# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 215830Orig1s000

# OTHER REVIEW(S)

# MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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|---|---|
| Date of This Memorandum: | June 22, 2023 |
| Requesting Office or Division: | Division of Dermatology and Dentistry (DDD) |
| Application Type and Number: | NDA 215830 |
| Product Name, Dosage Form, and Strength: | Litfulo (ritlecitinib) capsule, 50 mg |
| Applicant/Sponsor Name: | Pfizer Inc. |
| TTT ID #: | 2022-453-1 |
| DMEPA 1 Team Leader: | Madhuri R. Patel, PharmD |

## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on May 26, 2023 for Litfulo. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels for Litfulo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

## 2 CONCLUSION

We previously recommended to revise the statement "Always dispense with medication guide" with "Dispense the accompanying Medication Guide to each patient" or a similar statement. However, per Applicant, this language is consistent with other Pfizer products. We find the rationale acceptable. We also previously recommended relocating "Keep in Original Package" from the side panel to the Principal Display Panel (PDP). However, the Applicant requests this remains side panel as this is where all information related to storage is located. We find the rationale acceptable. The Applicant implemented all of our other recommendations and we have no additional recommendations at this time.

2 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[a] Patel, M. Label and Labeling Review for Litfulo (NDA 215830). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JAN 13. TTT ID No.: 2022-453.

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MADHURI R PATEL
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**Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)**
**Epidemiology: ARIA Sufficiency Templates**
**Version: 2018-01-24**

| | |
|---|---|
| Date: | June 16, 2023 |
| Reviewer: | Joel L. Wessfeld, MD MPH<br>Division of Epidemiology I |
| Team Leader: | Benjamin J. Booth, PhD MS<br>Division of Epidemiology I |
| Division Director: | Wei Hua, MD PhD MS MHS<br>Division of Epidemiology I |
| Subject: | Maternal and fetal outcomes |
| Drug Name: | ritlecitinib (LITFULO) |
| Application Type/Number: | NDA 215830 |
| Submission Number: | eCTD 0001 |
| Applicant/sponsor: | Pfizer |
| OSE TTT #: | 2023-4108 |

# Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

## 1. BACKGROUND INFORMATION

### 1.1. Medical Product

NDA 215830 seeks FDA approval for ritlecitinib as a treatment for alopecia areata in adults and adolescents 12 years and older. Ritlecitinib is a small molecule (molecular weight 457.55), which inhibits Janus kinase 3 (JAK3) and tyrosine kinases in the TEC family. The intracellular JAK3/TEC kinases transmit cytokine signals by phosphorylating certain gene transcription factors. Recommended for oral ingestion once daily, ritlecitinib has a mean terminal elimination half-life of 1.3 to 2.3-hours.

### 1.2. Describe the Safety Concern

Alopecia areata is an immune-mediated disease that targets anagen hair follicles and causes hair loss without scarring. With age of onset <40 years in >80% of patients, alopecia areata occurs more often in women than men.[a]

Consistent with labels for other JAK inhibitors, (b) (4)

PI Section 8.1 presents data from pre-clinical studies in:

- Pregnant rats that showed (1) no fetal developmental toxicity at maternal exposures equal to 16 times the maximum recommended human dose (MRHD) and (2) decreased fetal body weights and skeletal malformations at maternal exposures equal to 49 times MRHD.
- Pregnant rabbits that showed (1) no fetal developmental toxicity at maternal exposures equal to 12 times MRHD and (2) decreased fetal body weights, visceral and skeletal malformations, and delayed ossification at maternal exposures equal to 55 times MRHD.
- Rats that showed (1) no maternal or fetal developmental toxicity at maternal exposures (gestation day 6 through lactation day 20) equal to 14 times MHRD and (2) lower postnatal survival and lower offspring body weights at maternal exposures equal to 41 times MRHD.

A review completed by the Division of Pediatrics and Maternal Health (DPMH) found limited human data (12 maternal exposures during clinical studies) about the consequences of using ritlecitinib during pregnancy.[b]

[a] Roca Catherine, M Dinatale, and LP Yao, Division of Pediatric and Maternal Health Review, filed under NDA 215830 on [PENDING] (DARRTS Reference ID: [PENDING]).

[b] *Ibid.*

Noting the potential for use of ritlecitinib by women in reproductive age groups, DPMH cited "the limited data collected in clinical trials" as rationale for recommending two studies to be conducted as postmarketing requirements (PMRs), a pregnancy exposure registry study and a complimentary pregnancy study using a different design.[c] Outcomes of interest include major congenital malformation, spontaneous abortion, stillbirth, pre-term birth, and small for gestational age.

### 1.3. FDAAA Purpose (per Section 505(o)(3)(B))

| *Purpose (place an "X" in the appropriate boxes; more than one may be chosen)* | |
|---|---|
| Assess a known serious risk | |
| Assess signals of serious risk | |
| Identify unexpected serious risk when available data indicate potential for serious risk | X |

## 2. REVIEW QUESTIONS

### 2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
☐ No approved indication, but practitioners may use product off-label in pregnant women
☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
☒ No approved indication, but use in women of childbearing age is a general concern

### 2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

### 2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☒ Electronic database study without chart review (*e.g.*, retrospective cohort study using claims or electronic medical record data or a case-control study nested in a pre-existing pregnancy or birth defect registry)

[c] Mastroyannis, *op cit*.

☒ Other, please specify: Additional pregnancy study using a different design (e.g., case-control study in a pre-existing pregnancy or birth defect registry

**2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?**

☐ Study Population
☐ Exposures
☒ Outcomes (pregnancy registry)
☒ Covariates (pregnancy registry)
☒ Analytical Tools (electronic database/additional pregnancy study)

*For any checked boxes above, please describe briefly:*

Outcomes: ARIA lacks access to medical records. A pregnancy registry entails collection of detailed patient information. A requirement for detailed patient information necessitates data collection not possible in the Sentinel Distributed Database (SDD). The patient information requirement covers both details about (1) drug and concomitant exposures (e.g., precise timing of specific exposures in relation to days before or after pregnancy onset) and (2) outcomes of interest (e.g., specific type of congenital malformation). Pregnancy registry requirements for accurate classification of congenital malformation outcomes necessitate independent review of primary source documents by physicians with special training or expertise in clinical genetics or birth defects.

Covariates: Unlike a pregnancy registry, SDD provides incomplete information about critical covariates (e.g., smoking, folate supplementation, and family history of birth defects).

Analytical Tools: The requested PMRs target more than one outcome, including major congenital malformations (MCM), spontaneous abortions, stillbirths, small for gestational age, and preterm birth. Moreover, the MCM outcome covers several subclasses of potential interest (e.g., congenital malformation of the circulatory system, congenital malformation of the nervous system, or cleft lip and cleft palate). ARIA might address the complexity presented by multiple discrete outcomes by means of an appropriate data mining approach. However, a suitable data mining approach (e.g., TreeScan) is not yet available for signal detection of birth defects and other pregnancy outcomes in ARIA.

**2.5. Please include the proposed PMR language in the approval letter.**

PMR #1: Collect data from a prospective pregnancy exposure registry, preferably a disease-based multiproduct pregnancy registry, using a cohort analysis that compares the maternal, fetal, and infant outcomes of women with alopecia areata exposed to ritlecitinib during pregnancy with unexposed comparator population(s) (b) (4) Align the study protocol with protocol(s) outside the US to reach the target sample size. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortion, stillbirths, elective terminations, preterm births, small-for gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes described in the protocol will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

PMR #2: Conduct an additional pregnancy study that uses a different design from the Pregnancy Exposure Registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to ritlecitinib during pregnancy compared to an unexposed control population.

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**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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# Division of Pediatrics and Maternal Health Review

**Date:** 4/27/2023 **Date consulted:** 3/23/2023

**From:** Catherine Roca, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health

**Through:** Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatrics and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health (DPMH)

**To:** Division of Dermatology and Dentistry (DDD)

**Drug:** LITFULO (ritlecitinib) capsules

**NDA :** 215830

**Applicant:** Pfizer, Inc.

**Subject:** Pregnancy and Lactation Labeling

**Proposed Indication:** Treatment of alopecia areat (b) (4)

**Materials Reviewed:**

- DPMH consult request dated March 23, 2023. DARRTS Reference ID 5146674.
- Applicant's application and proposed labeling submitted June 24, 2022.

- DPMH labeling review for OLUMIANT (baricitinib), Jean Limpert, MD February 5, 2021, DARRTS Reference ID 4742935, and Addendum to the DPMH OLUMIANT (baricitinib) review, Jean Limpert, MD, dated March 23, 2021, DARRTS Reference ID 4768173.[1]

**Consult Question:** "In addition to reviewing section 8 of the PI for which we'd like your assistance, it was recently determined that an ARIA assessment is needed as there are planned PMRs. One of the PMRs will involve a pregnancy registry and, another, a retrospective cohort study using claims, medical records, or a case control study relating to gestational and congenital safety/risk. The DEPI reviewer for this ARIA assessment would like DPMH input on these matters."

## INTRODUCTION AND BACKGROUND

On June 24, 2022, Pfizer Inc., submitted an original new drug application (NDA) 215830 for ritlecitinib for the treatment of alopecia areata. DDD consulted DPMH March 23, 2023, to assist with the Pregnancy and Lactation subsections of labeling and to provide feedback on postmarketing commitments.

Relevant Regulatory History

- Ritlecitinib is a Janus kinase (JAK) 3 and tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family inhibitor for the proposed indication of the treatment of alopecia areat (b) (4)
- Ritlecitinib was granted Breakthrough Therapy Designation on July 31, 2018.

Drug Characteristics

- Ritlecitinib is a Janus kinase (JAK) 3 and tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell development and function. Upon activation JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATS) which modulate intracellular activity including gene expression. The TEC kinase family are also intracellular enzymes which transmit signals arising from various immune receptors modulating intracellular activity including gene expression.

  Ritlecitinib irreversibly and selectively inhibits JAK 3 and the TEC kinase family by blocking the adenosine triphosphate (ATP) binding site. In cellular settings, Ritlecitinib specifically inhibits cytokine-induced STAT phosphorylation mediated by JAK3-dependent receptors and spare receptor signaling independently of JAK3. Additionally, ritlecitinib inhibits signaling of immune receptors dependent on the TEC kinase family members. Ritlecitinib inhibits cytolytic activity and production of interferon gamma in natural killer (NK) cells and CD8+ T cells via inhibition of TEC kinase family members. Ritlecitinib treatment reduced inflammatory peribulbar clusters of CD3+ T cells and

[1] The OLUMIANT consult review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.

CD8+ T cytotoxic T cells as well as reduced NKG2D+NL and CD8+ T cells surrounding hair follicles. The relevance of inhibition of specific JAK or TEC family enzymes to therapeutic effectiveness is not currently known.

- 50mg oral capsule taken orally once daily.
- The molecular weight is 457.55 Daltons.
- The absorption is approximately 89% after oral administration with absolute bioavailability of ~64%; approximately 14% is protein-bound.
- The mean terminal half-life ranges between 1.3-2.3 hours.

**REVIEW**

***PREGNANCY***

Alopecia Areata (AA) and Pregnancy

Alopecia Areata is characterized by nonscarring hair loss of the scalp, face and/or body. Alopecia Totalis (AT) involves complete loss of scalp hair, and Alopecia Universalis (AU) involved the complete loss of scalp and body hair. The estimated prevalence in the United States is approximately 0.18% -0.22% of adults, and approximately 0.1% of children and adolescents.[2] The first onset is by age 40 in >80% of patients. The prevalence is higher among females compared to males.[3] A recent expert consensus study revealed a lack of high-quality randomized controlled trials for treatment of AA. Topical and intralesional agents such as corticosteroids are preferred in milder cases and in children. Systemic therapies include corticosteroids, cyclosporin, methotrexate, azathioprine and JAK inhibitors.[4]

AA is associated with other autoimmune diseases such as thyroid disease and lupus erythematosus. Data on AA during pregnancy are limited. Only two studies were located, both of which were from the Republic of Korea. These studies utilized the Korean National Health Insurance claims database and found that subsequent pregnancy rates among women diagnosed with AA after an initial pregnancy were lower than unaffected women,[5] and that pregnant women with AA had higher rates of spontaneous abortion, ectopic pregnancy, and pelvic inflammatory disease (the author's postulate that the increased risk for pelvic inflammatory disease was due to altered immune status) than women without AA.[6]

Nonclinical Experience

In an embryo-fetal development study in pregnant rats, oral administration of ritlecitinib from gestation days 6 to 17 decreased fetal body weights and caused fetal skeletal malformations (malformed vertebrae and ribs) and variations (delayed ossification) at doses ≥175 mg/kg/day (49 times the MRHD based on AUC comparison). Maternal toxicity (lower body weights) was

[2] McMichael AJ, Roberson ML. Characterizing epidemiology and burden in alopecia areata- making it count. JAMA Dermatol. 2023 Mar.1.online ahead of print.

[3] Mostaghimi A, et al. Trends in prevalence and incidence of alopecia areata, alopecia totalis and alopecia universalis among adults and children in a US employer-sponsored insured population. JAMA Dermatol. 2023:e230002.

[4] Meah N, et al. The alopecia areata consensus of experts (ACE) study: Results of an international expert opinion on treatments for alopecia areata. J Am Acad Dermatol. 2020;83(1):123-130.

[5] Kim JC, Choi JW. Impact of alopecia areata on subsequent pregnancy rate: a retrospective cohort study. Australasian J Dermatol. 2021;62(1):e121-123

[6] Cho SI, et al. Pregnancy outcomes in female patients with alopecia areata: a nationwide population-based study. J Invest Dermatol. 2021:141:1844-1847.

noted at 325 mg/kg/day (102 times the MRHD based on AUC comparison). There was no developmental toxicity at 75 mg/kg/day (16 times the MRHD based on AUC comparison).

In an embryo-fetal development study in pregnant rabbits, oral administration of ritlecitinib from gestation days 7 to 19 decreased mean fetal body weights and increased visceral malformations (malpositioned kidneys), skeletal malformations (supernumerary sternebrae, absent thoracic arch, and/or fused thoracic centra), and skeletal variations (delayed ossification) at 75 mg/kg/day (55 times the MRHD based on AUC comparison). There was no developmental toxicity at doses up to 25 mg/kg/day (12 times the MRHD based on AUC comparison).

In a pre- and postnatal development study in rats, oral administration of ritlecitinib from gestation day 6 through lactation day 20 had no effects on pre- and postnatal development at doses up to 75 mg/kg/day (14 times the MRHD based on AUC comparison). At 175 mg/kg/day (41 times the MRHD based on AUC comparison), ritlecitinib caused adverse lower postnatal survival and lower offspring body weights, which correlated with delayed sexual maturation in both sexes. Bred females in the $F_1$ generation also exhibited lower mean numbers of corpora lutea at 175 mg/kg/day.

Review of Data from the Clinical Trial Program

There were twelve cases of maternal exposure during pregnancy in the clinical development program. Of the twelve maternal exposures, there were:

- Six elective terminations
- Four spontaneous abortions (including one pregnancy exposed to placebo)
- One birth of a healthy, full-term infant
- One case with an unknown outcome

Review of Literature

*Applicant's Review of the Literature*

The Applicant did not provide a review of the published literature.

*DPMH's Review of the Literature*

DPMH performed a search of the published literature using the PubMed, Embase and Micromedex databases using the search terms "ritlecitinib" and "pregnancy," "congenital malformations," "stillbirth," "spontaneous abortion," and "pregnancy outcomes."

No published cases of ritlecitinib exposure during pregnancies were located in the literature search.

A search of the published literature using the terms, "JAK inhibitors" and "pregnancy" yielded the following results:

- In a report examining data from the tofacitinib safety databases for ulcerative colitis[7] and combined with previously reported data from safety databases for rheumatoid arthritis

[7] Mahadevan U, et al. Outcomes of pregnancies with maternal/paternal exposure in the tofacitinib safety databases for ulcerative colitis. Inflamm Bowel Dis. 2018;24(12):2494-2500.

and psoriasis,[8]there were a total of 74 exposed pregnancies. The outcomes were: 37 healthy newborns, 1 major congenital malformation (MCM) (pulmonary valve stenosis), 13 elective terminations, 12 spontaneous abortions, 11 lost to follow-up or pending end of pregnancy. An additional 42 reports from spontaneous reports or noninterventional studies reported 7 healthy newborns, 1 newborn with an MCM (ventricular septal defect), 1 elective termination, 3 spontaneous abortions and 33 cases lost to follow-up or pending at time of publication.

- A case report of a healthy newborn exposed to tofacitinib during the first trimester of gestational development.[9]
- A case report of pregnancy exposure to baricitinib through the 17th week of pregnancy. A healthy infant was born at 38 weeks' gestation.[10]

*Reviewer comment:*
*Nonclinical data on ritlecitinib use during pregnancy show an increased risk for fetal malformations in rats and rabbits at 49- and 55-times the MRHD. However, data at lower doses, 16-times and 12-times in rats and rabbits, respectively, did not demonstrate developmental toxicity. Data in human pregnancy are too limited to draw specific conclusions, but do not appear to report consistent findings of harm.*

***LACTATION***

Nonclinical Experience

After a single oral 30 mg/kg dose of ritlecitinib to lactating rats, ritlecitinib concentrations in milk over time were higher than those in plasma. The mean milk to plasma AUC ratio was 2.2.

Review of Data from the Clinical Trial Program

No cases of exposure to ritlecitinib during lactation were reported in the clinical trial program.

Review of Literature

*Applicant's Review of the Literature.*

The Applicant did not provide a literature review.

*DPMH's Review of Literature*

A search of the published literature was performed using the PubMed, Micromedex[11], and LactMed databases and HalesMeds.com[12] using the terms, "ritlecitinib" and "lactation," or "breastfeeding."

No information related to ritlecitinib, and lactation was found in the published literature. A search of the literature for other JAK-inhibitors and lactation did not yield any cases related to lactation.

[8] Clowse ME, et al. Pregnancy outcomes in the Tofacitinib Safety Databases for Rheumatoid Arthritis and Psoriasis. Drug Safety. 2016;39(8):755-62.
[9] Fernandez-Sanchez M, et al. Fetal exposure to tofacitinib during the first trimester: a healthy newborn case report. Birth Defects Res. 2021: 113(17):1275-1279.
[10] Costanzo G. Accidental exposure to the JAK-inhibitor baricitinib in rheumatoid arthritis: a case report. Allergy 2020;75 (Suppl 109):477.
[11] https://www micromedexsolutions.com, accessed 4/11/2023
[12] https://halesmeds.com, accessed 4/11/2023

*Reviewer comment:*
*There are no data on the presence of ritlecitinib in human milk, the effects on a breastfed infant or effects on milk production. Ritlecitinib is present in rat milk and has a milk: plasma ratio of 2, which could indicate that it accumulates in animal milk. Drug characteristics of ritlecitinib (a molecular weight below 800 Daltons, only 14% protein bounding) increase the likelihood that it passes into breast milk. Given the serious risk for adverse effects seen in adult, such as the increased risk for infections and malignancy, this reviewer recommends against breastfeeding during treatment with LITFULO and for 14 hours (6 half-lives) after the last dose.*

***FEMALES AND MALES OF REPRODUCTIVE POTENTIAL***

Nonclinical Experience

Ritlecitinib had no effects on female rat fertility at doses up to 200 mg/kg/day (55-times the MRHD) based on AUC comparison). Effects on male rat fertility were noted (higher preimplantation loss resulting in lower number of implantation sites and corresponding lower litter size in naïve females mated with ritlecitinib-dosed males) at 200 mg/kg/day (55 times the MRHD based on AUC comparison. No effects on male fertility were noted at doses up to 60 mg/kg/day (14 times the MRHD based on AUC comparison). No effects on spermatogenesis (sperm counts, production rate, motility, or morphology) were noted at any dose.

Review of Data from the Clinical Trial Program

There were no data reported on infertility with use of ritlecitinib from the clinical trials.

Review of Literature

*Applicant's Review of the Literature.*

The Applicant did not provide a literature review.

*DPMH's Review of Literature*

A search of the published literature was performed using the PubMed, Micromedex,[13] and Embase databases using the terms, "ritlecitinib" and "fertility," or "hormonal contraception."

No cases related to effects of ritlecitinib on either fertility or hormonal contraception were found in the search of the published literature.

The applicant's labeling states that (b) (4)

*Reviewer comment:*
*Nonclinical data did not demonstrate adverse effects on fertility except in male animals at multiples of 55-times the MRHD. Drug interaction studies performed by the Applicant did not show an adverse effect on hormonal contraception. Fertility studies in human are not available.*

*Nonclinical findings do not demonstrate an increased risk of MCMs at doses of ritlecitinib 16- and 12-times the MRHD in rats and rabbits, respectively. Currently proposed labeling*

[13] https://www micromedexsolutions.com, accessed 4/11/2023

*recommends* [redacted] (b) (4) *DPMH disagrees with this approach. Given the lack of adverse developmental outcomes in the nonclinical data at doses of ritlecitinib that were 16- and 12 times the MRHD in rats and rabbits, respectively, DPMH recommends that* [redacted] (b) (4) *not be included in labeling. Animal fertility data can remain in Section 13.*

**DISCUSSION AND CONCLUSIONS**

Pregnancy

Nonclinical reproductive toxicity studies demonstrated major congenital malformations with exposure to higher doses of ritlecitinib in rats and rabbits (49- and 55-times the MRHD, respectively); however, at doses of ritlecitinib that were 16- and 12-times the MRHD in rats and rabbits, respectively, there was no evidence of fetotoxicity. Human data from the clinical trials program are too limited to determine a risk associated with the use of ritlecitinib during pregnancy but do not appear to report consistent findings of harm.
Labeling will include a Pregnancy Exposure Registry heading (when the registry information is available), Risk Summary, and Data subheadings.

Given the anticipated use of ritlecitinib in females of reproductive potential who may become pregnant, and the limited data collected in clinical trials, postmarketing studies should be considered. DPMH recommends that a pregnancy exposure registry study be conducted along with a complimentary pregnancy study of a different design (such as a retrospective cohort study using claims or electronic medical records data or a case-control study) to assess major congenital malformations, spontaneous abortions, stillbirths, small-for-gestational age, preterm birth and other adverse maternal and fetal outcomes in women with alopecia areata exposed to ritlecitinib during pregnancy compared to an unexposed population. For more information, the reader is referred to the May 2019 FDA Draft Guidance for Industry Postapproval Pregnancy Safety Studies.[14]

Lactation

There are no data on the use of ritlecitinib during lactation. Ritlecitinib is present in rat milk with a milk: plasma ratio of ~2. When a drug is present in animal milk, it is likely to be present in human milk. Based on the physical properties of ritlecitinib (molecular weight < 800 Daltons, low (14%) protein binding), is likely to pass into breast milk. Given the serious risks seen in adults treated with ritlecitinib, such as infections and malignancy, the proposed labeling recommends against breastfeeding. DPMH agrees with the recommendation not to breastfeed.

Given that ritlecitinib will be used in females of reproductive potential, DPMH recommends a PMR for a clinical lactation study. Since the current recommendation is that women taking ritlecitinib should not breastfeed, DPMH recommends a milk-only study that enrolls only healthy volunteers or breastfeeding women prescribed ritlecitinib who are willing to discontinue breastfeeding. This type of study would be useful to evaluate the amount of transfer, if any, into breast milk. If there is no detectable transfer, such a finding could potentially allow for breastfeeding women to take ritlecitinib. For more information the reader is referred to the

[14] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-pregnancy-safety-studies-guidance-industry

FDA draft Guidance for Industry Clinical Lactation Studies: Considerations for Study Design, published May 9, 2019. https://www.fda.gov/media/124749/download."[15]

Females and Males of Reproductive Potential

Nonclinical data do not show evidence of adverse effects on fertility, except in males at high (55-times the MRHD) doses. There are no published human data on the effects of ritlecitinib on fertility. Animal fertility data will be reported in Section 13 of labeling.

Data from the clinical trials program are insufficient to determine a risk of adverse effects of use of ritlecitinib during pregnancy. Although nonclinical reproductive toxicity studies demonstrated major congenital malformations with exposure to higher doses of ritlecitinib in rats and rabbits (49- and 55-times the MRHD, respectively), lower doses of ritlecitinib (16- and 12-times the MRHD in rats and rabbits, respectively) did not demonstrate fetotoxicity. The Applicant's proposed labeling recommends (b) (4) Based on the nonclinical data demonstrating a lack of adverse effects at doses of ritlecitinib that were 16- and 12 times the MRHD in rats and rabbits, respectively, DPMH disagrees with the Applicant's proposed language (b) (4) will not be added to the labeling.

**POSTMARKETING REQUIREMENTS (PMR) RECOMMENDATIONS:**

- Conduct prospective pregnancy exposure registry cohort analyses in the US population that compares the maternal, fetal, and infant outcomes of women with alopecia areata exposed to ritlecitinib during pregnancy with a control population of women with alopecia areata who have not been exposed to ritlecitinib before or during pregnancy. The primary outcome of the study will be major congenital malformations (MCMs). Additional outcomes include spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational age infants, and other adverse maternal or fetal outcomes, including infant postnatal growth and development though the first year of life.
- Conduct an additional pregnancy outcomes study that uses a different study design (for example a retrospective cohort study using claims or electronic medical record data or a case-control study) to assess major congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational age infants in women exposed to ritlecitinib during pregnancy compared to an unexposed control population.
- Perform a lactation study (milk only) in in lactating women who have received ritlecitinib to assess concentrations of ritlecitinib in breast milk using a validated assay and to assess the effects on the breastfed infants

**LABELING RECOMMENDATIONS**

DPMH revised subsections 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

**DPMH Proposed Pregnancy and Lactation Labeling**

[15] https://www fda.gov/regulatory-information/search-fda-guidance-documents/clinical-lactation-studies-considerations-study-design

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**M E M O R A N D U M**

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

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DATE: May 02, 2023

TO: Kendall Marcus, MD
Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation

Harpeet Singh, MD
Director
Division of Oncology II
Office of Oncologic Diseases

FROM: Kara A. Scheibner, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Kimberly A. Benson, Ph.D.
Deputy Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Remote regulatory assessment (RRA) of (b) (4) (b) (4)

## 1. RRA Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote regulatory assessment (RRA)[1] of the analytical portion of studies B7981029 (NDA 215830, ritlecitinib/PF-06651600) (b) (4) (b) (4)

I did not observe any objectionable conditions during the RRA. Therefore, I conclude that data from the audited studies are reliable.

[1] One set of tools for oversight of regulated products used during the pandemic has been remote regulatory assessments (RRAs). The term "RRA" describes a category of activities for which FDA may use different terminologies, but all are considered to be types of RRAs, including "remote record reviews" and "remote interactive evaluations."

## 2. Reviewed Studies

**Study B7981029 (NDA 215830)**
"A Phase 1, Randomized, Open-Label, Cross-Over, Single-Dose Study to Evaluate the Bioequivalence of Candidate Capsule Formulations of PF-06651600 to Tablets and Estimate the Effect of High-Fat Meal on Bioavailability in Healthy Participants"

Sample Analysis Period: 03/03/2021 – 09/10/2021

(b) (4)

## 3. Scope of RRA

OSIS scientist Kara A. Scheibner, Pharmacologist, reviewed the analytical portion of the above studies conducted at (b) (4) (b) (4)

The RRA included an examination of records and processes for method validation, and study sample analysis. The RRA also included interviews with the firm's management and staff and a virtual tour of the facilities. In addition, I reviewed the firm's SOPs, data security of electronic records, and sample receipt and accountability.

## 4. RRA Observations

At the conclusion of the RRA, I did not observe any objectionable conditions. No items were discussed with firm's management during the RRA close-out meeting.

### 4.1 Specific concerns from OND

The bioequivalence audit consult for study B7981029 (NDA 215830) specifically requested that OSIS assess the events related to the lack of analysis for PK samples from 41 subjects. During the RRA, I discussed the incident and reviewed relevant documentation to ascertain why the PK samples were not analyzed. During shipment of study samples collected from subjects (b) (4) from the clinical site in the United States to (b) (4), the samples were stored in a warehouse belonging to the shipping

company (b) (4) while awaiting customs clearance. Dry ice was supposed to be replenished as needed, but the box containing the samples was stored in a non-temperature-controlled area, and thus, dry ice was not replenished, resulting in thawed samples. Upon discovery of the thawed samples, dry ice was added, and the samples were refrozen. (b) (4) Pfizer used data from the temperature logger inside the shipment to assess timing and temperature conditions to which the samples were exposed (**Exhibit 1**). (b) (4) created a series of additional cumulative analyte stability experiments in an attempt to recreate sample conditions (**reported in method validation B7989003, Addendum 2**). (b) (4) provided method validation Amendment 3 during the RRA, that describes the incident and cumulative stability assessment plan (**Exhibit 2**). However, integrity of the analyte could not be demonstrated under these cumulative stability conditions. Thus, Pfizer opted not to analyze the samples, and re-opened subject recruitment and enrollment for the study. Correspondence between (b) (4) and Pfizer regarding this incident is included herein as **Exhibit 3**.

Draft: KAS 05/02/2023
Edit: MFS 05/02/23; KAB 05/02/2023

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https://ecmsweb.fda.gov/webtop/drl/objectId/0b0026f881cf932e
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KIMBERLY A BENSON
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**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Medical Policy**

# PATIENT LABELING REVIEW

| | |
|---|---|
| Date: | March 13, 2023 |
| To: | Jennifer Harmon, PharmD<br>Regulatory Project Manager<br>**Division of Dermatology and Dentistry (DDD)** |
| Through: | LaShawn Griffiths, MSHS-PH, BSN, RN<br>Associate Director for Patient Labeling<br>**Division of Medical Policy Programs (DMPP)** |
| | Sharon Mills, BSN, RN, CCRP<br>Senior Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)** |
| From: | Laurie Buonaccorsi, PharmD<br>Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)** |
| | David Foss, PharmD, MPH, BCPS, RAC<br>Regulatory Review Officer<br>**Office of Prescription Drug Promotion (OPDP)** |
| Subject: | Review of Patient Labeling: Medication Guide (MG) |
| Drug Name (established name): | LITFULO (ritlecitinib) |
| Dosage Form and Route: | capsules, for oral use |
| Application Type/Number: | NDA 215830 |
| Applicant: | Pfizer Inc. |

# 1 INTRODUCTION

On June 24, 2022, Pfizer Inc. submitted for the Agency's review an original New Drug Application (NDA) 215830 for LITFULO (ritlecitinib) capsules, with a proposed indication for the treatment of alopecia areata.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on August 11, 2022 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for LITFULO (ritlecitinib) capsules.

# 2 MATERIAL REVIEWED

- Draft LITFULO (ritlecitinib) capsules MG received on October 24, 2022, and received by DMPP and OPDP on March 2, 2023.
- Draft LITFULO (ritlecitinib) capsules Prescribing Information (PI) received on October 24, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 2, 2023.
- Approved CIBINQO tablets, OLUMIANT tablets, OPZELURA cream, and RINVOQ extended-release tablets comparator labeling dated February 9, 2023, June 13, 2022, July 18, 2022, and October 21, 2022, respectively.

# 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6$^{th}$ to 8$^{th}$ grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8$^{th}$ grade reading level.

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

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the MG is consistent with the approved comparator labeling where applicable.

## 4 CONCLUSIONS

The MG is acceptable with our recommended changes.

## 5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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SHARON R MILLS
03/13/2023 02:20:25 PM

LASHAWN M GRIFFITHS
03/13/2023 02:29:56 PM

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

# ****Pre-decisional Agency Information****

# Memorandum

**Date:** March 9, 2023

**To:** Jennifer Harmon, Regulatory Project Manager, Division of Dermatology and Dentistry (DDD)

Hamid Tabatabai, Clinical Reviewer, DDD

**From:** David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:** Jim Dvorsky, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for LITFULO™ (ritlecitinib) capsules, for oral use

**NDA**: 215830

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**Background:**

In response to DDD's consult request dated August 11, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original NDA submission for Litfulo.

**PI/Medication Guide:**

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on March 2, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide, and comments will be sent under separate cover.

**Carton and Container Labeling**:

OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on March 9, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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DAVID F FOSS
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**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology (OSE)**
**Office of Pharmacovigilance and Epidemiology (OPE)**

# Epidemiology Review of Final Study Reports

| | |
|---|---|
| Date: | February 14, 2023 |
| Reviewer: | Joel L. Weissfeld, MD MPH<br>Division of Epidemiology I |
| Team Leader: | Benjamin J. Booth, PhD MS<br>Division of Epidemiology I |
| Associate Director: | Wei Hua, MD PhD MS MHS<br>Division of Epidemiology I |
| Drug Name: | ritlecitinib (LITFULO®) |
| Subject: | Real World Data Cohorts of Patients with Hospital-Treated Alopecia Areata (AA) to Characterize the Patient Population and Contextualize Safety Events within the Ritlecitinib AA Clinical Development Program (B7981049)<br><br>Epidemiology and Risk Characterization of Alopecia Areata via External Patient Cohorts Within a US Administrative Database (B7981051) |
| Application Type/Number: | NDA 215830 |
| Applicant/sponsor: | Pfizer |
| OSE TTT#: | 2022-3039 |

TABLE OF CONTENTS

## EXECUTIVE SUMMARY

Responding to a request from the Division of Dermatology and Dentistry (DDD), the Division of Epidemiology I (DEPI) reviewed the final reports from two epidemiological studies submitted by an NDA applicant to support the safety of ritlecitinib (LITFULO®) in adolescent and adult patients with alopecia areata (AA).

AA is an immune-mediated disease that targets anagen hair follicles and causes hair loss without scarring. Ritlecitinib is an orally bioavailable inhibitor of Janus kinase 3 (JAK3) and tyrosine kinases in the TEC family. The NDA applicant (Pfizer) seeks approval to market ritlecitinib for treatment of AA in ≥12-year-old patients.

NDA 215830 included the reports from two observational cohort studies that used similar methods but different electronic healthcare data sources to estimate adverse event (AE) incidence rates in patients with AA. NDA 215830 used these rates as external references for treatment-emergent AE incidence in clinical studies of ritlecitinib.

DEPI found general alignment between evidence presented in the NDA Summary of Clinical Safety (SCS) and the reports from the two observational studies.

DEPI advised that DDD might reasonably choose to include—in the Multi-Disciplinary Review and Evaluation for NDA 215830—a cautiously interpreted presentation of evidence enabled by the two observational studies. But DEPI also advised that DDD not use this evidence to eliminate certain AEs from consideration as identified or potential risks from ritlecitinib treatment.

## 1 INTRODUCTION

Responding to a request from the Division of Dermatology and Dentistry (DDD), the Division of Epidemiology I (DEPI) reviews the final reports from two epidemiological studies submitted by an NDA applicant to support the safety of ritlecitinib (LITFULO®) in adolescent and adult patients with alopecia areata (AA).

AA is an immune-mediated disease that targets anagen hair follicles and causes hair loss without scarring. Ritlecitinib is an orally bioavailable inhibitor of Janus kinase 3 (JAK3) and tyrosine kinases in the TEC family. The NDA applicant (Pfizer) seeks approval to market ritlecitinib for treatment of AA in ≥12-year-old patients. Pfizer presents ritlecitinib as a small molecule with "a narrow spectrum of cytokine inhibition."[a]

To support NDA 215830, Pfizer commissioned two epidemiologic studies to generate external reference values for "the rates of identified and potential risks of interest in the ritlecitinib

[a] NDA 215830, Clinical Overview, p 12.

clinical program."[b]

Meeting with DEPI on January 5, 2023, DDD's Medical Officer clarified the scope of the consult request to DEPI by expressing interest in data presented in Table 52 of the NDA Summary of Clinical Safety (SCS). SCS Table 52 summarizes incidence rates for safety events of interest in ritlecitinib-treated patients pooled from five clinical studies alongside incidence rates estimated by the epidemiological studies for similarly labeled safety events.

## 2 REVIEW METHODS AND MATERIALS

Documents submitted to NDA 215830 (eCTD 0001) on November 14, 2022:

- Summary of Clinical Safety (SCS), Module 2.7.4
- Non-Interventional (NI) Final Study Report: Real World Data Cohorts of Patients with Hospital-Treated Alopecia Areata (AA) to Characterize the Patient Population and Contextualize Safety Events within the Ritlecitinib AA Clinical Development Program (B7981049), 20-December-2021, Module 5.3.5.4
- Non-Interventional (NI) Final Study Report: Epidemiology and Risk Characterization of Alopecia Areata via External Patient Cohorts Within a US Administrative Database (B7981051), 20-December-2021, Module 5.3.5.4

## 3 REVIEW RESULTS

### 3.1 Study Overview

Two studies, Danish Study B7981049 and U.S. Study B7981051, used similar methods but different electronic healthcare data sources to provide information about patients with a diagnosis of alopecia areata (AA). See **APPENDIX 1** and **APPENDIX 2** for tabular summaries of B7981049 and B7981051, respectively.

### 3.2 Study Objectives

Both studies sought to (1) estimate AA incidence and prevalence, (2) characterize AA patients, and (3) calculate incidence rates for certain AEs in patients with AA. DEPI's assessment focuses on the latter objective as the matter pertinent to DDD's review of NDA 215830.

### 3.3 Study Methods

3.3.1 Study Setting

B7981049 describes a cohort study in four population-based data sources for Denmark. The

[b] NDA 215830, Clinical Summary of Safety, Contextualization of Safety Data, Section 2.7.4.1.6.1, pp 43-45.

Danish Civil Registration System identified the Danish resident population by date of birth, sex, and residential status. The Danish National Patient Registry provided coded information about the diagnoses and procedures recorded for patients admitted to hospital or attending a hospital outpatient clinic. The Danish Health Services Prescription Database provided information about the drugs dispensed by outpatient pharmacies. The Danish Register of Causes of Death listed underlying and contributing causes of death.

B7981051 describes a cohort study in Optum Clinformatics® Data Mart (CDM), a database of administrative health claims for patients covered by U.S. commercial health insurance or Medicare Advantage.

3.3.2 Eligibility Criteria

Both B7981049 and B7981051 indexed patient cohorts by first diagnosis code for AA (ICD-CM L63). B7981049 restricted analysis to patients with first AA diagnosis recorded in a 1995 to 2016 timeframe.[c] B7981051 restricted analysis to patients with ≥2 healthcare encounters on different dates during a 01-October-2016 to 20-September-2020 timeframe.

Both B7981049 and B7981051 (1) restricted cohort entry to patients ≥12 years in age, (2) required ≥12 years of pre-index data, and (3) excluded patients with any healthcare encounter with ICD-10 L65 (Other nonscarring hair loss) or L66 (Cicatricial alopecia) listed as a diagnosis. B7981051 also excluded patients with (1) unknown sex, race, or date of birth and (2) required ≥180 days of post-index follow-up.

3.3.3 Outcome Variables

Both B7981049 and B7981051 specified a common set of AEs including (1) sensorineural hearing loss, (2) serious infection, (3) herpes zoster, (4) malignancy except non-melanoma skin cancer (NMSC), (5) major adverse cardiovascular event (MACE), (6) deep vein thrombosis (DVT), and (7) pulmonary embolism (PE).

The MACE composite included (1) cardiovascular death, (2) myocardial infarction, (3) unstable angina, (4) ischemic stroke, (5) hemorrhagic stroke, (6) heart failure, and (7) coronary revascularization.

Except for coronary revascularization (defined by procedure code), B7981049 and B7981051 defined AEs by inpatient or outpatient diagnosis code. The serious infection and heart failure AEs required diagnosis associated with hospital admission.

None of the documents submitted to NDA 215830 provided the code sets used to identify the

[c] Further restricted to 1995 to 2011 timeframe for analysis of major adverse cardiovascular events (MACE). The MACE composite included cardiovascular death. At the time analysis, B7981049 had cause of death information through 2011 only.

AEs of interest.

3.3.3 Other Variables

Stratifying variables included (1) year of AA diagnosis, (2) sex, (3) age, and (4) AA subtype (alopecia totalis/universalis, AT/AU).[d]

Both B7981049 and B7981051 defined a patient subgroup deemed similar to clinical study patients for NDA 215830 by excluding patients with (1) a dispensing or administration of certain medications during the six months before AA diagnosis, (2) certain diagnoses, (3) recent infection or surgery, or (4) pregnancy. See **APPENDIX 3**.

3.3.4 Statistical Analysis

Both B7981049 and B7981051 calculated incidence as the number of patients with an AE divided by total person-time at risk (with follow-up ending upon first AE; death, disenrollment, or end to study period). By design, incidence rate calculations for certain AEs (e.g., malignancy, MACE, DVT, and PE), but not other AEs (e.g., serious infection and herpes zoster) excluded patients with a pre-index indicator for the AE of interest.

**3.4 Study Results**

3.4.1 Context

The Summary of Clinical Safety (SCS) for NDA 215830 used B7981049 and B7981051 as external references for treatment-emergent AE rates observed in an All Exposure Pool (AEP), which combined safety data from five clinical studies of ritlecitinib (four AA trials and one vitiligo trial).

3.4.2 Demographics

Results summarized by DEPI (Table 1) show lower median age and higher percentage AT/AU in ritlecitinib-treated patients (AEP) than patients from external reference populations (U.S. Study B7981051 and Danish Study B7981049).

Table 1: Demographic characteristics of patients in All Exposure Pool (AEP; by ritlecitinib dose) and external cohorts, U.S. Study B7981051 and Danish Study B7981049.

| | **Ritlecitinib AEP** | | **U.S. Study B7981051** | | **Danish Study B7981049** | |
|---|---|---|---|---|---|---|
| | **50 mg** | **Any Dose** | **AA** | **TS** | **AA** | **TS** |
| N | 1,521 | 1,628 | 8,784 | 5,370 | 2,778 | 2,232 |
| Age, years, P50 (IQR) | 35 (24, 47) | 35 (24, 47) | 43 (32, 59) | 40 (30, 55) | 39 (27, 52) | 38 (26, 51) |
| Age <18 years, n (%) | 172 (11.3) | 181 (11.1) | 398 (4.5) | 296 (5.5) | 302 (10.9) | 278 (12.5) |

[d] Alopecia totalis or universalis subtype identified by first AA encounter (ICD-10 L63.0 or L63.1).

| | | | | | | |
|---|---|---|---|---|---|---|
| Sex, male, n (%) | 583 (38.3) | 632 (38.8) | 3,904 (44.4) | 2,621 (48.8) | 1,025 (36.9) | 879 (39.4) |
| AT/AU, n (%) | 502 (33.0) | 533 (32.7) | 599 (6.8) | 342 (6.4) | 472 (17.0) | 377 (16.9) |

**SOURCE:** ISS Tables AEP.14.1.2.1, AEP.14.1.2.2; b7981051-report-body: Table 2 (pp 23-27); b7981049-report-body: Table 3 (pp 30-32)
**ABBREVIATIONS:** AA – alopecia areata cohort; AT/AU – areata totalis or universalis; IQR – interquartile range; P50 – median; TS – trial-similar AA cohort

### 3.4.3 Incidence Rates for Safety Events of Interest

Table 2 reproduces data shown in SCS Table 52 as corrected by NDA Clinical Information Amendment received on November 14, 2022. Table 2 and SCS Table 52 summarize incidence rates for safety events of interest in ritlecitinib-treated patients pooled from five clinical studies alongside incidence rates estimated by B7981051 and B7981049 for similarly labeled safety events. Except where indicated by bolded type and explanatory footnote, SCS Table 52 aligns with information in supporting documents including the (1) NDA Integrated Summary of Safety (**APPENDIX 4**), (2) report from Study B7981051 (**APPENDIX 5**), and (3) report from Study B7981049 (**APPENDIX 6**).

Table 2: SCS Table 52. Incidence Rates for Safety Events of Interest in AEP All 50 mg Group and Two External AA Cohorts (US and Danish Trial-Similar Cohorts), by Age Category.

| Safety Events | Categories | AEP All 50 mg IR/100 PY (95% CI) | US TS AA Cohort IR/100 PY (95% CI) (n=5370) | Danish TS AA Cohort IR/100 PY (95% CI) (n=2232) |
|---|---|---|---|---|
| Serious Infection | All ages | 0.66 (0.35, 1.14) | 1.15 (0.95, 1.39) | 1.8 (1.61, 2) |
| | ≥12 to <18 years | 0.81 (0.13, 2.79) | 0.35 (0.09, 1.39) | 1.54 (1.06, 2.17) |
| | ≥18 years | 0.64 (0.32, 1.16) | 1.2 (0.99, 1.45) | 1.83 (1.63, 2.05) |
| HZ | All ages | 1.17 (0.74, 1.76) | 0.55 (0.42, 0.73) | 1.14 (0.99, 1.3) |
| | ≥12 to <18 years | No observed cases | No observed cases | 0.96 (0.59, 1.46) |
| | ≥18 years | 1.34 (0.85, 2.03) | 0.59 (0.45, 0.78) | 1.16 (1, 1.34) |
| HS | All ages | 1.72 (1.19, 2.41) | 1.29 (1.08, 1.55) | Not calculated |
| | ≥12 to <18 years | No observed cases | 0.17 (0.02, 1.23) | Not calculated |
| | ≥18 years | 1.97 (1.37, 2.77) | 1.37 (1.14, 1.64) | Not calculated |
| Malignancy (excluding NMSC) | All ages | 0.37 (0.16, 0.75) | 1 (0.82, 1.23) | 0.56 (0.46, 0.68) |
| | ≥12 to <18 years | No observed cases | No observed cases | 0.17 (0.05, 0.45) |
| | ≥18 years | 0.42 (0.18, 0.86) | 1.07 (0.87, 1.31) | 0.61 (0.5, 0.74) |
| BCC | All ages | 0.16 (0.03, 0.45) | 0.59 (0.45, 0.77) | 0.11 (0.07, 0.17) |
| | ≥12 to <18 years | No observed cases | No observed cases | No observed cases |
| | ≥18 years | 0.18 (0.04, 0.52) | 0.63 (0.49, 0.83) | 0.13 (0.08, 0.19) |
| SCC | All ages | 0.06 (0.00, 0.29) | 0.39 (0.28, 0.54) | 0.02 (0.01, 0.05) |
| | ≥12 to <18 years | No observed cases | No observed cases | No observed cases |
| | ≥18 years | 0.06 (0.00, 0.33) | 0.42 (0.3, 0.58) | 0.02 (0.01, 0.06) |
| Female Breast Cancer | All ages | 0.36 (0.11, 0.88) | 0.29 (0.17, 0.49) | 0.14 (0.08, 0.23) |
| | ≥12 to <18 years | No observed cases | No observed cases | No observed cases |
| | ≥18 years | 0.40 (0.12, 0.98) | 0.31 (0.18, 0.52) | 0.16 (0.09, 0.26) |
| MACE | All ages | 0.15 (0.03, 0.43) | 1.2 (0.99, 1.45) | 0.58 (0.44, 0.74) |
| | ≥12 to <18 years | No observed cases | 0.17 (0.02, 1.23) | No observed cases |
| | ≥18 years | Not calculated | 1.27 (1.05, 1.53) | 0.65 (0.5, 0.83) |
| PE | All ages | 0.06 (0.00, 0.29) | 0.07 (0.03, 0.14) | 0.04 (0.01, 0.07) |
| | ≥12 to <18 years | No observed cases | No observed cases | No observed cases |

| Safety Events | Categories | AEP All 50 mg IR/100 PY (95% CI) | US TS AA Cohort IR/100 PY (95% CI) (n=5370) | Danish TS AA Cohort IR/100 PY (95% CI) (n=2232) |
|---|---|---|---|---|
| | ≥18 years | 0.07 (0.00, 0.33) | 0.07 (0.03, 0.15) | 0.04 (0.02, 0.08) |
| Arterial Thrombosis | All ages | 0.09 (0.01, 0.33) | 0.05 (0.02, 0.13) | 0.02 (0.01, 0.05) |
| | ≥12 to <18 years | No observed cases | No observed cases | 0.04 (0, 0.24) |
| | ≥18 years | 0.10 (0.01, 0.37) | 0.06 (0.02, 0.14) | 0.02 (0, 0.05) |
| Peripheral Neuropathy | All ages | 0.21 (0.06, 0.52) | **4.9 (4.4, 5.3) [2]** | Not calculated |
| | ≥12 to <18 years | No observed cases | **1.6 (0.8, 3.1) [2]** | Not calculated |
| | ≥18 years | 0.24 (0.07, 0.59) | **5.1 (4.6, 5.6) [2]** | Not calculated |
| Paresthesia / Dysesthesia | All ages | 1.19 (0.76, 1.78) | **3.2 (2.9, 3.6) [2]** | Not calculated |
| | ≥12 to <18 years | 0.46 (0.02, 2.28) | **0.2 (0, 1.2) [2]** | Not calculated |
| | ≥18 years | 1.29 (0.82, 1.96) | **3.4 (3.1, 3.9) [2]** | Not calculated |
| Sensorineural Hearing Loss | All ages | **0.85 (0.49, 1.39) [1]** | 2.72 (2.4, 3.09) | 0.32 (0.24, 0.41) |
| | ≥12 to <18 years | No observed cases | **1.23 (0.59, 2.59) [3]** | 0.09 (0.01, 0.32) |
| | ≥18 years | 0.98 (0.57, 1.59) | 2.82 (2.49, 3.21) | 0.35 (0.26, 0.45) |

**SOURCE:** Clinical Information Amendment, submitted to NDA 215830 (eCTD 0010) on November 14, 2022.
**ABBREVIATIONS:** AA – alopecia areata cohort; AEP – All Exposure Pool; BCC – basal cell carcinoma; CI – confidence interval; HS – herpes simplex; HZ – herpes zoster; IR – incidence rate; MACE – major adverse cardiovascular event; NMSC – non-melanoma skin cancer; PE – pulmonary embolism; PY – person-years; SCC – squamous cell carcinoma; TS – trial-similar AA cohort
**FOOTNOTES:**
1. Result not found by DEPI in Integrated Safety Summary (ISS).
2. Result not found by DEPI in final study report from B7981051.
3. Final study report from B7981051 shows result as 1.23 (0.59, 2.58).

## 4 DISCUSSION

NDA 215830 includes reports from two observational cohort studies that used similar methods but different electronic healthcare data sources to estimate AE incidence rates in patients with AA. NDA 215830 then uses these rates as external references for treatment-emergent AE incidence in clinical studies of ritlecitinib. The SCS (pp 150-156) discusses these NDA elements under the heading "contextualization of risk."

As reproduced in Table 2 (above), SCS Table 52 summarizes data used by NDA 215830 to contextualize risk. The Clinical Overview (Benefit-Risk Summary) and SCS refer to these data (in SCS Table 52) when making assertions about AE incidence in ritlecitinib-treated patients relative to external control. As indicated in Table 3, NDA 215830 asserts:

- lower incidence in treated patients for serious infection, malignancy excluding NMSC, and MACE.
- higher incidence in treated patients for herpes zoster, herpes simplex, and female breast cancer.
- incidence in treated patients similar to external control for PE.
- mixed results for sensorineural hearing loss.

Table 3: Assertions in NDA 215830 about incidence for safety events of interest in clinical study patients (All Exposure Pool, AEP) relative to two external controls, U.S. Study B7981051 and Danish Study B7981049. Down arrow (↓) indicates incidence lower in AEP than external control, up arrow (↑) indicates incidence higher in AEP than external control, and plus-minus sign (±) indicates incidence similar in AEP and external control.

| Safety Event | External Reference | |
|---|---|---|
| | U.S. | Danish |
| Serious infection | ↓ | ↓ |
| Herpes zoster | ↑ | ± |
| Herpes simplex | ↑ | N.A. |
| Malignancy (excluding NMSC) | ↓ | ↓ |
| Female breast cancer | ± | ↑ |
| MACE | ↓ | ↓ |
| Pulmonary embolism | ± | ± |
| Sensorineural hearing loss | ↓ | ↑ |

**SOURCE:** Clinical Overview, Section 2.5.5.4. Adverse Events of Interest, pp 66-74; Clinical Information Amendment, p 8.
**ABBREVIATIONS:** MACE – Major Adverse Cardiovascular Event; N.A. – not applicable; NMSC – non-melanoma skin cancer

To support DDD's review of ritlecitinib safety, DEPI cross-checked data in SCS Table 52 against supporting documents. With one major exception, SCS Table 52 and supporting documents aligned. SCS Table 52 presented results attributed to U.S. Study B7981051 for two AEs, (1) peripheral neuropathy and (2) paresthesia and dysesthesia. DEPI could not locate these results in the B7981051 study report.

Datasets for the observational studies were not submitted. Therefore, DEPI was not able to cross-check results presented in observational study reports against output from independent analysis of patient-level data.[e]

The SCS (p 43) acknowledges limitations by noting that the "observational data sources may differ in patient characteristics, duration of follow-up, data collection and reporting conventions." The SCS notes further that the "external databases were not adjudicated."

One type of limitation pertains to possible differences between the AEP safety pool and reference populations with respect to underlying risks for the AEs of interest. DEPI notes

[e] Except for squamous cell carcinoma (SCC) in ≥18-year-old patients, DEPI successfully used ADaM (Analysis Data Model) datasets to reproduce AE counts and PY totals for the All Exposure Pool (AEP). DEPI identified two ≥18-year-old patients with SCC (B7981019/10411001 and B7981032/10413006). ISS Table AEP.14.3.1.2.1.1.age shows only one ≥18-year-old patient with SCC. See **APPENDIX 7** for SAS code and output.

possibly important differences with respect to age (Table 1). In addition, reports from B7981049 and B7981051 provide information about other characteristics. For example, U.S. Study B7981051 reported baseline prevalence rates for MACE risk factors, such as hyperlipidemia (26.9%), hypertension (25.4%), and diabetes mellitus (9.1%). The SCS, however, provides for comparison no information about these baseline comorbidities in AEP patients.

To calculate incidence for certain AEs (e.g., malignancy, MACE, DVT, and PE), the observational studies excluded patients with a baseline indicator for the AE of interest.[f] Conceptually, the observational studies expressed incidence for these AEs in terms of the number of patients with an AE that first manifests clinically after the date of AA diagnosis. For patients in clinical studies, the SCS expressed incidence in terms of treated patients who experienced recurrence of an AE previously experienced before start of treatment in addition to patients who experienced an AE for the first time during treatment.

A more critical type of limitation pertains to methods used to identify AEs of interest. Clinical studies (1) ascertained AEs of interest by specific item on study questionnaires or transparent search of AE reports and (2) formally adjudicated certain outcomes by central review of primary medical data (e.g., malignancy, MACE, venous thromboembolism, sensorineural hearing loss, and other neurological AEs).[g] Without further scrutiny, observational studies identified AEs of interest by diagnosis and procedure codes in routinely collected healthcare data. DEPI confidently states that the set of AEs identified by codes includes some false positives (not truly AEs). In addition, code definitions plausibly operated with imperfect sensitivity (thereby failing to detect a certain number of true AEs). Additional information would be needed to determine the net effect of these two types of error on estimates of AE incidence.

None of the documents submitted to NDA 215830 provided the code sets used by observational studies to identify AEs of interest. This lack of transparency precludes any assessment of comparability between terms used to ascertain AEs in clinical studies and codes used to define similarly labeled AEs in healthcare data.

As noted above, the Benefit-Risk Summary in the Clinical Overview for NDA 215830 includes as evidence the observations summarized by DEPI in Table 3. The NDA's Benefit-Risk Summary, however, provides no indication (discernable to DEPI) as to the weight or importance attached by Pfizer to this evidence. Because of limitations previously noted, DDD should attach little weight to this evidence when making its own benefit-risk determination. Taken alone, the evidence summarized herein in no way eliminates any one of the AEs of interest as an identified

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[f] The observational studies used diagnosis codes in healthcare data to identify events of interest. In some instances, the presence of a diagnosis code in healthcare data might refer to follow-up healthcare for a patient with an old condition and not to initial healthcare for a patient with a new event. A cohort study might exclude patients with a baseline indicator for a study outcome in order to improve the specificity of diagnosis codes for incident (new) events.

[g] For search terms used by clinical studies to identify AEs of interest, see Excel spreadsheet (b798-scs-aeois-meddra-v24-searchterms-v-22nov2021.xlsx), submitted to NDA 215803, eCTD 0001, Module 5.3.5.3.

or potential risk from ritlecitinib treatment.

When referenced against risks measured in two observational studies, none of the risks measured during ritlecitinib treatment (in AEP patients) appeared (subjectively to DEPI) distinctly or clearly excessive. Though the evidence might not eliminate an AE as an identified or potential risk, DDD might accept SCS Table 52 as evidence of absence of alarmingly excessive risk.

## 5 CONCLUSIONS

Except for two neurological AEs of interest, evidence presented in SCS Table 52 aligns with evidence presented in supporting documents, including the reports from two observational studies.

## 6 RECOMMENDATIONS FOR DDD

DDD might reasonably choose to include—in the Multi-Disciplinary Review and Evaluation for NDA 215830—a cautiously interpreted presentation of evidence summarized as SCS Table 52. DDD should not regard results presented in SCS Table 52 as evidence that eliminates certain AEs as identified or potential risks from ritlecitinib treatment.

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Oussova T / Kettl D / Tabatabai H / Harmon J (DDD)

## APPENDIX 1: Tabular Summary of B7981049

| Domain | Summary |
|---|---|
| 1.1 Objectives/Aims/Scope | Research Objectives (paraphrased by DEPI)<br>• To estimate incidence and prevalence of alopecia areata (AA)<br>• To characterize patients with AA<br>• To calculate AE incidence rates in patients with AA |
| 1.2.1 Study Design | |
| 1.2.1.1 Type | cohort study |
| 1.2.1.2 Data Source | Health registers for Denmark |
| 1.2.1.3 Study Period | 1995-2016 for outcomes other than MACE and 1995-2011 for MACE |
| 1.2.1.4 Selection Standards | • age ≥12 years<br>• residence in Denmark ≥12 months<br>• inpatient stay or hospital outpatient clinic visit with ICD-10 L63 (Alopecia areata) listed as primary or secondary diagnosis<br>• no inpatient stay with ICD-10 L65 (Other nonscarring hair loss) or L66 (Cicatricial alopecia)<br>• no AA diagnosis before 1995 |
| 1.2.1.5 PHI | data anonymized |
| 1.2.2 Setting | population-based |
| 1.2.3 Exposure/Intervention | not applicable |
| 1.2.4 Adverse Events (AEs) | sensorineural hearing loss; serious infection (SI); herpes zoster (HZ) infection; any primary malignancy (except NMSC); BCC; SCC; malignant lymphoma; breast cancer; cervical carcinoma in situ; MACE; cardiovascular death; acute myocardial infarction; unstable angina; ischemic stroke; hemorrhagic stroke; heart failure; PCI or CABG; DVT; PE; ATE; death (any cause) |
| 1.2.5 Covariates | calendar year; age; sex; AA subtype; trial similarity |
| 1.2.6 Sample Size | N=2,778 (overall); N=2,232 (trial similar) |
| 1.2.7 Statistical Analyses | AE incidence calculated as number of patients with AE divided by total person-time at risk (follow-up ending upon first AE, death, emigration, or end to study period) |
| 1.2.8 Study Results | AE incidence (per 100 person-years) in trial-similar cohort: SI 1.80; HZ 1.14; malignancy except NMSC 0.56; MACE 0.58 |

**ABBREVIATIONS:** AE – adverse event; ATE – arterial thromboembolism; BCC – basal cell carcinoma; CABG – coronary artery bypass graft surgery; DVT – deep vein thrombosis; ICD-10 – International Classification of Disease, 10th Revision; MACE – Major Adverse Cardiovascular Event; NMSC – non-melanoma skin cancer; PCI – percutaneous coronary intervention; PE – pulmonary embolism; PHI – protected health information; SCC – squamous cell carcinoma

## APPENDIX 2: Tabular Summary of B7981051

| Domain | Summary |
|---|---|
| 1.1 Objectives/Aims/Scope | Research Objectives (paraphrased by DEPI)<br>• To estimate incidence and prevalence of alopecia areata (AA)<br>• To characterize patients with AA<br>• To calculate AE incidence rates in patients with AA |
| 1.2.1 Study Design | |
| 1.2.1.1 Type | cohort study |
| 1.2.1.2 Data Source | Optum Clinformatics® Data Mart (CDM) |
| 1.2.1.3 Time Period | 01-October-2016 – 20-September-2020 |
| 1.2.1.4 Selection Standards | • age ≥12 years<br>• known sex, race, and date of birth<br>• ≥365 days database enrollment<br>• ≥2 healthcare encounters on different dates with ICD-10 L63 (Alopecia areata) listed as a diagnosis (index date defined by date of first encounter)<br>• ≥180 days post-index follow-up<br>• no healthcare encounters with ICD-10 L65 (Other nonscarring hair loss) or L66 (Cicatricial alopecia) |
| 1.2.1.5 PHI | data anonymized |
| 1.2.2 Setting | U.S. patients covered by commercial health insurance or Medicare Advantage |
| 1.2.3 Exposure/Intervention | not applicable |
| 1.2.4 Outcomes | sensorineural hearing loss (including deafness or hypoacusis); serious infection (SI); herpes zoster (HZ) infection; herpes simplex infection; any primary malignancy (except NMSC); BCC; SCC; cervical carcinoma in situ; malignant melanoma; lymphoma; breast cancer; MACE; cardiovascular death; acute myocardial infarction; unstable angina; any stroke; heart failure; coronary revascularization; DVT; PE; ATE; death (any cause) |
| 1.2.5 Covariates | calendar year; age; sex; race; AA subtype; trial similarity |
| 1.2.6 Sample Size | N=8,784 (overall); N=5,370 (trial similar) |
| 1.2.7 Statistical Analyses | AE incidence calculated as number of patients with AE divided by total person-time at risk (follow-up ending upon first AE, death, end to Optum enrollment, or end to study period) |
| 1.2.8 Study Results | AE incidence (per 100 person-years) in trial-similar cohort: SI 1.14; HZ 0.55; malignancy except NMSC 1.00; MACE 1.20 |

**ABBREVIATIONS:** AE – adverse event; ATE – arterial thromboembolism; BCC – basal cell carcinoma; ICD-10 – International Classification of Disease, 10th Revision; DVT – deep vein thrombosis; MACE – Major Adverse Cardiovascular Event; NMSC – non-melanoma skin cancer; PE – pulmonary embolism; PHI – protected health information; SCC – squamous cell carcinoma

**APPENDIX 3: Specifications for Trial-Similar Cohort**

Danish Study B7981049 and U.S. Study B7981051 identified Trial-Similar Cohorts by using all available pre-index data (unless specified otherwise) to exclude patients with:

- A record of dispensing/administration of the following medications within 6 months prior to study index: JAKi (tofacitinib, baricitinib, upadacitinib, filgotinib, ruxolitinib), non-b-cell selective lymphocyte-depleting agents (alemtuzumab), rituximab, other immunomodulary agents (alefacept, certolizumab, etanercept, adalimumab, anakinra, abatacept, infliximab, golimumab, ustekinumab, apremilast), immune suppressants (cyclosporine A, azathioprine, methotrexate, sulfasalazine, mycophenolate mofetil, everolimus, ibrutinib), intralesional, oral, or injectable corticosteroids (betamethasone, hydrocortisone, cortisone, prednisone, prednisolone, triamcinolone, methylprednisolone, dexamethasone, budesonide, fludrocortisone), 5α-reductase inhibitors, oral minoxidil, spironolactone, vaccination with a live or attenuated live vaccine, attenuated rotavirus vaccine, varicella (chickenpox) vaccine, attenuated typhoid fever vaccine, oral polio vaccine, measles, mumps, rubella (MMR) vaccine, vaccinia (smallpox) vaccine, zoster vaccine live.

- Any history of malignancies with the exception of NMSC or cervical carcinoma in situ.

- Any history of lymphoma, or leukemia.

- B7981049: Any history (single episode) of disseminated herpes zoster or disseminated herpes simplex (hospital-treated) or recurrent (more than one episode of) localized dermatomal herpes zoster. B7981051: Any history (single episode) of herpes zoster or herpes zoster simplex.

- Any history of serious infection requiring hospitalization within 6 months of the index date.

- Any surgery within 1 month of the index date.

- B7981049: Any hospital diagnosis of human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C infection. B7981051: Any diagnosis of human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C infection.

- B7981049: Any hospital diagnosis of alcohol/substance abuse (does not include tobacco abuse). B7981051: Any diagnosis of alcohol/substance abuse (does not include tobacco abuse).

- Pregnancy (any pregnancy-related diagnoses 9 months before or after index date).

## APPENDIX 4: Treatment-emergent adverse events in All Exposure Pool

Ritlecitinib All Exposure Pool (AEP) – number of patients (n) with treatment-emergent adverse event (AE), patient-years at risk (PYs), AE incidence rates (IRs), and 95% confidence intervals (CIs), by age group.[1]

| | Ritlecitinib All Exposure Pool (AEP) – All Ages | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 50 mg (N=1,521) | | | | Any Dose (N=1,628) | | | |
| **Adverse Event** | **n** | **PYs** | **IR** | **95% CI** | **n** | **PYs** | **IR** | **95% CI** |
| Serious infection | 12 | 1,875 | 0.66 | 0.35-1.14 | 14 | 2,204 | 0.64 | 0.36-1.05 |
| Herpes zoster | 21 | 1,861 | 1.17 | 0.74-1.76 | 23 | 2,190 | 1.05 | 0.68-1.56 |
| Herpes simplex | 32 | 1,856 | 1.72 | 1.19-2.41 | 44 | 2,175 | 2.02 | 1.48-2.70 |
| Malignancy except NMSC | 7 | 1,880 | 0.37 | 0.16-0.75 | 7 | 2,212 | NA | NA |
| Basal cell carcinoma | 3 | 1,879 | 0.16 | 0.03-0.45 | 3 | 2,211 | 0.14 | 0.03-0.38 |
| Squamous cell carcinoma | 1 | 1,880 | 0.06 | 0.00-0.29 | 1 | 2,212 | 0.05 | 0.00-0.23 |
| Female breast cancer [2] | 4 | 1,169 | 0.36 | 0.11-0.88 | 4 | 1,375 | 0.29 | 0.09-0.71 |
| MACE | 3 | 1,880 | 0.15 | 0.03-0.43 | 3 | 2,212 | 0.14 | 0.03-0.38 |
| Pulmonary embolism | 1 | 1,880 | 0.06 | 0.00-0.29 | 1 | 2,212 | 0.05 | 0.00-0.23 |
| Arterial thromboembolism | 2 | 1,880 | 0.09 | 0.01-0.33 | 2 | 2,212 | 0.09 | 0.01-0.30 |
| Peripheral neuropathy | 4 | 1,878 | 0.21 | 0.06-0.52 | 5 | 2,207 | 0.23 | 0.07-0.50 |
| Paresthesia and dysesthesia | 22 | 1,864 | 1.19 | 0.76-1.78 | 27 | 2,188 | 1.23 | 0.82-1.77 |
| Sensorineural hearing loss | 15 | 1,869 | NA | NA | 18 | 2,198 | NA | NA |

| | Ritlecitinib All Exposure Pool (AEP) – Age 12-17 years | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 50 mg (N=172) | | | | Any Dose (N=181) | | | |
| **Adverse Event** | **n** | **PYs** | **IR** | **95% CI** | **n** | **PYs** | **IR** | **95% CI** |
| Serious infection | 2 | 242 | 0.81 | 0.13-2.79 | 3 | 285 | 1.05 | 0.27-2.87 |
| Herpes zoster | 0 | 243 | 0.00 | 0.00-1.38 | 0 | 287 | 0.00 | 0.00-1.04 |
| Herpes simplex | 0 | 243 | 0.00 | 0.00-1.38 | 0 | 287 | 0.00 | 0.00-1.04 |
| Malignancy except NMSC | 0 | 243 | 0.00 | 0.00-1.38 | 0 | 287 | 0.00 | 0.00-1.04 |
| Basal cell carcinoma | 0 | 243 | 0.00 | 0.00-1.38 | 0 | 287 | 0.00 | 0.00-1.04 |
| Squamous cell carcinoma | 0 | 243 | 0.00 | 0.00-1.38 | 0 | 287 | 0.00 | 0.00-1.04 |
| Female breast cancer [3] | 0 | 130 | 0.00 | 0.00-2.69 | 0 | 157 | 0.00 | 0.00-1.91 |
| MACE [5] | 0 | | | | 0 | | | |
| Pulmonary embolism | 0 | 243 | 0.00 | 0.00-1.38 | 0 | 287 | 0.00 | 0.00-1.04 |
| Arterial thromboembolism | 0 | 243 | 0.00 | 0.00-1.38 | 0 | 287 | 0.00 | 0.00-1.04 |
| Peripheral neuropathy | 0 | 243 | 0.00 | 0.00-1.38 | 0 | 287 | 0.00 | 0.00-1.04 |
| Paresthesia and dysesthesia | 1 | 242 | 0.46 | 0.02-2.28 | 1 | 286 | 0.35 | 0.01-1.73 |
| Sensorineural hearing loss | 0 | 243 | 0.00 | 0.00-1.38 | 0 | 287 | 0.00 | 0.00-1.04 |

| Adverse Event | Ritlecitinib All Exposure Pool (AEP) – Age ≥18 years | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 50 mg (N=1,349) | | | | Any Dose (N=1,447) | | | |
| | n | PYs | IR | 95% CI | n | PYs | IR | 95% CI |
| Serious infection | 10 | 1,633 | 0.64 | 0.32-1.16 | 11 | 1,918 | 0.57 | 0.30-1.01 |
| Herpes zoster | 21 | 1,619 | 1.34 | 0.85-2.03 | 23 | 1,903 | 1.21 | 0.78-1.79 |
| Herpes simplex | 32 | 1,614 | 1.97 | 1.37-2.77 | 44 | 1,888 | 2.33 | 1.71-3.10 |
| Malignancy except NMSC | 7 | 1,637 | 0.42 | 0.18-0.86 | 7 | 1,924 | 0.36 | 0.16-0.73 |
| Basal cell carcinoma | 3 | 1,636 | 0.18 | 0.04-0.52 | 3 | 1,923 | 0.16 | 0.03-0.43 |
| Squamous cell carcinoma | 1 | 1,638 | 0.06 | 0.00-0.33 | 1 | 1,925 | 0.05 | 0.00-0.26 |
| Female breast cancer [4] | 4 | 1,039 | 0.40 | 0.12-0.98 | 4 | 1,218 | 0.33 | 0.10-0.80 |
| MACE [5] | 3 | | | | 3 | | | |
| Pulmonary embolism | 1 | 1,638 | 0.07 | 0.00-0.33 | 1 | 1,925 | 0.05 | 0.00-0.26 |
| Arterial thromboembolism | 2 | 1,638 | 0.10 | 0.01-0.37 | 2 | 1,925 | 0.10 | 0.01-0.35 |
| Peripheral neuropathy | 4 | 1,635 | 0.24 | 0.07-0.59 | 5 | 1,920 | 0.26 | 0.09-0.58 |
| Paresthesia and dysesthesia | 21 | 1,622 | 1.29 | 0.82-1.96 | 26 | 1,901 | 1.37 | 0.90-1.98 |
| Sensorineural hearing loss | 15 | 1,627 | 0.98 | 0.57-1.59 | 18 | 1,911 | 0.94 | 0.57-1.47 |

**SOURCE:** SCS Tables 43 and 52; ISS Tables AEP.14.3.1.2.1.1, AEP.14.3.1.2.1.1.age, AEP.14.3.1.5.2.1, AEP.14.3.1.5.2.1.age, AEP.14.3.1.5.4.age, AEP.14.3.1.5.6, AEP.14.3.1.5.6.age, AEP.14.3.1.5.7, AEP.14.3.1.5.7.age, AEP.14.3.1.5.8.age, AEP.14.3.1.5.10, AEP.14.3.1.5.10.age, AEP.14.3.1.5.14.sex, AEP.14.3.1.5.14.sex.age

**ABBREVIATIONS:** MACE – Major Adverse Cardiovascular Event; NMSC – non-melanoma skin cancer; NA – not available

**FOOTNOTES:**

1. IRs adjusted for study size and CIs determined by mid-p gamma method. See Appendix 3 in Integrated Analysis Plan (iAP) for Clinical Safety in Alopecia Areata (AA).
2. N=938 and 996 female patients in 50 mg and Any Dose group, respectively.
3 N=92 and 98 female patients in 50 mg and Any Dose group, respectively.
4. N=846 and 898 female patients in 50 mg and Any Dose group, respectively.
5. The ISS (as Table AEP.14.3.1.5.5.age) presents results for adjudicated cardiovascular events in three categories, Fatal MACE, Non-Fatal MACE, and Non-MACE. The ISS does not present results for the composite outcome of fatal or non-fatal MACE. See **APPENDIX 7** for AE patient counts and PY totals for the composite (fatal or non-fatal) MACE AE as determined by DEPI analysis of ADaM datasets.

## APPENDIX 5: Adverse Events in U.S. Study B7981051

U.S. Study B7981051 – number of patients (n) with adverse event (AE), patient-years at risk (PYs), AE incidence rates (IRs), and 95% confidence intervals (CIs), by age group. [1]

| | U.S. Study B7981051 – All Ages | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Alopecia Areata Cohort (N=8,784) | | | | | Trial-Similar Cohort (N=5,370) | | | | |
| **Adverse Event** | **N** | **n** | **PYs** | **IR** | **95% CI** | **N** | **n** | **PYs** | **IR** | **95% CI** |
| Serious infection | 8,784 | 281 | 15,196 | 1.85 | 1.65-2.08 | 5,370 | 105 | 9,174 | 1.14 | 0.95-1.39 |
| Herpes zoster | 8,784 | 119 | 15,352 | 0.78 | 0.65-0.93 | 5,370 | 51 | 9,223 | 0.55 | 0.42-0.73 |
| Herpes simplex | 8,784 | 294 | 15,105 | 1.95 | 1.74-2.18 | 5,370 | 118 | 9,123 | 1.29 | 1.08-1.55 |
| Malignancy except NMSC | 8,324 | 181 | 14,467 | 1.25 | 1.08-1.45 | 5,370 | 92 | 9,177 | 1.00 | 0.82-1.23 |
| Basal cell carcinoma | 8,636 | 118 | 15,081 | 0.78 | 0.65-0.94 | 5,307 | 54 | 9,106 | 0.59 | 0.45-0.77 |
| Squamous cell carcinoma | 8,703 | 79 | 15,259 | 0.52 | 0.42-0.65 | 5,336 | 36 | 9,186 | 0.39 | 0.28-0.54 |
| Female breast cancer | 4,776 | 39 | 8,543 | 0.46 | 0.33-0.63 | 2,749 | 14 | 4,840 | 0.29 | 0.17-0.49 |
| MACE | 8,425 | 234 | 14,603 | 1.60 | 1.40-1.82 | 5,254 | 107 | 8,949 | 1.20 | 0.99-1.45 |
| Pulmonary embolism | 8,743 | 30 | 15,419 | 0.19 | 0.14-0.28 | 5,360 | 6 | 9,273 | 0.06 | 0.03-0.14 |
| Arterial thromboembolism | 8,769 | 13 | 15,491 | 0.08 | 0.05-0.15 | 5,368 | 5 | 9,293 | 0.05 | 0.02-0.13 |
| Sensorineural hearing loss | 8,784 | 507 | 14,826 | 3.42 | 3.14-3.73 | 5,370 | 244 | 8,963 | 2.72 | 2.40-3.09 |

| | U.S. Study B7981051 – Age 12-17 years | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Alopecia Areata Cohort (N=398) | | | | | Trial-Similar Cohort (N=296) | | | | |
| **Adverse Event** | **N** | **n** | **PYs** | **IR** | **95% CI** | **N** | **n** | **PYs** | **IR** | **95% CI** |
| Serious infection | 398 | 2 | 776 | 0.26 | 0.06-1.03 | 296 | 2 | 576 | 0.35 | 0.09-1.39 |
| Herpes zoster | 398 | 0 | 778 | 0.00 | NA | 296 | 0 | 578 | 0.00 | NA |
| Herpes simplex | 398 | 5 | 772 | 0.65 | 0.27-1.56 | 296 | 1 | 576 | 0.17 | 0.02-1.23 |
| Malignancy except NMSC | 398 | 0 | 778 | 0.00 | NA | 296 | 0 | 578 | 0.00 | NA |
| Basal cell carcinoma | 398 | 0 | 778 | 0.00 | NA | 296 | 0 | 578 | 0.00 | NA |
| Squamous cell carcinoma | 398 | 0 | 778 | 0.00 | NA | 296 | 0 | 578 | 0.00 | NA |
| Female breast cancer | 197 | 0 | 395 | 0.00 | NA | 149 | 0 | 291 | 0.00 | NA |

| Adverse Event | U.S. Study B7981051 – Age 12-17 years | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Alopecia Areata Cohort (N=398) | | | | | Trial-Similar Cohort (N=296) | | | | |
| | N | n | PYs | IR | 95% CI | N | n | PYs | IR | 95% CI |
| MACE | 398 | 1 | 776 | 0.13 | 0.02-0.91 | 296 | 1 | 576 | 0.17 | 0.02-1.23 |
| Pulmonary embolism | 398 | 0 | 778 | 0.00 | NA | 296 | 0 | 578 | 0.00 | NA |
| Arterial thromboembolism | 398 | 0 | 778 | 0.00 | NA | 296 | 0 | 578 | 0.00 | NA |
| Sensorineural hearing loss | 398 | 8 | 769 | 1.04 | 0.52-2.08 | 296 | 7 | 570 | 1.23 | 0.59-2.58 |

| Adverse Event | U.S. Study B7981051 – Age ≥18 years | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Alopecia Areata Cohort (N=8,386) | | | | | Trial-Similar Cohort (N=5,074) | | | | |
| | N | n | PYs | IR | 95% CI | N | n | PYs | IR | 95% CI |
| Serious infection | 8,386 | 279 | 14,420 | 1.93 | 1.72-2.18 | 5,074 | 103 | 8,598 | 1.20 | 0.99-1.45 |
| Herpes zoster | 8,386 | 119 | 14,574 | 0.82 | 0.68-0.98 | 5,074 | 51 | 8,645 | 0.59 | 0.45-0.78 |
| Herpes simplex | 8,386 | 289 | 14,333 | 2.02 | 1.80-2.26 | 5,074 | 117 | 8,547 | 1.37 | 1.14-1.64 |
| Malignancy except NMSC | 7,926 | 181 | 13,689 | 1.32 | 1.14-1.53 | 5,074 | 92 | 8,599 | 1.07 | 0.87-1.31 |
| Basal cell carcinoma | 8,238 | 118 | 14,303 | 0.83 | 0.69-0.99 | 5,011 | 54 | 8,528 | 0.63 | 0.49-0.83 |
| Squamous cell carcinoma | 8,305 | 79 | 14,481 | 0.55 | 0.44-0.68 | 5,040 | 36 | 8,609 | 0.42 | 0.30-0.58 |
| Female breast cancer | 4,579 | 39 | 8,149 | 0.48 | 0.35-0.66 | 2,600 | 14 | 4,549 | 0.31 | 0.18-0.52 |
| MACE | 8,027 | 233 | 13,827 | 1.69 | 1.48-1.92 | 4,958 | 106 | 8,373 | 1.27 | 1.05-1.53 |
| Pulmonary embolism | 8,345 | 30 | 14,641 | 0.20 | 0.14-0.29 | 5,064 | 6 | 8,695 | 0.07 | 0.03-0.15 |
| Arterial thromboembolism | 8,371 | 13 | 14,713 | 0.09 | 0.05-0.15 | 5,072 | 5 | 8,716 | 0.06 | 0.02-0.14 |
| Sensorineural hearing loss | 8,386 | 499 | 14,057 | 3.55 | 3.25-3.88 | 5,074 | 237 | 8,393 | 2.82 | 2.49-3.21 |

**SOURCE:** b7981051-appendix4-tables Tables 1 and 4
**ABBREVIATIONS:** MACE – Major Adverse Cardiovascular Event; NMSC – non-melanoma skin cancer; NA – not available
**FOOTNOTES:**
1. IRs validated by DEPI by application of the Rothman-Greenland method. Rothman KJ, Greenland S. Modern Epidemiology, 2nd Edition. Lippincott-Raven Publishers, Philadelphia, 1998.

## APPENDIX 6: Adverse Events in Danish Study B7981049

Danish Study B7981049 – number of patients (n) with adverse event (AE), patient-years at risk (PYs), AE incidence rates (IRs), and 95% confidence intervals (CIs), by age group. [1]

| | Danish Study B7981049 – All Ages | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Alopecia Areata Cohort (N=2,778) | | | | | Trial-Similar Cohort (N=2,232) | | | | |
| **Adverse Event** | **N** | **n** | **PYs** | **IR** | **95% CI** | **N** | **n** | **PYs** | **IR** | **95% CI** |
| Serious infection | 2,778 | 478 | 21,610 | 2.21 | 2.02-2.42 | 2,232 | 327 | 18,203 | 1.80 | 1.61-2.00 |
| Herpes zoster | 2,778 | 299 | 22,709 | 1.32 | 1.17-1.48 | 2,232 | 215 | 18,910 | 1.14 | 0.99-1.30 |
| Herpes simplex | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Malignancy except NMSC | 2,639 | 134 | 22,808 | 0.59 | 0.49-0.70 | 2,222 | 109 | 19,458 | 0.56 | 0.46-0.68 |
| Basal cell carcinoma | 2,745 | 28 | 23,924 | 0.12 | 0.08-0.17 | 2,207 | 22 | 19,764 | 0.11 | 0.07-0.17 |
| Squamous cell carcinoma | 2,778 | *** | *** | 0.02 | 0.00-0.04 | 2,232 | *** | *** | 0.02 | 0.01-0.05 |
| Female breast cancer | 1,708 | 20 | 14,689 | 0.14 | 0.08-0.21 | 1,353 | *** | *** | 0.14 | 0.08-0.23 |
| MACE | 1,808 | 83 | 13,055 | 0.64 | 0.51-0.79 | 1,465 | 63 | 10,951 | 0.58 | 0.44-0.74 |
| Pulmonary embolism | 2,769 | 14 | 24,199 | 0.06 | 0.03-0.10 | 2,227 | *** | *** | 0.04 | 0.01-0.07 |
| Arterial thromboembolism | 2,771 | *** | *** | 0.03 | 0.01-0.06 | 2,228 | *** | *** | 0.02 | 0.01-0.05 |
| Sensorineural hearing loss | 2,690 | 78 | 23,350 | 0.33 | 0.26-0.42 | 2,165 | 61 | 19,269 | 0.32 | 0.24-0.41 |

| | Danish Study B7981049 – Age 12-17 years | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Alopecia Areata Cohort (N=302) | | | | | Trial-Similar Cohort (N=278) | | | | |
| **Adverse Event** | **N** | **n** | **PYs** | **IR** | **95% CI** | **N** | **n** | **PYs** | **IR** | **95% CI** |
| Serious infection | 302 | 41 | 2,313 | 1.77 | 1.27-2.41 | 278 | *** | *** | 1.54 | 1.06-2.17 |
| Herpes zoster | 302 | 26 | 2,382 | 1.09 | 0.71-1.60 | 278 | 21 | 2,198 | 0.96 | 0.59-1.46 |
| Herpes simplex | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Malignancy except NMSC | 299 | *** | *** | 0.16 | 0.04-0.41 | 278 | *** | *** | 0.17 | 0.05-0.45 |
| Basal cell carcinoma | 302 | 0 | 2,532 | 0.00 | 0.00-0.15 | 278 | *** | *** | 0.00 | 0.00-0.16 |
| Squamous cell carcinoma | 302 | *** | *** | 0.00 | 0.00-0.15 | 278 | *** | *** | 0.00 | 0.00-0.16 |
| Female breast cancer | 165 | *** | *** | 0.00 | 0.00-0.27 | 150 | *** | *** | 0.00 | 0.00-0.30 |
| MACE | 185 | 0 | 1,311 | 0.00 | 0.00-0.28 | 169 | 0 | 1,206 | 0.00 | 0.00-0.31 |

| Adverse Event | Danish Study B7981049 – Age 12-17 years | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Alopecia Areata Cohort (N=302) | | | | | Trial-Similar Cohort (N=278) | | | | |
| | N | n | PYs | IR | 95% CI | N | n | PYs | IR | 95% CI |
| Pulmonary embolism | 302 | *** | *** | 0.00 | 0.00-0.15 | 278 | *** | *** | 0.00 | 0.00-0.16 |
| Arterial thromboembolism | 302 | *** | *** | 0.04 | 0.00-0.22 | 278 | *** | *** | 0.04 | 0.00-0.24 |
| Sensorineural hearing loss | 298 | *** | *** | 0.16 | 0.04-0.41 | 274 | *** | *** | 0.09 | 0.01-0.32 |

| Adverse Event | Danish Study B7981049 – Age ≥18 years | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Alopecia Areata Cohort (N=2,476) | | | | | Trial-Similar Cohort (N=1,954) | | | | |
| | N | n | PYs | IR | 95% CI | N | n | PYs | IR | 95% CI |
| Serious infection | 2,476 | 437 | 19,298 | 2.26 | 2.06-2.49 | 1,954 | *** | *** | 1.83 | 1.63-2.05 |
| Herpes zoster | 2,476 | 273 | 20,327 | 1.34 | 1.19-1.51 | 1,954 | 194 | 16,712 | 1.16 | 1.00-1.34 |
| Herpes simplex | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Malignancy except NMSC | 2,340 | *** | *** | 0.64 | 0.53-0.76 | 1,944 | *** | *** | 0.61 | 0.50-0.74 |
| Basal cell carcinoma | 2,443 | 28 | 21,392 | 0.13 | 0.09-0.19 | 1,929 | *** | *** | 0.13 | 0.08-0.19 |
| Squamous cell carcinoma | 2,476 | *** | *** | 0.02 | 0.01-0.05 | 1,954 | *** | *** | 0.02 | 0.01-0.06 |
| Female breast cancer | 1,543 | *** | *** | 0.15 | 0.09-0.23 | 1,203 | *** | *** | 0.16 | 0.09-0.26 |
| MACE | 1,623 | 83 | 11,744 | 0.71 | 0.56-0.88 | 1,296 | 63 | 9,745 | 0.65 | 0.50-0.83 |
| Pulmonary embolism | 2,467 | *** | *** | 0.07 | 0.04-0.11 | 1,949 | *** | *** | 0.04 | 0.02-0.08 |
| Arterial thromboembolism | 2,469 | *** | *** | 0.03 | 0.01-0.06 | 1,950 | *** | *** | 0.02 | 0.00-0.05 |
| Sensorineural hearing loss | 2,392 | *** | *** | 0.36 | 0.28-0.45 | 1,891 | *** | *** | 0.35 | 0.26-0.45 |

**SOURCE:** b7981049-report-body Tables 8-13, 16, 18, 27, 28

**ABBREVIATIONS:** *** – suppressed in source document to hide small cell counts; MACE – Major Adverse Cardiovascular Event; NMSC – non-melanoma skin cancer; NA – not available

**FOOTNOTES:**

1. IRs validated by DEPI (where possible) by application of Ulm's method (exact method based on a relationship between the $\chi^2$ and Poisson distributions). Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). Am J Epidemiol 131(2):373-375, 1990.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

| | |
|---|---|
| Date of This Review: | January 13, 2023 |
| Requesting Office or Division: | Division of Dermatology and Dentistry (DDD) |
| Application Type and Number: | NDA 215830 |
| Product Name, Dosage Form, and Strength: | Litfulo (ritlecitinib) capsule, 50 mg |
| Product Type: | Single Ingredient Product |
| Rx or OTC: | Prescription (Rx) |
| Applicant/Sponsor Name: | Pfizer Inc. |
| FDA Received Date: | June 24, 2022 and October 24, 2022 |
| TTT ID #: | 2022-453 |
| Acting DMEPA 1 Team Leader: | Madhuri R. Patel, PharmD |
| DMEPA 1 Associate Director for Nomenclature and Labeling: | Mishale Mistry, PharmD, MPH |

## 1 REASON FOR REVIEW

As part of the approval process for Litfulo (ritlecitinib) capsule, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Litfulo Prescribing Information (PI), Medication Guide (MG), and container labels for areas of vulnerability that may lead to medication errors.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

| Table 1. Materials Considered for this Review | |
|---|---|
| Material Reviewed | Appendix Section (for Methods and Results) |
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B – N/A |
| Human Factors Study | C – N/A |
| ISMP Newsletters* | D – N/A |
| FDA Adverse Event Reporting System (FAERS)* | E – N/A |
| Other | F – N/A |
| Labels and Labeling | G |

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the Prescribing Information (PI), Medication Guide (MG), and container labels. We note the container labels can be improved to prevent wrong drug errors and facilitate product identification.

## 4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Prescribing Information (PI) and Medication Guide (MG) are acceptable from a medication error perspective. However, we find the proposed container labels can be improved and we provide recommendations below in Section 4.1 for the Applicant to address our concerns.

### 4.1 RECOMMENDATIONS FOR PFIZER INC.

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

A. Container Labels

1. As currently presented, the proposed container label states “Always dispense with medication guide” and does not state how the medication guide will be provided. We recommend revising this statement to read “Dispense the accompanying Medication Guide to each patient” or a similar statement in accordance with 21 CFR 208.24(d).
2. We recommend revising the statement, “ (b) (4) See accompanying prescribing information.” to “Dosage: See accompanying Prescribing Information.” to ensure consistency with terminology in the Prescribing Information.
3. Consider relocating “Keep in Original Package” from the side panel to the Principal Display Panel (PDP).
4. We note the GTIN number is located above the 2D data matrix, while the other human-readable product identifiers (Exp, Lot, SN) are located below 2D data matrix. The GTIN number should appear with the other human-readable product identifiers. Additionally, we note that for the trade container label, the other human readable product identifiers (Exp, Lot, SN) are located near the linear barcode. Please ensure the linear barcode is surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).
5. We recommend you review the Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021) available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Litfulo received on October 24, 2022 from Pfizer Inc..

| Table 2. Relevant Product Information for Litfulo | |
|---|---|
| Initial Approval Date | N/A |
| Active Ingredient | ritlecitinib |
| Indication | treatment of alopecia areat (b) (4) |
| Route of Administration | oral |
| Dosage Form | capsule |
| Strength | 50 mg |
| Dose and Frequency | 50 mg orally once daily |
| How Supplied | 28 count bottle |
| Storage | Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (59°F to 86°F). Keep in original package. |
| Container Closure | bottle |

## APPENDIX G. LABELS AND LABELING

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

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Litfulo labels and labeling submitted by Pfizer Inc..

- Container Label received on June 24, 2022
- Professional Sample Container Label received on June 24, 2022
- Prescribing Information and Medication Guide (Images not shown) received on October 24, 2022, available from \\CDSESUB1\EVSPROD\nda215830\0006\m1\us\lab-1469-0-3-lab-1525-0-2-combined-clean.pdf

### G.2 Label and Labeling Images

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[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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# Clinical Inspection Summary

| | |
|---|---|
| **Date** | 1/10/2023 |
| **From** | Stephanie Coquia, MD<br>Michele Fedowitz, MD, Acting Team Leader<br>Jenn Sellers, MD, PhD, Acting Branch Chief<br>Good Clinical Practice Assessment Branch (GCPAB)<br>Division of Clinical Compliance Evaluation (DCCE)<br>Office of Scientific Investigations (OSI) |
| **To** | Hamid Tabatabai, MD, Clinical Reviewer<br>David Kettl, MD, Clinical Team Leader<br>Jennifer Harmon, Regulatory Project Manager<br>Division of Dermatology and Dentistry (DDD) |
| **NDA #** | 215830 |
| **Applicant** | Pfizer Inc. |
| **Drug** | Ritlecitinib |
| **NME (Yes/No)** | Yes |
| **Therapeutic Classification** | Janus kinase (JAK) 3 and tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family inhibitor |
| **Proposed Indication** | Treatment of alopecia areata in adults and adolescents 12 years or older |
| **Consultation Request Date** | 08/25/2022 |
| **Summary Goal Date** | 01/23/2023 |
| **Action Goal Date** | 06/07/2023 |
| **PDUFA Date** | 06/23/2023 |

## I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Pfizer Inc., submitted clinical data from study b7931015 (NCT 03732807) to the Agency in support of a New Drug Application (NDA 215830) for ritlecitinib.

Three clinical investigators were selected for clinical inspections; they were high enrolling sites with high treatment effect. The sites comprised investigators from the U.S. (Drs. Lugo-Somolinos and Nossa) and Canada (Dr. Saint-Cyr Proulx). All inspections were conducted on-site.

The inspections did not find significant concerns regarding the management of the clinical trial or Good Clinical Practice (GCP) or regulatory compliance, and based on the results of these inspections, data generated by the inspected clinical investigators appear acceptable in support of the proposed indication.

# II. BACKGROUND

Pfizer Inc. seeks approval for a new drug application for ritlecitinib. In support of the NDA, the Applicant submitted clinical data from study b7931015. The following is a summary of the study protocol and key study information relevant to the clinical inspections.

Study b7931015 was a randomized, double-blind, placebo-controlled trial in subjects with alopecia areata (AA) having ≥50% scalp hair loss (i.e., total Severity of Alopecia Tool (SALT) score ≥50). In addition to adults, adolescent subjects 12 years and older were enrolled. Following a 24-week treatment period (after which the primary endpoint was assessed), a 24-week extension phase commenced. In this extension phase, subjects originally randomized to placebo were administered Ritlecitinib. The subjects were thus randomized to the following seven treatment arms:

1. 200 mg once daily for 4 weeks followed by 50 mg once daily for 44 weeks
2. 200 mg once daily for 4 weeks followed by 30 mg once daily for 44 weeks
3. 50 mg once daily for 48 weeks
4. 30 mg once daily for 48 weeks
5. 10 mg once daily for 48 weeks (for exposure response only)
6. placebo for 24 weeks followed by 200 mg once daily for 4 weeks and 50 mg once daily for 20 weeks (pbo-200/50 mg)
7. placebo for 24 weeks followed by 50 mg once daily for 24 weeks (pbo-50 mg).

Twice as many subjects were randomized to arms 1-4 (n=120) as compared to arms 5-7 (n=60).

The primary objective of the study was to evaluate the efficacy of ritlecitinib compared to placebo on regrowth of lost hair (as measured by an absolute SALT Score ≤20) at Week 24, in adult and adolescent AA subjects with ≥50% scalp hair loss at enrollment (i.e., SALT score ≥50).

The primary endpoint was response based on an absolute SALT Score ≤20 at Week 24 (i.e., ≤20% scalp hair loss).

Key secondary objectives and endpoints included:

- Efficacy and response based on an absolute SALT Score ≤10 at Week 24 (i.e., ≤10% scalp hair loss)
- Improvement in regrowth of eyebrows and/or eyelashes at Week 24 as measured by improvements in Eyebrow Assessment (EBA) and Eyelash Assessment (ELA) scores.

The above assessments for efficacy (SALT, EBA, and ELA) were performed by trained raters

at baseline and at pre-specified timepoints up to 48 weeks.

A total of 118 study sites participated in this study, including 29 sites in the United States (US), 11 sites in China (CHN), 11 sites in Canada (CAN), 8 in Russia (RUS), 7 sites in Australia (AUS), and 4 sites in Chile (CHL). 715 subjects were in the safety population.

# RESULTS

**1. Dr. Etienne Saint-Cyr Proulx (Site 1045)**
3530 Boulevard Saint-Laurent
Montreal, QUEBEC H2X 2V1 CAN

Inspection Dates: October 31-November 4, 2022

This investigator was inspected as a routine PDUFA inspection for Study b7931015. This was the first FDA inspection for this investigator.

There were 30 subjects screened and 18 subjects enrolled, randomized, and treated at the site (12 screen failures); 17 subjects completed the study, and one subject (Subject (b) (6)) was discontinued after 48 weeks of treatment due to declining follow up due to COVID-19.

The source documents were reviewed for all 18 subjects enrolled for informed consent, eligibility, concomitant medications, adverse events, and protocol adherence. Reviewed records included informed consent forms, adverse event reports, and randomization and kit assignments. Primary and key secondary efficacy endpoint source data were reviewed for all subjects. All source documents were in hardcopy format.

Study-related documents also reviewed included training logs; the Signature Sheet and Delegation of Duties Log; IRB approval documents; central lab certifications; financial disclosure forms; subject visit accountability logs; pharmacy master accountability log; temperature log; correspondence between the site, monitors, and the sponsor; and monitoring visit documentation.

The source data available at the inspected clinical site for the primary efficacy endpoint [the proportion of subjects with an absolute Severity of Alopecia Tool (SALT) Score ≤20] and the key secondary endpoints [Eyebrow Assessment and Eyelash Assessment] were compared to the data listings in the submission and there were no discrepancies. There was no evidence of under-reporting of adverse events or protocol deviations. No unblinding occurred during the study.

**2. Dr. Aida Lugo-Somolinos (Site 1024)**
410 Market St
Chapel Hill, NC 27516 USA

Inspection Dates: November 14-18, 2022

This investigator was inspected as a routine PDUFA inspection for Study b7931015. This was the first FDA inspection for this investigator.

A total of 16 subjects were screened; 13 subjects were enrolled into the study. Nine subjects completed the study and four (4) did not complete the study for the following reasons: two were lost to follow-up, one was discontinued by the investigator, and one withdrew consent.

The source documents and eCRFs were reviewed for all screened subjects for informed consent, eligibility, physical exam and laboratory tests, adverse events, protocol deviations, and concomitant medications. Adverse event data for all subjects was verified. Primary and key secondary endpoint data were reviewed for all subjects who completed the study. Most of the study records were on paper worksheets which were then entered into the eCRFs within 24 hours.

Study-related documents also reviewed included those related to IRB approval and other related submissions, site monitoring, investigational product accountability, clinical site training, site responsibility delegation, financial disclosures, and correspondences with either the sponsor or monitor.

The source data available at the inspected clinical site for the primary efficacy endpoint and the secondary endpoints were compared to the data listings in the submission and there were no discrepancies. There was no evidence of under-reporting of adverse events or protocol deviations.

**3. Dr. Robert Nossa (Site 1037)**
60 Pompton Ave
Verona, NJ 07044 USA

Inspection Dates: December 5-8, 2022

This investigator was inspected as a routine PDUFA inspection for Study b7931015. This was the first FDA inspection for this investigator.

A total of 26 subjects were screened for the study. Sixteen subjects were enrolled and treated at the site; 13 subjects completed the study, one subject (Subject (b) (6)) completed to week 48, and two subjects withdrew consent.

The source documents were reviewed for all enrolled subjects pertaining to eligibility criteria, informed consent, protocol deviations, and adverse events. Subject-related source data included screening results, adverse event forms, correspondence between the subjects and subject's families with the study coordinator, laboratory results, subject questionnaires, and subject diaries. Primary and key secondary endpoint data at Week 24 were reviewed.

Study-related documents also reviewed included the protocol and amendments, training documentation, investigator agreement, financial disclosure, IRB submissions and approvals, sponsor/monitor correspondence, test article accountability, and training documentation.

The source data available at the inspected clinical site for the primary efficacy endpoint and the secondary endpoints were compared to the data listings in the submission and there were no discrepancies. There were no deficiencies or under-reporting of results, protocol deviations, or adverse events.

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Office of Scientific Investigations

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