CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219155Orig1s000

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 Review:	May 2, 2025
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 219155
Product Name, Dosage Form, and Strength:	Anzupgo (delgocitinib) cream, 2%
Applicant Name:	LEO Pharma A/S
FDA Received Date:	April 4, 2025
TTT ID #:	2024-10221-1
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

LEO Pharma A/S submitted revised container labels and carton labeling received on April 4, 2025 for Anzupgo. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Anzupgo (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

LEO Pharma A/S implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Patel, M. Label and Labeling Review for Anzupgo (NDA 219155). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 MAR 26. TTT ID: 2024-10221.

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/s/

MADHURI R PATEL
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YEVGENIYA M KOGAN
05/02/2025 08:38:42 AM

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

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

Memorandum

Date: May 1, 2025

To: Kim Searcy, Regulatory Project Manager, Division of Dermatology and Dentistry (DDD)

Jessica M. Nguyen, Clinical Reviewer, DDD
Kapil D. Verma, Clinical Reviewer, DDD

Matthew White, Associate Director for Labeling, DDD

From: Montherson L. Saint Juste, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for ANZUPGO® (delgocitinib) cream, for topical use

NDA: 219155

Background:
In response to DDD's consult request dated February 3, 2025, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for ANZUPGO® (delgocitinib).

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on April 17, 2025, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover on April 23, 2025.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on May 1, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Montherson L. Saint Juste at 301-796-1200 or Montherson.SaintJuste@fda.hhs.gov.

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MONTHERSON L SAINT JUSTE
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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:	April 22, 2025
To:	Kim Searcy Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	Barbara Fuller, MSN, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Montherson L. Saint Juste, PharmD, MS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ANZUPGO (delgocitinib)
Dosage Form and Route:	cream, for topical use
Application Type/Number:	NDA 219155
Applicant:	LEO Pharma A/S

1 INTRODUCTION

On July 23, 2024, LEO Pharma A/S submitted for the Agency's review an original New Drug Application (NDA) 219155 for ANZUPGO (delgocitinib) cream with proposed indication for the topical treatment of moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable.

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 February 4, 2025, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ANZUPGO (delgocitinib) cream.

2 MATERIAL REVIEWED

- Draft ANZUPGO (delgocitinib) cream PPI received on July 23, 2024, and received by DMPP and OPDP on April 17, 2025.
- Draft ANZUPGO (delgocitinib) cream Prescribing Information (PI) received on July 23, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 17, 2025.

3 REVIEW METHODS

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

In our collaborative review of the PPI we:

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

4 CONCLUSIONS

The PPI 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 PPI 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 PPI.

Please let us know if you have any questions.

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MONTHERSON L SAINT JUSTE
04/22/2025 04:01:14 PM

BARBARA A FULLER
04/23/2025 08:20:32 AM

Clinical Inspection Summary

Date	4/8/2025
From	Stephanie Coquia, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Jessica Nguyen, MD, Clinical Reviewer Kapil (Dev) Verma, MD, Clinical Reviewer Melinda McCord, MD, Clinical Team Leader Kimberle Searcy, Regulatory Project Manager Division of Dermatology and Dentistry (DDD)
NDA #	219155
Applicant	Leo Pharma Inc.
Drug	Delgocitinib
NME (Yes/No)	Yes
Therapeutic Classification	Janus kinase inhibitor
Proposed Indication	For the treatment of moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable.
Consultation Request Date	9/13/2024
Summary Goal Date	4/23/2025
Action Goal Date	7/23/2025
PDUFA Date	7/23/2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Leo Pharma Inc., submitted clinical data from Study DELTA 1 (NCT04871711) and DELTA 2 (NCT04872101) to support a New Drug Application (NDA 219155) for delgocitinib. The proposed indication is for the treatment of moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable.

Five clinical investigators (Drs. Devani, Lesiak, Radny, Silvestre, and Leitz) were inspected.

The inspections did not find significant concerns regarding the conduct of the clinical trial or GCP or regulatory compliance. Based on the results of these inspections, data generated by the inspected clinical investigators appear acceptable in support of the proposed indication.

II. BACKGROUND

Leo Pharma Inc. seeks approval of an NDA for delgocitinib. In support of this NDA, the Applicant submitted clinical data from two phase 3 studies, DELTA 1 and DELTA 2. The following is a summary of the study protocols and key study information relevant to the clinical inspections.

Study Design

These were randomized, double-blind, vehicle-controlled, parallel-group, multi-site, phase 3 trials confirming the efficacy and evaluating the safety of twice-daily delgocitinib cream compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe CHE.

The trial consisted of a screening period (1 to 4 weeks), a 16-week treatment period, and a 2-week off-treatment period for safety (in those subjects who did not transfer to the long-term extension trial).

Objectives and Endpoints

The **primary objective** of each trial was to confirm the efficacy of twice-daily applications of delgocitinib cream compared with cream vehicle in the treatment of adult subjects with moderate to severe CHE.

The **primary endpoint** of each trial was the Investigator's Global Assessment for CHE treatment success (IGA-CHE TS) defined as an IGA-CHE score of 0 (clear) or 1 (almost clear) at Week 16 with a ≥ 2-step improvement from baseline.

The **secondary objective** was to confirm the health-related quality of life and efficacy of twice-daily applications of delgocitinib cream compared with cream vehicle in the treatment of adult subjects with moderate to severe CHE.

Secondary endpoints of interest included: Reduction in Hand Eczema Symptom Diary (HESD) weekly average scores from baseline at Week 16. The HESD was assessed daily for 6 items: itch, pain, cracking, redness, dryness, and flaking.

Eligibility Criteria

- ≥18 years at screening
- Diagnosis of CHE, defined as hand eczema that had persisted for more than 3 months or returned twice or more within the last 12 months
- Disease severity graded as moderate (3) to severe (4) at screening and baseline according to IGA-CHE
- HESD itch score (weekly average) ≥ 4 at baseline
- Documented recent history of inadequate response to treatment with topical corticosteroids

(TCS) at any time within 1 year before the screening visit or for whom TCS are documented to be otherwise medically inadvisable

- None of the following:
  - Concurrent skin disease on the hands, including clinically significant infection
  - Active atopic dermatitis (AD) requiring medical treatment in regions other than the hands and feet
  - Active psoriasis on any part of the body
  - Hyperkeratotic hand eczema in combination with a history of psoriasis on any part of the body

Study Conduct

DELTA 1 database lock was November 17, 2022. There were 51 sites in six countries (Canada, France, Germany, Italy, Poland, and the United Kingdom) that enrolled subjects. The first subject visit was May 10, 2021. The last subject visit was October 31, 2022.

DELTA 2 database lock was January 25, 2023. There were 49 sites in seven countries (Belgium, Canada, Denmark, Germany, the Netherlands, Poland, and Spain) that enrolled subjects. The first subject visit was May 25, 2021. The last subject visit was January 6, 2023.

III. RESULTS

1. **Dr. Alim Devani (CAN1568, DELTA 1)**
   8500 Blackfoot Trail S.E., Suite 310
   Calgary, Alberta, Canada T2J 7E1

   Inspection Dates: December 9 – 11, 2024

   This investigator was inspected as a BIMO Review-based inspection for Study DELTA 1. This was the first FDA inspection for this investigator.

   At the site, 23 subjects were screened, and 18 were enrolled into the study. Records from all 18 enrolled subjects were reviewed. Subject-related records reviewed included informed consent forms (ICFs), investigational product (IP) accountability records, progress notes, laboratory reports, subject diaries, audit trails, and documentation of efficacy, adverse events (AEs), eligibility, randomization, subject discontinuations, concomitant medications, demographics, and medical history.

   Study-related records reviewed included the protocol, IP accountability records, correspondence with the sponsor and monitor, regulatory records, delegation of authority log, screening and enrollment log, sponsor and research ethics board correspondence, and documentation of laboratory accreditation, protocol deviations, and staff training.

   There were no discrepancies identified in the submitted data when compared to the source data for subjects. The primary and secondary efficacy data were verifiable. No unreported AEs,

concomitant medications, or protocol deviations were identified.

Based on the results of the inspection, the data generated at Dr. Devani's site appear acceptable in support of the proposed indication in the NDA.

2. **Dr. Aleksandra Lesiak (POL0771, DELTA 1)**
   Ul. Kosciuszki 93
   Lodz, Lodzkie, 90-346, Poland

   Inspection Dates: January 6 – 10, 2025

   This investigator was inspected as a BIMO Review-based inspection for Study DELTA 1. This was the first FDA inspection for this investigator.

   Of the 17 subjects screened at the site, 15 were enrolled into the study. The ICFs for all 17 screened subjects were reviewed, and study records of all 15 enrolled subjects were reviewed. Subject-related records reviewed included laboratory reports, AE reports, questionnaires, worksheets, and documentation of medical history, concomitant medications, physical examinations, and IP dispensation.

   Study-related records reviewed included the protocol, ethics committee (EC) and monitor correspondence, training records, delegation of authority log, enrollment log, protocol deviation log, IP accountability and storage temperature logs, and reports to the sponsor.

   There were no discrepancies identified in the submitted data when compared to the source data for subjects. No unreported AEs, concomitant medications, or protocol deviations were identified.

   Based on the results of the inspection, the data generated at Dr. Lesiak's site appear acceptable in support of the proposed indication in the NDA.

3. **Dr. Peter Radny (Site DEU0751, DELTA 2)**
   Charlottenstrasse 12/1 Friedrichshafen
   Friedrichshafen, Baden-wurttemberg, 88045 Germany

   Inspection Dates: December 2 – 6, 2024

   This investigator was inspected as a BIMO Review-based inspection for Study DELTA 2. This was the first FDA inspection for this investigator.

   Of the 16 subjects screened at the site, 15 were enrolled into the study. The records of all 16 subjects were reviewed. Subject-related records reviewed included ICFs, eCRFs, visit notes, laboratory reports, questionnaires, AE/SAE logs, and documentation of demographics, medical history, concomitant medications, vital signs, physical examination, and IP administration.

   Study-related records reviewed included the protocol, IEC documentation, signed protocol

acknowledgement form, financial disclosure forms, IP temperature logs, training records, correspondence with the sponsor, delegation of authority log, screening and enrollment log, notes to file, and documentation of sponsor monitoring activities and protocol deviations.

There was one unreported AE of headache in Subject (b) (6), who received delgocitinib.

Reviewer comment: This is a topical product with negligible absorption (per the proposed prescribing information); this unreported AE is unlikely to change the study's overall conclusion on safety.

Otherwise, there were no discrepancies identified in the submitted data when compared to the subject source data. The IGA-CHE and HESD scores were verifiable. No unreported protocol deviations were identified.

Based on the results of the inspection, the data generated at Dr. Radny's site appear acceptable in support of the proposed indication in the NDA.

4. **Dr. Nicolas Leitz (Site DEU0995, DELTA 2)**
   Marienstrabe 1, Leitz Treatment
   Stuttgart, Baden-wurttemberg, 70178 Germany

   Inspection Dates: December 9 – 13, 2024

   This investigator was inspected as a BIMO Review-based inspection for Study DELTA 2. This was the first FDA inspection for this investigator.

   Of the 36 subjects screened at the site, 33 were enrolled and randomized into the study. Subject-related records were reviewed for 23 enrolled subjects and included ICFs, visit notes, laboratory reports, questionnaires, ECGs, eCRFs, and documentation of eligibility, IP administration, and AEs.

   Study-related records reviewed included the protocol, IEC documentation, financial disclosure forms, signed protocol acknowledgement form, delegation of authority log, screening and enrollment log, training records, notes to file, IP accountability records, temperature logs, correspondence with the sponsor, and documentation of sponsor monitoring activities, AE reporting, and protocol deviations.

   There was one unreported AE of gastrointestinal infection in Subject (b) (6), who received delgocitinib.

   Reviewer comment: This is a topical product with negligible absorption (per the proposed prescribing information); this unreported AE is unlikely to change the study's overall conclusion on safety.

   Otherwise, there were no discrepancies identified in the submitted data when compared to the source data for subjects. The IGA-CHE and HESD scores were verifiable. No unreported

protocol deviations were identified. ECGs documented as being performed in the eCRF were located at the site.

Based on the results of the inspection, the data generated at Dr. Leitz's site appear acceptable in support of the proposed indication in the NDA.

5. **Dr. Juan Silvestre (Site ESP1017, DELTA 2)**
Avenida Pintor Baeza 12
Alicante, Spain 3010

Inspection Dates: January 13 – 17, 2025

This investigator was inspected as a BIMO Review-based inspection for Study DELTA 2. This was the first FDA inspection for this investigator.

Subject-related records reviewed for the 22 enrolled subjects included ICFs, laboratory reports, AE reports, IP dispensation records, questionnaires, worksheets, and documentation of medical history, physical examinations, and concomitant medications.

Study-related records reviewed included the protocol, IP accountability records, temperature logs, monitor and IEC correspondence, training records, delegation of authority log, screening and enrollment log, protocol deviation log, and financial disclosure forms.

There were no discrepancies identified in the submitted data when compared to the source data for subjects. No unreported AEs, concomitant medications, or protocol deviations were identified.

Based on the results of the inspection, the data generated at Dr. Silvestre's site appear acceptable in support of the proposed indication in the NDA.

{See appended electronic signature page}

Stephanie Coquia, M.D.
Primary reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Michele Fedowitz, M.D.
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Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
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cc:

Review Division /Division Director/Jill Lindstrom, MD
Review Division /Project Manager/Kimberle Searcy
Review Division/Cross Discipline Team Lead/Melinda McCord, MD
OSI/Office Director/David Burrow
OSI/ GCP Program Analysts/Yolanda Patague

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JENN W SELLERS
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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)

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Date of This Review:	March 26, 2025
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 219155
Product Name, Dosage Form, and Strength:	Anzupgo (delgocitinib) cream, 2%
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	LEO Pharma A/S
FDA Received Date:	July 23, 2024 and March 7, 2025
TTT ID #:	2024-10221
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 INTRODUCTION

As part of the approval process for Anzupgo (delgocitinib) cream, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Anzupgo Prescribing Information (PI), Patient Package Insert (PPI), container label(s), and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B

3 CONCLUSION

We evaluated the proposed Anzupgo Prescribing Information (PI) and Patient Package Insert (PPI) and determined that they are acceptable from a medication error perspective.

However, the proposed Anzupgo container labels and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for LEO Pharma A/S in Section 4.

4 RECOMMENDATIONS FOR LEO PHARMA A/S

A. General Comments (Container Label(s) and Carton Labeling)

1. The "Rx only" statement is bolded. Overuse of bold font may diminish its effect on prominence for more important product information. Reserve the use of bolded font only for the most important product information on the label and labeling; remove the bolded font from the "Rx only" statement.

B. Container Label(s)

1. The net quantity statement is in close proximity to the product strength. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Product selection or dosing errors can occur if the net quantity statement is mistaken for the product strength, leading to under- or over-dosing. We recommend relocating the net quantity statement away from and less prominent than the product strength, such as to the bottom right of the principal display panel. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

2. As currently presented, the format for the expiration date is not defined. We are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).

C. Carton Labeling

1. We recommend removing the following statement for consistency with the Prescribing Information and container label: "Before first use, screw off the cap, peel off the seal and screw the cap back on."
2. The placeholder for the lot number is missing. Lot number statement is required on the immediate container AND carton labeling when there is sufficient space per 21 CFR 201.10(i)(1). Add the placeholder for the lot number in accordance 21 CFR 201.10(i)(1).
3. The placeholder for the expiration date is missing. The label of an official drug product shall bear an expiration date per USP General Chapter <7>. Add the placeholder for the expiration date in accordance with USP General Chapter <7>. The USP Chapter <7>Labeling requires the expiration date to appear on the immediate container and all other packaging. When all-numeric dates are used, they must be formatted using the year, the month, and, if applicable, the day, separated by hyphens or forward slashes in one of the following formats: YYYY-MM-DD or YYYY-MM. When alphanumeric dates are used, months must be displayed using at least three letters in one of the following formats: YYYY-MMM-DD or YYYY-MMM. We recommend you ensure that there are no other numbers located in close proximity to the expiration date. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the expiration date format you intend to use.
4. The product identifier is missing. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in

both a human-readable form and machine-readable (2D data matrix barcode) format. We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling. Ensure the NDC, serial number, lot number, expiration date, and 2D data matrix barcode placeholders are included as part of the product identifier.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Anzupgo received on March 7, 2025 from LEO Pharma A/S.

Table 2. Relevant Product Information for Anzupgo	
Initial Approval Date	N/A
Active Ingredient	delgocitinib
Indication	topical treatment of moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable
Dosage Form	cream
Strength	2%
Route of Administration	topical
Dose and Frequency	Apply a thin layer twice daily to clean and dry (b) (4) affected areas on the hands and wrists. (b) (4) for topical use only. Avoid contact with eyes, mouth, or other mucous membranes. If contact with mucous membranes occurs, rinse thoroughly with water.
How Supplied	cream is a white to slightly brown cream containing 2% delgocitinib and is supplied in the following sizes: 30 g laminated tubes: NDC 50222-280-30 60 g laminated tubes: NDC 50222-280-60
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Do not freeze.
Container Closure	15 g, 30 g and 60 g laminate tubes tube body is constructed from a (b) (4) laminate with an aluminum barrier layer tube is fitted with a (b) (4) flip-top cap

APPENDIX B. LABELS AND LABELING

B.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 Anzupgo labels and labeling submitted by LEO Pharma A/S.

- Prescribing Information received on March 7, 2025, available from \\CDSESUB1\EVSPROD\nda219155\0023\m1\us\draft-labeling-text-uspi-track.docx
- Patient Package Insert received on July 23, 2024, available from \\CDSESUB1\EVSPROD\nda219155\0001\m1\us\draft-labeling-text-ppi.pdf
- Container label(s) received on July 23, 2024
- Carton labeling received on July 23, 2024
- Professional Sample Container Label received on July 23, 2024
- Professional Sample Carton Labeling received on July 23, 2024

B.2 Container Label(s) and Carton Labeling Images

Container Label(s):

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

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MADHURI R PATEL
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YEVGENIYA M KOGAN
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health Review

Date: March 18, 2025 **Date consulted:** August 26, 2024

From: Kerry R. Shaab, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatrics and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatrics and Maternal Health

To: Division of Dermatology and Dentistry (DDD)

Drug: Anzupgo (delgocitinib)

NDA: 219155

Applicant: LEO Pharma Inc.

Subject: Pregnancy and Lactation Labeling

Indication: Topical treatment of moderate to severe chronic hand eczema in adults who had inadequate response to, or for whom topical steroids are not advisable.

Materials Reviewed:

- DPMH consult request, dated 8/26/2024. DARRTS Reference ID: 5437645.
- Applicant's background package and proposed labeling for NDA 219155, Sequence Number (SN) 0001, dated 7/23/2024.
- Applicant's response to DPMH Information Request (IR) dated 1/10/2025, SN 0012, submitted 1/31/2025.

Consult Question: "Please review the pregnancy data in the development program, provide recommendations for labeling and attend meetings."

I. INTRODUCTION AND BACKGROUND

On July 23, 2024, the Applicant, LEO Pharma Inc., submitted a 505(b)(1) New Drug Application (NDA) for Anzupgo (delgocitinib) for the treatment of moderate to severe chronic hand eczema in adults who had inadequate response to, or for whom topical steroids are not advisable. DDD consulted the Division of Pediatrics and Maternal Health (DPMH) on August 26, 2024, to assist with the Pregnancy and Lactation subsections of labeling.

Relevant Regulatory History

- Delgocitinib was originally developed by Japan Tobacco (JT) and formulated as an ointment. In November 2014, JT and LEO Pharma entered into a license agreement for delgocitinib, giving LEO Pharma the rights to research, develop, and commercialize delgocitinib for topical treatment in dermatological skin diseases globally, excluding Japan.
- Delgocitinib ointment was approved in January 2020 only in Japan, under the brand name Corectim which is currently approved for the topical treatment of adult and pediatric patients (≥ 6 months) with atopic dermatitis (AD).
- Delgocitinib cream was approved in the European Economic Area (EEA) through the centralized procedure on September 15, 2024. It was launched in Germany and Denmark in October 2024. Although it has been approved in the UK, Switzerland, and UAE, delgocitinib cream has not been launched in these countries/territories yet.
- Delgocitinib cream was granted Fast Track Designation by the FDA on June 20, 2020.

Drug Characteristics[1]

Drug class	Janus kinase (JAK) inhibitor
Mechanism of Action	Inhibits the activity of JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). JAK signaling involves recruitment of signal transducers and activators of transcription (STATs) to cytokine receptors, activation, and subsequent localization of STATs to the nucleus leading to expression of cytokine-response genes to induce specific biological responses in target cells. The (b) (4) is not currently known.
Proposed dosage form and administration	2% Cream Each gram of Anzupgo contains 20 mg of delgocitinib. Apply a thin layer twice daily to clean and dry (b) (4) affected areas on the hands and wrists.
Molecular weight	310.35 g/mol

[1] NDA 219155, draft Annotated Labeling with DDD review team edits, review ongoing.

Half-life	21 hours (average following repeated topical application)
% protein bound	22 – 29%
Bioavailability	(b) (4)

Chronic Hand Eczema (CHE)

- Chronic hand eczema refers to hand eczema that persists for more than 3 months or recurs two or more times within a 12-month time frame. CHE is the most frequent occupational skin disease, especially among workers exposed to "wet work", such as health care workers, food handlers, and hairdressers.[2]
- A recent systematic review and meta-analysis revealed a lifetime prevalence of 14.5%, a 1-year prevalence of 9.1% and a point prevalence of 4% of hand eczema in European and North American populations. It has been shown that the occurrence of hand eczema was 1.5- to 2-fold higher in females than males. The average age of onset is in the early to mid-twenties.[3] In up to two-thirds of individuals affected by hand eczema, the disease becomes chronic.[4]
- The pathophysiology of chronic hand eczema is multifactorial with current or past atopic dermatitis and excessive or prolonged exposure to irritants or allergens being major risk factors. Trying to identify the underlying cause of hand eczema can aid with treatment.[4]
- In general, hand eczema often requires different treatments than eczema elsewhere on the body because the skin on the hands is thicker and more commonly exposed to irritants and allergens. A first-line treatment for mild to moderate chronic hand eczema is high potency or super high potency topical corticosteroids in conjunction with frequent and liberal use of emollients and moisturizers. Moderate-to-severe cases of CHE are often refractory to topical treatments. Patients with severe or recalcitrant hand eczema that does not respond to super potent topical corticosteroids may require systemic therapies, including oral corticosteroids, immunosuppressants and immunomodulators, retinoids or phototherapy.[2,5] Currently, there are no FDA-approved treatments specifically for moderate to severe CHE.
- Hand eczema has a very prolonged course. The reported average duration is approximately 12 years. CHE may have significant psychosocial consequences, such as social stigma, long-term sick leaves, involuntary job rotation, and early retirement, and a profound impact on quality of life.[2]

[2] Sheehan, M. Chronic Hand Eczema. In:UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed 3/3/2025)
[3] Quaade AS, Simonsen AB, Halling A-S, Thyssen JP, Johansen JD. Prevalence, incidence, and severity of hand eczema in the general population – A systematic review and meta-analysis. Contact Dermatitis. 2021; 84: 361–374. https://doi.org/10.1111/cod.13804
[4] Weidinger, S, Novak, N. Hand eczema. The Lancet, Volume 404, Issue 10470, 2024, Pages 2476-2486, ISSN 0140-6736, https://doi.org/10.1016/S0140-6736(24)01810-5.
[5] Dubin C, Del Duca E, Guttman-Yassky E. Drugs for the Treatment of Chronic Hand Eczema: Successes and Key Challenges. Ther Clin Risk Manag. 2020 Dec 31;16:1319-1332. doi: 10.2147/TCRM.S292504. Erratum in: Ther Clin Risk Manag. 2021 Mar 18;17:233. doi: 10.2147/TCRM.S303302. PMID: 33408476; PMCID: PMC7780849.

II. REVIEW

PREGNANCY

Nonclinical Experience

The nonclinical team reviewed the Applicant's submission and provided the following information:

In the female rat Fertility and Early Embryonic Development (FEED) study, the NOAEL for early embryonic development was 3 mg/kg/day (110 times the exposure at the maximum recommended human dose (MRHD) based on AUC comparison).

In the rat and rabbit Embryo-Fetal Development (EFD) studies, delgocitinib did not cause adverse effects in the offspring when administered orally during the period of organogenesis at dose exposures 120- and 193-times exposure at the MRHD based on AUC comparison in pregnant rats and rabbits, respectively.

In the Pre- and Postnatal Development (PPND) study, pregnant rats were dosed from implantation through weaning by oral gavage at dose levels of 3, 10, and 30 mg/kg/day. No significant maternal toxicity was noted at 30 mg/kg/day (1555 times the MRHD based on AUC comparison). Extended gestation period, a decrease in the birth index, and an increase in the number of dead newborns were observed at 30 mg/kg/day. In the newborn pups, a decrease in the viability and reduced pup weights were noted during the early postnatal period at 30 mg/kg/day (1555 times the MRHD based on AUC comparison) as well. The NOAEL for the rat PPND study was 10 mg/kg/day (378 times the MRHD based on AUC comparison). No effects on the behavior or the reproductive performance of F_1 offspring were observed at any dose levels tested.

The reader is referred to the full nonclinical review by Kevin Ebert, Ph.D.

> ***Reviewer Comment:***
> *The adverse effects seen in the animal reproduction studies occurred at dose exposures greater than 100 times the clinical exposure at the recommended human dose. These substantial safety margins suggest low risk of reproductive toxicity to humans/in patients treated with topical delgocitinib cream.*

Review of Pharmacovigilance Database

Delgocitinib cream clinical development program:

The Applicant reported 13 pregnancy cases during the clinical development program of delgocitinib cream 20 mg/g as of December 31, 2024. The summary of birth outcomes are as follows with details provided in Table 1 below:[6,7]

- Elective abortions n=3
- Spontaneous abortions n=2
- Live births n=4
    - 40 1/7-week gestational age "normal newborn"
    - 39 5/7-week gestational age SGA (birth weight 2.79 kg), "normal newborn"
    - 39-week gestational age "live birth" with "no fetal complications"
    - 38-week gestational age "normal newborn"

[6] NDA 219155, Module 2.7.4, Summary of Clinical Safety, p. 295-299.
[7] NDA 219155, SN 0012, Applicant's response to DPMH IR, dated 1/10/2025, submitted 1/31/2025.

- Ongoing pregnancies n=2
- Cases lost to follow-up n=2

Table 1: Pregnancy Cases from the delgocitinib cream Clinical Drug Development Program[8]

Trial ID/ Subject ID/ Age/Country	**Trial Period where pregnancy occurred**	**Pregnancy Outcome**	**Obstetric History**	**Permanent discontin – uation of delgocitinib cream**	**Comments**
LP0133-1402/ (b) (6) /35 years/ Germany	Treatment period	Elective abortion	3 live births, 2 induced abortions, and 1 spontaneous abortion	Yes	Subject became pregnant on an unknown date and had an induced abortion at gestational week 7.
LP0133-1402/ (b) (6) /46 years/ Germany	Treatment period	Elective abortion	2 live births with normal outcomes	Yes	Approximately 1 month after last dose of delgocitinib cream, subject discovered pregnancy. The subject did not wish to continue with the pregnancy and had a planned abortion at gestational week 9 without complications.
LP0133-1403/ (b) (6) /37 years/ Canada	Treatment period	Elective abortion	2 live births	Yes	Subject reported a spontaneous conception and wished to continue with the pregnancy. Prenatal test results confirmed Down's syndrome/Trisomy 21 in the fetus, and the subject had an elective abortion. Investigator and sponsor considered the event not related to the delgocitinib cream. The obstetrician considered the chromosomal abnormality to be associated with the subject's age.
LP0133-1403/ (b) (6) /40 years/ Spain	Off treatment	Spontaneous abortion	1 live birth with previous obstetric complication (cesarean)	Yes	The subject had her LMP during the off-treatment period and had planned to continue with the pregnancy. Subject had a spontaneous abortion at gestational week 9 +6 days. The investigator considered the event as not related to delgocitinib cream.
LP0133-1403/ (b) (6) /24 years/ France	Off treatment [subject on treatment at the next (early termination) visit]	Spontaneous abortion	1 live birth	Yes	Subject had LMP 3 days after the last dose of delgocitinib cream. At < 4 gestational weeks, the subject had a spontaneous abortion. The investigator considered the event as not related to delgocitinib cream.
LP0133-1402/ (b) (6) /39 years/ Spain	Treatment period	Normal newborn	2 live births (1 cesarean due to induction failure, 1 vacuum delivery); No	Yes	Subject had LMP approximately 1 month prior to last dose of delgocitinib cream. The subject wished to continue with the pregnancy. No risks identified with the pregnancy. Planned induction

[8] Source: Reviewer's table based on information from Module 2.7.4 p. 295-299 and Applicant's response to DPMH IR, dated 1/10/2025, p. 15 and p. 22-27.

Trial ID/ Subject ID/ Age/Country	Trial Period where pregnancy occurred	Pregnancy Outcome	Obstetric History	Permanent discontin – uation of delgocitinib cream	Comments
			stillbirths, no previous fetal/neonatal abnormalities/co ngenital anomalies		at gestational week 40+1 due to advanced maternal age (40 years). An emergency cesarean section was performed due to the risk of loss of fetal wellbeing, non-progression of labor, and suspicion of fetal head malposition. The subject gave birth to a live male baby weighing 3.46 kgs and Apgars 10 and 10.
LP0133-1403/ (b) (6) /34 years/ Spain	Off treatment	Normal newborn	1 live birth and 1 abortion; No previous obstetric complications, no previous fetal, neonatal or congenital anomalies.	Yes	Subject was in the off-treatment period and had stopped treatment with delgocitinib cream 2 days prior to LMP. The subject has risk factors: smoking and obesity (BMI:44). The subject gave birth to a live male baby by vaginal delivery at gestational week 39 + 5 after being admitted for planned induction of labor. The newborn weighed 2.79 kgs (reported as small for the gestational age) with Apgars 9, 10 and 10. No reported adverse events during pregnancy or pregnancy complications.
LP0133-1528/ (b) (6) / 25 years/ France	After completing treatment	Live birth	None	N/A	Subject became pregnant and had LMP 181 days after first dose and 41 days after last dose of delgocitinib cream. There are no known risks associated with the pregnancy. Subject had completed treatment with delgocitinib cream. Subject gave birth via vaginal delivery to one child at week 39. No AEs or pregnancy complications experienced during pregnancy. No fetal complications.
LP0133-1528/ (b) (6) / 23 years/ Spain	On treatment	Normal newborn	1 spontaneous abortion and 1 live birth	N/A	Subject became pregnant and had LMP 149 days after first dose and 20 days prior to last dose of delgocitinib cream. There were no known risks associated with the pregnancy. The subject had completed treatment with delgocitinib cream when the pregnancy was discovered. Planned cesarean section at gestational age week 38, without any complications.
LP0133-1528/ (b) (6) / 27 years/ Spain	Off treatment	Ongoing	None	N/A	Subject became pregnant on an unknown date and had LMP 143 days after first dose of delgocitinib cream and 26 days after last dose of delgocitinib cream. Expected delivery date is currently unknown. There are

Trial ID/ Subject ID/ Age/Country	Trial Period where pregnancy occurred	Pregnancy Outcome	Obstetric History	Permanent discontin – uation of delgocitinib cream	Comments
					no known risk factors associated with the pregnancy.
LP0133-2283/ (b) (6) / 37 years/ China	On treatment	Ongoing	1 induced abortion	Yes	Subject became pregnant and had LMP on (b) (6), 80 days after first dose and 34 days prior to last dose of open-label delgocitinib cream. Expected delivery date is (b) (6)
Trial 2283/ (b) (6) / 41 years/ Asian	On treatment	Planned elective abortion – lost to follow-up	2 live births	Yes	Onset date of LMP was 12 days before the first dose of delgocitinib cream. Subject exposed to delgocitinib cream for 3 ½ weeks prior to discontinuation. Subject refused to sign a pregnancy ICF or to provide follow-up information. Elective abortion planned 2 weeks after discontinuation date.
Trial 2283/ (b) (6) / 33 years/ Asian	On treatment	Ongoing – lost to follow-up	2 live births with no previous obstetric complications and no fetal/neonatal or congenital anomalies	Yes	Subject's LMP date was 11 days after first dose of blinded delgocitinib cream. Delgocitinib cream discontinued 4 weeks later. (Approximately 5 ½ weeks of IMP exposure). Subject planned to continue with the pregnancy. Subject refused to sign a pregnancy ICF or to provide follow-up. Smoker until (b) (6)

The Applicant concluded that "given the confounding factors for all cases and the negligible systemic exposure of delgocitinib cream observed in CHE patients in the PK Trial 2285, these events were not considered to be caused by treatment with delgocitinib cream 20 mg/g."

Delgocitinib cream postmarketing experience in Germany and Denmark[9]:
As of December 31, 2024, the Applicant reported that no postmarketing cases of delgocitinib exposure during pregnancy have been received after the launch of delgocitinib cream in October 2024.

Delgocitinib ointment (Corectim) postmarketing experience in Japan[10,11]*:*
Japan Tobacco (JT) is responsible for reporting delgocitinib exposures during pregnancy to the Applicant and to follow-up on the pregnancy until after delivery or termination. Based on the postmarketing data as of December 31, 2024, cumulatively, there have been 52 pregnancies in 51 females treated with Corectim. There is very limited information. According to the Applicant, for the majority of reports (50 out of 52), no adverse events or adverse outcomes were reported with the pregnancy. There were 2 separate pregnancies in a 37-year-old female which occurred

[9] NDA 219155, SN 0012, Applicant's response to DPMH IR, dated 1/10/2025, p. 14.
[10] NDA 219155, Module 5.3.6, Reports of Postmarketing Experience from CORECTIM, p. 5 and p. 19.
[11] NDA 219155, SN 0012, Applicant's response to DPMH IR, dated 1/10/2025, p. 16.

1.5 years apart and both resulted in spontaneous abortions. The first spontaneous abortion occurred at an unknown gestation week. The second spontaneous abortion occurred at gestation week 10. Important relevant information such as maternal obstetric history, course of events, and other relevant medical history was not reported. The patient had one 5-gram "dispension" of Corectim prescribed for a 6-month period but there are no details on the actual use. Her concomitant medications included oral tokishakuyakusan (a traditional Japanese herbal medicine), oral tocopheryl acetate, and topical heparinoid. All the concomitant medications were used on unspecified dates for unknown indications. The patient's physician considered both spontaneous abortions not related to Corectim but rather due to the patient's age.

According to the Applicant, none of the individual pregnancy outcomes with delgocitinib ointment raised any safety concerns. In addition, the systemic exposure was comparable between delgocitinib ointment (Corectim) for atopic dermatitis and delgocitinib cream 20 mg/g for chronic hand eczema, and thus, the safety information for Corectim helps to inform the safety of delgocitinib cream.

> ***Reviewer Comment:***
> *DPMH agrees with the Applicant's conclusion that none of the individual pregnancy outcomes with either delgocitinib cream or delgocitinib ointment raise specific safety concerns. With respect to participant* (b) (6) *(Trial ID LP0133-1528), the participant's LMP was 26 days after the last dose of delgocitinib cream. Based on a systemic clearance of 5x half-life of delgocitinib cream, the drug likely cleared maternal circulation before embryonic development, and thus, the final pregnancy outcome was not pursued. There is limited clinical data on delgocitinib exposure during pregnancy and the limited clinical data are insufficient to draw meaningful safety conclusions about the effects of delgocitinib during pregnancy.*

Review of Literature

Applicant's Review:

The Applicant performed a cumulative literature search with the following strategy:

- Databases: Ovid MEDLINE and Embase;
- Search terms: ("LEO 124249" or LEO124249 or LEO-124249 or "JT 052" or JT052 or JT-052 or "JTE 052" or JTE052 or JTE-052 or JT052A or JT-052A or "JT 052A" or "JTE 052A" or JTE052A or JTE-052A or delgocitinib or Anzupgo or Corectim and (fertilit* or infertilit* or contraception* or contraceptives*) and (pregnan* or (birth and defect*) or congenital or malformation* or stillbirth* or abortion* or miscarriage* or ((fetal or foetal) and loss) and (breastfeeding or (breast and feeding) or (breast and milk) or (mammary and gland*) or lactation) or delgocitinib/ and (exp pregnancy/ or lactation/ or drug exposure during lactation/ or exp breast feeding/ or breast milk/ or "Milk, Human"/ or exp fertility/ or exp infertility/ or exp Contraception/ or exp contraceptive agent/ or exp Contraceptive Agents/ or exp congenital disorder/ or exp "Congenital, Hereditary, and Neonatal Diseases and Abnormalities"/ or exp abortion/ or Aborted Fetus/ or exp Fetal Death/ or exp fetus death/)
- Limits: No limits specified

The Applicant's literature search identified 18 articles none of which reported clinical trials or observational studies investigating the use of delgocitinb in pregnant women. Supplementary searches conducted in ReproTox and TERIS for the chemical name "delgocitinib" did not yield any relevant information.

DPMH review:
DPMH conducted a search of published human studies in PubMed and Embase, using the search terms "delgocitinib" and "pregnancy", "pregnancy outcomes", "pregnant", "major birth defects", "birth defects", "congenital malformations", "congenital anomalies", "teratogenicity", "miscarriage", "spontaneous abortion", "elective abortion", "pregnancy loss", "stillbirth", "fetal loss", "fetal demise", "fetotoxicity", "safety events", and "adverse events". No relevant publications were found.

In addition, DPMH conducted a search for delgocitinib in Micromedex[12], Reprotox[13], TERIS[14], Shepard's[15], and Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*[16]. No information was found.

Reviewer comment:
The Applicant's review is adequate.

LACTATION
Nonclinical Experience
Delgocitinib was excreted in the milk of lactating rats following a single oral dose of 1 mg/kg delgocitinib administered on lactation day 12. Drug exposure was approximately 2.5-fold greater in rat milk than in plasma based on AUC comparison.

The reader is referred to the full nonclinical review by Kevin Ebert, Ph.D.

Reviewer Comment:
The presence of delgocitinib in rat milk was demonstrated following a single oral dose of delgocitinib to lactating rats.
As mentioned in the Pregnancy section of this review, during the postpartum/nursing phase of the pre- and postnatal development study where delgocitinib was administered to pregnant rats from the period of implantation to weaning, adverse effects in the newborn pups were observed during the early postnatal period at doses approximately 1500 times the MRHD based on AUC comparison. According to the nonclinical review team, it would not be possible to clearly distinguish between the effects from in utero exposure and lactational exposure because toxicity was still noted after weaning and the milk:plasma ratios were greater than 1.0.

[12] Truven Health Analytics information, http://www.micromedexsolutions.com Accessed 1/8/2025.
[13] Reprotox Website: www.Reprotox.org. Accessed 1/8/2025.
[14] TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 1/8/2025.
[15] Shepard's database. Truven Health Analytics. Micromedex Solutions. Accessed 1/8/2025.
[16] Briggs, Gerald G., Craig V. Towers, and Alicia B. Forinash. Briggs Drugs in Pregnancy and Lactation: a Reference Guide to Fetal and Neonatal Risk. 12th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2021.

Review of Pharmacovigilance Database

Delgocitinib cream clinical development program:

According to the Applicant, no delgocitinib exposures via lactation were reported in any of the clinical trials.[17]

Delgocitinib ointment (Corectim) postmarketing experience in Japan:

As of August 25, 2024, a total of 40 "maternal exposures during breast feeding/exposure via breast milk" in females treated with Corectim had been reported in the postmarketing setting. The Applicant reported that "very limited information was available in the reports, however, no associated AEs in infants/neonates were reported."[18] There were no further details.

> ***Reviewer Comment:***
> *There is limited clinical data on delgocitinib exposure in lactating individuals. No exposures were reported during clinical drug development program. Although missing details, no safety concerns have been identified from reports of exposure in lactating individuals in the delgocitinib ointment postmarketing setting in Japan. In two Phase 1 trials (Trial NBX1-1 and Trial 1409) evaluating PK parameters, tolerability and safety following the oral administration of delgocitinib to healthy subjects, there were no serious adverse events reported. The relative bioavailability of delgocitinib following topical application is approximately 0.6% compared to oral administration. The low relative bioavailability and low systemic exposure in individuals treated with topical delgocitinib suggest that the presence of delgocitinib in breast milk is likely to be low, resulting in a low relative infant dose in the breast fed infant.*

Review of Literature

Applicant's review:

Refer to the Pregnancy section of this review for the Applicant's literature search parameters. The Applicant did not identify any published clinical literature related to delgocitinib use in lactating women. Supplementary searches conducted in Reprotox and LactMed for the chemical name "delgocitinib" did not yield any relevant information.

DPMH review:

DPMH conducted a search of published human studies in PubMed and Embase, using the search terms "delgocitinib" and "lactating", "lactation", "nursing", "breastfeeding", "breastfed", "breast fed", "neonates", and "infants". No relevant publications were found.

In addition, DPMH conducted a search for delgocitinib in Micromedex[12], Reprotox[13], Hale's *Medications and Mothers' Milk*[19], the Drugs and Lactation Database (LactMed)[20], and Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*[16]. No information was found.

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[17] NDA 219155, Module 2.5, Clinical Overview, p. 102.
[18] NDA 219155, Module 5.3.6 Reports of Postmarketing Experience from CORECTIM, p. 19 and Module 5.3.6 Addendum, p. 9.
[19] Hale, Thomas W. Hale's Medications and Mother's Milk 2021: A Manual of Lactational Pharmacology. 19th ed. New York: Springer Publishing Company, 2020. www.halesmeds.com. Accessed 1/8/2025.
[20] Drugs and Lactation Database (LactMed). Accessed 1/8/2025.

Reviewer comment:
The Applicant's review is adequate.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Delgocitinib was not mutagenic in a bacterial mutagenicity assay (the Ames test) and did not cause chromosomal aberration in human peripheral lymphocytes in vitro or in rat bone marrow cells in vivo.

A Fertility and Early Embryonic Development (FEED) study was conducted in rats. In the male rat fertility study, there were no effects on male fertility observed at oral doses up to 30 mg/kg/day (approximately 1300 times the MRHD based on AUC comparison). In the female rat fertility study, effects on female fertility including a decrease in number of corpora lutea, a decrease in number of implantations, and a decrease in fertility index were observed at 100 mg/kg/day (5897 times the MRHD based on AUC comparison). No adverse effects on fertility were noted at 30 mg/kg/day (1087 times the MRHD based on AUC comparison).

The reader is referred to the full nonclinical review by Kevin Ebert, Ph.D.

Reviewer Comment:
Although effects on female fertility were seen in the female rat fertility study, these effects occurred at dose exposures approximately 5000 times the clinical exposure at the maximum recommended human dose. Based on this substantial safety margin, delgocitinib cream is not expected to affect human fertility.

Review of Pharmacovigilance Database

Delgocitinib cream clinical development program and postmarketing experience[7]:
Per the Applicant, to identify relevant cases reporting effects on male or female fertility, a search in the pharmacovigilance database on MedDRA SMQs Fertility disorders and SMQ Sexual dysfunction was performed. No cases were identified from the delgocitinib cream development program or the postmarketing safety database for delgocitinib cream.

Delgocitinib ointment (Corectim) postmarketing experience in Japan[7]:
For Corectim ointment, 6 postmarketing cases from Japan were identified. Of the 6, 3 patients were between the ages of 19 and 50 years old, as well as one additional patient of unknown age. These cases reported "amenorrhea" in a 50-year-old, "genital discomfort" in a 40-49-years-old, "hypoaesthesia" in a 19-year-old, and "hypoaesthesia" in a person of unknown age. The case reports contained limited information, and all were considered "non-serious". The Applicant concluded that "none of the identified cases suggest that delgocitinib affects fertility."

Reviewer comment:
DPMH agrees with the Applicant that none of the identified cases suggest that delgocitinib affects fertility. The identified cases are missing pertinent information, including patient sex, frequency and duration of use of Corectim, application site, timing of use in relation to the onset of the adverse event, reversibility of the adverse event, and use of concomitant medications.

Review of Literature

Applicant's review:

Refer to the Pregnancy section of this review for the Applicant's literature search parameters. The Applicant did not identify any published clinical literature with relevant safety information related to males and females of reproductive potential.

DPMH review:

DPMH conducted a search of published human studies in PubMed and Embase, using the search terms "delgocitinib" and "fertility", "infertility", "decreased sperm count", "contraception", "oral contraceptives", "effects on fertility", and "reproduction".

In addition, DPMH conducted a search for delgocitinib in Micromedex[12], Reprotox[13], and TERIS[14]. No relevant publications or additional information on the effects of delgocitinib on human fertility or interactions with hormonal contraceptives were found in the literature search.

Reviewer comment:

The applicant's review is adequate.

III. DISCUSSION AND CONCLUSIONS

Pregnancy

Based on the nonclinical data, delgocitinib does not appear to be teratogenic in rats or rabbits. The adverse effects observed in the animal reproduction studies included post-implantation loss, decreased number of live embryos, increased fetal loss, a decrease in fetal weights, as well as a decrease in the viability and suppression of growth in the newborn pups during the early postnatal period. However, all these observed effects occurred at exposures greater than 100 times the clinical exposure at the maximum recommended human dose. The safety margins in the nonclinical studies suggest that no appreciable risks are to be expected in humans following topical delgocitinib treatment.

Although no safety concerns have been raised by the pregnancy exposure case reports in either the clinical drug development program for delgocitinib cream or the postmarketing experience with delgocitinib ointment, there are insufficient data on delgocitinib use in pregnancy to allow assessment of a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

Given population-based studies indicate that hand eczema occurs more frequently in females with an average age of onset in the early to mid-twenties, and in up to two-thirds of individuals affected by hand eczema, the disease becomes chronic, chronic hand eczema affects females of reproductive potential. Thus, the use of delgocitinib cream during pregnancy is anticipated. While reproductive toxicity is considered a class effect of JAK inhibitors, the low systemic exposure demonstrated in clinical PK studies and the substantial nonclinical safety margins suggest the appreciable risk in humans following topical delgocitinib treatment is low. Consequently, adverse effects during pregnancy would not be expected. As such, DPMH does not recommend postmarketing requirement (PMR) pregnancy safety studies. Monitoring for

safety signals through requested drug pharmacovigilance of pregnancy exposures and literature review is reasonable.

Lactation

Lactation data for delgocitinib are not currently available for humans. In nonclinical studies, after oral administration, delgocitinib was present in the milk of lactating rats. Although there were no lactational exposures reported during the clinical drug development program for delgocitinib cream, no safety concerns have been identified from the limited reports of lactational exposures in the delgocitinib ointment postmarketing setting. As mentioned, females of reproductive potential can develop chronic hand eczema, so use of delgocitinib cream during lactation is anticipated. The low systemic exposure after topical application of delgocitinib cream in a lactating female would likely result in a low amount of delgocitinib in breast milk, and thus, would not be expected to result in clinically relevant exposure of the breastfed infant to delgocitinib. However, serious adverse findings, including risks of serious infections, thrombocytopenia, anemia, and neutropenia, have been reported in adults treated with oral JAK inhibitors. As such, it is important to collect human lactation data for delgocitinib. DPMH recommends issuing a PMR for a clinical milk-only lactation study. The data obtained from a clinical milk-only lactation study would be helpful in determining the amount of delgocitinib present in human breastmilk. If a clinical milk-only lactation study demonstrates a clinically important amount of delgocitinib in breast milk, further study to examine systemic exposure in the breastfed infant may be needed in the future.

Females and Males of Reproductive Potential

There are no available human data to suggest delgocitinib adversely effects male or female fertility. Animal fertility studies do not indicate any adverse effects at clinical exposures. In addition, animal reproduction studies do not indicate an increased risk for embryo-fetal toxicity at clinical exposures. Based on the safety margins observed in the nonclinical studies and the low systemic exposure demonstrated in clinical PK studies, no appreciable risks to human fertility are expected following topical delgocitinib treatment. In addition, there is no evidence of fetal harm that would require pregnancy testing prior to delgocitinib use. Therefore, DPMH recommends omitting labeling subsection 8.3 Females and Males of Reproductive Potential.

POSTMARKETING REQUIREMENTS (PMR) SUGGESTED LANGUAGE

- **Lactation Study**: Perform a milk-only lactation study in lactating women who have received delgocitinib to measure concentrations of delgocitinib in breast milk using a validated assay. Assess the effects on the breastfed infant, if available, based on study population.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on 3/6/2025. DPMH recommendations are below and reflect the discussions with DDD. DPMH refers to the final NDA action for final labeling.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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03/21/2025 09:31:32 AM

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03/21/2025 09:36:30 AM

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03/24/2025 10:20:37 AM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 219155
Submission Number	1
Submission Date	9/23/2024
Date Consult Received	1/13/2025
Drug Name	Anzupgo (delgocitinib)
Indication	Topical treatment of moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable.
Therapeutic Dose	Twice-daily application of 20 mg/g delgocitinib cream
Clinical Division	DDD
Protocol Review	Link

Note: Any text in the review with a light background should be considered to be copied from the Applicant's document.

This review responds to your consult dated 1/13/2025 regarding the Applicant's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND 135351 dated 10/21/2020 in DARRTS;
- Investigator's brochure (NDA 219155 / SN0001; link);
- Proposed label (NDA 219155 / SN0001; link);
- Cardiac safety report (NDA 219155 / SN0001; link);
- Clinical study report (NDA 219155 / SN0001; link);
- QT evaluation checklist (NDA 219155 / SN0001; link); and
- Highlights of clinical pharmacology and cardiac safety (NDA 219155 / SN0001; link).

1 SUMMARY

Delgocitinib did not prolong the QTc interval based on concentration-QTc analysis of study LP0133-1409 – see Table 1 for overall results. These data can be used as a substitute for a TQT study (ICH E14 Q&A 5.1).

Study LP0133-1409 was a phase 1 clinical trial to evaluate QTcF prolongation and proarrhythmic potential of delgocitinib following oral administration in healthy subjects. The highest dose of 12 mg provided 193-fold high clinical exposure. Data were analyzed

using concentration-QTc analysis as the primary analysis, which did not suggest that delgocitinib is associated with large mean increases in the QTcF interval (section 4.5). The findings of the primary analysis are further supported by the lack of QTc prolongation in by-time analysis (section 4.3) and categorical analysis (section 4.4).

Table 1: Summary of findings

<table>
<tr><td>QT assessment pathway</td><td>☐ Thorough QT study
☒ Substitute for thorough QT study (5.1)
☐ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>• No intrinsic/extrinsic factors have clinically relevant effect on exposure thus high clinical exposure scenario is same as observed exposure after therapeutic dose of 20 mg/g delgocitinib cream applied topically twice-daily (section 3.1)
• The highest dose of 12 mg after oral administration in clinical QT study 1409, covers the maximum anticipated therapeutic exposure (Cmax) by 193-fold.
<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Concentration</th><th>ΔΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>ΔΔQTcF</td><td>Highest therapeutic or clinical trial dosing regimen</td><td>0.5 ng/mL</td><td>1.3</td><td>(-0.9 to 3.4)</td></tr>
<tr><td>ΔΔQTcF</td><td>Delgocitinib 12 mg (Highest dose in QT assessment)</td><td>96.4 ng/mL</td><td>2.8</td><td>(0.1 to 5.5)</td></tr>
</table></td></tr>
<tr><td>In vitro and In vivo findings</td><td>Integrated nonclinical risk assessment was not performed.</td></tr>
</table>

2 RECOMMENDATIONS

2.1 PROPOSED LABEL

Below are proposed edits to the label submitted to SN0001 (link).

Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At 193 times the mean maximal concentration provided by the recommended topical dose, clinically significant QTc interval prolongation was not observed. (b) (4)

Reviewer's comment: We propose to use labeling language for this product consistent with the "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry" draft guidance (link).

3 APPLICANT'S SUBMISSION

3.1 OVERVIEW

Delgocitinib (ANZUPGO®, cream, for topical use, MW: 310.35 g/mol) is a Janus kinase (JAK) inhibitor that targets the activity of all 4 members of the JAK family of enzymes consisting of JAK1, JAK2, JAK3, and TYK2 in a concentration dependent manner indicated for the topical treatment of moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable. [redacted] The product is formulated as cream ([redacted] form) containing 20 mg delgocitinib (per gram) for topical application. The recommended dosage is twice-daily application of 20 mg/g delgocitinib cream to clean and dry [redacted] affected areas.

The CS-IRT reviewed the QT assessment proposal previously (DARRTS 10/21/2020). The Applicant proposed to evaluate the QT effects in Study LP0133-1409, a phase-1, randomized, double-blind, placebo-controlled, parallel-group, single-dose, single-center, clinical study in healthy subjects. An oral (capsule) formulation was used for this study. The maximum dose proposed was 12 mg single dose. We found the study design and analysis plan acceptable. In this submission, the Applicant submitted cardiac safety report for Study LP0133-1409. Concentration-QTc was used as the primary analysis.

3.1.1 Clinical Pharmacology

See highlights of clinical pharmacology and cardiac safety (link).

After topical application twice daily, delgocitinib cream 20 mg/g showed minimal systemic exposure at both Day 1 and Day 8. Overall, the geometric mean Cmax was similar at Day 1 and Day 8, whereas geometric mean AUC0-12 was slightly higher at Day 8 compared with Day 1. The exposure at Week 16 was 48% lower than that at Week 1 (Study 1402), suggesting that there is no accumulation of delgocitinib over time in subjects with CHE. Median T_{max} is 0.9 hours on Day 1 and 7.9 hours on Day 8 for parent. The geometric mean of t1/2 was 203 hours and primary elimination route is renal, 70-80% unchanged. There are no relevant metabolites.

Following single ascending oral doses of 1.5–12 mg delgocitinib, plasma concentrations increased rapidly, with T_{max} being observed between 0.833- and 1.00-hours post-dose. The geometric mean $T_{1/2}$ was below 3 hours in all dose groups (range: 2.02–2.85 hours), with individual subject values all below 5 hours. The systemic exposure of delgocitinib (based on AUC and C_{max}) increased proportionally with the dose after single oral dosing of 1.5–12 mg delgocitinib in healthy adult subjects (Study 1409).

For this topically applied drug C_{max} and AUC were not investigated for different population and no population PK analysis was done. For the pivotal trial 1402, PK samples were collected in 313 subjects at three different weeks 2-6 hours after dosing. Based on this data a mixed models for repeated measures (MMRM) where conducted. Three factors were identified to be correlated to exposure. These are age, baseline disease severity score, and delgocitinib consumption (dose per application). However, given the low level of exposure, these factors are considered to be of no clinical relevance. No DDI studies were conducted. No effect of food intake on the PK of delgocitinib was observed.

Table 2. Summary of Dose and Exposure Assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	20 mg/g BID, topical cream	0.5 ng/mL ($C_{max,ss}$)
Applicant's High clinical exposure scenario	No intrinsic/extrinsic factors have clinically relevant effect on exposure	N/A
Highest dose in QT assessment*	12 mg, single dose, oral capsule	96.4 ng/mL
C_{max} Ratio	193	

*GM after 12 mg single oral dose (Study 1409)

3.1.2 Nonclinical Safety Pharmacology Assessments

The Applicant evaluated the effects of delgocitinib on hERG current in the study report (P100986, link). The hERG current was assessed at room using manual patch clamp assay.

The reduction in hERG current at the highest concentration tested (30 µM) was 10%. This concentration provides over 20,000-fold (MW: 310.35 g/mol; PB: 27% [at 3 µg/mL, one third of 30 µM]) the high clinical exposure scenario (0.5 ng/mL, see Table 2). Assuming a Hill coefficient of 1, this corresponds to an IC50 of 270 µM and a safety margin over 200,000-fold.

The in vivo QT study (P100985, link) assessed the effects of delgocitinib on ECG parameters following single oral doses to conscious telemetrized male dogs (n=4). The lowest dose tested was 0.3 mg/kg and the highest dose tested was 3 mg/kg. No statistical difference was noted in HR and ECG parameters (PQ interval, QRS duration, QT interval and QTc) at any dose compared to the control. Increased heart rate and decreased blood pressure were noted in the 3 mg/kg group.

In a single dose toxicokinetic study in dogs (10113, link), C_{max} was 0.2 µg/mL at 0.3 mg/kg and was 2.0 µg/mL at 3 mg/kg. The free C_{max} (PB%: 20% in dogs) of 3 mg/kg was over 4,000-fold the free C_{max} of the high clinical exposure scenario.

3.2 APPLICANT'S RESULTS

3.2.1 By-Time Analysis

The Applicant conducted IUT by-time analysis base on MMRM model. In the highest dose group (12 mg), LS mean ΔΔQTcF ranged from 2.1 ms (at 1-hour post-dose) to 5.2 ms (at 4 hours post-dose). The primary analysis for delgocitinib was based on exposure-response analysis, please see section 3.2.3 for additional details.

Reviewer's comment: *Since the number of subjects was relatively small, the reviewer evaluated the ΔQTcF effect using descriptive nonparametric statistics. The results were similar as the results based on MMRM. In the highest dose group (12 mg), LS mean ΔΔQTcF ranged from 1.5 ms (at 1-hour post-dose) to 5.7 ms (at 4 hours post-dose). The largest upper limit of CI of ΔΔQTcF was 12.0 ms (at 12-hour post-dose). Please see section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

Not Applicable.

3.2.1.1.1 QT Bias Assessment

The Applicant conducted a method bias sensitivity analysis by comparing fully automated ECG measurements (using the iCOMPAS software) to ECG measurement technique using Early Precision QT (EPQT) at their central ECG laboratory. Bias was evaluated using Bland-Altman (BA) plots. The relationship between the means and differences of the QTc interval measured by the 2 methods were investigated by robust regression using an M estimator. The Applicant's results indicated that the bias was minimal and unlikely to negatively impact the result of the concentration-QT analysis.

3.2.2 Categorical Analysis

There were no significant outliers per the Applicant's analysis for QTc (i.e., >500 msec or >60 msec over baseline), HR (<50 or >100 beats/min and 25% over baseline), PR (>200 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline) based on either change from baseline or categorical analyses.

Reviewer's comment: *The reviewer's analysis had slightly different threshold for HR (>100 beats/min) and PR (>220 msec and 25% over baseline). The analysis also showed no significant outliers for QTc, HR, PR and QRS intervals. Please see section 4.4 for additional details.*

3.2.3 Exposure-Response Analysis

The Applicant did not use the model recommended in the white paper. Compared to the white paper model, the Applicant's model excluded the intercept term. The results of the Applicant's analysis show an absence of significant QTc prolongation where the effect on ΔΔQTcF was predicted to be 2.79 ms (90% CI: -0.20 to 5.78) for 12 mg delgocitinib (96.4 ng/mL).

Reviewer's comment: *We used white paper model without random slope, as the model with random slope did not converge. Despite the difference between reviewer and Applicant's models, the results from the 2 analyses are consistent (See section 4.5.1)*

3.2.4 Safety Analysis

In Study LP0133-1409, 40 subjects received treatment with 8 subjects in each dose group (placebo, delgocitinib 1.5 mg, 3 mg, 6 mg, and 12 mg single dose). No SAEs or severe AEs were reported, and no subjects were withdrawn due to an AE. There were no AEs of SMQ Torsade de pointes/QT prolongation.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The Applicant used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| >10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Digital ECG waveforms were submitted for review. The ECGs were read semi-automatically by a central reader in a blinded manner. Compared to the ECG warehouse algorithm, we did not observe significant bias in QT measurements and the ECG acquisition and interpretation for this study is therefore acceptable.

4.2.2 QT Bias Assessment

The Applicant did not report QTc bias (section 3.2.1.1.1). This is consistent with our assessment (section 4.2.1).

4.3 BY-TIME ANALYSIS

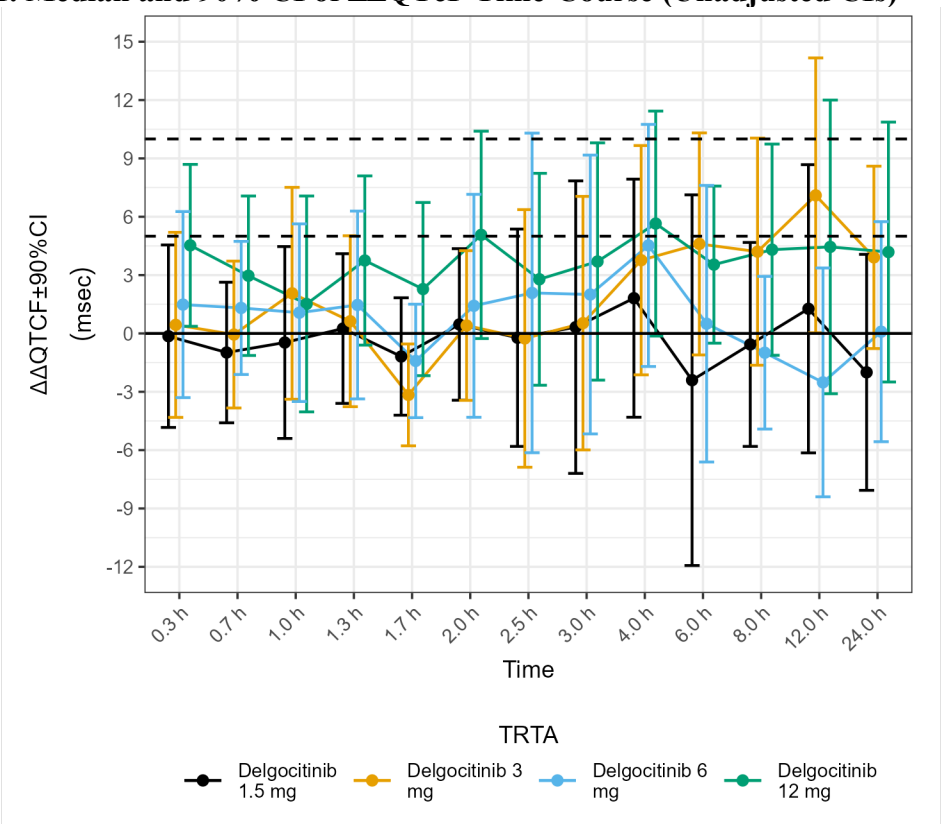
The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

Since the number of subjects was relatively small, e.g. delgocitinib 1.5 mg (n = 8), delgocitinib 3 mg (n = 8), delgocitinib 6 mg (n = 8), delgocitinib 12 mg (n = 8) and placebo (n = 8). The reviewer evaluated the ΔQTcF effect using descriptive nonparametric statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups.

Figure 1. Median and 90% CI of ΔΔQTcF Time-Course (Unadjusted CIs)



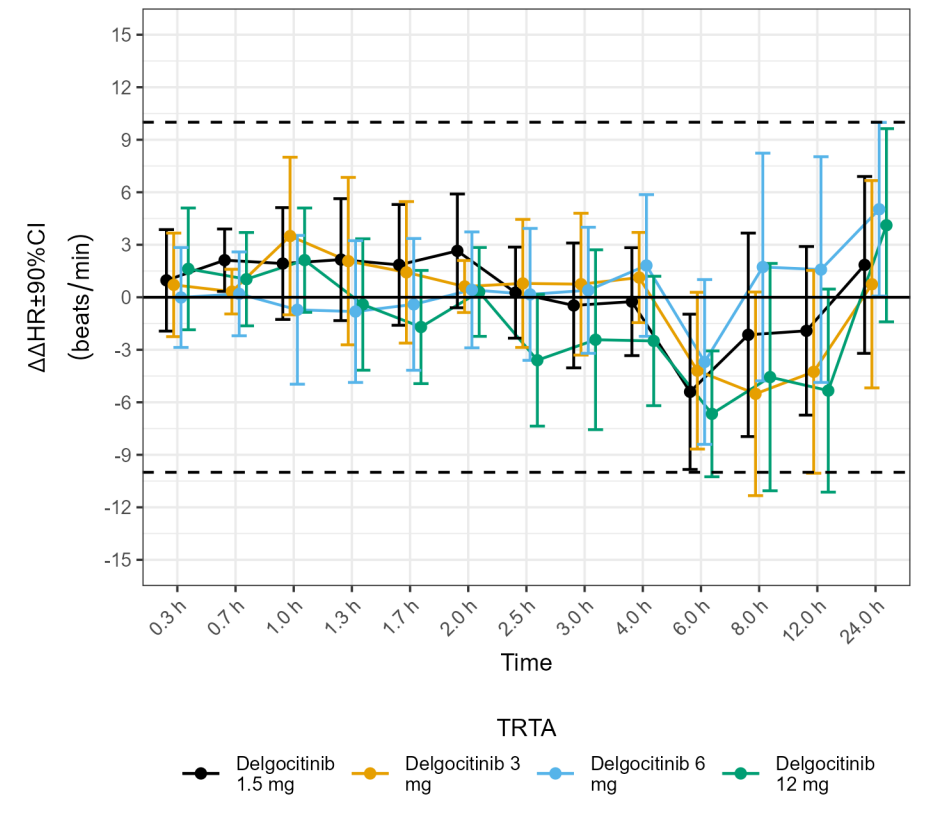
4.3.1.1 Assay Sensitivity

By-time analysis for assay sensitivity is not applicable as the study did not include moxifloxacin control

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

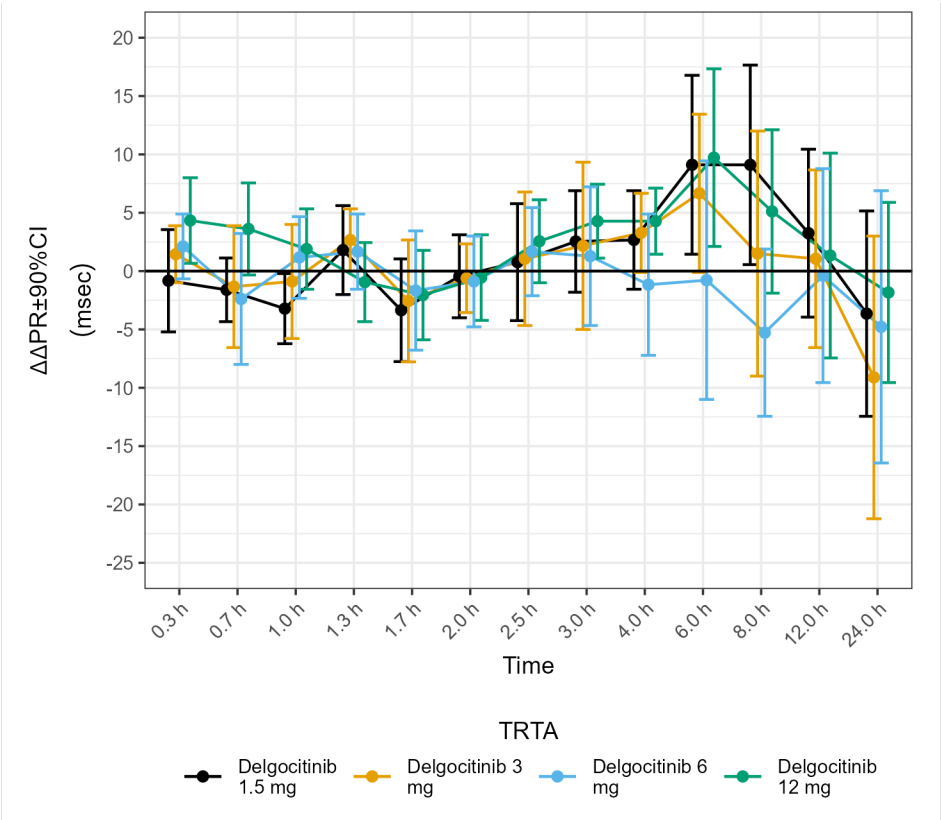
Figure 2. Median and 90% CI of ΔΔHR Time-Course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

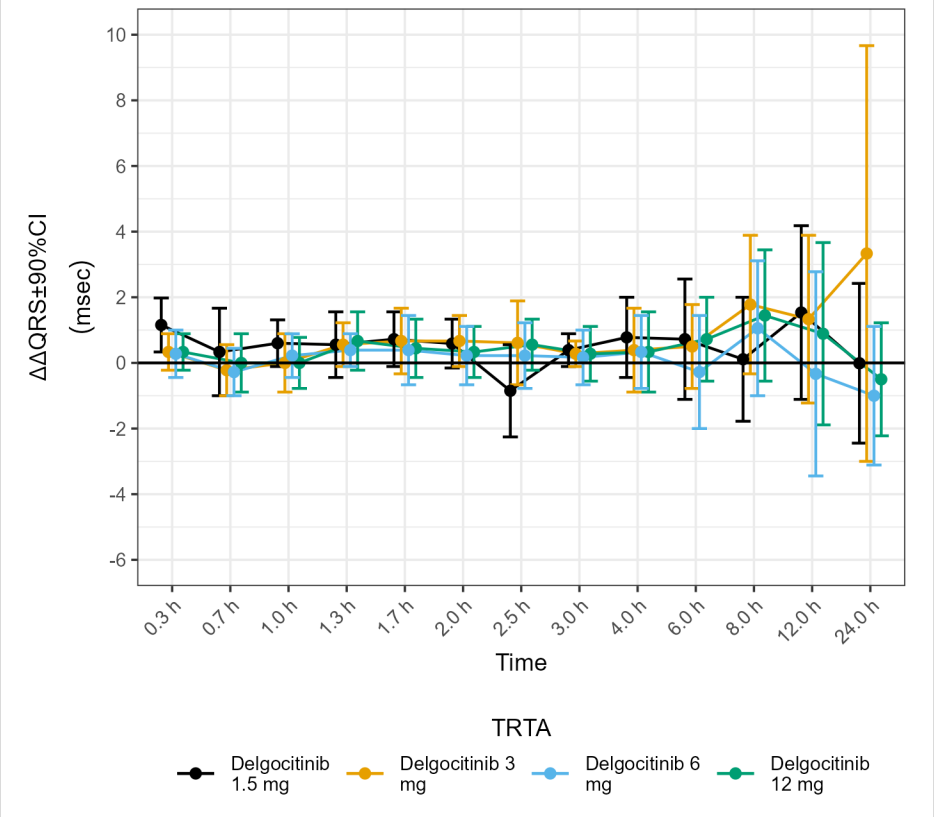
Figure 3. Median and 90% CI of ΔΔPR Time-Course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4. Median and 90% CI of ΔΔQRS Time-Course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs.

4.4.1 QTc

None of the subjects had QTcF value >450 msec. None of the subjects had ΔQTcF value >30 msec.

4.4.2 HR

None of the subjects had HR value >100 beats/min.

4.4.3 PR

None of the subjects had PR value >220 msec.

4.4.4 QRS

None of the subjects had QRS value >120 msec.

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK. A total of thirty-two (32) subjects, n= 8 for each dose group including 1.5, 3, 6 and 12 mg who had adequate pharmacokinetic data

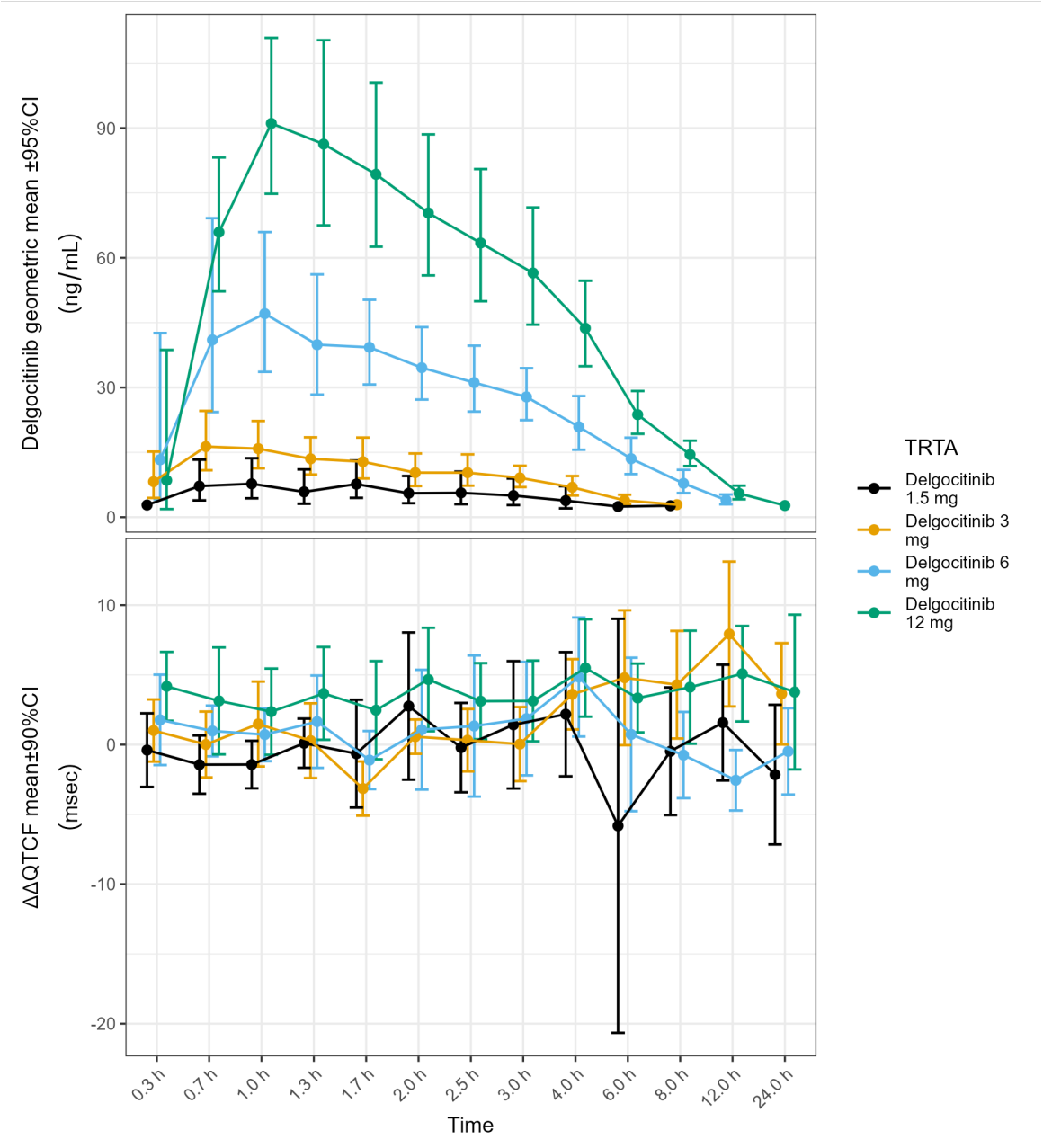
which contributed to the Delgocitinib pharmacokinetic analysis and constitute the pharmacokinetic analysis population. No subjects were excluded from the analysis.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔΔQTcF; and 3) absence of a nonlinear relationship.

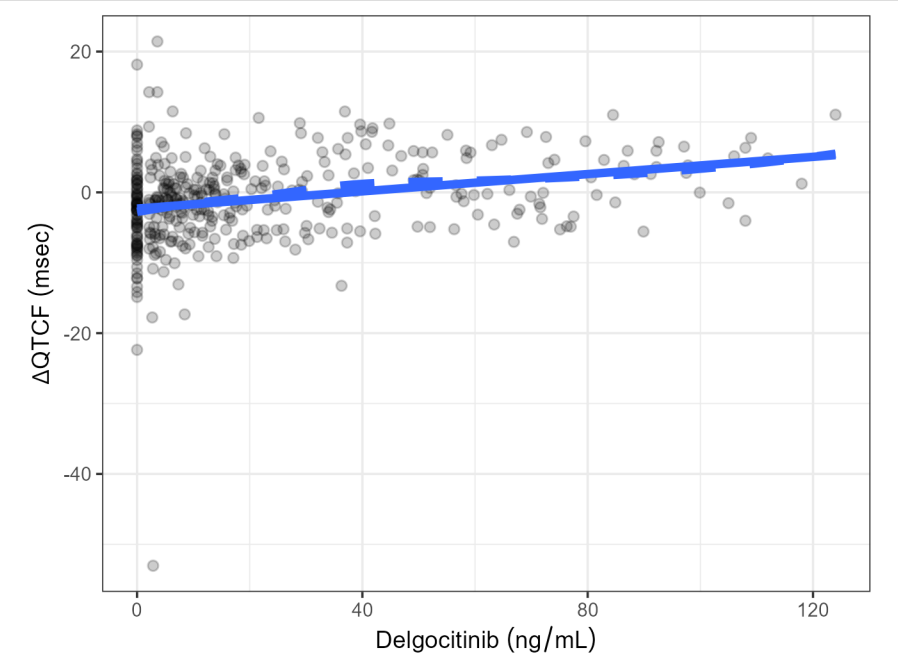
Figure 2 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and ΔΔQTcF. There seem to be a delay of 3 hours between C_{max} and the largest ΔΔQTcF for the 3 mg dose group. This is not observed with other doses. Since the ΔΔQTcF profiles are essentially flat, there is no dose-ΔΔQTcF relationship, and no 3 consecutive time points have means ΔΔQTcF >5 msec the observed delay in the 3 mg treatment group has no meaningful impact on characterizing linearity of the C-QTc relationship. Figure 6 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Figure 5. Time-Course of Drug Concentration (Top) and QTcF (Bottom)[1]



[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6. Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Since the white paper model did not converge, we applied the white paper model without random slope. Predictions from the concentration-QTcF model are provided in Table 4. The overall results of the reviewer analysis were comparable with the Applicant's predicted values.

Figure 7. Goodness-of-Fit Plot for QTcF

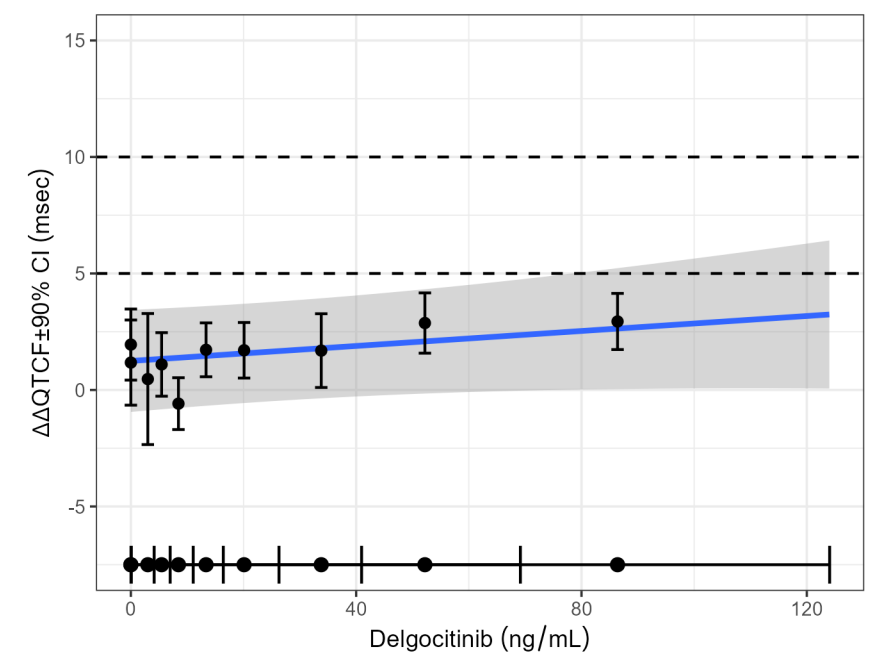


Table 3. Predictions From Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	Delgocitinib (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Highest therapeutic or clinical trial dosing regimen		0.5	1.3	(-0.9 to 3.4)
Delgocitinib 12 mg (Highest dose in QT assessment)	1	96.4	2.8	(0.1 to 5.5)

4.5.1.1 Assay Sensitivity

Assay sensitivity is demonstrated by 193-fold exposure margin between the highest dose in QTc assessment and the maximum recommended dosing regimen.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

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

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/s/

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