose-limiting.
- Lymphoid depletion observed in the thymus, spleen, and lymph nodes correlated with reductions of lymphocyte counts and was considered monitorable in a clinical setting.

- Minimal erosion and subacute/chronic inflammation in the tongue was observed for males and females at ≥ 20 mg/kg/day. These findings were considered monitorable in a clinical setting.
- Systemic exposure to UPA (AUC and C_{max}) generally increased in a greater than dose proportional manner for the range of doses tested. Slight drug accumulation was observed on Day 178. Mean AUC values for male and female rats at 20 mg/kg/day on Day 178 were 3.83 and 6.84 $\mu\text{g}\cdot\text{hr}/\text{mL}$, respectively, or 5.32 $\mu\text{g}\cdot\text{hr}/\text{mL}$ for males and females combined.
- A NOAEL of 20 mg/kg/day was established for this study based upon observed histopathological findings in the kidneys at 50 mg/kg/day.

Dog

Study title: 4-Week Oral Toxicity Study of A-1293543 in Beagle Dogs with a 4-Week Recovery Period (Study No. TB11-225, GLP)

Key Study Findings

- In a 4-week oral toxicity study, dogs (4/sex/group) were administered UPA at oral doses of 0, 0.5, 1.5, 3, and 5 mg/kg/day.
- No treatment-related effects were observed on body weight, ophthalmology, clinical chemistry, urine chemistry, and gross pathology.
- A slight decrease in spleen, thymus, and ovary organ weights was observed for males and/or females at ≥ 3 mg/kg/day. The decrease in spleen and thymus organ weights correlated with histopathological findings in these tissues.
- A slight decrease in lymphocyte, basophil, and eosinophil counts were observed in males and females in all drug-treated groups and were attributed to the immunosuppressive (pharmacodynamic) effects of UPA.
- The target organs of toxicity for UPA were identified as the bone marrow, spleen, thymus, and lymph nodes.
- Hypocellularity in the bone marrow was observed for males and/or females at ≥ 3 mg/kg/day UPA. This finding was reversible.
- Decreased lymphocytes in the lymph nodes (i.e., mandibular, trachea-bronchial, mesenteric), spleen, and thymus were observed for males and/or females at ≥ 3 mg/kg/day UPA. These findings were attributed to the immunosuppressive (pharmacodynamic) properties of the drug. These findings were considered monitorable in a clinical setting.
- Mixed cell infiltration in the popliteal lymph nodes was observed in males and/or females at ≥ 3 mg/kg/day UPA.
- A NOAEL of 5 mg/kg/day was established for this study. The observed effects were attributed to the pharmacodynamic effects of the drug and were considered monitorable in a clinical setting.

Study title: 39-Week Oral Toxicity Study of A-1293543 (b) (4) in Beagle Dogs (Study No. TB12-042, GLP)**Key Study Findings**

- In a 39-week chronic oral toxicity and toxicokinetic study, dogs (4/sex/group) received UPA at oral doses of 0, 0.1, 0.5, and 1.5 mg/kg/day.
- Clinical observations of skin swelling of the forepaws and hindpaws) were observed for male and female dogs in the 0.5 and 1.5 mg/kg/day treatment groups.
- One male animal (#4005) in the 1.5 mg/kg/day group had dosing suspended on Day 219 due to observed significant skin lesions that included cutaneous inflammation and demodicosis. This animal also exhibited increased neutrophil levels with the presence of immature precursors from Days 182-217.
- Increased white blood cell counts, neutrophil counts, and monocyte levels were observed for males and/or females in the 1.5 mg/kg/day group relative to control animals throughout the treatment period.
- Dose-dependent decreases in red blood cell, hemoglobin, and hematocrit values were observed for males and females in the 1.5 mg/kg/day treatment group relative to control animals throughout the treatment period.
- Increased incidences of interdigital cysts were observed in the skin of males (i.e., front and rear paws) in the 0.5 and 1.5 mg/kg/day treatment groups and in females (i.e., rear paws only) administered 0.5 mg/kg/day UPA compared to control animals. These findings correlated with histopathological findings in the skin of the interdigital spaces of the paws in these treatment groups.
- The target organs of toxicity for UPA were identified as the skin, popliteal LN, precapsular LN, spleen, and thymus. These findings were attributed to the immunosuppressive effects of UPA and are considered monitorable in a clinical setting.
- A dose-dependent increase in severity of mixed, multifocal cell inflammation in the interdigital skin was observed for males in all UPA treatment groups relative to control animals at the scheduled sacrifice in Week 39.
- An increased incidence and severity of mixed cell inflammation was observed in the precapsular and popliteal lymph nodes of males and/or females in the 0.5 and 1.5 mg/kg/day treatment groups.
- A decrease in lymphocytes in the spleen and thymus were observed for males in the 0.5 and 1.5 mg/kg/day treatment groups.
- Systemic exposure to UPA increased in an approximate dose-proportional manner for both males and females at the range of doses tested on Days 1, 35, 218, and 272.
- A NOAEL of 1.5 mg/kg/day was established for this study.

7 Genetic Toxicology

GLP-compliant *in vitro* and *in vivo* genetic toxicology studies were conducted with upadacitinib. These genetic toxicology studies were reviewed under IND 114,717 and brief summaries are provided below. Refer to the Pharmacology and Toxicology Review of IND 114,717 by Dr. Asoke Mukherjee dated December 3, 2013 for further information.

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Bacterial Reverse Mutation Assay with A-1293543 Free Form (Study No. R&D/11/1293)

Key Study Findings

- The selection of bacterial tester strains was considered adequate per the ICH S2(R1) Guidance.
- Upadacitinib was tested up to the limit dose of 5000 µg/plate ± S9.
- Positive controls produced expected increases of revertant colony counts (i.e., at least a 3-fold increase of revertant colonies compared to control).
- Upadacitinib at doses up to 5000 µg/plate in the presence and absence of S-9 mix was not mutagenic in the Ames assay.

7.2 *In Vitro* Assays in Mammalian Cells

Study title: In Vitro Mammalian Chromosome Aberration Test with A-1293543 Free Form (Study No. R&D/11/1294)

Key Study Findings

- Upadacitinib was studied in a chromosomal aberration assay in human peripheral blood lymphocytes in the presence and absence of S-9 mixture.
- The assay was conducted at 4 hr incubation in the presence and absence of S-9 mixture and 20 hr incubation in the absence of S-9 mixture.
- Positive controls exhibited statistically significant increases in aberrant cells.
- Upadacitinib was not clastogenic for the aberration of chromosomes in the presence and absence of S-9.
- A significant increase in numerical aberrations (i.e., polyploidy or aneuploidy) was observed under conditions without metabolic activation at 4 or 20 hr incubations.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: Rat Bone Marrow Micronucleus Test with A-1293543 Free Form (Study No. R&D/12/350)

Key Study Findings

- Based on the results of a dose-range finding study, the maximum dose in the definitive study with male rats was 150 mg/kg (oral).
- Piloerection was observed at 150 mg/kg during the study. No mortality was observed.
- The positive control increased the frequency of micronucleated PCEs.
- The study was considered valid.
- No treatment-related increases in the frequency of micronucleated PCEs or cytotoxicity were observed.
- Upadacitinib was not clastogenic in the *in vivo* rat micronucleus assay

8 Carcinogenicity

The Sponsor conducted a carcinogenicity evaluation of upadacitinib in a 26-week oral study in transgenic (TgRas) mice and a 104-week oral study in rats. The Executive Carcinogenicity Assessment Committee (ECAC) concurred with the doses and designs of the studies (see Carcinogenicity Special Protocol Assessment Agreement Letters dated April 30, 2015 and July 27, 2016 for further information).

The 26-week mouse and 104-week rat carcinogenicity studies were submitted and reviewed under IND 114,717; a brief synopsis of these studies is included below (see Pharmacology and Toxicology Review of IND 114,717 by Dr. Brett Jones dated March 26, 2019 for further information). Briefly, the CDER ECAC concurred that the carcinogenicity studies were adequate, noting prior approval of the protocols. The Committee also concurred that there were no drug-related neoplasms in males or females in either the 26-week mouse or 104-week rat carcinogenicity studies (see ECAC meeting minutes submitted under NDA 211675 dated March 8, 2019 for further information).

Study title: A-1293543 Free Form [ABT-494]: A 26-Week Oral Gavage Carcinogenicity Study in Model 001178-T (Hemizygous) CByB6F1-TG(HRAS)2JIC Mice (Study No. TD16-088)

Key Study Findings

- In a 26-week oral carcinogenicity study, male and female CB6F1-TgN mice (25/sex/group, 15/sex/group for MNU positive control) received UPA at doses of 0, 5, 10, and 20 mg/kg/day.
- Dose selection was based on data from 7- and 28-day toxicity studies in CByB6F1-Tg(HRAS)2Jic (wild-type) mice.
- Positive control mice received a single intraperitoneal injection of 75 mg/kg N-nitroso-N-methylurea on Study Day 1.
- There were no statistically significant test article-related tumor findings in male or female mice.
- Mean AUC exposure of UPA after oral administration of high dose UPA was 844 ng*hr/mL and 1440 ng*hr/mL, for males and females, respectively.
- The ECAC concurred with the doses and design of the study (see Special Protocol Agreement dated July 27, 2016).
- The duration of the treatment was adequate (i.e., 26 weeks for males and females).
- The CB6F1-TgN mouse is considered an acceptable model for 26-week oral carcinogenicity studies.
- The CB6F1-TgN mouse achieved systemic exposures to UPA after oral administration.

Study title: 104-Week Oral Dose (Gavage) Carcinogenicity Study with A-1293543 Hydrate C in Sprague Dawley Rats (Study No. TA15-032)

Key Study Findings

- In a 104-week oral carcinogenicity study, male and female SD rats (70 rats/sex/group) received UPA at doses of 0, 4, 7.5, and 15 mg/kg/day (males) and 0, 3, 7.5, and 20 mg/kg/day (females).
- Dose selection was based on the results of a 6-month toxicology study in which SD rats received UPA by oral gavage at doses of 0, 5, 20, or 50 mg/kg/day.
- There were no test article-related effects on mortality.
- There were no statistically significant test article-related tumor findings in male and female rats.
- Mean AUC exposure of UPA following oral administration at the high dose 1293543 was 1.67 µg*hr/mL (15 mg/kg/day) and 4.17 µg*hr/mL (20 mg/kg/day), for males and females, respectively.
- The ECAC concurred with the doses and design of the study (see Carcinogenicity Special Protocol Agreement dated April 30, 2015).
- The duration of treatment was adequate (i.e., 99-101 weeks for males and 100 weeks for females).
- The SD rat is considered an acceptable model for 2-year oral carcinogenicity studies.

- The SD rat achieved systemic exposures to UPA following oral administration.

9 Reproductive and Developmental Toxicology

Reproductive and developmental toxicology studies were conducted with upadacitinib in rats (fertility and early embryonic development; embryo-fetal development; and pre-/post-natal development) and rabbits (embryofetal development). These studies were reviewed under IND 114,717 and brief summaries are provided below. Refer to the Pharmacology and Toxicology Review of IND 114,717 by Dr. Brett Jones dated January 24, 2019 for further information.

9.1 Fertility and Early Embryonic Development

Study title: An Oral Fertility Study with A-1293543 (b) (4) in Rats (Study No. TA13-312)

Key Study Findings

- This GLP-compliant oral fertility study in rats evaluated UPA at doses of 0 (vehicle), 5, 25, 50 (males), and 75 mg/kg/day (females) administered for 14 days prior to mating (males and females), through mating and post-mating periods (males), and through mating period to GD7 (females)
- During the pre-mating period (Study days 11-15), a 28% and 29% decrease in body weight gain was observed for males in the 25 and 50 mg/kg/day treatment groups, respectively. At 5 mg/kg/day, UPA was associated with a 47% decrease in body weight gain in males during the post-mating period (study days 32-36). The decreased body weight gains were considered adverse; therefore, a paternal NOAEL was not achieved.
- At 75 mg/kg/day, UPA was associated with a 49% decrease in body weight gain in females during the gestation period. The decreased body weight gain was considered adverse; therefore, the maternal NOAEL was 25 mg/kg/day UPA.
- No clear test article-related effects on male or female mating and fertility indices were observed in the study; therefore, 50 mg/kg/day and 75 mg/kg/day UPA were considered as the NOAELs for male and female fertility, respectively.
- The mid dose level of 25 mg/kg/day UPA was associated with increased post-implantation loss, an increased number of resorptions, and decreased mean number of live concepti per litter. The severity of these effects was more pronounced at 75 mg/kg/day (i.e., 6 dams with all resorptions, 82% post-implantation loss, and mean of just 2 viable fetuses per litter). These effects were considered adverse and the NOAEL for early embryonic development was considered as 5 mg/kg/day UPA.

9.2 Embryonic Fetal Development

Study title: An Oral Developmental Toxicity Study with A-129343 (b) (4) in Rats, including a Toxicokinetic Evaluation (Study No. TA12-095)

Key Study Findings

- This GLP-compliant oral EFD study in rats evaluated UPA at doses of 0 (vehicle), 5, 25, and 75 mg/kg/day administered from GD 6-17.
- There was no maternal mortality in this study, and no test article-related effects on body weight changes or food consumption. Despite the lack of maternal toxicity, the study was considered acceptable based on the clear identification of embryo-fetal toxicity.
- Treatment with 75 mg/kg/day UPA was associated with a significant decrease in mean litter fetal body weight at GD 20.
- Upadacitinib was associated with increased skeletal malformations (25 and 75 mg/kg/day groups) and variations (all doses).
- The most prominent skeletal fetal malformations induced by UPA were misshapen forelimbs (humerus) and bent scapula. Skeletal malformations at the high dose included absent vertebra (cervical vertebra), bent forelimbs (radius), and bent and misshapen hindlimbs (femur).
- Skeletal fetal variations of bent and rudimentary ribs, additional ossification of the neural arch (cervical vertebra), and not ossified sternebra (sternum) were observed in all treatment groups. Additional skeletal variations in the pectoral girdle, ribs, skull, and thoracic vertebra were also observed at ≥ 25 mg/kg/day.
- Upadacitinib drug exposure on GD 16 increased in a greater than dose-proportional manner between 5 and 75 mg/kg/day. T_{max} was 1 hr postdose.
- The NOAEL in the study for maternal toxicity was 75 mg/kg/day (AUC 33.4 $\mu\text{g}\cdot\text{hr}/\text{mL}$) and the NOAEL for developmental toxicity was unable to be determined (i.e., < 5 mg/kg/day). Based upon the identification of treatment-related skeletal malformations in the absence of maternal toxicity, UPA was judged to be teratogenic in rats.

Study title: A-1293543 Free Form: A Low Dosage Oral Developmental Toxicity Study in Rats, including a Toxicokinetic Evaluation (Study No. TA17-026)

Key Study Findings

- This low dosage oral developmental toxicity study in rats, evaluated UPA at doses of 0 (vehicle), 1.5, and 4 mg/kg/day administered on GD 6-17.
- No maternal mortality was observed at any dose.
- One female in the 1.5 mg/kg/day group (Animal #2524) and two females in the 4 mg/kg/day group (Animal #3501 and #3502) were submitted for veterinary consult due to body weight loss on GD, 15, 12, and 13, respectively.
- No test-article related effects on any Cesarean section parameters were observed.
- No external or visceral malformations were observed at any treatment dose.

- One single fetus (#12) from a 4 mg/kg/day female (Animal #3519) exhibited skeletal malformations of bent humerus, bent radius, bent ulna, misshapen tympanic ring, misshapen neural arches (thoracic vertebra) and fused neural arches (cervical vertebra). These findings were considered treatment-related and adverse based on consistency with the findings at ≥ 5 mg/kg/day in the prior study.
- The NOAEL for maternal toxicity was established at 4 mg/kg/day (AUC 629 ng*hr/mL).
- The NOAEL for developmental toxicity was established at 1.5 mg/kg/day (AUC 115 ng*hr/mL).

Study title: An Oral Developmental Toxicity Study with A-129343 (b) (4) in Rabbits, including a Toxicokinetic Evaluation (Study No. TE12-096)

Key Study Findings

- This oral EFD study in rabbits, evaluated UPA at doses of 0 (vehicle), 2.5, 10, and 25 mg/kg/day administered from GD 7-19.
- Four does aborted in the 25 mg/kg/day group and this was attributed UPA.
- A 35% decrease in body weight gain was observed in the 25 mg/kg/day group from GD 7-20 which correlated with a significant decrease in food consumption. A clear dose-response was not observed, but the body weight effects at the high-dose were considered adverse.
- Treatment with 25 mg/kg/day UPA was associated with significant changes in several parameters recorded at Cesarean section including significant increases in post-implantation loss, total and early resorptions and significant decreases in fetal body weight and gravid uterine weight.
- An increase in fetal visceral malformations (i.e., thoracic cavity) and skeletal variations and malformations (i.e., sternum) were observed in offspring from the 25 mg/kg/day group.
- UPA exposure on GD 18 increased in a greater than dose-proportional manner from 2.5-25 mg/kg/day. T_{max} was 1 hr for each dose group.
- The NOAEL in the study for maternal and developmental toxicity was 10 mg/kg/day (AUC 881 ng*hr/mL).

9.3 Prenatal and Postnatal Development

Study title: An Oral (Gavage) Pre-/Postnatal Developmental Toxicity Study of A-1293543 (ABT-494) in Rats, including a Postnatal Behavioral/Functional Evaluation Study (Study No. TA16-197)

Key Study Findings

- In a rat PPND study, four groups of 22 virgin-mated female Sprague-Dawley rats (F0 generation) were treated by oral administration with 0 (control), 2.5 (low dose), 5, (mid-dose), and 10 (high dose) mg/kg/day UPA from GD 6 to LD 20.

- In the F0 generation, the mean gestation length was comparable in all groups (about 22 days) as was the mean number of implantation sites (about 13). The mean number of pups delivered per litter was similar across groups (about 12).
- In the F0 generation, toxicokinetic evaluation on LD 14 indicated that following oral administration of UPA, systemic exposure of UPA generally increased with dose (less than dose proportional between 2.5 and 5 mg/kg/day).
- On LD 14, the mean UPA plasma concentration in F1 pups was below the lower limit of quantitation (<5.25 ng/mL) for the control and 2.5 mg/kg/day groups. On LD 14, the mean UPA plasma concentration in F1 pups was 4.32 ng/mL for the 5 mg/kg/day groups and 10.9 ng/mL for the 10 mg/kg/day groups.
- F1 generation female and male body weights of drug treated groups (postweaning) were unaffected.
- There was no effect of drug treatment of the F0 mothers on the postweaning sexual maturation/development of F1 males (assessed by preputial separation and body weight at time of occurrence) and F1 females (assessed by vaginal opening and body weight at time of occurrence).
- There was no effect of drug treatment of the F0 mothers on the postweaning behavioral assessment of F1 offspring as assessed by the acoustic startle test (to evaluate habituation), the motor activity test (to evaluate ambulation and fine movement), and the water maze test (to evaluate learning capacity and memory).
- There was no effect of drug treatment of the F0 mothers on fertility in the F1 offspring.
- There was no effect of drug treatment of the F0 mothers on numbers of corpora lutea, implantations, pre- and post-implantation losses, and live fetuses evaluated for pregnant F1 females.
- The NOAEL for maternal and pre-/post-natal toxicity was the high dose (10 mg/kg/day).

10 Special Toxicology Studies

Study Title: T-Cell Dependent Antibody Response Assay using A-1293543 Free Base (Hemihydrate) in Sprague-Dawley Rats (Study No. TA15-053, GLP)

The aim of this investigation was to evaluate if UPA can modulate a T-cell dependent antibody response (TDAR) in Sprague-Dawley rats, and to evaluate the reversibility of any observed test article related effects. Upadacitinib free base was administered to SD rats (10/sex/group) at dosages of 0, 5, 30 or 60 mg/kg/day by oral gavage. One cohort of animals at each dosage was administered test item for 8 weeks (main study animals), and utilized for a T-cell dependent antibody response assay conducted during the last four weeks of the dosing phase. Additional cohorts of animals at dosages of 0 and 60 mg/kg/day were administered test item for 4 weeks, followed by a 16-week recovery phase. A TDAR assay was conducted during the last 4 weeks of the recovery phase. A separate cohort of animals was administered cyclosporin A (immunosuppressant) at 25 mg/kg/day by oral gavage during Days 21 to 55 of the dosing phase. No test article related deaths occurred during the study. Body weight gain was decreased (-14%) for

males in the 60 mg/kg/day group relative to control animals. These changes were reversible. Dose-dependent decreases in mean lymphocyte counts were observed at \geq 5 mg/kg/day on Days 23 and 50. These changes were reversible. Upadacitinib administration produced dose-dependent decreases in mean anti-KLH IgM and IgG concentrations relative to control animals. These effects were reversible. Therefore, UPA suppressed the anti-KLH IgM and IgG T-cell dependent antibody response under the conditions of the study.

Study Title: Neutral Red Uptake Phototoxicity Assay of A-1293543 (b) (4) in Balb/c 3T3 Mouse Fibroblasts (Study No. TX13-260, GLP)

The aim of the investigation was to evaluate the phototoxicity potential of UPA as measured by the relative reduction in viability of Balb/c 3T3 mouse fibroblasts exposed to UPA and ultraviolet radiation (UVR), as compared with the viability of fibroblasts exposed to UPA in the absence of UVR. Promethazine was used as the positive control.

Upadacitinib did not demonstrate phototoxic potential by the Photoirritancy Factor (PIF) and Mean Photo Effect (MPE) criteria. According to the Sponsor's report, all cell survival and OD₅₄₀ results met the OECD 432 criteria and the promethazine cytotoxicity and phototoxicity criteria were met according to the Test Facility historical control, indicating the assay was valid. Upadacitinib was present in the 1.78 and 100 mg/mL formulations used for the definitive assays at concentrations acceptable for use in the assay.

11 Integrated Summary and Safety Evaluation

AbbVie Inc. submitted an original 505(b)(1) NDA on December 18, 2018, for upadacitinib (ABT-494, A-1293543) as an extended-release tablet for oral use. Upadacitinib is a JAK inhibitor proposed for the treatment of adult patients with moderately to severely active RA. Upadacitinib is proposed as monotherapy or in combination with methotrexate or other conventional synthetic DMARDs. The planned dose of upadacitinib is 15 mg once daily taken orally.

The nonclinical safety program for upadacitinib included pharmacology, PK, general toxicology, carcinogenicity assessment, genetic toxicology, reproductive and developmental toxicology, and special toxicology studies. An integrated summary of this information is provided below.

PK/ADME

Designated PK studies were conducted with UPA in CByB6F1-Tg(HRAS)2Jic wild-type mice, Sprague-Dawley rats, New Zealand white rabbits, beagle dogs, and cynomolgus monkeys. Oral bioavailability was moderate in rats (31%) and higher in both monkeys (59%) and dogs (77%). The mean $t_{1/2}$ of UPA ranged from 1-3 hrs in rats, dogs, and monkeys following IV dosing. Upadacitinib exhibited moderate to high plasma clearance and high volumes of distribution. In repeat dose studies of upadacitinib in mice, rats, rabbits, and dogs, UPA exposure (C_{max} and AUC) increased in greater than a dose-

proportional manner across a range of doses. No UPA accumulation was observed following repeat dosing. No sex differences in UPA exposure were observed in mice and dogs; however, in rats AUC values were higher in females than males.

Upadacitinib exhibited low plasma protein binding in all nonclinical species examined. In a placental transfer and lacteal excretion study with radiolabeled UPA in pregnant rats, UPA distributed into the placenta, uterus, amniotic sac, and fetal tissues at 4 hrs following oral dosing.

Unchanged UPA was the primary component in circulation in all species (i.e., >79% plasma radioactivity in humans). The glucuronide metabolite M4 (i.e., 13%) was the major metabolite in human plasma. It was not considered a safety concern. All human metabolites were observed in nonclinical species. Upadacitinib was primarily cleared via the biliary or renal routes of excretion. Upadacitinib was a weak inducer of CYP3A4 at clinically relevant doses.

Pharmacology

In a cell-free isolated enzyme assay, the *in vitro* potency of upadacitinib towards JAK1, JAK2, and JAK3 at 0.1 mM ATP was 0.043 μ M, 0.12 μ M, and 2.3 μ M, respectively. Therefore, UPA displayed 2.8-fold selectivity for JAK1 vs. JAK2 and 53-fold selectivity for JAK1 vs. JAK3 (at 0.1 mM ATP). However, JAK1 and JAK2 were both inhibited at < 0.0032 μ M (lower limit of detection) at 0.001 mM ATP. In human leukocytes, UPA inhibited cytokine induced STAT phosphorylation mediated by JAK1/JAK3 and JAK1/JAK1 with comparable potencies.

The Sponsor has described UPA in their submission and proposed draft label as a (b) (4). Based upon the findings described above, this nonclinical reviewer recommends that (b) (4) be removed from the draft label. This would avoid promotional labeling language and maintain consistency with other previously approved JAK inhibitor products (e.g., baricitinib, tofacitinib) in this Established Pharmacologic Class.

In a concanavalin-induced IFN γ *in vivo* rat model assessing the effects on IL-2 signaling, upadacitinib inhibited IFN γ induction with an ED₅₀ of 0.4 mg/kg. In an AIA *in vivo* rat model, oral treatment with UPA resulted in a dose-dependent inhibition of paw swelling, with >90% inhibition observed at 10 mg/kg. A histological examination of the left paws and ankles from rats revealed that UPA at \geq 3 mg/kg/day significantly improved joint morphology (i.e., synovial hypertrophy/inflammation, cartilage damage, and bone erosion).

Safety Pharmacology

Upadacitinib was tested in a battery of safety pharmacology studies. In a neurobehavioral study, UPA decreased motor activity in rats at an oral dose of 100 mg/kg. In a cardiovascular study in conscious dogs, UPA increased heart rate at an oral dose of 5 mg/kg. No effects on respiratory were observed.

General Toxicology

The safety of UPA was evaluated in a number of GLP-compliant repeat-dose oral toxicology studies in Sprague-Dawley rats (4-weeks and 26-weeks) and beagle dogs (4-weeks and 39-weeks). For the purposes of this integrated summary, significant and/or common findings observed in the repeat-dose toxicology studies in rats and dogs (39-week study only) are briefly summarized below.

Significant dose-limiting mortality was observed with UPA administered at oral doses of 100 and 200 mg/kg/day in the 4-week toxicology study in rats. Treatment-related adverse microscopic findings of moderate to marked, multifocal, diffuse liver necrosis in the liver were observed in animals with early mortality at 100 mg/kg/day. Treatment-related adverse findings of minimal to marked degeneration/regeneration of the renal tubular epithelium of the kidney was also observed for rats at 100 mg/kg/day. This finding was reversible. From the assessment of a standard panel of hematology parameters, test article related effects were observed on red blood cell (RBC) mass and lymphocyte counts. At Week 4, RBC mass were decreased at 100 mg/kg/day UPA for females. This decrease was generally reversible. At Week 4, lymphocyte counts were decreased in all treatment-related groups, in a dose-related manner. These decreases were generally reversible at the end of the recovery period.

In a 26-week toxicology study, rats were administered UPA at doses of 0, 5, 20, or 50 mg/kg/day. The target organs of toxicity for UPA were identified as the kidneys, thymus, spleen, and lymph nodes (mandibular, medial iliac, mediastinal, and mesenteric). Minimal to moderate tubular degeneration/regeneration in the kidneys was observed for males and females in the 50 mg/kg/day treatment groups. Similar to the finding observed at 100 mg/kg/day in the 4-week rat study, this kidney finding was also considered adverse and dose-limiting. At Week 26, decreases in lymphocyte counts were observed for males and females at 50 mg/kg/day UPA and correlated with decreased lymphoid organ weights and decreased numbers of lymphocytes in the thymus, spleen, and lymph nodes. At Week 26, RBC mass and reticulocytes were decreased for males (≥ 20 mg/kg/day) and females (50 mg/kg/day). These findings were considered monitorable in a clinical setting. A NOAEL of 20 mg/kg/day was established for this study based upon observed adverse histopathological findings in the kidneys at 50 mg/kg/day. Mean systemic exposure at 20 mg/kg/day was 5320 ng*hr/mL. This exposure provides a safety margin of approximately 13 times the exposure at the proposed clinical dose (see Table 7).

Upadacitinib was administered to beagle dogs at oral doses of 0, 0.1, 0.5, and 1.5 mg/kg/day for up to 39 weeks. The skin was identified as a target organ of toxicity. Increased incidences of interdigital cysts were observed in the skin of males in the 0.5 and 1.5 mg/kg/day treatment groups and in females administered 0.5 mg/kg/day. A dose-dependent increase in severity of mixed, multifocal cell inflammation in the interdigital skin was observed for males in all UPA treatment groups. One male animal (#4005) in the 1.5 mg/kg/day group had dosing suspended on Day 219 due to observed significant skin lesions that included cutaneous inflammation and demodicosis. These findings were attributed to the immunosuppressive effects of UPA and were considered

monitorable in a clinical setting. Other target organs of toxicity were identified as the popliteal lymph node (LN), precapsular LN, spleen, and thymus. No treatment-related effects on kidneys have been observed in dogs. An increased incidence and severity of mixed cell inflammation was observed in the precapsular and popliteal lymph nodes of males and/or females at ≥ 0.5 mg/kg/day. A decrease in lymphocytes in the spleen and thymus were observed for males at ≥ 0.5 mg/kg/day. These findings were also attributed to the immunosuppressive effects of UPA and were considered monitorable in a clinical setting. A NOAEL of 1.5 mg/kg/day was established for this study. Mean systemic exposure at 1.5 mg/kg/day was 888 ng*hr/mL. This exposure provides a safety margin of approximately 2 times the exposure at the proposed clinical dose (see Table 7).

Genetic Toxicology

Upadacitinib was non-mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay and was negative in an *in vitro* chromosomal aberration assay for structural chromosomal aberrations. A significant increase in polyploidy was observed under conditions without metabolic activation (4 or 20 hr exposures); however, upadacitinib was negative in a subsequent *in vivo* rat micronucleus assay.

Carcinogenicity

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

Reproductive and Developmental Toxicity

The reproductive and developmental toxicity of upadacitinib was evaluated in: (1) an oral developmental toxicity study in rats (2 studies), (2) an oral developmental toxicity study in rabbits, and (3) an oral pre-/postnatal developmental (PPND) toxicity study in rats. An oral fertility study in rats was also conducted.

In an initial oral embryo-fetal development (EFD) study in rats at doses of 0, 5, 25, and 75 mg/kg/day UPA, no maternal toxicity was observed. However, UPA was associated with fetal skeletal malformations and variations at all doses. Due to the observed fetal malformations at all treatment doses, the NOAEL for developmental toxicity in this study was unable to be established.

In a second low dosage oral EFD study in rats at doses of 0, 1.5, and 4 mg/kg/day UPA, one single fetus (#12) from a 4 mg/kg/day female (Animal #3519) exhibited skeletal malformations of bent humerus, bent radius, bent ulna, misshapen tympanic ring, misshapen neural arches (thoracic vertebra) and fused neural arches (cervical vertebra). These findings were considered treatment-related and adverse based on consistency with the findings at ≥ 5 mg/kg/day in the prior study. The NOAEL for maternal toxicity was 4 mg/kg/day. The NOAEL for developmental toxicity was 1.5 mg/kg/day.

In the oral EFD study in rabbits, UPA was administered at doses of 0, 2.5, 10, and 25 mg/kg/day. Embryo lethality observed at 25 mg/kg/day was considered adverse and test article related. In addition, UPA at 25 mg/kg/day was associated with increased post-implantation loss and total/early resorptions and decreased fetal body weight and gravid uterine weight. Fetal visceral malformations (i.e., thoracic cavity) and skeletal variations and malformations (i.e., sternum) were observed in offspring at 25 mg/kg/day. The NOAEL for maternal and developmental toxicity was determined to be 10 mg/kg/day.

In the oral PPND study with pregnant rats, UPA at doses up to 10 mg/kg/day produced no evidence of maternal toxicity or embryotoxicity/fetal malformations. The NOAEL for maternal toxicity was the high dose (10 mg/kg/day) and the NOAEL for the PPND study was the high dose (10 mg/kg/day).

In an oral fertility study in rats at doses of 0, 5, 25, 50 (M), and 75 (F) mg/kg/day UPA, no test article-related effects on male or female mating and fertility indices were observed; therefore, 50 mg/kg/day and 75 mg/kg/day UPA were considered as the NOAELs for male and female fertility, respectively. Doses of 25 mg/kg/day UPA or greater were associated with increased post-implantation loss, an increased number of resorptions, and decreased mean number of live concepti per litter. These effects were considered adverse and the NOAEL for early embryonic development was considered as 5 mg/kg/day UPA.

Upadacitinib is teratogenic in rats and rabbits and is associated with skeletal malformations in rats at doses of ≥ 4 mg/kg/day in the absence of maternal toxicity and cardiac malformations in rabbits concurrent with maternal toxicity. The finding of teratogenicity in rats and rabbits at clinically relevant exposures indicates a serious risk for human fetal toxicity. This was not an unexpected finding due to the pharmacological activity of upadacitinib and similar findings reported for other JAK inhibitors. However, the nonclinical reviewer considered the embryo-fetal toxicity data with upadacitinib as comparatively more concerning than previously approved JAK inhibitor products (e.g., tofacitinib, baricitinib) based on the observed lower exposure margins to proposed clinical dose levels.

At a Safety Mid-Cycle Meeting on March 4, 2019, the nonclinical safety concerns regarding the observed teratogenicity of upadacitinib at exposures similar to the proposed clinical dose levels in both rats and rabbits were presented and subsequently discussed with the clinical review team and other associated review team members. The review team agreed that the observed embryo-fetal toxicity data with upadacitinib represented a significant safety concern that potentially warranted inclusion in the Warnings and Precautions (Section 5) of the label, particularly given the abundance of women of childbearing potential in the RA population. It was agreed that a consult request be submitted to the Division of Pediatric and Maternal Health (DPMH) to review this embryo-fetal toxicity issue for possible inclusion into the Warnings and Precautions section of the proposed product label. The Division submitted a DPMH request for consultation on April 11, 2019.

In the DPMH consult review, the reviewer stated that a higher level of concern regarding the animal findings for upadacitinib is reasonable based upon the lower exposure margins to proposed clinical dose levels. The precedent regarding labeling for other approved products in the class of small molecule kinase inhibitors (e.g., for oncologic indications) was also considered. These products exhibit similar exposure ratios to that observed with upadacitinib and carry Warnings and Precautions for embryo-fetal toxicity in their approved labels. Therefore, based on the guidance and precedent established with other approved small kinase inhibitor products, DPMH stated that labeling for upadacitinib should include a Warning and Precaution for embryo-fetal toxicity. DPMH provided a proposed labeling recommendation for Section 5 of the upadacitinib product label. Refer to the DPMH consult review for NDA 211675 dated April 19, 2019 for further information.

Special Toxicology Studies

In a GLP-compliant TDAR assay, upadacitinib suppressed the anti-KLH IgM and IgG T cell-dependent antibody response. The observed treatment-related effects on decreased body weight gain, decreased circulating lymphocytes, and suppression of the T cell-dependent antibody response were reversible.

Recommendation

From the nonclinical perspective, the application is recommended for approval. No additional nonclinical studies are recommended.

Labeling

Nonclinical sections of the product label will be evaluated in a separate review. As discussed above, the nonclinical reviewer recommends that a Warning and Precaution for embryo-fetal toxicity be included in the proposed product label for upadacitinib.

Table 7. Upadacitinib Safety Margins

Study	Endpoint	Daily Dose	AUC (ng*hr/mL)	Exposure Margin Clinical Oral Dose of 15 mg (QD) (AUC _{0-24hr} = 396 ng*hr/mL) ^A
				AUC
General Toxicology				
6-month Rat	NOAEL (M/F)	20 mg/kg	5320	13.4
9-month Dog	NOAEL (M/F)	1.5 mg/kg	888	2.2
Developmental and Reproductive Toxicology				
Male and Female Fertility and Early Embryonic Development in Rats (No TK Data)	NOAEL (maternal)	25 mg/kg	8720 (est.) ^D	22.0
	NOAEL (male fertility)	50 mg/kg	12,000 (est.) ^B	30.3
	NOAEL (female fertility)	75 mg/kg	33,400 (est.)	84.3
	NOAEL (early embryonic development)	5 mg/kg	680 (est.) ^C	1.7
Embryo-Fetal Development in Rats	NOAEL (maternal)	75 mg/kg	33,400	84.3
	NOAEL (embryo-fetal development)	None (<5 mg/kg)	-	-
Embryo-Fetal Development in Rats (Low Dose)	NOAEL (maternal)	4 mg/kg	629	1.6
	NOAEL (embryo-fetal development)	1.5 mg/kg	115	0.3
Embryo-Fetal Development in Rabbits	NOAEL (maternal)	10 mg/kg	881	2.2
	NOAEL (embryo-fetal development)	10 mg/kg	881	2.2
Pre-/Postnatal Development in Rats	NOAEL (maternal)	10 mg/kg	1090	2.8
	NOAEL (reproductive)	10 mg/kg	1090	2.8

^AMean steady state plasma exposure following administration of upadacitinib (15 mg, QD) in adult RA patients (R&D/18/0165).

^BEstimated AUC exposure based upon mean AUC exposure observed in male rats on Day 178 in 26-week rat study (AUC = 12,100 ng*hr/mL).

^CEstimated AUC exposure based upon mean AUC exposure observed in female rats at 5 mg/kg in Embryo-Fetal Development Study (AUC = 629 ng*hr/mL) (Study No. TA12-095).

^DEstimated AUC exposure based upon mean AUC exposure observed in female rats at 25 mg/kg in Embryo-Fetal Development Study (AUC = 8720 ng*hr/mL) (Study No. TA12-095).

Table 8. Adverse endpoints for upadacitinib relative to proposed clinical dose

Study	Adverse Endpoints	Daily Dose	AUC (ng*hr/mL)	Exposure Margin Clinical Oral Dose of 15 mg (QD) (AUC ₀₋₂₄ = 396 ng*hr/mL) ^A
				AUC
General Toxicology				
6-month Rat	<ul style="list-style-type: none"> Renal degeneration Lymphocytic decrease 	50 mg/kg	17,000	42.9
9-month Dog	<ul style="list-style-type: none"> Immunosuppression (monitorable) 	1.5 mg/kg	888	2.2
Developmental and Reproductive Toxicology				
Male and Female Fertility and Early Embryonic Development in Rats (No TK Data)	<ul style="list-style-type: none"> Decreased BW gain (maternal) 	75 mg/kg	33,400 (est.)	84.3
	<ul style="list-style-type: none"> None (male fertility) 	50 mg/kg	12,000 (est.) ^B	30.3
	<ul style="list-style-type: none"> None (female fertility) 	75 mg/kg	33,400 (est.)	84.3
	<ul style="list-style-type: none"> Increased postimplantation loss Increased resorptions Decreased no. live concepti (early embryonic development) 	25 mg/kg	8720 (est.) ^C	22.0
Embryo-Fetal Development in Rats	<ul style="list-style-type: none"> None (maternal) 	75 mg/kg	33,400	84.3
	<ul style="list-style-type: none"> Skeletal fetal malformations and variations (embryo-fetal development) 	5 mg/kg	680	1.7
Embryo-Fetal Development in Rats (Low Dose)	<ul style="list-style-type: none"> None (maternal) 	4 mg/kg	629	1.6
	<ul style="list-style-type: none"> Skeletal malformation (one female) (embryo-fetal development) 	4 mg/kg	629	1.6
Embryo-Fetal Development in Rabbits	<ul style="list-style-type: none"> Four does aborted Decreased BW gain Increased postimplantation loss, total and early resorptions 	25 mg/kg	5950	15.0

	<ul style="list-style-type: none"> • Decrease in fetal BW and uterine weight (maternal) 			
	<ul style="list-style-type: none"> • Increased fetal visceral malformations • Increased skeletal variations and malformations (embryo-fetal development) 	25 mg/kg	5950	15.0
Pre-/Postnatal Development in Rats	<ul style="list-style-type: none"> • None (maternal) 	10 mg/kg	1090	2.8
	<ul style="list-style-type: none"> • None (reproductive) 	10 mg/kg	1090	2.8

^AMean steady state plasma exposure following administration of upadacitinib (15 mg, QD) in adult RA patients (R&D/18/0165).

^BEstimated AUC exposure based upon mean AUC exposure observed in male rats on Day 178 in 26-week rat study (AUC = 12,100 ng*hr/mL).

^CEstimated AUC exposure based upon mean AUC exposure observed in female rats at 25 mg/kg in Embryo-Fetal Development Study (AUC = 8720 ng*hr/mL) (Study No. TA12-095).

12 Appendix/Attachments

Appendix 1: Special Protocol Assessment (ECAC Meeting Minutes) Dated March 8, 2019, for Committee Discussion and Recommendations for 26-Week Oral Carcinogenicity Study in Mice and 104-Week Oral Carcinogenicity Study in Rats

Executive CAC

Date of Meeting: March 5, 2019

Committee: Karen Davis Bruno, Ph.D., OND IO, Chair
Paul Brown, Ph.D., OND IO, Member
Tim McGovern, Ph.D., OND IO, Member
Ronald Wange, Ph.D., OND IO, Member
Ikram Elayan, Ph.D., DPP, Alternate Member
Andrew Goodwin, Ph.D., DPARP, PharmTox Supervisor
Brett Jones, Ph.D., DPARP, Presenting Reviewer

Also present: Feng Zhou, Ph.D., DBVI

Author of Minutes: Brett Jones, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 211,675; IND # 114,717

Drug Name: Upadacitinib (A-1293543, ABT-494)

Sponsor: AbbVie Inc.

Background:

Upadacitinib is an orally available small molecule Janus kinase (JAK) inhibitor being developed for the treatment of rheumatoid arthritis.

Tg rasH2 Mouse Carcinogenicity Study:

AbbVie Inc., conducted a 26-week bioassay in CByB6F1-Tg(HRAS)^{2Jic} mice (25/sex/group, 15/sex for MNU positive control) with upadacitinib administered by oral gavage at doses of 0 (0.2% (w/v) hydroxypropyl methylcellulose [HPMC] in deionized water), 5, 10, and 20 mg/kg/day for males and females. These doses received concurrence from the CDER Executive Carcinogenicity Assessment Committee (ECAC; see IND 114,717 Meeting Minutes dated July 27, 2016). Positive control mice received a single intraperitoneal injection of 75 mg/kg N-nitroso-N-methylurea on study Day 1.

There was no effect of upadacitinib on survival. Upadacitinib was not tumorigenic in Tg.rasH2 mice at doses up to 20 mg/kg/day in males and females.

Rat Carcinogenicity Study:

The Sponsor conducted a 104-week bioassay in Sprague-Dawley rats (70 rats/sex/group) with upadacitinib administered by oral gavage at doses of 0 (0.2% (w/v) hydroxypropyl methylcellulose [HPMC] in deionized water), 4, 7.5 or 15 mg/kg/day (Males), or 0, 3, 7.5, or 20 mg/kg/day (Females). These doses received concurrence from the CDER ECAC (see IND 114,717 Meeting Minutes dated April 30, 2015). The study was stopped at Week 99-101 (males) and Week 100 (females) due to deaths in treatment groups, in accordance with ECAC recommendations.

There was no effect of upadacitinib on survival. Upadacitinib was not tumorigenic in rats at doses up to 15 mg/kg/day in males and 20 mg/kg/day in females.

Executive CAC Recommendations and Conclusions:

Tg rasH2 Mouse Carcinogenicity Study

- The Committee concurred that the carcinogenicity study was adequate, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms in the 26-week Tg rasH2 mouse study in either males or females.

Rat Carcinogenicity Study

- The Committee concurred that the carcinogenicity study was adequate, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms in males or females in the 104-week study.

Karen Davis Bruno, PhD
Chair, Executive CAC

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

/s/

BRETT R JONES
05/21/2019 03:10:59 PM

ANDREW C GOODWIN
05/21/2019 03:19:07 PM
I concur

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 211675
Supporting document/s: SDN 0002
Applicant's letter date: December 18, 2018
CDER stamp date: December 18, 2018
Product: Upadacitinib (ABT-494)
Indication: Rheumatoid Arthritis
Applicant: AbbVie Inc.
Review Division: Division of Pulmonary, Allergy, and
Rheumatology Products
Reviewer: Brett Jones, PhD
Supervisor/Team Leader: Andrew Goodwin, PhD
Division Director: Sally Seymour, MD
Project Manager: Nina Ton, PharmD

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 211675 are owned by [name of applicant] or are data for which AbbVie Inc., has obtained a written right of reference. Any information or data necessary for approval of NDA 211675 that AbbVie Inc., does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 211675.

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APPEARS THIS WAY ON ORIGINAL

1 Executive Summary

1.1 Introduction

Upadacitinib is a small molecule inhibitor of Janus-associated kinase (JAK) being developed for the treatment of moderately to severely active rheumatoid arthritis (RA).

This review was conducted to provide a safety assessment of additional potentially genotoxic impurities in the drug substance as requested by the API reviewer, Dr. Sam Bain.

A Pharmacology and Toxicology Review of IND 114717 by Dr. Jessica Bonzo (review dated January 11, 2019) previously provided a safety assessment/qualification of several potentially genotoxic impurities in the drug substance. Briefly, a combination of *in silico* (Q)SAR assessment, *in vitro* bacterial mutagenicity (Ames) testing, compound-specific risk assessment, and other scientific principles justifications were submitted by the Sponsor and subsequently reviewed to categorize each impurity according to ICH M7(R1) Guidance. FDA QSAR analysis was requested for 51 structures, of which two impurities (b) (4) were identified as a concern. An Information Request (IR) was forwarded to the Sponsor requesting further justification for the use of the mini Ames assay for these impurities. Following consultation with the CDER Genetic Toxicology Subcommittee, the Sponsor's response was considered insufficient and a second IR was forwarded requesting additional justification. In response to the IR, the Sponsor stated that the impurities were successfully controlled by scientific principles. Of 33 impurities tested by the mini Ames assay, four were positive/equivocal for mutagenicity (b) (4). The Sponsor stated that (b) (4) were controlled per the ICH M7 (R1) guidance. Two different lots (b) (4) provided conflicting mutagenicity results and the FDA QSAR analysis resulted in a "no-call". The Sponsor responded to the IR with additional information detailing the control of the substance by purge factor analysis. Refer to the Pharmacology and Toxicology Review of IND 114717 by Dr. Jessica Bonzo (review dated January 11, 2019) for further information.

A Pharmacology and Toxicology Review of IND 114717 by Dr. Asoke Mukherjee (review dated December 3, 2013) provided a safety assessment of ABT-494 in an Ames assay, *in vitro* mammalian chromosome aberration assay, and an *in vivo* micronucleus assay. Several impurities of toxicological concern were also reviewed. Refer to the Pharmacology and Toxicology Review of IND 114717 by Dr. Asoke Mukherjee (review dated December 3, 2013) for further information.

1.2 Brief Discussion of Nonclinical Findings

1.3 Recommendations

1.3.1 Approvability

NA

1.3.2 Additional Non Clinical Recommendations

None.

2 Drug Information

2.1 Drug

Generic Name

Upadacitinib

Code Name

ABT-494; A-1293543

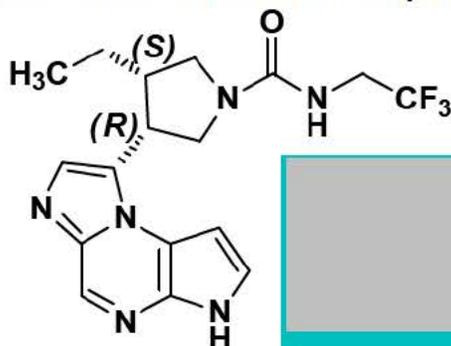
Chemical Name

(3S,4R)-3-Ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazine-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrate (2:1)

Molecular Formula/Molecular Weight

C₁₇H₁₉F₃N₆O · (b) (4)

Structure or Biochemical Description



Pharmacologic Class

Janus kinase (JAK) inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 114717

2.5 Comments on Impurities/Degradants of Concern

In an email communication dated March 8, 2019, the API reviewer, Dr. Sam Bain, provided a table of potential mutagenic impurities for the drug substance (b) (4) (see table below). A nonclinical review of the compounds identified that several of the structures were previously evaluated in the Pharmacology and Toxicology Review of IND 114,717 by Dr. Jessica Bonzo (review dated January 11, 2019) (or are (b) (4) included in the review). In addition, a number of the structures are classified as (b) (4) compounds with no alerts in either Derek or CASE Ultra analyses, or classified (b) (4) and which present no toxicological concerns.

A CDER/OTS/OCP/DARS Computational Toxicology (Q)SAR consultation was submitted for 4 impurities:

(b) (4)

Table 1. Potential mutagenic impurities for the drug substance upadacitinib

(b) (4)



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(b) (4)

The (Q)SAR assessment of mutagenic potential for the compounds was consistent with recommendations described in the ICH M7(R1) guideline. Briefly, the Sponsor predicted all chemicals to be negative for bacterial mutagenicity. The CDER/OTS/OCP/DARS consultation agreed with the Sponsor's conclusions (see tables below).

Table 2. CDER/OTS/OCP/DARS Computational Toxicology Consultation (Q)SAR assessment of mutagenic potential of four impurities in the drug substance upadacitinib

No.	Chemical Name	Sponsor's Bacterial Mutagenicity Expert Prediction	Agency's Bacterial Mutagenicity Expert Prediction
1	(b) (4)	-	-
2	(b) (4)	-	-
3	(b) (4)	-	-
4	(b) (4)	-	-

Table 3. CDER/OTS/OCP/DARS Computational Toxicology Consultation bacterial mutagenicity (Q)SAR predictions

No.	Chemical Name	Structure	Bacterial Mutagenicity Predictions				Comments
			DX	LMA	CU	Overall Expert	
1	(b) (4)	(b) (4)	-	-	-	-	(b) (4) is predicted to be negative for bacterial mutagenicity.
2	(b) (4)	(b) (4)	-	-	-	-	(b) (4) is predicted to be negative for bacterial mutagenicity.
3	(b) (4)	(b) (4)	-*	-	NC	-	(b) (4) is predicted to be negative for bacterial mutagenicity. DX identified an (b) (4) was unable to generate a prediction (b) (4) and CU (b) (4) however, information from the structurally similar analogs was able to address these data gaps and support an overall negative conclusion.
4	(b) (4)	(b) (4)	-	NC	Eqv	-	(b) (4) is predicted to be negative for bacterial mutagenicity based on the application of expert knowledge. CU generated an equivocal prediction due to the (b) (4) however, the positive training set structures from which the alert was derived were found to contain additional alerting features. Sufficient evidence was obtained from the other models to support an overall negative prediction for bacterial mutagenicity.

¹ - = negative; -* = negative with unclassified features; Eqv = equivocal; NC = test chemical features are not adequately represented in the model training data set, leading to a no call.

The API reviewer, Dr. Sam Bain also provided a second table of other identified impurities for the drug substance upadacitinib (see table below).

Table 4. Other identified impurities for upadacitinib

(b) (4)

(b) (4)

1

(b) (4)

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3 Studies Submitted

3.3 Previous Reviews Referenced

Pharmacology and Toxicology Review of IND 114,717 by Dr. Jessica Bonzo dated January 11, 2019

Pharmacology and Toxicology Review of IND 114,717 by Dr. Asoke Mukherjee dated December 3, 2013

11 Integrated Summary and Safety Evaluation

This review provides a safety assessment of impurities in the upadacitinib drug substance (as identified by the API reviewer, Dr. Sam Bain), based on data submitted by the Sponsor and other available information. The drug product will be administered by the oral route.

Overall, based on review of the nonclinical data, this review did not identify any mutagenic or non-mutagenic impurities that pose a safety concern for the chronic administration of 15 mg/day upadacitinib in RA patients.

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

/s/

BRETT R JONES
04/22/2019 12:44:23 PM

ANDREW C GOODWIN
04/22/2019 12:57:55 PM
I concur