

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

220149Orig1s000

OTHER REVIEW(S)



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
ARIA Sufficiency Memorandum for Pregnancy Safety Concerns**

Date: March 16, 2026

Product Name: Icotyde (icotrokinra)

Application Type/Number: NDA 220149

Sponsor/Applicant: Janssen Biotech, Inc.

NEXUS Task Tracking Tool ID #: 2025-15580

Reviewer: Sally Peprah, PhD MSPH
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Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

NDA 220149 seeks approval for Icotyde (icotrokinra). Icotrokinra is 13-amino acid peptide composed of natural and unnatural amino acids. It is a small molecule interleukin-23 receptor (IL-23R) antagonist that binds directly to IL-23R and prevents IL-23p19 from engaging its receptor, thereby inhibiting proximal IL-23R signaling and downstream effector functions (e.g., cytokine secretion) involved in the pathogenesis of plaque psoriasis. The proposed indication for icotrokinra is for the treatment of adults and pediatric patients 12 years of age and older with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

1.2. Describe the Safety Concern

Psoriasis and Pregnancy

The Division of Pediatrics and Maternal Health (DPMH) in their Pregnancy and Lactation Labeling Review of icotrokinra¹ noted that psoriasis is a chronic inflammatory skin disease that affects about 3% of the global population. Although it can occur at any age, the incidence rate of psoriasis is highest in the age groups between 15 to 39 years and 50 to 69 years. Women and men are equally affected by psoriasis, and, among the female population, about 75% of patients develop the disease before reaching 40 years of age. Therefore, psoriasis commonly occurs in women of reproductive age. Pregnancy may impact the severity of the disease. Psoriasis improves in pregnancy in 40% to 60% of patients, worsens in 10% to 20%, and remains stable in the remainder. In the postpartum period, psoriasis severity remains the same or worsens in most patients. Topical treatment with emollients or moisturizers and a low- or medium-potency topical corticosteroid is the first-line intervention for pregnant patients with limited psoriasis. Ultraviolet B (UVB) phototherapy is the preferred treatment for pregnant patients with more severe symptoms. The effect of maternal psoriasis on pregnancy outcomes remains uncertain.

Nonclinical Experience

Based on the nonclinical review, in the Embryofetal Development (EFD) study conducted in rats, there were no adverse effects on embryofetal development observed at any doses tested, resulting in a no-observed-adverse-effect level (NOAEL) of 1000 mg/kg/day (297-times the maximum recommended human dose (MRHD) based on AUC). In the EFD study conducted in rabbits, pregnancy losses and an increased incidence of fetal skeletal malformation (fused ribs) were observed at 500 mg/kg/day (157-times the MRHD based on AUC), resulting in a NOAEL of 200 mg/kg/day (27-times the MRHD based on AUC). In a pre- and postnatal development (PPND) study, icotrokinra was administered orally to pregnant rats from implantation through weaning at doses up to 200 mg/kg/day (127-times the MRHD based on AUC). There were no maternal or reproductive developmental effects observed, and, thus, the NOAEL for maternal toxicity in F0 rats and pre- and postnatal developmental toxicity for F1 rats was 200 mg/kg/day.

¹ Division of Pediatrics and Maternal Health (DPMH) in their Pregnancy and Lactation Labeling Review of Icotyde (icotrokinra). Filed on December 17, 2025, under NDA 220149 (DARRTS Ref ID #: 5712684).



Review of Applicant's Pharmacovigilance Database

The Applicant reported five pregnancy cases with maternal exposure during the icotrokinra clinical development program. The birth outcomes included two live births, one elective abortion, and two unknown outcomes.^{2,3} Details of the pregnancy cases are summarized in DPMH's PLLR.⁴ Based on a review of these cases, DPMH concluded that "icotrokinra exposure during early pregnancy occurred in four of the five pregnancy cases, including the two cases resulting in healthy newborns with no reported congenital anomalies, and the two cases in which the pregnancy outcomes are unknown."⁵ There are insufficient pregnancy data from the clinical development program to inform the safety of icotrokinra use in pregnancy".⁶

Review of Literature

Applicant's Review of Literature

The Applicant did not perform a literature search.

FDA Review of Literature

DPMH conducted a search of published human studies in PubMed and Embase, using the search terms "icotrokinra" 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", "adverse pregnancy outcomes", "prematurity" and "low birth weight". No relevant publications were found.

In addition, DPMH conducted a search for icotrokinra in Micromedex⁷, ReproTox⁸, TERIS⁹, Shepard's¹⁰, and Briggs' Drugs in Pregnancy and Lactation: A reference guide to fetal and neonatal risk¹¹. No information was found.

On February 17, 2026, DEPI ran an independent search of the literature in PubMed using the search terms utilized by DPMH without restriction to a specific time period and no relevant articles were identified.

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

- ☐ Assess a known serious risk
- ☐ Assess signals of serious risk
- ☒ Identify unexpected serious risk when available data indicate potential for serious risk

² NDA 220149, Module 2.7.4, Summary of Clinical Safety and 5.3.5.3 Safety Narratives.

³ Applicant's response to DPMH October 14, 2025 IR. Submitted to NDA 220149 (eCTD Seq # 0015) on October 29, 2025.

⁴ See footnote 1.

⁵ Ibid.

⁶ Ibid.

⁷ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed by DPMH on October 07, 2025.

⁸ Reprotox Website: www.Reprotox.org. Accessed by DPMH on October 07, 2025.

⁹ TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed by DPMH on October 07, 2025.

¹⁰ Shepard's: A Catalog of Teratogenic Agents, accessed via Micromedex. Accessed by DPMH on October 07, 2025.

¹¹ Briggs GG, Freeman RK, Towers CV, Forinash AB. Briggs drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Lippincott Williams & Wilkins; 2021 Feb 18.



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

2.2. Regulatory Goal¹²

- ☐ Signal evaluation of specific outcome(s) – *implementation of a full epidemiological analysis to thoroughly evaluate the causal relationship between exposure to the medical product and the health outcome of interest.*
- ☐ Signal refinement of specific outcome(s) – *further investigation of an identified potential safety signal to determine whether evidence exists to support a relationship between the medical product exposure and the health outcome.*
- ☒ Signal identification – *detection of new and unexpected potential medical product safety concerns and may be for a **targeted or multiple** safety concern(s)/health outcome(s).*
 - ☐ Targeted evaluation of specific safety concern
 - ☒ Simultaneous identification of multiple infant and maternal adverse outcomes

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
- ☒ Other, please specify: A descriptive pregnancy safety study (DPSS), defined as a protocol-driven uncontrolled (single-arm) observational cohort study that collects detailed data for descriptive analysis. Specifically, the DPSS will assess pregnancy and maternal complications, and adverse effects on the developing fetus, neonate, and infant. In addition, infant outcomes through at least the first year of life will be assessed.

¹² Definitions adapted from: Robb MA, Racoosin JA, Sherman RE, Gross TP, Ball R, Reichman ME, Midthun K, Woodcock J. The US Food and Drug Administration's Sentinel Initiative: expanding the horizons of medical product safety. *Pharmacoepidemiol Drug Saf.* 2012 Jan;21 Suppl 1:9-11. doi: 10.1002/pds.2311. PMID: 22262587.



2.4. Identify the epidemiologic domain(s) where ARIA is not sufficient and provide a rationale on ARIA insufficiency for those epidemiologic domain(s). Then, provide an assessment of the overall ARIA sufficiency.

Epidemiologic Domain	Explanation on ARIA insufficiency
☐ Study Population	
☒ Exposures (and Comparators)	Exposures/Outcomes/Covariates: Descriptive pregnancy safety studies use targeted questionnaires to collect detailed and specific information about important confounders (e.g., body mass index and illicit drug use) and the timing of drug exposures in relation to well defined pregnancy outcomes. Data elements considered appropriate for collection by targeted questionnaire include study drug and concomitant drug exposures during pregnancy and results from newborn physical examinations. Data collection occurs at pre-determined intervals (e.g., at study enrollment, mid-point of pregnancy, estimated delivery date, 3-6 months postpartum, and 12 months postpartum). Well-documented case narratives that include detailed clinical information acquired directly from primary sources (e.g., medical records and providers) facilitate causal assessment of relationships between drug exposures during pregnancy and adverse outcomes from pregnancy. ARIA precludes use of targeted questionnaires for data collection.
☒ Outcomes	
☒ Covariates	
☐ Analytic Tools	
Overall ARIA sufficiency determination	
☒ Insufficient	
☐ Sufficient	

2.5. If ARIA is deemed insufficient, include the PMR language to be included in the approval letter.

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Icotyde (icotrokinra) during pregnancy to assess risk of pregnancy and maternal complications, and adverse effects on the developing fetus, neonate, and infant. Assess infant outcomes through at least the first year of life. The minimum number of patients will be specified in the protocol.

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/s/

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DIVISION of Dermatology and Dentistry
Associate Director for Labeling Review of the
Prescribing Information

Product Title	ICOTYDE (icotrokinra) tablets, for oral use
Applicant	Janssen Biotech, Inc.
Application/Supplement Number	NDA 220149
Type of Application/Submission ¹	New drug application
Is Proposed Labeling in “Old” Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Proposed Indication(s) (if applicable)	TRADENAME is an interleukin-23 (IL-23) receptor antagonist peptide indicated for the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy.
Approved Indication(s)	ICOTYDE is an interleukin-23 (IL-23) receptor antagonist indicated for the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who weigh at least 40 kg who are candidates for systemic therapy or phototherapy.
Date FDA Received Application	July 18, 2025
Review Classification (Priority/Standard)	Priority
Action Goal Date	March 18, 2026
Review Date	March 16, 2026
Reviewer	Matthew White

INTRODUCTION

This Associate Director for Labeling (ADL) review is for new NDA 220149, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NDA 220149 for ICOTYDE (icotrokinra) tablets. ICOTYDE is an interleukin-23 (IL-23) receptor antagonist indicated for the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who weigh at least 40 kg who are candidates for systemic therapy or phototherapy.

LABELING HISTORY

Icotrokinra is a first-in-class oral peptide that selectively binds to the IL-23R to competitively antagonize the binding of IL-23.

A list of approved product labeling considered for this review is below.

Appication Number Product Name	Mechanism of Action	Indication
BLA 761061 TREMFA (guselkumab) injection, for subcutaneous or intravenous use	Interleukin-23 antagonist	For the treatment of: - adults and pediatric patients 6 years of age and older who also weigh at least 40 kg with moderate-to-severe plaque psoriasis and who are candidates for systemic therapy or phototherapy. - adults and pediatric patients 6 years of age and older who also weigh at least 40 kg with active psoriatic arthritis. - adults with moderately to severely active ulcerative colitis. - adults with moderately to severely active Crohn's disease.
BLA 761105; 761262 SKYRIZI (risankizumab-rzaa) injection, for subcutaneous or intravenous use	Interleukin-23 antagonist	For the treatment of: - moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. - active psoriatic arthritis in adults. - moderately to severely active Crohn's disease in adults. - moderately to severely active ulcerative colitis in adults.
BLA 761067 ILUMYA (tildrakizumab-asmn) injection, for subcutaneous use	Interleukin-23 antagonist	For the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
BLA 761279 OMVOH (mirikizumab-mrkz) injection, for intravenous or subcutaneous use	Interleukin-23 antagonist	for the treatment of: - moderately to severely active ulcerative colitis in adults - moderately to severely active Crohn's disease in adults
STELARA (ustekinumab) injection, for subcutaneous or intravenous use	Interleukin-12 and -23 antagonist	For the treatment of Adult patients with: - moderate to severe plaque psoriasis (PsO)who are candidates for phototherapy or systemic therapy. - active psoriatic arthritis (PsA). (1.2) - moderately to severely active Crohn's disease (CD). - moderately to severely active ulcerative colitis.(1.4)

The Applicant submitted the proposed labeling on July 18, 2025. To start labeling discussions, Carton and Container labeling comments were conveyed to the Applicant on December 18, 2025. The Agency proposed USPI and Patient Information were conveyed to the Applicant on January 30, 2026. Agreed upon labeling was submitted on March 14, 2026.

DMEPA 1 completed their consult review on October 27, 2025. Labeling recommendations for the USPI and Carton and Container labeling are included in this review. A memo to this review was completed on December 31, 2025.

The Interdisciplinary Review Team for Cardiac Safety Studies completed their consult review on October 22, 2025. Labeling recommendations for subsection 12.2 are included in this review.

The Maternal Health Team completed their consult review on . Labeling recommendations for subsections 8.1, 8.2 and section 17 are included in this review.

The Division of Gastroenterology completed their consult review on . Labeling recommendations for section 5 and subsection 6.1 are included in this review.

OPDP completed their consult review on January 22, 2026. Labeling recommendations for the USPI and Carton and Container labeling are included in this review.

The Patient Labeling Team completed their review on January 22, 2026. Labeling recommendations for the Patient Information are included in this review.

REVIEW

This review describes the updates implemented to the PI to help ensure that it:

- Is compliant with Physician Labeling Rule (PLR) [including the Pregnancy and Lactation Labeling Rule (PLLR)] requirements,²
- Is consistent with labeling guidance recommendations³ and with CDER labeling policies, as appropriate,
- Conveys the essential scientific information needed for safe and effective use of the drug,
- Is clinically meaningful and scientifically accurate,
- Is a useful communication tool for health care practitioners, and
- Is consistent with other PI with the same active moiety, drug class, or similar indication, as appropriate

The following groups provided input to the review of the labeling:

Regulatory Project Manager	Tina Whang, PharmD
Nonclinical Reviewer	Yen-Ming Chan, PhD
Nonclinical Supervisor	Jianyong Wang, MD, PhD
Office of Clinical Pharmacology Reviewer(s)	Youssef Mousa, PhD
Office of Clinical Pharmacology Team Leader(s)	Chinmay Shukla, PhD
Clinical Reviewer	Kathleen Butler, MD
Clinical Team Leader	Mary Kim, MD
Statistical Reviewers	Daeyoung Lim, PhD Youn Kyeong Chang, MS
Statistical Secondary Reviewer	Kathleen Fritsch, PhD
Cross-Disciplinary Team Leader	Mary Kim, MD
Deputy Division Director (DPT-II)	Carmen Booker, PhD

² See [January 2006 Physician Labeling Rule](#); 21 CFR [201.56](#) and [201.57](#); and [December 2014 Pregnancy and Lactation Labeling Rule](#) (the PLLR amended the PLR regulations). For applications with labeling in non-PLR “old” format, see 21 CFR [201.56\(a\) and \(e\)](#) and [201.80](#).

³ See [Prescription Drug Labeling Resources](#) website for PLR labeling guidances. When final, guidances represent the FDA’s current thinking on a topic. Applicants can use an alternative approach if it satisfies statutory and regulatory requirements.

Division Director (OCP)	Jianmeng Chen, MD, PhD
Division Director or Division Signatory (DDD)	Jill Lindstrom, MD, FAAD, Tatiana Oussova, MD, MPH
Deputy Director for Safety (DDD)	Tatiana Oussova, MD, MPH
Office Director (or Designated Signatory Authority)	Nikolay Nikolov, MD

Additional Reviewers of Application

OPQ	Biopharm: Kamrun Nahar, PhD/Tapash Ghosh, PhD DP: Austin Yu, PhD/Baoqing Ma, PhD DS: Sophie Rubashkin, PhD/Lawrence Perez, PhD EA: Xiaoqin Wu, PhD/ James Laurenson, PhD Manufacturing/Facility: Md Abdullah Mahmud, PhD/Zhaoyang Meng, PhD RBPM: Esther Jones, BSN, RN/Janell Artis, PharmD
Pharmacometrics	Ye Xiong, PhD/Jiang Liu, PhD
Immunogenicity	Bruce Huang, PhD/Seth Thacker, PhD
QT-IRT	Eliford Kitabi, PhD/Sonia Pahwa, PhD/Lars Johannesen, MS/Christine Garnett, PharmD
DMPP	Jessica Chung, PharmD, MS/Barbara Fuller, MSN, BSN, RN/Laurie Buonaccorsi, PharmD
OPDP	Montherson Saint Juste, PharmD/Eunice Chung-Davies, PharmD, MBA/James Dvorsky, PharmD, MPH
DPMH - Maternal	Kerry Shaab, MD/Tamara Johnson, MD
DPMH - Pediatrics	Karen Fratantoni, MD/Shetarra Walker, MD/George Greeley, MS, MBA /John Alexander, MD, MPH DPMH RPMs: Aniya Diggs/Anissa Davis-Williams
Division of Gastroenterology	Jaime Wolfe, MD/Irena Lavine/MD/Juli Tomaino, MD, MS

The attached PI shows differences between the Applicant's proposed PI, received July 18, 2025, and the Agreed upon PI, received March 14, 2026.

This review includes a high-level summary of the rationale for major changes to the PI as compared with the Applicant's draft PI (see the table below).

Full Prescribing Information Sections¹	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)²
1 INDICATIONS AND USAGE	Included a weight restriction (at least 40 kg) for pediatric patients 12 years of age and older. The pediatric use regulatory statements in the Pediatric Use subsection and the recommended dosage statements in the D&A section state that the conditions of use for ICOTYDE are only for pediatric patients 12 years of age and older who weigh at least 40 kg.

	The conditions of use in Sections 1 and 2 and subsection 8.4 should be consistent. Thus, if there is a weight restriction for pediatric patients then this restriction should be in all of the appropriate sections/subsection of labeling.
2 DOSAGE AND ADMINISTRATION	Under the subheading <u>Recommended Evaluation and Immunizations Prior to Treatment Initiation</u>, included instructions to consider evaluating patients for TB prior to initiating treatment with ICOTYDE and instructions to complete all age-appropriate vaccinations according to current immunization guidelines. This is consistent with instructions included in other IL-23 antagonist labeling (TREMFYA, SKYRIZI). It is also consistent with draft guidance for industry: <i>Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format</i> (January 2023) which states, when certain dosage- and administration-related information is particularly critical to the safe and effective use of the drug (e.g., lack of knowledge of the information or nonadherence to a recommendation could have serious consequences for patients), this information should appear as the first information presented within the DOSAGE AND ADMINISTRATION section.
4 CONTRAINDICATIONS	No major changes were made.
5 WARNINGS AND PRECAUTIONS	Added a Warning and Precaution for Infections given the mechanism of action for IL-23 antagonism and potential risk of serious infection. Added a Warning and Precaution for Tuberculosis. The clinical program under this NDA was not specifically designed to reliably rule out this risk. We acknowledge the shifting viewpoint in the dermatology community regarding tuberculosis testing for IL-23 antagonists prior to starting treatment. This shifting viewpoint for the IL-23 antagonists is being considered actively within the Agency. Under the Warning and Precaution for Immunizations, included the statement, “Medications that interact with the immune system may increase the risk of infection following administration of live vaccines.” to reflect current labeling practices. Refer to the Clinical section of the unireview for additional information.
6 ADVERSE REACTIONS	Under subsection 6.1 Clinical Trials Experience, included the following most common $\geq 1\%$ adverse reactions: headache, nausea, Cough, fungal infection, and fatigue. Included the following less common ($<1\%$) adverse reactions: gastritis, abdominal discomfort, and one fatal case involving upper gastrointestinal bleeding in a subject with underlying risk factors.

	Refer to the Clinical section of the unireview and consult review from the Division of Gastroenterology for additional information.
8 USE IN SPECIFIC POPULATIONS	Subsection 8.1 Pregnancy and 8.2 Lactation were modified per the recommendations of the Nonclinical review team and the Division of Pediatrics and Maternal Health. Refer to the nonclinical sections of the unireview and the MHT review for additional information. Under subsection 8.4 Pediatric Use, revised the pediatric indication statement for consistency with Sections 1 and 2. The summary of the basis for approval for pediatric patients was modified to state that the approval was in part on extrapolation from clinical trials in adult subjects. Under subsection 8.6 Renal Impairment, included instructions to monitor for potential adverse reactions when ICOTYDE is used in patients with an estimated glomerular filtration rate (eGFR) <60 mL/min. Removed (b) (4). Refer to the Clinical Pharmacology section of the unireview for additional information.
10 OVERDOSAGE	Removed the subsection because it did not include specific overdose data that would be useful to the HCP.
12 CLINICAL PHARMACOLOGY	Revised subsection 12.1 based on the recommendations of the Nonclinical review team. Removed (b) (4). Inclusion of Kd was deemed acceptable. Refer to the Nonclinical section of the unireview for additional information. Revised subsection 12.2 Pharmacodynamics, subsection 12.3 Pharmacokinetics, and 12.6 Immunogenicity based on the recommendations of the Clinical Pharmacology Review team. Refer to the Clinical Pharmacology section of the unireview for additional information.
13 NONCLINICAL TOXICOLOGY	Revised subsection 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility based on the recommendations of the Nonclinical review team. Refer to the Nonclinical section of the unireview for additional information
14 CLINICAL STUDIES	Revised the presentation of the efficacy results based on the recommendations of the Biostatistics Review team. Refer to the Biostatistics section of the unireview for additional information.
17 PATIENT COUNSELING INFORMATION	References to the Patient Information were changed to Medication Guide due to the risk of infections and for consistency with the other IL-23 antagonists.

	Included subheadings for Infections and Tuberculosis to correspond with changes made to Section 5. Included a Pregnancy subheading to correspond with edits made to subsection 5.1.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	In Section 11, included more physical attributes (isoelectric point, solubility at different pH ranges) of the API. Included an equivalency statement for the hydrochloride salt.

¹ The product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.

² For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved. The finalized PI was compared to the currently approved PI and the Applicant's draft PI).

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/s/

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Division of Gastroenterology (DG) Consult Addendum

Date: March 11, 2026

DG consult memo: December 26, 2025

To: Kathleen Butler, MD, Medical Officer, Division of Dermatology and Dental (DDD)

Mary Kim, MD, Lead Physician, DDD

From: Jaime Wolfe, MD, Medical Officer, DG

Through: Irena Lavine, MD, Acting Lead Physician, DG

Juli Tomaino, MD, MS, Deputy Division Director, DG

Drug: Icotrokinra, NDA 220149

Proposed indication: Icotrokinra is an orally administered cyclic peptide under development for the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy.

Updated Regulatory history:

The Division of Gastroenterology (DG) clinical team continues to collaborate with the Division of Dermatology and Dental (DDD) clinical team during labeling negotiations with the Applicant on the potential risk of gastrointestinal (GI) bleeding with the use of interleukin-23 receptor (IL23R) antagonist, icotrokinra, based on the occurrence of four adverse events during the clinical trials: (1) esophageal variceal bleeding (fatal), (2) nonspecific hematemesis (fatal), (3) rectal bleeding, and (4) gastric ulcer perforation. Refer to the DG consult memo, dated December 26, 2025, for discussion of these cases, assessment of the potential causal relationship between the adverse events and icotrokinra use, and DG's labeling recommendations.

FDA issued an information request (IR), dated October 17, 2026, for the Applicant to provide additional details regarding the serious GI events. In their response the Applicant indicated that one of the fatal cases with "nonspecific hematemesis" (subject (b) (6) [case 2 in the consult below]) was reported by family to have "not a big amount" of blood surrounding the time to death. In addition, the subject had underlying electrocardiogram abnormalities and received a concomitant medication

that is associated with cardiac conduction abnormalities in the days leading up the fatal event (refer to Applicant's response, received January 8, 2026, to IR issued by FDA). Therefore, the case lacks sufficient detail to conclude that the fatal outcome was related to GI bleeding.

FDA sent labeling comments on January 30, 2026, recommending the addition of a Warnings and Precautions, 5.1 Upper Gastrointestinal Bleeding based on the rationale that it is important to inform patients and providers of these serious events which they may not expect in the intended patient population with psoriasis; and although there were confounding factors in all cases, uncertainty remains regarding whether icotrokinra could have contributed to the GI bleeding events and the gastric ulcer perforation. This is the first oral drug in class and while we acknowledge that GI irritation was not observed in the nonclinical studies, it remains unknown whether icotrokinra exacerbated the serious GI events in the four subjects with underlying predisposition to GI bleeding and ulcer perforation. In addition, FDA recommended the inclusion of the four serious GI adverse events in section 6.1 (b) (4)

The Applicant provided a response to FDA's labeling comments on February 6, 2026, proposing that labeling is not warranted in Section 5 Warnings and Precautions or Section 6 Adverse Reactions based on the Applicant's report that the incidence rate and types of GI AEs observed in the icotrokinra program are consistent with the rates and types of events in the overall psoriasis population; the presence of confounding factors for the serious cases; the lack of a common clinical pattern or mechanism; the lack of biological plausibility; and a GI safety profile from the icotrokinra psoriasis program that does not indicate an imbalance in related GI events between drug and placebo groups.

FDA responded with labeling comments sent on February 27, 2026, and agreed to remove upper GI bleeding from the Warnings and Precautions section of the icotrokinra label given the multiple confounding factors present in each of the cases, resulting in a significant amount of uncertainty as to whether icotrokinra increases the risk of GI bleeding or other serious GI adverse events (e.g., ulcer perforation). However, FDA retained these events in Section 6.1 (b) (4), as a causal association to the study drug cannot be entirely ruled out. Furthermore, given the seriousness of the cases with two cases resulting in fatality, the FDA included the cases in the label.

The Applicant submitted a response on March 4, 2026, to FDA's labeling comments, sent on February 27, 2026, including additional rationale to support their disagreement with the inclusion of GI bleeding (upper gastrointestinal bleeding, nonspecific hematemesis, rectal bleeding) and gastric ulcer perforation as adverse reactions in the United States Prescribing Information (USPI), including:

- Additional exposure data from psoriasis (PsO) and psoriatic arthritis (PsA) icotrokinra studies: Additional 2,041 person-years of icotrokinra safety data from the Phase 2 and Phase 3 psoriatic program (including blinded data from the ongoing

Phase 3 psoriasis study PSO3006) and ongoing blinded PsA Phase 3 studies (PSA3001 and PSA3002) in which no new cases of serious GI bleeding or ulcerative events have occurred (Appendix 3).

- Clinicaltrials.gov data from 223 psoriasis studies including 137,122 person-years, and psoriasis registries data (PSOLAR, 89,321 person-years; CorEvitas, 18,224.9 person-years) showing rates of serious GI bleeding (new data) and GI events of interest similar to the observed rates in the icotrokinra program (Table 4, Appendix 4).¹

DG's assessment:

There remains a significant amount of uncertainty regarding the relatedness of serious GI events to icotrokinra use. The additional data provided by the Applicant does not indicate the presence of a safety signal for serious GI bleeding with icotrokinra use across the psoriasis development program and the Applicant reports that the rates of serious GI bleeding and ulceration in the icotrokinra program are consistent with that expected in the psoriasis studies and registries (although there is some variation in reported rates in the literature). We also acknowledge the presence of multiple confounding factors in the four cases of serious GI events (i.e., upper GI bleeding, nonspecific hematemesis,² rectal hemorrhage, and gastric ulcer perforation), the clinical heterogeneity of the events (e.g., types of events, duration of therapy with icotrokinra), and the lack of a known pharmacologic mechanism associated with icotrokinra or other IL-23R antagonists.

However, given the severity of the events (including two fatalities), the lack of data to better inform the potential risk(s) conferred by icotrokinra given that it is the first oral drug in class, as well as the uncertainty as to whether icotrokinra may increase the propensity for gastrointestinal irritation or bleeding in patients with underlying risks for bleeding or ulcers, it would be reasonable to include the events descriptively in Section 6 of the USPI. We recommend noting in the label that the cases were confounded and the subjects had underlying reasons for bleeding or ulcer perforation. In addition, we recommend noting in the label that a causal association between icotrokinra and these reactions has not been established. Alternatively, given that the rate of GI bleeding identified is lower than the expected rate in the general population, the presence of multiple confounding factors, and the clinical heterogeneity (e.g., types of events, duration of therapy with icotrokinra) in the four cases of serious GI events (i.e., upper GI variceal bleeding, nonspecific hematemesis, rectal hemorrhage, and gastric perforation), it would be reasonable not to describe the GI events in the label at this time. Postmarketing surveillance appears reasonable to further assess this unexpected potential risk.

¹ From the Applicant, "Response to 27 February 2026-PSO-Labeling-Comments," dated March 4, 2026

² GI event in subject (b) (6) described as "nonspecific hematemesis" due to lack of details related to the case description.

We also agree with the Applicant's proposal to implement enhanced pharmacovigilance monitoring of serious GI adverse events including GI bleeding, ulceration, and perforation, and to establish an external, blinded adjudication committee to systematically review potential serious events.

Correction to DG's original consult memo:

DG would like to make a correction to our original response to Question 1 in the "DG Consult Memo," dated December 26, 2025, as noted by the changes in text identified in bold and strikeout shown below:

Question 1: Is this observation within the expected rate of fatal or serious upper GI bleed in this study population size, and specifically are there any concerns with 2 deaths and 1 SAE all occurring on active drug vs no cases on placebo?

*Death from upper GI bleeding has been reported in the literature to occur with an annual incidence of approximately 80 to 150 per 100,000 population, with an estimated mortality rate of 2% to 10% (Stanley, 2019). Based on the pooled safety population of 1864 subjects across the four clinical trials of the phase 3 program in patients with psoriasis (1296 subjects who received icotrokinra and 568 subjects who received placebo), the two fatalities that were attributed to upper GI bleeding and the SAE of acute perforated ulcer with peritonitis represented 2/1864 (0.11%) subjects and 1/1864 (0.05%) subject, respectively. Therefore, the rate of GI bleeding identified in the icotrokinra PsO development program is **lower than** the expected rate in the general population. ~~of the same size; however, the rate of fatal GI bleeding exceeds the expected rate in the general population of the same size.~~*

Division of Gastroenterology Consult Memo

Date: December 23, 2025

To: Kathleen Butler, MD, Medical Officer, Division of Dermatology and Dental (DDD)
Mary Kim, MD, Lead Physician, DDD

From: Jaime Wolfe, MD, Medical Officer, Division of Gastroenterology (DG)

Through: Irena Lavine, MD, Acting Lead Physician, DG
Juli Tomaino, MD, MS, Deputy Division Director, DG

Subject: Evaluation of a potential safety risk of gastrointestinal bleeding with icotrokinra

Drug Product(s):	Name	Application	Application Holder/Sponsor ¹
	Icotrokinra	NDA 220149	Janssen Biotech, Inc.

Proposed Product Indication:	Icotrokinra is an orally administered cyclic peptide under development for the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy.
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Date Requested: July 18, 2025

I. Consultation Request

The Division of Dermatology and Dental (DDD) requests the Division of Gastroenterology (DG) consultation to evaluate potential safety risks of gastrointestinal (GI) bleeding with use of icotrokinra in patients with moderate to severe plaque psoriasis, including two deaths attributed to upper GI bleeding and two serious adverse events (SAEs; perforated gastric ulcer with peritonitis and rectal hemorrhage), all of which occurred on study drug.

Specifically, the DG team was asked to provide input on the following:

1. Is this observation within the expected rate of fatal or serious upper GI bleed in this study population size, and specifically are there any concerns with 2 deaths and 1 SAE all occurring on active drug vs no cases on placebo?

¹ In the body of this review, the terms "Sponsor" and "Applicant" will refer to Janssen Biotech, Inc., unless otherwise indicated.

2. Could you please comment on the risk factors these cases had for upper GI bleed vs known risk factors in this population for UGI bleed? In particular, the Sponsor attributes increased risk of upper GI bleed from psychiatric medications in the fatal case of the 49-year old male was not aligned with review of the adverse effect profile of those drugs (which seem primarily to be associated with nausea and vomiting).
3. Any further investigations or monitoring recommended for UGI bleed or GI adverse events?

Materials reviewed for this consultation include:

Scientific literature, Applicant's submission (SDN 1) dated July 18, 2025, safety reports submitted through the FDA Adverse Event Reporting System (FAERS), labeling and/or safety data and other select documents from the NDA submissions for approved IL-23 receptor antagonists.

II. Background

Icotrokinra (JNJ-77242113) is a first-in-class, orally administered peptide that selectively binds to the IL-23 receptor (IL-23R) to competitively antagonize the binding of IL-23.² Icotrokinra is a new molecular entity (NME) in development for the treatment of moderate-to-severe plaque psoriasis, psoriatic arthritis, moderately to severely active ulcerative colitis, and moderately to severely active Crohn's disease.

This consult is being conducted as part of a New Drug Application (NDA) for icotrokinra for the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy. DDD has requested that DG evaluate the risk factors for GI bleeding in the three cases (two deaths and one SAE) who experienced upper GI bleeding and received the study drug. Of note, the 120-day safety update (submitted by the Applicant on November 12, 2025) included an additional SAE of lower GI bleeding (PT: rectal hemorrhage, reported with the nonserious adverse events [AEs] of diverticulum and hemorrhoids).

IL-23 antagonists have been used to treat a variety of chronic inflammatory diseases. Presently, there are several IL-23 antagonists administered via subcutaneous or intravenous routes that are approved for the treatment of plaque psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease. There is no known association between IL-23 antagonists and GI bleeding, and there is not a plausible biologic explanation to suspect that the drug may have caused the events.

Nonclinical data

Per discussion with the DDD clinical team, the nonclinical studies did not indicate signs of gastrointestinal toxicity in rats and monkeys with a 60-fold margin over human exposure.

Clinical data

² From Applicant, NDA 220149 *Clinical Overview*.

The safety and tolerability of icotrokinra has been evaluated in four phase 3, adequate and well-controlled, randomized trials in subjects with plaque psoriasis:³

1. PSO3001- Multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of icotrokinra 200 mg once daily; includes adults and adolescents (≥ 12 years to < 18 years and weighing ≥ 40 kg) with a total BSA $\geq 10\%$, total PASI ≥ 12 , and total IGA ≥ 3 who were candidates for phototherapy or systemic treatment. Screened: 837, randomized 684 (618 adults and 66 adolescents).
2. PSO3002- Multicenter, randomized, double-blind, placebo- and comparator-controlled (deucravacitinib 6 mg) trial to evaluate the efficacy and safety of icotrokinra vs. deucravacitinib vs. placebo to demonstrate superiority to deucravacitinib; adults only with a total body surface area (BSA) $\geq 10\%$, total Psoriasis Area and Severity Index (PASI) ≥ 12 , and total Investigator's Global Assessment (IGA) ≥ 3 who were candidates for phototherapy or systemic treatment. Planned: 750, screened 986, randomized 774.
3. PSO3003- Multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of icotrokinra 200 mg once daily dose; includes adults and adolescents (≥ 12 years to < 18 years and weighing ≥ 40 kg); inclusion of subjects with plaque psoriasis with at least moderate special area (scalp, genital, and/or hand/foot) involvement defined as overall BSA $\geq 1\%$, IGA score ≥ 2 , and at least one of the following: scalp-specific Investigator's Global Assessment [ss-IGA] ≥ 3 , and/or Physician Global Assessment of hands and/or feet [hf-PGA] ≥ 3 . Planned 300, screened 366, randomized 311.
4. PSO3004- Multicenter, randomized, double-blind, placebo- and comparator controlled (deucravacitinib 6 mg) trial to evaluate the efficacy and safety of icotrokinra vs. deucravacitinib vs. placebo to demonstrate superiority to deucravacitinib; adults only with PASI ≥ 12 , IGA ≥ 3 , and BSA $\geq 10\%$, who were candidates for phototherapy or systemic treatment. Planned 675, screened 917, randomized 731.

Overall, 2,367 subjects ≥ 12 years of age with plaque psoriasis were exposed to icotrokinra; 1,849 (78.1%) were exposed for at least 6 months, and 648 (27.4%) were exposed for at least 1 year in pooled PSO3001, PSO3002, PSO3003, and PSO3004. A total of 72 adolescent subjects, ≥ 12 to < 18 years of age, were exposed to icotrokinra.⁴

Icotrokinra is not approved or marketed in any country.

III. Case Narratives and Assessments

There were two deaths attributed to upper gastrointestinal bleeding and one SAE of acute gastric ulcer perforation with peritonitis reported in the controlled clinical trials in subjects that received

³ From NDA 220149 Clinical Filing Review, Dr. Kathleen Butler, September 12, 2025.

⁴ From NDA 220149, Summary of Clinical Safety, Section 1.2.

icotrokinra. In addition, the 120-day safety update included an SAE of lower gastrointestinal bleeding (PT: rectal hemorrhage).

Based on the narratives provided in the initial NDA submission, it was not clear that these events could be reasonably attributed to risk factors related to the patients' medical and/or lifestyle history (e.g., concomitant medications, alcohol intake). Therefore, the team sent an information request (IR) to the Applicant on October 17, 2025, to submit the following information:

1. A summary table of the proportion of subjects who experienced the gastrointestinal-related adverse events specified below. Provide the data for the icotrokinra groups by dose vs. placebo that have been reported for the psoriasis and psoriatic arthritis development programs for icotrokinra. If data are available from the ulcerative colitis and Crohn's disease programs, provide a similar table.

- Gastritis
- Peptic ulcer disease
- Gastrointestinal bleed/hemorrhage
- Hematemesis/blood in vomit
- Melena/tarry stool/black stool
- Bloody stool
- Gastrointestinal ulcer
- Gastrointestinal perforation
- Mallory-Weiss tear
- Peritonitis
- Thrombocytopenia

2. Additional medical history for subjects (b) (6)

including the following or lack thereof:

- History of gastrointestinal disease and/or risks factors for gastrointestinal bleeding, including: gastritis; gastric and/or intestinal ulcer; gastrointestinal bleeding (e.g., hematemesis, melena); chronic vomiting; chronic abdominal pain; thrombocytopenia; anemia; Helicobacter pylori
- History of endoscopy (upper and colonoscopy) including indication for Procedure
- History of non-steroidal anti-inflammatory (NSAID), corticosteroid, and/or acetylsalicylic acid use
- Autopsy report

Applicant's IR response, received October 24, 2025

1. The Applicant indicated that the icotrokinra clinical development program includes studies in healthy volunteers (phase 1), subjects with plaque psoriasis (PsO; phase 2

and 3), ulcerative colitis (UC; phase 2), and psoriatic arthritis (phase 3). Across seven placebo-controlled studies in subjects with PsO (phase 2 and 3) and UC (phase 2) through Week 16 (with 1,762 icotrokinra-treated subjects and 698 placebo-treated subjects), a total of 7/1,762 (0.4%) subjects who received icotrokinra and 1/698 (0.1%) subjects who received placebo reported at least one of the adverse events (12 PTs above) identified for this query. Of these 7 subjects treated with icotrokinra, the reported AEs included gastritis (6), hematemesis (1), and the 1 subject who received placebo reported the AE of peptic ulcer (1).

The Applicant reported that no cases of the following selected AEs were reported in subjects who received icotrokinra through Week 16: peptic ulcer, gastrointestinal hemorrhage, melaena, feces discolored, hematochezia, gastrointestinal ulcer, gastrointestinal perforation, Mallory-Weiss syndrome, peritonitis, or thrombocytopenia. Furthermore, none of the selected AEs were identified at higher doses (300 mg, 400 mg, or 1,000 mg); thus no dose-response relationship was identified.

Reviewer Comment:

Although the placebo sample size is small (as compared to the icotrokinra sample size), there is not an imbalance in the number of subjects who reported at least one of the specified GI related AEs between the icotrokinra and placebo arms in the seven placebo-controlled studies in subjects with psoriasis and UC. Of note, based on the results reported by the Applicant in response to the IR, there were no occurrences of serious GI events, including GI bleeding, gastrointestinal ulcer, or gastrointestinal perforation, across the placebo-controlled trials in the icotrokinra development programs other than the 2 deaths and 1 SAE of gastric ulcer perforation that are the focus of this consult. We note that the analyses included in this response from the Applicant do not include data from the 120-day safety update.

2. Based on the information provided in the NDA submission and the IR above, the four cases of GI bleeding are summarized below:

Case 1. (b) (6) (Death)

A 49-year-old male with a history of parkinsonism, obesity, hypertension, bipolar disorder, intellectual disability, and abnormal ECG Q wave who experienced a fatal event associated with hematemesis on Study Day 17. The subject developed an SAE of tremor on Study Day 3; due to worsening tremor the study drug was discontinued on Study Day 12, with some improvement in neurological symptoms. The subject was hospitalized on Study Day 17 for the SAE of hematemesis. According to the CSR, the subject reportedly “*woke up oriented and talking, had breakfast and a juice in the middle of the morning, but had little acceptance of the lunch meal. At 3:00 PM, after the afternoon snack, the first dark colored emetic episode occurred, followed by two more dark colored, jet emetic episodes. The [participant] suffered two*

cardiorespiratory arrests, evolving to death (Source: CIOMS).” An autopsy report was not able to be obtained, however, a death certificate identified the cause of death as “*Part I: A: Upper digestive hemorrhage, B: Gastroesophageal varices rupture. Part II: psoriasis - Parkinson's disease.*”⁵

No known history of alcohol or smoking. Concomitant medications included benserazide hydrochloride/levodopa, lithium carbonate, aripiprazole, primidone, and losartan. Family history included intestinal cancer in his older brother. No reported subject history of gastritis, gastric/intestinal ulcer, GI bleeding, chronic vomiting, chronic abdominal pain, thrombocytopenia, anemia, or *Helicobacter pylori* infection. The investigator did not report a history of endoscopy or use of NSAIDs, acetylsalicylic acid, or corticosteroids.

Reviewer Comment:

The subject’s cause of death was determined to be bleeding from ruptured gastroesophageal varices. It is unlikely that the variceal bleeding was related to icotrokinra use as gastroesophageal varices typically develop over a longer period of time compared to the subject’s short duration of exposure to the study drug (12 days). Mortality during the acute variceal bleeding episode is high and ranges from 16% to 24% (Reverter, 2014). Rupture of gastroesophageal varices is generally due to portal hypertension, and not likely to be precipitated by mucosal irritation from icotrokinra use. Additionally, review of the subject’s concomitant medications does not indicate that they appear to increase the risk of GI bleeding in this subject (e.g., no known history of peptic ulcer disease). The subject’s cause of death was likely unrelated to icotrokinra use.

Case 2. (b) (6) (Death)

A 72-year-old male with a history of hypertension, obesity, former tobacco use, current alcohol use, and varicose veins who experienced a fatal event associated with gastrointestinal hemorrhage on Study Day 385. According to the CSR, “*It was reported that the participant had nausea for two days, followed by vomiting since the previous night, including episodes of black vomit; this was accompanied by loss of consciousness and sudden cardiac arrest; chest compressions were initiated initially but had ceased by the time of arrival of emergency medical services* (Source: CIOMS).”

Concomitant medications at study entry included acetylsalicylic acid (75 mg daily for four years) and the subject was reported to be using an anticoagulant (drug not specified) at the time of death. The subject had a history of concomitant alcohol use

⁵ From the Applicant, “Response to FDA IR,” October 17, 2025.

(50 mL liquor and 1 can beer per week since (b) (6)), former cigarette use (7 packs of cigarettes/week for 23 years; 23 pack years), and a history of gastrointestinal problems (not otherwise specified). Per the investigator, the subject did not report a medical history of gastritis, gastric and/or intestinal ulcer, gastrointestinal bleeding (e.g., hematemesis, melena), chronic vomiting, chronic abdominal pain, thrombocytopenia, anemia, or *Helicobacter pylori*, nor a history of endoscopy or NSAID or corticosteroid use. A primary care physician for the subject could not be contacted to inquire about additional medical records or history not previously disclosed. An autopsy was not performed.

Reviewer Comment:

The subject's use of acetylsalicylic acid, alcohol, and tobacco are known risk factors for the development of peptic ulcer disease (Csordas, 2013; Peterson, 1986). Gastric ulcers have also been associated with obesity and coronary artery disease (Garrow, 2009). Due to these confounding factors that were present in this subject, causality of death to icotrokinra is not established.

Case 3. (b) (6) (SAE)

A 68-year-old male with a history of obesity, and current cigarette and alcohol use who experienced an SAE of gastric ulcer perforation on Study Day 271. Study drug was discontinued on the day of the event and the subject was discharged from the hospital on Study Day 295. No concomitant medications. Per the investigator, the subject did not report a medical history of gastritis, gastric and/or intestinal ulcer, gastrointestinal bleeding (e.g., hematemesis, melena), chronic vomiting, chronic abdominal pain, thrombocytopenia, anemia, or *Helicobacter pylori*. The investigator did not report a history of endoscopy or NSAID or corticosteroid use.

Reviewer Comment:

This case of SAE of peptic ulcer with perforation represented an incidence of 1/1864 (0.05%) total subjects across the four clinical trials in the phase 3 psoriasis program, which is lower than the incidence of GI ulcer with perforation in the general population.⁶ We also note the presence of multiple confounding factors for gastric ulcer, including obesity and cigarette and alcohol use, which prevent the establishment of causality to icotrokinra use.

Case 4. (b) (6) (SAE)

A 65-year-old white female with a history of ureteric dilatation (left renal ectasia), hysterectomy (b) (6), bariatric surgery due to obesity (b) (6), and *Helicobacter pylori* infection (b) (6) who experienced lower GI bleeding (PT: rectal hemorrhage) on

⁶ The incidence of the peptic ulcer disease has been reported in the literature to be 1.5-3%, with 2%-14% of the ulcers leading to perforation and acute illness (Chung KT and Shelat V. Perforated peptic ulcer-an update. World J Gastrointest Surg. 2017 Jan 27;9(1):1-12).

Study Day 503, reported along with the nonserious AEs of diverticulum and hemorrhoids. The subject reported one bowel movement with soft, dark brown/black stool on the same day (Study Day 503). On Study Day 507, the subject was admitted to the hospital following an “episodic vegetive episode with abundant dark brown/black stool containing clots.” No reported abdominal pain, vomiting, or other associated symptoms. The subject’s hemoglobin was 8.90, leukocyte count was 81010 and platelet count was 20600 (units and normal ranges not provided). Upper endoscopy and contract [sic] enhanced abdominal computed tomography scan did not identify a source of bleeding.

On the same day, the subject had another episode of dark stool and blood count showed a hemoglobin of 7.50 (units not provided); colonoscopy showed diverticulosis and two internal hemorrhoids reported as nonserious adverse events of diverticulum (reported term: diverticulosis) and hemorrhoids. Icotrokinra was continued. The event of rectal hemorrhage was reported as resolved on Study Day 508. On Study Day 510, the subject’s hemoglobin had improved to 10.9 (units not provided), and the subject was discharged from the hospital on Study Day 512 with a hemoglobin of 10.3

No concomitant medications at the time of study entry, however, the subject used acetylsalicylic acid from Study Day 55-62.

Reviewer Comment:

The clinical history of painless, large-volume, dark brown/black stool is consistent with colonic diverticular bleeding, particularly if the bleeding source is located on the right side of the colon. A diagnosis of colonic diverticular bleeding in this subject, however, is presumptive given that no active bleeding or stigmata of recent GI bleeding were noted on colonoscopy, and no active bleeding was seen on CT.

It is unlikely that hemorrhoids were the source of bleeding as it would have been associated with hematochezia (i.e., as opposed to brown/black stool), and more profuse bleeding that would lead to a decrease in the subject’s hemoglobin.

We also note the subject’s history of *Helicobacter pylori* infection, a risk factor for peptic ulcer disease. However, upper endoscopy at the time of the event did not reveal an ulcer or other source of bleeding.

Given the identification of colonic diverticulosis as a possible source of GI bleeding, causality of the event to icotrokinra is not established.

IV. DG Responses to Consultation Questions from DDD

DDD requests DG input regarding the potential GI-related safety risk of upper gastrointestinal bleeding with the use of IL23R antagonist, icotrokinra, based on the occurrence of two deaths attributed to upper gastrointestinal bleeding and one SAE of acute gastric ulcer perforation with peritonitis that were reported in the controlled clinical trials in subjects that received icotrokinra. In addition, the recently submitted 120 day safety update included an SAE of lower gastrointestinal bleeding (PT: rectal hemorrhage).

We have the following responses to the questions from DDD:

Question 1: Is this observation within the expected rate of fatal or serious upper GI bleed in this study population size, and specifically are there any concerns with 2 deaths and 1 SAE all occurring on active drug vs no cases on placebo?

Death from upper GI bleeding has been reported in the literature to occur with an annual incidence of approximately 80 to 150 per 100,000 population, with an estimated mortality rate of 2% to 10% (Stanley, 2019). Based on the pooled safety population of 1864 subjects across the four clinical trials of the phase 3 program in patients with psoriasis (1296 subjects who received icotrokinra and 568 subjects who received placebo), the two fatalities that were attributed to upper GI bleeding and the SAE of acute perforated ulcer with peritonitis represented 2/1864 (0.11%) subjects and 1/1864 (0.05%) subject, respectively. Therefore, the rate of GI bleeding identified in the icotrokinra PsO development program is consistent with the expected rate in the general population of the same size; however, the rate of fatal GI bleeding exceeds the expected rate in the general population of the same size.

Review of the literature does not indicate an increased risk of GI bleeding in the intended treatment population (i.e., adults with psoriasis). It is concerning that all 4 cases of these serious GI events occurred in subjects that received icotrokinra, and not placebo. We also acknowledge our discussion with our dermatological colleagues that these serious GI events are not commonly reported in clinical trials in patients with psoriasis.

Question 2: Could you please comment on the risk factors these cases had for UGI bleed vs. known risk factors in this population for UGI bleed? In particular, the Sponsor attributes increased risk of UGI from psychiatric medications in the fatal case of the 49-year old male was not aligned with review of the adverse effect profile of those drugs (which seem primarily to be associated with nausea and vomiting).

Known risk factors for upper GI bleeding were present in each of the cases, resulting in potential confounding (refer to Section III, Case Narratives, for a detailed discussion). However, icotrokinra cannot be excluded as contributing to GI adverse reactions with serious outcomes given the imbalance observed in these events between the drug and placebo arms of the trials.

We do not agree with the Applicant's assessment of the 49-year old male who died from esophageal variceal bleeding, attributing the increased risk of upper GI bleeding to psychiatric medications. This subject was receiving concomitant medications that included benserazide hydrochloride/levodopa, lithium carbonate, aripiprazole, primidone, and losartan. Levodopa has been associated with an increased risk of GI bleeding in patients who have a history of peptic ulcer disease (Gandhi, 2023); however, this subject did not have a known history of peptic ulcer disease. Although cases of thrombocytopenia have been reported in patients with Parkinson's disease who are treated with levodopa (Shahrestani, 2022), this subject did not have thrombocytopenia at the time that could have contributed to his GI bleeding. Review of the literature and prescription drug labels for the subject's other concomitant medications did not indicate that these medications are associated with an increased risk of severe GI bleeding. Therefore, we do not attribute this subject's fatal upper GI bleeding to concomitant psychiatric medications, but rather to bleeding from gastroesophageal varices.

Question 3: Any further investigations or monitoring recommended for UGI bleed or GI adverse events?

We do not recommend any further investigations or monitoring for upper GI bleeding or GI adverse events at this time. There was no trend in the risk factor(s) in the affected subjects that indicate a specific increased risk with icotrokinra use, and the affected subjects had coexisting conditions or concomitant medications that could have contributed to the GI bleeding events. Therefore, it is challenging to provide specific recommendations regarding how and/or in whom to monitor for these potential risks.

V. Overall Summary and Recommendations:

There remains uncertainty as to whether icotrokinra increases the risk of GI bleeding or other serious GI adverse events (e.g., ulcer perforation) as multiple confounding factors were present in each of the cases, and furthermore, there is no known pharmacologic mechanism associated with icotrokinra or other IL-23 antagonists that would support an increased risk of GI bleeding. However, there is some basis to believe that there is a causal relationship as these events only occurred in subjects that received icotrokinra, and the subject population (i.e., patients with psoriasis) is not considered to be at risk for GI bleeding or other serious GI adverse events.

Per the FDA guidance for industry - *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2006),⁷ “[f]or serious adverse events that are unusual in the absence of drug therapy (e.g., liver failure, agranulocytosis, rhabdomyolysis, idiopathic thrombocytopenic purpura, intussusception), there is a basis to believe there is a causal relationship between the event and the drug at a very low rate of occurrence. Therefore, these events are generally listed in the adverse reactions section even if there are only one or two reported events, unless it is clear that a causal relationship can be

⁷ We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

excluded.” We therefore recommend that the events of upper gastrointestinal bleeding (1 case of esophageal variceal bleeding; fatal, 1 case of nonspecific hematemesis; fatal), lower gastrointestinal bleeding (1 case of rectal bleeding), and gastric ulcer perforation (1 case) be included in the USPI in the ADVERSE REACTIONS, Clinical Trials Experience subsection as low frequency, serious adverse reactions.

We present the following language for your consideration for inclusion in Section 6.1 of the USPI, under (b) (4)

(b) (4)

During discussions with DDD, they communicated that it is unusual to have SAEs, including death, in clinical trials of PSO. They felt that it would be important to communicate these ARs beyond Section 6.1 of the PI. DDD drafted the following proposal and requested feedback from DG:

(b) (4)

DG defers to DDD as to whether a W&P is needed. We have the following suggestions if DDD recommends proceeding with a W&P:

- *Consider discussing the two fatal cases and the timing of the events in relation to study drug.*
- *Suggest HCPs and patients monitor for new onset or worsening GI symptoms in patients with known risk factors for GI bleeding and instruct patients to seek immediate medical attention for these symptoms.*
- *If a serious GI event is suspected, discontinue drug, and refer patients for additional evaluation, as clinically indicated.*

Labeling negotiations are ongoing at the time that this consult was finalized. DG is continuing to collaborate with DDD on finalizing labeling language.

References:

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/s/

JAIME L WOLFE
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IRENA G LAVINE
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JULI A TOMAINO
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JAIME L WOLFE
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03/12/2026 04:11:15 PM

Clinical Inspection Summary Addendum

Date	2/23/2026
From	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	Kathleen Butler, MD, Clinical Reviewer Mary Kim, MD, Clinical Team Leader Tina Whang, Regulatory Project Manager Division of Dermatology and Dentistry (DDD)
NDA #	220149
Applicant	Janssen Biotech Inc.
Drug	Icotrokinra
NME (Yes/No)	Yes
Therapeutic Classification	Interleukin (IL)-23 receptor antagonist peptide
Proposed Indication	For the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy
Consultation Request Date	8/29/2025
CIS filed in DARRTs	1/23/2026
Action Goal Date	3/17/2026
PDUFA Date	3/18/2026

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

This is an addendum to the Clinical Inspection Summary for NDA 220149 filed into DARRTS on January 23, 2026.

The Division of Dermatology and Dentistry received in IND 156446 on January 23, 2026, sponsor's report of potential GCP non-compliance issues at Site US10098 (Paul W. Wallace), which participated in Study 77242113PSO3004 (ADVANCE 2) supporting NDA 220149. The sponsor reported three allegations regarding: (1) confidential source document removal by the study coordinator; (2) accuracy of subject discontinuations; and (3) patient-reported outcome data reliability.

On January 28, 2026, based on OSI's recommendation, the review division issued an Information Request requiring the sponsor to conduct a 100% source data audit at Dr. Wallace's site that enrolled 8 subjects in Study 77242113PSO3004. The Sponsor responded to the information request on February 2, 2026, and February 11, 2026. **This addendum evaluates the Sponsor's initial allegation report and responses to the FDA Information Request. It also provides OSI's recommendations to the review division.**

Sponsor's Audit Findings and Assessments

The Sponsor's audit of the efficacy data revealed GCP concerns affecting both clinician-reported and patient-reported outcomes. Specifically, the principal investigator (PI) verbally relayed the primary efficacy endpoint assessments to the study coordinator, who then entered the data directly into the site's iPad using the PI's username and password and signed on his behalf. There was no independent documentation at the site to verify that the PI had personally observed each participant's skin condition at the time of assessment, and no independent verification that the verbal communication of scores to the coordinator was accurate. Date and timestamp analysis of daily Psoriasis Symptoms and Signs Diary (PSSD) symptom scores (secondary efficacy endpoint data) revealed multiple irregularities, including compressed completion windows, sequential entries within minutes across participants, and identical completion sequences for 4 participants on 11 days. (*See **Sponsor's Audit of Efficacy Data** below, for full details*).

The safety data audit examined subject dosing and all safety parameters. PK concentration data demonstrated all participants received study drug as assigned. The 100% source data audit did not identify previously unreported adverse events. Central laboratory reports were reviewed, and safety parameters were verified, and all safety data were verifiable and deemed reliable. (*See **Sponsor's Audit of Safety Data** below, for full details*)

Sponsor's Corrective Actions, Data Analysis and Labeling Proposal

Based on the data audit findings, the Sponsor closed Site US10098 and proceeded with all required site-closure activities. The sponsor conducted a sensitivity analysis which showed that the efficacy data at this site had no impact on the overall efficacy results of Study 77242113PSO3004. Nevertheless, the sponsor proposed to exclude all efficacy data (co-primary and key secondary endpoints) from this site in the United States Prescribing Information (USPI) as a precaution. They proposed to retain all safety data from Site US10098 because the audit verified the reliability the safety data.

OSI's Assessments and Recommendations

While there is no evidence that the efficacy data are fraudulent, the data entry practice at the site, i.e., the study coordinator entering data using the PI's credentials and signing on his behalf, is concerning because it does not preserve the unique identity of the PI's entry or the attributability of the data. The cause of the pattern irregularities regarding the daily patient diary data (PSSD 24-hour assessments) is unknown.

As per our email to the review division dated on January 28, 2026, we recommended the review division conduct sensitivity analysis of the efficacy data. We defer to the review division regarding if the efficacy data of this site should be included in the USPI.

The safety data from Site US10098 appeared to be reliable and may be retained in the NDA safety analyses.

*The study coordinator's removal of participant source documents (GCP non-compliance allegation #1) appears to be a privacy issue and does not appear to impact safety or efficacy data. The issue of subject discontinuations (GCP non-compliance allegation #2) occurred after the data cutoff (January 2025) for the study and the 120-day Safety Update (July 2025) and therefore should not impact the efficacy or safety data for the current application. (see **GCP Non-Compliance Issues** below, for full details).*

II. Background

Janssen Biotech Inc. submitted clinical data from three clinical studies, 77242113PSO3001 (LEAD), 77242113PSO3002 (ADVANCE 1), and 77242113PSO3004 (ADVANCE 2) to support a New Drug Application (NDA 220149) for icotrokinra. Three clinical investigators (Drs. Toth, Brzewski, and Weyergraf) were inspected and the results of these inspections are detailed in the Clinical Inspection Summary filed 1/23/2026.

On January 23, 2026, the Sponsor notified the FDA of potential GCP non-compliance issues at Site US10098 (Principal Investigator: Dr. Paul W. Wallace, Wallace Medical Group, Inc., Los Angeles, CA) participating in Study 77242113PSO3004 (ADVANCE 2), a pivotal Phase 3 trial supporting NDA 220149 for icotrokinra via General Correspondence.

Study Design and Endpoints

ADVANCE 2 was a Phase 3, randomized, double-blind, active comparator- and placebo-controlled, parallel-group, multicenter, interventional study in adults with moderate to severe plaque psoriasis; deucravacitinib was the active comparator.

Primary Endpoints and Key Secondary Endpoints/ Clinician-Reported Outcomes:

The co-primary endpoints were Investigator's Global Assessment (IGA) [score of 0 or 1 and ≥ 2 grade improvement from baseline at week 16] and Psoriasis Area and Severity Index (PASI) [Week 16] which were investigator assessments. These assessments were also components of the key secondary endpoints.

Secondary Endpoints / Patient-Reported Outcomes (PRO):

Secondary endpoints included patient-reported outcomes (PRO) such as the Psoriasis Symptoms and Signs Diary (PSSD) symptom score. PRO assessments were to be completed by the participant who was provided with an electronic device to enter study-related data.

Study Conduct

For ADVANCE 2, 114 sites enrolled at least 1 subject. The study was initiated March 9, 2024, and was ongoing at the time of NDA submission; efficacy data were submitted through Week 24, and safety data were submitted through January 6, 2025.

At Site US10098, 10 subjects were screened, 8 randomized, 7 discontinued, and 1 was active at the time of initial notification (January 23, 2026). The 8 enrolled subjects represented approximately 1% of randomized participants in Study 77242113PSO3004 (total enrollment, 731 subjects).

GCP allegations and FDA Information Request

On January 23, 2026, the Sponsor notified the FDA of potential GCP non-compliance issues at Site US10098, which participated in the ADVANCE 2 Study only. The initial communication detailed three potential allegations: (1) source document removal by a former study coordinator, removing protected patient information from the site; (2) questionable accuracy of subject discontinuations, with 7 out of 8 subjects discontinued within a one-month period; and (3) patient reported outcome data accuracy: uncertainty whether subjects had completed PRO questionnaires.

On January 28, 2026, and based on OSI's recommendation, the review division issued an Information Request requiring a 100% source data audit of the site including verification of both safety and efficacy data (co-primary and key secondary endpoints), and a detailed analysis of the GCP non-compliance issues, including root cause, scope, and impact on the study and the overall NDA. The Sponsor responded in two parts: Part 1 on February 2, 2026, and Part 2 on February 11, 2026.

III. GCP Non-Compliance Issues

Issue 1: Source Document Removal

Sponsor's Findings (January 23, 2026, initial notification and February 2, 2026, response to FDA Information Request):

The former study coordinator removed confidential documents from the site, including participant source documents, on October 22, 2025. All documents were returned to the site on October 28, 2025. The Sponsor verified document return on October 31, 2025, and November 7, 2025. The site PI sent certified letters to all seven discontinued participants notifying them of the privacy breach.

OSI Assessment:

The study coordinator's removal of participant source documents appears to be a privacy issue. While the Sponsor did not provide information about which specific documents were

*removed or why, the removal does not appear to impact safety or efficacy, as all documents were returned to the site within six days which was verified by the Sponsor. The PI appropriately notified affected participants, and the Sponsor took corrective actions at the site (see **Summary: Sponsor Actions**, below).*

Issue 2: Subject Discontinuation Accuracy

Sponsor's Findings (January 23, 2026, initial notification and February 2, 2026, response to FDA Information Request):

Seven of eight randomized participants were discontinued between September-October 2025. On 31 December 2025, the PI sent certified letters to the seven discontinued participants informing them of removal of their source documents (Issue #1, above) and requesting that they contact the site regarding their discontinuation status. As of January 6, 2026, four of the seven discontinued participants had responded to certified letters sent by the PI, and all four verbally confirmed they never chose to discontinue from the trial.

OSI Assessment:

*The Sponsor did not include details in their February 11, 2026 data audit findings. Therefore, we do not know who made these discontinuations and the rationale. Nevertheless, these discontinuations occurred after the data cutoff (January 2025) and the 120-day Safety Update (July 2025) and therefore do not impact the efficacy or safety data for the current application. (see **Summary: Sponsor Actions**, below).*

Issue 3: Patient Reported Outcome (PRO) Data Reliability:

Sponsor's Findings (January 23, 2026, initial notification and February 2, 2026, response to FDA Information Request):

During a December 11, 2025, Week 76 visit, the remaining active participant ((b) (6)) voluntarily reported that he had never completed patient questionnaires on the site tablet or used the study-supplied device for daily diary entries. This impacted inputs potentially affecting all visits from May 9, 2024 (enrollment) through the Week 64 visit (August 28, 2025), prior to the study coordinator transition.

Sponsor's Audit of Efficacy Data (February 11, 2026, response to FDA Information Request):

On February 2-5, 2026, the Sponsor conducted a 100% source data review, including (for efficacy):

- Source documentation review and timestamp analysis of data entry, including assessment of visit-related time entries for plausibility, sequence, and consistency
- Central statistical surveillance comparing data trends and reporting patterns
- Participant interviews (conducted February 6, 2026; 3 of 8 participants contacted)

Sponsor's Audit Findings:

Clinician-Reported Outcome (ClinRO) for Co-Primary Efficacy Endpoint Data (PASI and IGA)

PASI and IGA evaluations were to be collected via direct data entry into the site's eCOA iPad. During the data audit, the PI indicated that although he personally performed the efficacy assessments, he verbally relayed the results to the study coordinator, who then entered the data directly into the site's iPad using the investigator's username and password and signed on behalf of the investigator. There was no independent documentation to verify that the PI had personally observed each participant's skin condition at the time of assessment, and no independent verification that the verbal communication of scores to the coordinator was accurate.

Date and timestamp analysis identified a subset of data entry outliers in which ClinRO assessments were entered approximately 3 to 4 hours prior to the corresponding visit assessments (i.e., laboratory samples, vital signs, investigational product dispensing). No contemporaneous source documentation existed for PASI and IGA assessments (due to direct eCOA entry).

OSI Assessment:

While there is no evidence that the data are fraudulent, the process at the site for data entry of the primary endpoint is problematic. The investigator did not personally enter PASI or IGA assessments into the electronic database. Instead, the study coordinator entered data using the investigator's credentials and signed assessments on behalf of the principal investigator, constituting a 21 CFR Part 11 violation. This practice does not preserve the unique identity of the PI's entry or the attributability of the data.

Furthermore, verbally relaying the assessments introduces potential for transcription errors, creating the potential for inaccurate recording of data; and there was no independent verification that the verbal communication of scores by the PI to the study coordinator was accurately entered in the eCOA.

*As per our January 28, 2026 email, we recommend the review division conduct a sensitivity analysis of the efficacy data. We defer to the review division on regarding if the efficacy data of this site should be included in the USPI. (see **Summary: Sponsor Actions**, below).*

Patient-Reported Outcome (PRO) for Key Secondary Efficacy Endpoint Data: Psoriasis Symptoms and Signs Diary (PSSD)

PROs were to be collected via direct data entry. PSSD 24-hr recalls were to be collected via provided handheld device or via an app downloaded by the participant. Remaining PROs including the PSSD 7-day recall were to be collected via direct data entry on the site's iPad. documentation was not available, as this information was recorded through direct entry into the electronic data capture system.

Participant Interviews

The Sponsor evaluated the PRO data for all participants at the site. Three of eight participants were able to be contacted for interviews, which were conducted on February 6, 2026. During the interviews, all three participants reported that they did not complete their PSSD 24-hour assessments. Additionally, these 3 participants reported not completing ePROs (including

PSSD 7-day recall) utilizing the site's iPad. One participant indicated completion of ePRO responses on paper while at the site; and another participant indicated that site staff verbally asked psoriasis symptom questions. However, there were no source documents at the site to substantiate this process.

Timestamp and Data Trend Analysis

The Sponsor identified the following irregularities:

PSSD 7-Day Recall

For a subset of subjects, the ePRO assessments were entered approximately 3 to 4 hours prior to the corresponding visit assessments (i.e., laboratory samples, vital signs, investigational product dispensing).

Daily PSSD (24 hour) Diary Entries:

1. Compressed Time Window - All participants' entries were completed within a shorter timeframe each day compared to other study sites.
2. Sequential Entry Pattern - Multiple participants repeatedly completed diaries within 3 minutes of each other, an anomaly when compared to patterns at other sites.
3. Repetitive Completion Sequence –The same four participants completed their diaries in identical order on 11 separate days.

OSI Assessment:

The cause of the observed irregularities regarding compressed completion windows, sequential entry pattern and repetitive completion sequence is unknown.

Sponsor's Audit of Safety Data (February 11, 2026, response to FDA Information Request):

On February 2-5, 2026, the Sponsor conducted a 100% source data review of safety data, including:

- Pharmacokinetic (PK) concentration data for all 8 enrolled participants
- Medical histories (source documents and eCRF)
- Adverse events (completeness and accuracy)
- Concomitant medications
- Vital signs
- Laboratory values (compared to central laboratory reports)
- Protocol-specified safety evaluations

Audit Results and Conclusions

PK concentration data for all 8 enrolled participants confirmed that each participant was exposed to the assigned study intervention as intended. Medical histories were documented in source documents and the eCRF for all 8 enrolled participants. The Sponsor verified all safety parameters, including adverse events, concomitant medications, vital signs, and laboratory values. Records confirmed that protocol-specified safety evaluations were performed, and that appropriate participant safety monitoring occurred throughout study conduct. **The review did not identify any previously unreported adverse events.** Central laboratory reports were

reviewed and verified, providing independent confirmation of laboratory values recorded in the database. All safety data were verifiable and reliable.

OSI Assessment:

The safety data from Site US10098 are deemed reliable. PK data provide objective evidence that participants received study drug and attended visits. Central laboratory reports provide independent verification of laboratory values. The 100% source data review confirmed all adverse events were appropriately documented and reported.

We recommend that safety data from Site US10098 be retained in the NDA safety database and safety analyses for the current NDA indication.

Summary: Sponsor Actions (February 11, 2026, response to FDA Information Request)

Based on the data audit findings, the Sponsor closed Site US10098 and proceeded with all required site-closure activities. The Sponsor conducted a sensitivity analysis and proposed to exclude all efficacy data (co-primary and key secondary endpoints) from this site in the USPI. Safety data from Site US10098 will be retained in the NDA safety database, as the comprehensive safety data review confirmed the reliability and verifiability of all safety parameters.

The Sponsor identified inadequate Principal Investigator oversight as the root cause of the GCP non-compliance issues at Site US10098.

{See appended electronic signature page}

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

/s/

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02/23/2026 01:57:53 PM

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02/23/2026 02:02:03 PM

Memorandum of Assessment – Immunogenicity Consult [NDA 220149 icotrokinra; Janssen]

NDA Number:	220149
eCTD/SDN	0001/01
Submission(s):	Link
Subject:	Icotrokinra (JNJ-77242113)
Date(s) received:	18-July-2025
Consults:	Immunogenicity Consultation Request issued by OND/DDD
Date of Consult:	09-September-2025
Requesters:	Tina Whang, CDER/OND/ORO/DROII
Primary Assessor:	Bruce Huang, CDER/OPQ/OPQR/DPQRIII
Secondary Assessor:	Seth Thacker, CDER/OPQ/OPQR/DPQRIV
Applicant:	Janssen Biotech, Inc.; Horsham, PA, USA
Product:	Icotrokinra, 200 mg oral film-coated immediate-release tablet, administered once daily
Indication:	Treatment for moderate to severe plaque psoriasis (PsO) in adults and pediatric patients 12 years old and older

Immunogenicity Executive Summary and Recommendation(s):

The CDER/OND/DDD requested the OPQR immunogenicity team's assessment of the anti-drug antibody (ADA) and neutralizing antibody (NAb) assays used to evaluate immunogenicity in icotrokinra (JNJ-77242113; Janssen Biotech, Inc.) Phase 3 clinical trials (PSO3001, PSO3002, PSO3003, PSO3004). Immunogenicity testing was conducted at two contract research organizations: (b) (4) for U.S. patient samples, and (b) (4) for Chinese patient samples from trial PSO3001.

The ADA assays used for icotrokinra Phase 3 immunogenicity testing at (b) (4) and (b) (4) are fit for purpose and the data is acceptable for making a regulatory decision for NDA 220149 approval. The ADA assays are adequately validated with appropriate sensitivity, precision, and a successful 10/10 cross-validation concordance across laboratories. The NAb assays have demonstrated some deficiencies including inadequately justified LPC selections, hemolysis intolerance, and potentially inadequate drug tolerance relative to expected patient residual drug levels. Both the ADA and NAb assays have limited validation testing for robustness and interference by common serum contaminants (hemolysis, lipemia, bilirubin).

To fully understand how the limitations of the assay may be impacting on results from the NAb assay the sponsor could be asked to identify how many of the samples tested exhibited hemolysis or had levels of icotrokinra above the drug tolerance of the assay.

The potential impact of the poor drug tolerance could lead to the underestimation of NAb positive samples; however, given the lack of observed clinical impact on efficacy or safety in the trials the importance of addressing the adequacy of the drug tolerance of the assay may not be needed.

It is unlikely that these analytical deficiencies will significantly compromise patient safety given icotrokinra's low observed immunogenicity, the NAb assay's bias toward false positivity rather than false negativity, and lack of observed clinical impact on efficacy or safety in trials.

While there remains some identified validation gaps which are not ideal from an analytical perspective, they are not assessed to be so severe as to justify withholding approval given the favorable clinical immunogenicity profile, low intrinsic immunogenic potential of this orally-administered macrocyclic peptide drug, and absence of safety signals related to immunogenicity in the Phase 3 trials. Therefore, the assays are considered fit-for-purpose for characterizing the immunogenicity profile of icotrokinra in patients with moderate to severe plaque psoriasis.

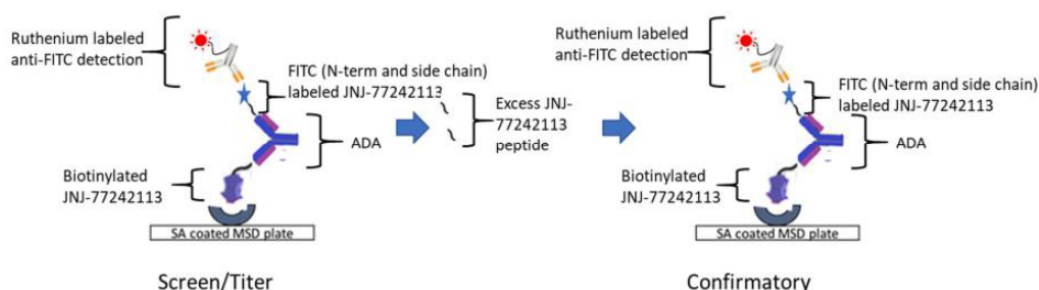
Background: Icotrokinra (JNJ-77242113) is a macrocyclic peptide molecule organically synthesized from 4 proteinogenic and 9 nonproteinogenic amino acids that selectively binds to IL-23 receptor (IL-23R) to competitively antagonize binding with IL-23, and is proposed as an orally-administered 200 mg coated tablet. The IL-23R target of icotrokinra is found on multiple types of immune cells, and upon stimulation with IL-23, triggers signals that promote cell proliferation, survival, and secretion of pro-inflammatory cytokines such as IL-17 and IL-22. Inhibition of IL-23R signal transduction by administration of icotrokinra is intended to suppress the release of proinflammatory cytokines and chemokines involved in pathogenesis of plaque psoriasis (PsO).

The structure of icotrokinra has no known endogenous counterpart, therefore the potential for cross-reactivity with existing physiological proteins is predicted to be low. The Applicant predicted low cross-reactivity potential using EpiScreen DC:T cell assay studies (Abzena [Cambridge] Ltd., Cambridge, UK), which were not submitted in the NDA, and could not be assessed or determined to be fit for purpose by the Agency. Nevertheless, because of the organo-synthetic nature of icotrokinra, post-translational modifications such as glycosylation are not predicted, and it is anticipated that there is low likelihood of specific higher order molecular structures, such as aggregates or oligomers, which further decreases potential immunogenic risk. Additionally, the film-coated solid tablet formulation of icotrokinra lessens the probability of drug interaction with leachable packaging components, and the intended oral administration of icotrokinra eliminates some of the most common immunology-related risk factors of drug administration, such as infusion and/or injection site reactions. Furthermore, the continuous daily nature of the proposed treatment scheme and the route of administration lowers the potential immunogenicity risk of the product. However, the novel structure of the drug, as well as the recognized etiology of PsO which includes a generally over-active pro-inflammatory systemic immune environment in patients, could potentially induce product related immunogenicity. To address the potential immunogenicity of this product the sponsor is measuring ADA levels in subjects undergoing treatment with icotrokinra. The Sponsor developed ADA assays and submitted validation packages for these assays to monitor for immunogenicity against icotrokinra in administered patients. Preliminary immunogenicity assays for ADA testing of patient samples collected during Phase 1 and 2 studies were developed by Janssen R&D; however, to support the large-scale multi-site international Phase 3 trials (PSO3001, PSO3002, PSO3003, PSO3004), the ADA testing method was transferred to (b) (4) for analysis of U.S. patient samples, and (b) (4) for analysis of Chinese patient samples (Phase 3 trial PSO3001, only).

Immunogenicity Consult Request: The CDER/OND/ORO/DROII division requested via [consult](#) (DARRTS Ref. ID: 5655957) for OPQR immunogenicity team to analyze the assays/methods used, as well as conclusions reached, regarding the immunogenicity testing of patients administered with icotrokinra.

Anti-drug antibody (ADA) assays: The Applicant stated that both the (b) (4) and (b) (4) ADA assays that were used for evaluating the Phase 3 trial patient specimen materials were transferred from the original Janssen developmental ADA assay. All assays are based on the Meso Scale Discovery (MSD) electrochemiluminescence (ECL) bridging immunoassay principle using acid dissociation of samples, with screening, confirmatory, and titration components (see cartoon below, reproduced from the (b) (4) ADA method validation report):

Figure 1: JNJ-77242113 ADA Assay: Screening and Specificity Methods



Biotinylated drug (JNJ-77242113; icotrokinra) is immobilized on streptavidin-coated MSD plates. The plates are then used to capture potential ADA from human serum samples that were acid-treated to dissociate ADA from specific or non-specific binding partners then neutralized. Captured ADA are detected by being “sandwiched” with added FITC-labelled JNJ-77242113, which are then bound by addition of ruthenium-labelled anti-FITC antibodies. In the presence of tripropylamine-containing read buffer, the ruthenium label of the anti-FITC antibodies emits chemiluminescent signal upon stimulation by electrical voltage to the MSD plate, revealing the presence of bound ADA (screening positivity). Samples that screen positive for ADA are further evaluated by confirmatory testing using excess unlabeled JNJ-77242113 to compete with the FITC-labelled JNJ-77242113 for binding to the immobilized ADA, resulting in diminishment of the ADA-associated ECL signal. Comparative assessments of the ADA assay validations relevant to the JNJ-77242113 Phase 3 trials performed in the U.S. ((b) (4) ADA assay) and China ((b) (4) ADA assay) are described in the table below. Overall immunogenicity data from the Phase 3 clinical trials is summarized at the end of this assessment memorandum.

Detection of Anti-Drug Antibodies (ADA) Against JNJ-77242113 in Human Patient Sera of Phase 3 clinical trials [ADA Assays: (b) (4)]			
Validation Parameter	(b) (4) ADA assay: Project #2329-16028	(b) (4) ADA assay: Report # (b) (4) J01-R5061	Assessor Comment
Contract research org. (CRO)	(b) (4)		The Janssen ADA testing method, which was used for their Ph1 and Ph2 studies, was transferred to (b) (4) and (b) (4) to support their large-scale Ph3 studies.

Associated clinical trials for JNJ-77242113	PSO3001, PSO3002, PSO3003, PSO3004 (USA)	PSO3001 (China)	<i>Only samples obtained from Chinese patients enrolled in PSO3001 (101 total subjects) were analyzed at (b) (4)</i>
ADA Assay principle	MSD ECL bridging immunoassay	MSD ECL bridging immunoassay	<i>The ADA assays utilized at (b) (4) and (b) (4) for P3 clinical trials were both transferred from the developmental ADA method initiated at Janssen R&D, which had been used for analyzing their preliminary P1 and P2 trial data.</i>
ADA Assay Sample Pretreatment (Acid dissociation)	Samples diluted using 100 mM glycine HCl	Samples diluted using 100 mM glycine HCl	<i>Acid dissociation is performed identically between the (b) (4) and (b) (4) assays.</i>
Matrix and negative control (NC)	Human serum, pooled normal human serum (obtained from (b) (4), and Sponsor), Lots NB255-04 (Pool), NB272-01, NB272-05, NB272-06, NB272-19; Receipt 31MAY2023, Exp. 30JUN2028, storage ≤ -20°C	Pooled normal human serum (b) (4); Individual healthy naïve normal human serum (nNHS) (b) (4) Individual Psoriasis Human Serum (Janssen), Individual Ulcerative Colitis Human Serum (Janssen)	<i>The listed sources of the matrices are applicable to the purpose – importantly, for the (b) (4) assay, sera is sourced from local supplies appropriate to the specified patient population.</i>
ADA Assay Surrogate Positive Control antibody (SPC)	- <u>Monoclonal (mAb) PC</u> : Anti-JNJ-77242113 mAb PTGGB4 human Chimeric IgG (Janssen R&D [Absolute antibody Ltd]; Lot T2206B03, exp/retest date 30-Mar-2032; storage -80°C) - <u>Polyclonal (pAb) PC</u> : Rabbit sera Anti-JNJ-77242113 pAb (Janssen R&D; Lots MOS00330106, MOS00330106_13Dec2023, exp/retest date 04-Mar-2026; storage -80°C)	- <u>Monoclonal (mAb) PC</u> : Anti-JNJ-77242113 mAb PTGGB4 human Chimeric IgG (Janssen R&D [Absolute antibody Ltd]; Lot T2206B03, exp date 30-Mar-2032; storage -70°C) - <u>Polyclonal (pAb) PC</u> : Rabbit sera Anti-JNJ-77242113 pAb (Janssen R&D; Lot MOS00330106_13Dec2023, exp/retest date 04-Mar-2026; storage -70°C)	<i>The same monoclonal and polyclonal PC are used at both (b) (4) and (b) (4) attempting to support the applicability of the principle and procedures across both sites. The use of two separate SPCs (mAb and pAb) in the validation intended to demonstrate a measure of robustness for broad detection capability over different antibody formats. The SPC were stored under adequate conditions at both sites. As described below, it was found at (b) (4) that the pAb SPC did not perform as reliably as the mAb SPC, and was largely marginalized. The reason for this discrepancy was not explored, and remains unexplained. It is possible that some matrix effect inherent to the sera used at the (b) (4) testing location might have negatively interacted with the pAb SPC. Nevertheless, the (b) (4) team performed the complete assay validation</i>

			<i>using the mAb SPC, with only limited utilization of the pAb.</i>
ADA Assay Study Drug	JNJ-77242113 Lot# MOS00397904 (Janssen Research & Development, LLC) Expiry: 05-May-2028 Storage: -80°C	JNJ-77242113 Lot# MOS00397904 (Janssen Research & Development, LLC) Expiry: 05-May-2028 Storage: -80°C	<i>The same lot of study drug was used for validation of both the (b) (4) and (b) (4) assays, which is acceptable.</i>
ADA Assay Low positive control (LPC)	Statistically determined using data of ≥ 5 sensitivity titration curves targeting 1% failure rate. <u>Chimeric mAb (5 measurements)</u> : 73.2 ng/ml (screening); 151.8 ng/ml (confirmatory) <u>Rabbit pAb (6 measurements)</u> : 176.2 ng/ml (screening); 295.2 ng/ml (confirmatory)	Statistically determined using data of 6 sensitivity titration curves targeting 1% failure rate using the Chimeric mAb PC. Concentration of <u>99.69 ng/ml</u> was chosen as conservative LPC for both screening and confirmatory assays. The (b) (4) analyses found the assay was more sensitive using the mAb PC (see Sensitivity parameter, below), and did not consistently use the pAb for validating all parameters.	<i>The strategy of using both mAb and pAb as controls is not disqualifying, because different antibodies have different characteristics, and successful validation with a variety of controls could demonstrate a measure of flexibility in the assay design. It is noteworthy that the calculated mAb LPC are different between the testing sites – this would typically be a concerning issue if the testing sites claimed they were validating the assay in completely identical fashion; however in this case an important differentiator is that the assay matrices at (b) (4) are different than those used at (b) (4) in accordance with the regional availability at the geographic locality of the testing, as well as heeding the prevailing heritage of the subjects involved in the testing at the Chinese clinical site. The difference in LPC concentration may not be ideal, but could be necessitated by biological factors unique to the patient population, as well as by local regulatory agencies requirement for provision of population-relevant validation data in case of application for approval in that market.</i>
ADA Assay Mid positive control (MPC)	<u>1,000 ng/ml</u> (both mAb and pAb)	<u>2,000 ng/ml</u>	
ADA Assay High positive control (HPC)	<u>10,000 ng/ml</u> (mAb); <u>20,000 ng/ml</u> (pAb)	<u>20,000 ng/ml</u>	
ADA Assay Acceptance Criteria (AC)	%CV $\leq$ 20.0 for controls; HPC>MPC>LPC	%CV $\leq$ 20.0 for controls; assay allows CV $\leq$ 25.0% for NC and diluent control	<i>CV$\leq$20.0% is standard for analytical assays. The allowance of CV$\leq$25.0% for NC and diluent control (b) (4) is not ideal, however it is reasonable that at low extremes of analytical range, minute variation of assay readout might result in amplified statistical anomaly, especially for assays that are highly sensitive.</i>
ADA Assay SPC Dose Curve / Hook Effect	SPC dose ranged from 3.9 to 2000 ng/ml (mAb and pAb); Hook effect evaluated for pAb up to 250,000 ng/ml, no	mAb dose ranged from 0.79 to 200 ng/ml, Hook effect evaluated up to 400,000 ng/ml mAb: descending signal trend	<i>The Hook effect for pAb and mAb were evaluated separately, split between (b) (4) (pAb) and (b) (4)</i>

	descending signal trend was observed	was detected beyond 50,000 ng/ml, however signal remained strongly positive throughout dose range up to the 400,000 ng/ml; pAb dose ranged from 3.13 to 400 ng/ml (no ultra-high concentration pAb was tested at (b) (4) .	<i>(mAb). While the split is not an ideal situation, the validation results for (b) (4) were acceptable in absence of any pAb signal hook. The mAb signal hook observed at (b) (4) remained strongly positive at ultra-high SPC concentration, and is assessed to be low-risk for any potential hazard of returning false-negative results.</i>
ADA Assay Minimum required dilution (MRD)	1:50	1:50	<i>The (b) (4) and (b) (4) assays use the same MRD, which is reasonable because the assays are derived from the same Jannson developmental method, which also used 1:50 MRD.</i>
ADA Assay Screening cut point (SCP)	Sera were obtained from 50 normal, 38 ulcerative colitis (UC), and 29 psoriasis (PSO) patients. 30 psoriatic arthritis (PA) patients were also analyzed separately, for comparison (all the diseases share chronic dysregulated inflammatory etiology). Using parametric 90% lower confidence limit targeting 5% FPR, SCP factor for normal, UC, and <u>psoriasis patient sera was calculated to be 1.06</u> , whereas SCP factor for PA patient sera was calculated to be 1.09. The 1.06 SCP (normal, UC, psoriasis) was chosen for the study.	Sera obtained from 50 normal healthy patients, 30 psoriasis patients, and 50 UC patients were analyzed for computation of parametric 90% one-sided lower confidence limit targeting 5% FPR, SCP factor was 0.98 for normal patients, <u>1.03 for psoriasis patients</u> , and 1.02 for UC patients.	<i>The SCP using the various normal and diseased patient sera was determined appropriately, targeting an adequate FPR rate of 5%. In addition to psoriasis patient SCP, UC patient SCP was also determined, possibly for use in monitoring ADA in patients receiving icotrokinra for treatment of further indications, in the future.</i>
ADA Assay Confirmatory cut point (CCP)	<u>13.0% inhibition</u> (Psoriasis, Normal, and Ulcerative Colitis); determined by addition of excess (2 µg/ml) drug, and calculating % inhibition compared to non-drug-spiked samples: non-parametric determination of CCP targeting 1% FPR.	<u>8.85% inhibition</u> (Psoriasis), 8.74% (UC), 7.07% (Healthy); determined by addition of excess (2 µg/ml) drug, and calculating % inhibition compared to non-drug-spiked samples: parametric determination of CCP targeting 1% FPR.	<i>The determination of CCP was performed adequately, using excess drug to competitively inhibit the assay readout, statistically targeting the appropriate 1% FPR. It was noted that the (b) (4) CCP calculation used a non-parametric determination, while the (b) (4) CCP calculation used a parametric method. The (b) (4) CCP %inhibition data set was not confirmed as normal and the skewness coefficient did not meet acceptance limits, therefore a nonparametric CCP statistical determination method was recommended, with 1% FPR. However, the (b) (4) CCP %inhibition data set was found to conform to normality, thus (b) (4) CCP was statistically determined by</i>

			<i>a parametric method, also with 1% FPR.</i>
ADA Assay Titer Cut Point (TCP)	1.213; normality in titer set was confirmed by Shapiro-Wilk test, and skewness coefficient of 0.214 demonstrated acceptable symmetry, for FPR of 0.1%.	1.45; normality of titer set was confirmed by Shapiro-Wilk test, and skewness coefficient of 0.361 demonstrated acceptable symmetry, for FPR of 0.1%.	<i>The determination of TCP was performed using FPR 0.1%, which is stringent, but allowable in accordance with the Agency guidance. The high stringency is not anticipated to result in high risk of false-negativity, as the only samples that will be tested for titration will be those that already confirmed positive by the Confirmatory Assay.</i>
ADA Assay Sensitivity	Sensitivity data was generated by ≥5 measurements by 2 analysts over 3 days, using 2-fold dilutions in NHS from 3.9 to 2,000 ng/ml - mAb PC PTGBB4: Screening: <u>24.783 ng/ml</u> Confirmatory: <u>53.038 ng/ml</u> - pAb PC Rabbit sera Anti-JNJ-77242113: Screening: <u>58.905 ng/ml</u> Confirmatory: <u>91.719 ng/ml</u>	Sensitivity was evaluated over 6 runs performed by 2 analysts on 3 days, using two-fold serial dilutions ranging from 0.79 to 200 ng/ml (PTGBB4 mAb) or 3.13 to 400 ng/ml (Rabbit sera pAb) in naïve normal human sera (nNHS) or assay diluent. - mAb in nNHS: <u>5.52 ng/ml</u> screening, <u>32.15 ng/ml</u> confirmatory - mAb in diluent: <u>0.79 ng/ml</u> screening, <u>11.61 ng/ml</u> confirmatory - pAb in nNHS: <u>18.49 ng/ml</u> screening, <u>109.74 ng/ml</u> confirmatory - pAb in diluent: <u>3.13 ng/ml</u> screening, <u>37.77 ng/ml</u> confirmatory	<i>The (b) (4) assay adequately met the Agency recommendation for sensitivity of at least 100 ng/ml using both mAb and pAb. The (b) (4) assay met the Agency recommendation except for the pAb confirmatory assay in nNHS, which carries a risk of failing to confirm positivity for ADA which are less than 109.74 ng/ml. The pAb (nNHS) confirmatory risk is mitigated somewhat by the pAb screening sensitivity that is still adequate to detect ADA at ≥18.49 ng/ml. Additionally, dilution of sample for the assay would not normally be performed using nNHS, as sample dilution would be performed using assay diluent, in order to reduce the potential for residual factors in the matrix to interfere with the assay.</i>
ADA Assay Drug Tolerance	Drug tolerance was evaluated by spiking ADA assay with drug (4 to 1024 ng/ml). - PTGBB4 mAb: All concentrations of mAb (100-10,000 ng/ml) tolerated up to 1,024 ng/ml drug. - Rabbit sera pAb: HPC (20,000 ng/ml) and MPC (1,000 ng/ml) tolerated up to 1,024 ng/ml drug; LPC (295 ng/ml) tolerated 64 ng/ml drug.	Drug tolerance was evaluated by spiking ADA assay with drug (19.54 to 20,000 ng/ml for mAb, 0.13 to 2,000 ng/ml for pAb). - PTGBB4 mAb: 2,000 ng/ml mAb tolerated up to 20,000 ng/ml drug in both screening and confirmatory assay, while 99.69 ng/ml mAb tolerated up to 1,250 ng/ml drug. - Rabbit sera pAb: 2,000 ng/ml pAb tolerated up to 2,000 ng/ml drug, while 100.00 ng/ml pAb tolerated up to 0.49 ng/ml drug.	<i>The Summary of Biopharmaceutical Studies section of the NDA stated that the concentration of residual drug in all samples analyzed was under 31.1 ng/ml. The (b) (4) tolerance study found that at mAb and pAb worst-case, the pAb LPC could tolerate up to 64 ng/ml drug, which safely exceeds the residual drug. The (b) (4) tolerance study was less optimistic, indicating that the maximum residual drug level may interfere with detection of ADA at close to the pAb LPC concentration. It is unknown if this observation has any clinical significance, as it has</i>

			<i>been documented that icotrokinra ADA (presumably at a level high enough for detection to overcome any potential interference by residual drug, thus potentially an underestimation of actual concentration) had no clinically meaningful impact on efficacy or safety to patients.</i>
ADA Assay Target Interference	Up to 200 ng/ml soluble IL-23R (the target of icotrokinra) was spiked into pAb PC samples, all LPC and HPC samples returned positive results, all NC samples returned negative results.	Up to 10,000 ng/ml soluble IL-23R was spiked into LPC and MPC mAb PC, with no negative results observed (thus no impact on positivity).	<i>IL-23R exists largely in membrane-bound form, with very little shedding, thus the potential of soluble IL-23R being found in sera at levels that could interfere with the ADA assays is low.</i>
ADA Assay Precision	Inter-assay precision was evaluated over 22 (DC and NC), 7 (mAb), 8 (pAb) runs on 4 days by 2 analysts using 6 replicates of each PC per run (screen/%inhib). Diluent control: 12.3% CV Neg. control: 12.2% CV mAb LPC: 16.6% / 10.8% CV mAb MPC: 19.7% / 10.0% CV mAb HPC: 15.8% / 0.1% CV pAb LPC: 16.8% / 13.0% CV pAb MPC: 15.6% / 5.1% CV pAb HPC: 15.4% / 0.1% CV Intra-assay precision was evaluated over 22 (DC and NC), or 6 (LPC, MPC, HPC) runs in hexuplicate (screen/%inhib). Diluent control: 2.9-9.8% CV Neg. control: 0.8-6.0% CV mAb LPC: 1.6-18.0% / 1.7-15.2% CV mAb MPC: 1.7-6.6% / 0.4-1.5% CV mAb HPC: 1.0-6.4% / 0.0-0.1% CV pAb LPC: 1.5-4.1% / 1.5-7.8% CV pAb MPC: 2.4-5.1% / 0.8-2.1% CV pAb HPC: 3.3-14.4% / 0.0-0.2% CV	Inter-assay precision was evaluated using 2 analysts on 2 different days using 6 sets of controls for 6 accepted runs (screen/%inhib). Diluent control: 7.3% CV Neg. control: 11.3% mAb LPC: 5.6% / 20.5% CV mAb MPC: 17.8% / 2.2% CV mAb HPC: 23.6% / 0.1% CV Intra-assay precision was evaluated using 6 accepted runs of the controls (screen/%inhib). Diluent control: 1.8% CV Neg. control: 3.1% CV mAb LPC: 3.3 / 8.3% CV mAb MPC: 4.7% / 0.7% mAb HPC: 11.2% / 0.1%	<i>In general, the (b) (4) assay demonstrates acceptable precision. Assessment of the evidence found that the study design was adequate, and that the inter- and intra-assay precision was sufficient to ensure that performance of the assay across multiple analysts, days, and instruments could be reasonably expected to return accurate results. The (b) (4) assay is also assessed to be reasonably precise for the purpose of evaluating immunogenicity of patient samples. Two instances of inter-assay precision values exceeding the pre-defined acceptance criteria (CV≤20.0%) were recorded, however in the case of the mAb LPC confirmatory assay, the amount is not large, and in the case of the mAb HPC assay, there exists little chance of compromise to patient safety due to a false negative finding.</i>
ADA Assay Selectivity	All individual samples in Normal, UC, PS, and PSA groups spiked at LPC level as well as spiking controls returned positivity (100% passing rate); all unspiked samples tested negative.	10/10 sera spiked with LPC or HPC tested positive, while unspiked blank samples tested negative.	<i>The ability of the assays to successfully differentiate samples with antibody from samples without antibody is supportive of assay validation.</i>
ADA Assay Stability	Three aliquots of LPC, HPC, and NC were subjected to six 12-hour freeze cycles with 30-120 minutes thaw cycles. All testing of the controls met acceptance criteria. Three aliquots of LPC, HPC and NC were stored on the	3 sets of HPC and LPC were cycled through seven rounds of freeze/thaw, assay results met acceptance criteria (Response of HPC > response of LPC ≥ SCP). Stability at 2- 8°C for 48 hours 14 minutes, and at RT for	<i>The ability of the ADA assays to successfully read samples that had been subjected to temperature excursions, and stored inappropriately is supportive of assay stability.</i>

	bench at room temperature for 18 hours and analyzed, meeting acceptance criteria. Further aliquots of LPC, HPC and NC were tested in the refrigerator for 18 hours, with no significant detriment to assay readout.	48 hours 15 minutes, were demonstrated by assay results meeting the acceptance criteria (Response of HPC > response of LPC ≥ SCP).		
ADA Assay Robustness	Variation in plate incubation and blocking times were tested; acceptable performance of the assay controls was achieved regardless.	Variations in plate mixing and incubation times were tested, with no effect on performance of the assay controls.	<i>The robustness testing that was performed supported assay validation though they were somewhat limited. Other variables that could have been tested include reaction temperature, pH, mixing times, to name a few.</i>	
ADA Assay Specificity	100 µg/ml irrelevant protein (RPGR peptide) and antibody (C3AB11, anti-JNJ-67571244) were spiked to NC, LPC, and HPC, with no interference observed.	Introduction of up to 100 µg/ml unrelated ADA or biologics (RPGR peptide) in the assay did not affect detection of the HPC, LPC or NC.	<i>High concentration of irrelevant antibody or biologics did not suppress the assay signal, indicating no non-specificity, and indicating low risk for false negativity.</i>	
ADA Assay Lipemia Resistance	pAb LPC samples in normal human sera spiked with either ~1100 mg/dL hemoglobin or >300 mg/dL triglycerides (one each) both tested positive.	Hemolyzed (2%) and lipemic (311.1mg/dL of triglycerides) were tested (3 times each) with LPC and HPC, no matrix effects of hemolysis or lipemia were observed.	<i>Hemolysis and lipemia testing appears somewhat inadequate at both (b) (4) and (b) (4). While the testing did not reveal matrix interference by blood or lipid products in the ADA assays, the testing did not employ sufficient samples at either site, thus confidence in the results is not absolute. During testing of the Janssen ADA method that was transferred to (b) (4) and (b) (4) 5/5 hemolyzed samples demonstrated resistance to hemolysis, and 5/5 lipemia samples demonstrated resistance to lipid. However, the effect of bilirubin in the samples on assay performance was not evaluated at any of the three sites, which ought to have been performed.</i>	
ADA Assay Hemolysis Resistance				
The Applicant sought to draw further comparison between the (b) (4) and (b) (4) ADA assays that were both based on the Applicant's original ADA assay CP2021V-054, that was only used for immunogenicity analysis of Phase 1 and 2 studies. Cross-validation between the Janssen (Johnson and Johnson Innovative Medicine (JJIM)) developmental ADA assay and the (b) (4) assay was performed by head-to-head screening and confirmatory analysis of 10 mock samples (see below).				
Summary of Mock Sample ADA Classification at JJIM, (b) (4) and (b) (4) Labs				
Sample Label	Sample contents	JJIM confirmatory classification	(b) (4) confirmatory classification	(b) (4) confirmatory classification
JNJ-2113Mock01	150 ng/mL PTGBB4 in nNHS	ADA positive	ADA positive	ADA positive
JNJ-2113Mock02	600 ng/mL PTGBB4 in nNHS	ADA positive	ADA positive	ADA positive

JNJ-2113Mock03	300 ng/mL PTGBB4 and 0.25 µg/mL JNJ-77242113 in nNHS	ADA positive	ADA positive	ADA positive
JNJ-2113Mock04	nNHS	ADA negative	ADA negative	ADA negative
JNJ-2113Mock05	600 ng/mL PTGBB4 and 0.75 µg/mL JNJ-77242113 in nNHS	ADA positive	ADA positive	ADA positive
JNJ-2113Mock06	300 ng/mL PTGBB4 in nNHS	ADA positive	ADA positive	ADA positive
JNJ-2113Mock07	0.25 µg/mL JNJ-77242113 in nNHS	ADA negative	ADA negative	ADA negative
JNJ-2113Mock08	300 ng/mL PTGBB4 and 0.75 µg/mL JNJ-77242113 in nNHS	ADA positive	ADA positive	ADA positive
JNJ-2113Mock09	0.75 µg/mL JNJ-77242113 in nNHS	ADA negative	ADA negative	ADA negative
JNJ-2113Mock10	150 ng/mL PTGBB4 and 0.25 µg/mL JNJ-77242113 in nNHS	ADA positive	ADA positive	ADA positive
<u>Assessor comment:</u> The results of the ADA cross-analysis of the same samples between JJIM, (b) (4) and (b) (4) demonstrated 10/10 agreement in confirmatory evaluation of the samples, which supports that the analytical ADA results obtained at (b) (4) and (b) (4) are comparable to those that would have been obtained by the JJIM laboratory.				
<u>Overall ADA assay assessment:</u> The two ADA assays utilized for the Phase 3 testing of JNJ-77242113 (icotrokinra) are adequately validated and assessed to be appropriate for immunogenicity testing sera of patients administered with icotrokinra. Importantly, several differences exist in the assays, such as the matrix sources, which is justifiable given the patient populations relevant to the clinical trial locations. There were slight issues with precision in the (b) (4) ADA assay, however they were assessed to be minor, with little potential impact to the accurate execution of the assay. Furthermore, validation of the assays in the face of potential serum contaminants (blood, lipid, bilirubin) could have been tested to a greater extent.				

Neutralizing antibody (NAb) assays: The basis of the NAb assay lays in the competitive binding of NAb to drug immobilized in wells of MSD plates, which blocks (neutralizes) the subsequent interaction of the MSD plate-immobilized drug with ruthenium-labeled soluble IL-23R that is added to the wells. In the absence of NAb, the ruthenium-labeled soluble IL-23R is uninhibited from binding to the MSD plate-immobilized drug, thus bringing ruthenium into connection with the MSD plate, which when electrified stimulates the ruthenium to emit luminescence. In contrast, when NAb is present, the MSD plate-immobilized drug is prevented (i.e. blocked/neutralized) from interacting with the ruthenium-labeled soluble IL-23R. Therefore, ruthenium is prevented from coming into connection with the MSD plate, does not receive electrical stimulation, and does not luminesce. Thus, the presence of NAb is revealed by the diminishment of ruthenium-labeled soluble IL-23R luminescent signal as compared to the brighter luminescent signal when NAb is absent.

Assessors comment: The magnitude of luminescent signal intensity will be inversely proportional to the abundance of NAb in the assay. More NAb will result in relatively less luminescent signal, while less NAb will result in relatively more luminescent signal.

Detection of Neutralizing Antibodies (NAb) Against JNJ-77242113 in Human Patient Sera of Phase 3 clinical trials [NAb Assays: (b) (4) and (b) (4)]			
Validation Parameter	(b) (4) NAb assay: Project #2329-160700	(b) (4) NAb assay: Report # (b) (4) J01-R5122	Assessor Comment

NAb Assay Contract research org. (CRO)	(b) (4) Statistical analyses for NAb assay cut point determinations was contracted to (b) (4)	(b) (4)	None.
Associated clinical trials for JNJ-77242113	PSO3001, PSO3002, PSO3003, PSO3004 (USA)	PSO3001 (China)	Only samples obtained from Chinese patients enrolled in PSO3001 (101 total subjects) were analyzed at (b) (4)
NAb Assay principle	MSD ECL bridging immunoassay	MSD ECL bridging immunoassay	The NAb assays utilized at (b) (4) and (b) (4) for P3 clinical trials were both transferred from the developmental ADA method initiated at Janssen R&D, which had been used for analyzing their preliminary P1 and P2 trial data.
NAb Assay Sample Pretreatment (Acid dissociation)	Samples are <u>pre-treated with acetic acid</u> to dissociate drug-NAb complexes, then neutralized with HEPES buffer containing biotinylated drug, which captures the dissociated NAb for subsequent immobilization on streptavidin-coated MSD plate surface.	Samples are <u>pre-treated with acetic acid</u> to dissociate drug-NAb complexes, then neutralized with HEPES buffer containing biotinylated drug, which captures the dissociated NAb for subsequent immobilization on streptavidin-coated MSD plate surface.	The same assay principle is employed at both (b) (4) and (b) (4) because the assay was transferred to both sites from Janssen.
NAb Assay Matrix and negative control (NC)	- Normal human serum Lot NB267-01 - Neg. Cont. / Bkgd. Cont. Lots NB288-01, NB288-02	Pooled normal human serum (b) (4); Individual healthy naïve normal human serum (nNHS) (b) (4) Individual Psoriasis Human Serum (Janssen), Individual Ulcerative Colitis Human Serum (Janssen)	The listed sources of the matrices are applicable to the purpose – for the (b) (4) assay, sera is sourced from local supplies appropriate to the specified patient population.
NAb Assay Surrogate Positive Control antibody (SPC)	Rabbit anti-JNJ-77242113 pAb, Lot MOS00431621, Lots NB288-01, NB288-02; Exp. 04-March-2026	pAb from rabbit serum 1082, Lot MOS00431621; Exp. 04-Mar-2026	Both (b) (4) and (b) (4) NAb assays use the rabbit pAb.
NAb Assay Study Drug	JNJ-77242113 Lot# MOS00397904 (Janssen Research & Development, LLC) Expiry: 05-May-2028 Storage: -80°C	JNJ-77242113 Lot# MOS00397904 (Janssen Research & Development, LLC) Expiry: 05-May-2028 Storage: -80°C	The same lot of study drug was used for validation of both the (b) (4) and (b) (4) assays, which is appropriate.
NAb Assay Low positive control (LPC)	Serial 2x dilutions of the PC (5000 to 78.13 ng/ml) were measured 8 times by 3 analysts over 2 days, with linear interpretation on the dose-response curves. The target LPC concentration was derived statistically based on population-specific cut-points targeting 1% FNR by the B2S contract laboratory.	350 ng/mL in undiluted pooled NHS: (b) (4) used a single LPC of 350 ng/mL for all populations based on combined population analysis that yielded a single cut point of 17.27%.	The disease-specific approach to LPC determination by (b) (4) is justified, recognizing that different immunological conditions could lead to different behavior in the assay, which is plausible. Targeting a 1% FNR is also justified. Rounding the concentrations to the nearest factor of 10 appears to be low-

	Normal/PSA LPC = 417 ng/ml; rounded to 420 ng/ml Psoriasis LPC = 1157 ng/ml; rounded down to 700 ng/ml UC LPC = 525 ng/ml (not rounded)		risk. However, the shift by (b) (4) for the Psoriasis-specific LPC from the calculated 1157 ng/ml to 700 ng/ml (highlighted) seems extreme. No scientific rationale was provided by (b) (4) and the potentially drastic change to the FNR was not addressed. The shift does bring the psoriasis LPC more in line with those of the other conditions. Additionally, it seems irregular that the 700 ng/ml LPC chosen for Psoriasis NAb assay is the same concentration as the chosen assay HPC. In Hook effect testing (see below) it was demonstrated that even PC concentration up to 20,000 ng/ml did not result in upward sloping of the response curve, so it was unclear why a higher HPC for Psoriasis was not chosen by (b) (4). In any case, from the perspective of direct patient risk, the change of LPC from 1157 ng/ml to 700 ng/ml for Psoriasis by (b) (4) does not alter the assay sensitivity, nor does it alter potential patient classification, because it does not affect the assay sensitivity or cut point. Therefore, it does not seem likely that using 700 ng/ml for the Psoriasis patient LPC by (b) (4) would directly affect the safety of clinical subjects. However, from a QC perspective, having a similar LPC and HPC eliminates the ability to have a multi-point control curve for evaluation of assay dose-response, which might render the assay as lacking a controlled dynamic range for psoriasis sera. Additionally, it poses potential issues with AC, as it is difficult to imagine that an ordered readout of controls requiring HPC < LPC would be possible. It seems that the (b) (4) team realized that the possibility of having HPC the same as LPC was awkward, and in cases when experimental designs called for HPC and LPC to be run in the same experiment, a different LPC was chosen, such as 420 ng/ml.
NAb Assay Mid positive control (MPC)	n/a	n/a	
NAb Assay High positive control (HPC)	700 ng/ml; 5,000 ng/ml (titer PC)	700 ng/mL in undiluted pooled NHS	

			On the other hand, the (b) (4) NAb assay LPC determination of 350 ng/mL lacks adequate scientific justification because no compelling narrative was found on how 350 ng/mL was derived for LPC or whether it achieves any target FNR. Despite the validation deficiency, the LPC inadequacy does not actually pose a direct risk to patient safety. Indeed, patient NAb classification remains based on the established NCP cut point threshold (see below), which is not affected in a day-to-day manner by the choice of LPC. Nevertheless, the failure to justify LPC concentration is difficult to ignore.
NAb Assay Acceptance Criteria (AC)	%CV ≤ 20.0%; HPC<LPC<NC LPC replicate mean %INH≥CP	Inter-replicate %CV ≤ 20.0; 50.82%INH≤HPC≤71.72%INH; 28.04%INH≤LPC≤49.06%INH NC<17.27%INH	The ACs that were chosen are generally appropriate.
NAb Assay SPC Dose Curve / Hook Effect	Assay sensitivity and LPC determination was conducted using eight series of 2-fold SPC dilution concentrations from 5,000 to 78.13 ng/ml; <u>no upward slope (hook effect) was observed</u> in dose curves with ultra-high SPC concentrations up to 20,000 ng/ml.	Assay sensitivity and LPC determination was conducted using six series of 3-fold SPC dilution concentrations from 10,000 to 0.00 ng/ml; <u>no upward slope (hook effect) was observed</u> in dose curves with ultra-high SPC concentrations up to 10,000 ng/ml.	The SPC dose curves are adequate to cover the range of the assay responses, and the lack of hook effect up to very high SPC concentrations are acceptable.
NAb Assay Minimum required dilution (MRD)	1:10	1:10	The 1:10 MRD used for both (b) (4) and (b) (4) NAb assays is consistent with that of the original Janssen NAb assay 1:10 MRD.
NAb assay cut point (NCP)	The (b) (4) NCP were determined using 152 individual serum samples representing normal subjects, and a spectrum of inflammatory diseased subject populations, including the proposed drug indication, psoriasis (below): 50 normal/healthy 29 psoriasis (PSO) 38 ulcerative colitis (UC) 35 psoriatic arthritis (PA) Twenty plates were analyzed by three analysts using two instruments, applying a targeted FPR of 1% after removal of outliers. The calculated %Inhibition NAb cut points were calculated using mixed-effects ANOVA by robust parametric (80% LCL) approach:	The (b) (4) NCP was calculated by estimating NAb reactivity of drug naïve serum samples collected from healthy and diseased subjects; 3 populations were tested: 33 male/17 female naïve individuals 23 male/27 female UC patients 27 male/3 female PSO patients Testing was performed by 2 operators on 3 days in 10 plates, generating 400 data points to compute the NCP. Mixed effects model applied to %inhibition results, statistical comparison showed no significant differences between means or variances. Thus NCP of 17.27% inhibition was used	The derivation of the (b) (4) NCPs was similar to Janssen in taking a separate population-based approach, recognizing that patients with different conditions may have unique immunological considerations. On the other hand, (b) (4) approach of combining all populations into one NCP is not unreasonable, given that they did not find statistically significant differences between the distinct populations. This result is plausible taking into consideration that the sera used by (b) (4) are all from a single country, with a population having fairly homogeneous heritage. The NCP calculated by (b) (4)

	• <u>Normal: 22.58%</u> • <u>PSO: 48.79%</u> • <u>UC: 29.84%</u> • <u>PA: 22.58%</u>	for all populations, corresponding with 1% FPR.	<i>turns out to be numerically somewhat lower than that of (b) (4) (and also that of the original Janssen NCP), which could be the source of the dramatically higher sensitivity of (b) (4) NAb assay (see section, below).</i>
NAb Assay Sensitivity	Calculated by linear interpolation of 2-fold dilution titration curves run in duplicate by 3 analysts on 2 separate days with sensitivities obtained by back-calculation: • <u>Normal/PA: 236 ng/ml</u> • <u>PSO: 599 ng/ml</u> • <u>UC: 313 ng/ml</u>	Determined by testing serial dilutions of SPC pAb 1082 (range 10,000 to 0 ng/mL) in pooled NHS. Two operators tested over 3 days in 6 assays. Percent inhibition data fitted using 4-PL curve model; sensitivity calculated as antibody concentration producing inhibition equal to NCP (17.27%). Result: The assay sensitivity determined to be <u>69.63 ng/mL</u> of pAb SPC in 100% pooled human serum.	(b) (4) <i>sensitivity is remarkably better than (b) (4) even meeting the Agency's recommendation for 100 ng/ml, which is usually not strictly enforced for NAb assays. All of the (b) (4) sensitivities are poorer than 100 ng/ml, but are within the same order of magnitude as the developmental Janssen NAb assay (204.3 ng/ml). It is possible that the "superior" sensitivity of the (b) (4) assay may be an advantage derived from the unique circumstance of it being built around sera samples taken from a relatively homogeneous population.</i>
NAb Assay Assay Drug Tolerance	Drug Tolerance evaluated at (b) (4) by preparing SPC and drug at different 2X concentrations, then mixing 1:1 and incubating for >1 hour at RT. Samples were then frozen for at least 12 hours at -80°C before analysis. Tolerance was reported as highest drug concentration where pAb SPC samples remained positive and NC samples remained negative: • <u>420 ng/mL pAb SPC tolerated up to 1.23 ng/mL drug</u> • <u>700 ng/mL pAb SPC tolerated up to 3.7 ng/mL drug</u>	Drug Tolerance evaluated at (b) (4) by preparing drug concentration series ranging from 0 to 200 ng/mL in undiluted pooled NHS, which were then mixed with pAb SPC at 1.0 and 2.0 µg/mL. Drug and antibody sample were mixed 1:1 for analysis; %INH was plotted against drug concentrations, curves were fitted by 4-PL model. • <u>0.5 µg/mL pAb SPC: tolerated ≤2.59 ng/mL drug</u> • <u>1.00 µg/mL pAb SPC: tolerated ≤7.09 ng/mL drug</u>	<i>As stated above, the Summary of Biopharmaceutical Studies section of the NDA stated that the concentration of residual drug in all samples analyzed was under 31.1 ng/ml, which may still exceed the NAb assay drug tolerances. However, the Summary of Clinical Pharmacology Studies document indicates that in most cases, patient C_{trough} were typically <1 ng/ml - therefore, if patient sample collection for immunogenicity is coordinated with the C_{trough} drug concentration (ie. collected just before receiving the daily dose), there is a good chance that the residual drug concentration in patients will be within the drug tolerance level of the NAb assays.</i>
NAb Assay Target (IL-23R) Interference	The NAb assay was spiked with sIL-23R up to 200 ng/ml; no interference detected in wells of pAb SPC, however at ≥100 ng/ml sIL-23R, false positives were observed in wells with no addition of SPC (0 ng/ml).	The NAb assay was spiked with sIL-23R up to 10,000 ng/ml in NHS; 4-PL curve fitting calculation showed target tolerance up to 51.96 ng/ml sIL-23R; sIL-23R concentrations higher than 51.96 ng/ml caused increasing NAb assay % inhibition, leading to false positivity readout.	<i>The (b) (4) and (b) (4) NAb assays both developed false positivity readings at high levels of sIL-23R (≥100 ng/ml, and ≥51.96 ng/ml). The extent to which sIL-23R could be found in human serum, even that of PSO, PA, or UC patients is not currently well characterized, but thought to</i>

			<i>be low. In any case, the potential for patient risk associated with false-positivity due to sIL-23R interference is regarded as less severe than if it was associated with false-negativity; and therefore the risk is acceptable.</i>
NAb Assay Precision	Precision was evaluated over 6 assay runs by 2 analysts over 3 days, using at least 6 replicates of each SPC, 12 wells of Normalization Control, and 12 wells of bkgd control per plate. <u>Intra-assay (Repeatability)</u> NC: 4.6-8.3% CV BC: 2.9-5.5% CV LPC (420ng/mL): 2.6-6.5% CV HPC (700ng/mL): 1.8-10.2% CV <u>Inter-assay (Reproducibility)</u> NC: 13.7% CV BC: 8.9% CV LPC (420ng/mL): 18.4% CV HPC (700ng/mL): 20.4% CV	Precision was evaluated over 3 runs by 2 analysts over 3 days, using 8 sets of each control including normalization control with 2 replicates/set/run. <u>Intra-assay (Repeatability)</u> NC: range 3.7-4.8% LPC: 2.6-5.5%CV across runs HPC: 2.8-3.6% CV across runs <u>Inter-assay(Reproducibility)</u> NC: range 3.7-4.8% LPC: 13.1%CV across runs HPC: 12.3% CV across runs	<i>Assay precision (both intra- and inter-) were demonstrated to be generally adequate at both (b) (4) and (b) (4). One concern was observed in a slight exceeding of acceptance criteria by the HPC testing at (b) (4) (highlighted in yellow), however the amount was fairly minor, and at high antibody concentration, it is plausible that even slight variations would be amplified to greater degree.</i>
NAb Assay Selectivity	10 samples were tested for each serum type with or without pAb PC: normal, PSO, UC. Normal: 10/10 samples were positive, 10/10 negatives were negative. PSO: 10/10 samples were positive, 10/10 negatives were negative. UC: 10/10 samples were positive, 10/10 negatives were negative.	10 samples were tested for each serum type with or without pAb PC: normal, PSO, UC. Normal: 10/10 samples were positive, 10/10 negatives were negative. PSO: 10/10 samples were positive, 10/10 negatives were negative. UC: 10/10 samples were positive, 10/10 negatives were negative.	<i>The ability of the assays to successfully differentiate samples with antibody from samples without antibody is supportive of assay adequate assay selectivity.</i>
NAb Assay Stability	Studies conducted using 3 aliquots each of NC, LPC, and HPC. <u>F/T stability</u>: 6 cycles of 12 hour freeze, thaw for 30 min to 2 hour; all samples tested as expected. <u>RT stability</u>: 17 hours RT storage; all samples tested as expected. <u>Refrigerator stability</u>: 17 hours refrigerated storage; all samples tested as expected. <u>Long term storage</u>: Relying on literature reports of antibody stability under freezing conditions for 2 or more years.	Studies conducted using 3 aliquots each of LPC, and HPC. <u>RT stability</u>: storage for >48 hours; all samples tested as expected. <u>Refrigerator stability</u>: storage for >48 hours; all samples tested as expected. <u>F/T stability</u>: 7 cycles of 12 hour freeze, thaw for at least 1 hour; all samples tested as expected	<i>The ability of the NAb assays to successfully read samples that had been subjected to temperature excursions, or stored inappropriately, is supportive of adequate assay stability.</i>
NAb Assay Robustness	Robustness was tested by varying incubation times for steps of acid dissociation, neutralization, plate incubation, and detector incubation, by up to $\pm 16.7\%$, built into the precision runs. Despite the variances in the incubation	The NAb assay tolerated various alterations of timing in the acid step, mix incubation step, blocking step, sample incubation step, and sulfo-tag incubation step. Time variations were generally 5-10 minutes; all assay performances were	<i>The robustness testing had sufficiently acceptable results, but the study design could have been more rigorous - for example, with variations in more parameters such as temperature, pipetting technique, and different lots of</i>

	timing, all precision runs met acceptance criteria, and no significant impact on assay performance was observed.	acceptable under the robustness testing.	<i>critical reagents. More rigor in the robustness testing would provide increased confidence in the robustness results.</i>
NAb Assay Specificity	Neither addition of irrelevant antibody C3AB11 nor irrelevant peptide RPGR caused false positivity or false negativity.	Unrelated ADA (GP5B7) and unrelated biologic (RPGR peptide 1) were used in the NAb assay, and all dilutions (up to 10,000 ng) of either unrelated substance failed to produce %INH above the cut point (all were tested negative)	<i>The Specificity testing results at both the (b) (4) and (b) (4) sites were supportive of adequate Specificity.</i>
NAb Assay Lipemia Resistance	Only 1 NAb SPC sample each was tested for lipemia (>300 mg/dL triglyceride) and hemolysis (~1100 mg/dL). <u>Lipemic</u> : 1/1 pooled sample passed. <u>Hemolytic</u> : the hemolysis sample was inconclusive because despite the %inhibition exceeding the NCP, the no-Ab (unspiked) control also tested positive (no-Ab control should test negative).	5 samples were tested for lipemia (~300 mg/dL triglyceride) and hemolytic (2% hemolysis). <u>Lipemia</u> : 5/5 samples passed <u>Hemolytic</u> : 5/5 samples FAILED (negative control wells tested positive); repeat assay resulted in 4/5 sample failures.	<i>The (b) (4) lipemia testing supported resistance to lipid contamination, though the sample size was limited to 1. Testing of 6 lipemic samples during the developmental stage of the NAb assay at Janssen demonstrated 6/6 NAb assay sample resistance to lipemia. Lipemia testing at (b) (4) used more samples (5) than at (b) (4) (only 1 sample), and all five (b) (4) lipemic test samples were successful.</i> <i>The (b) (4) hemolysis testing was inconclusive – though the single test of NAb SPC in hemolyzed environment was appropriately positive because of exceeding the NCP, the no-Ab control was a false-positive. It is not inconceivable that a false positive would occur, as FPR is built into the NCP calculation. However, the experiment was not reported to be repeated for verification at (b) (4)</i> <i>(b) (4) hemolysis testing was even more problematic, with a high false-positivity rate, exceeding what could plausibly be expected given the NCP FPR of 1%. However, having high FPR for the hemolysis aspect of the NAb assay may not be an overwhelming safety issue, as it does not affect the NCP, NAb assay sensitivity, or lead to risk of false negativity – it may even lessen the risk of false negativity by boosting false positivity. However, it may negatively affect the QC aspects of the assay, which could feed back into other aspects of the assay. It is</i>
NAb Assay Hemolysis Resistance			

		<i>noted that the original NAb assay hemolysis testing performed for the Janssen developmental NAb assay was similarly affected with poor hemolysis resistance. It is also noteworthy that the NAb assay 1:10 MRD is 5-times less than the ADA assay 1:50 MRD. It is possible that higher MRD, or more extreme measures such as specifying a SPEAD-type of sample pre-purification step for the NAb assay may help to alleviate the potential problem of interference by hemolysis. This would be a major undertaking that would likely necessitate a complete reevaluation of the entire NAb assay framework. Additionally, common serum contaminant testing such as bilirubin was not reported, which could be a further problem.</i>
<i><u>NAb Assay Overall Assessment:</u> The NAb assays of (b) (4) and (b) (4) each have some issues that may be difficult to overlook. Primarily, the choice of Psoriasis LPC by (b) (4) was not adequately explained or justified. Though it is not thought that the LPC choice by (b) (4) would explicitly impact on patient safety, as it should not have a direct effect on the assay sensitivity, or the judgement of whether a sample is positive or negative, it may have effect on the detection of irregularity with the assay instrument(s), which over time could result in quality control issues, and perturb the accurate function and/or readout of the assay. Another potentially serious issue is the seemingly intolerant state of the assays to contamination by products of hemolysis, which appeared to permeate both (b) (4) and (b) (4) going back even to the original developmental pre-Phase 3 NAb assay from Janssen. From an assay perspective, the hemolysis intolerance issue is a grave one; however from the perspective of clinical safety, the potential for serious harm to patients is less clear-cut. The experimental evidence seems to indicate that hemolysis products could result in inflated FPR of the assay, which is not in itself a major contributor to elevated patient risk. It could even be (optimistically) thought of as the opposite of risk – through inducing increased clinical vigilance and care for patients that appear to be developing NAb, even though the NAb may simply be artefactual from the effect of the assay. Ultimately, patient care should be dictated by clinical signs and symptoms, and it is beyond the expertise of the OPQR Immunogenicity team to make any supposition as to how patients will be clinically treated in response to immunogenicity assay results.</i>		

Summary of reported immunogenicity results from four Phase 3 trials of icotrokinra (reported in the [Integrated Summary of Immunogenicity](#)):

Overall Incidence of Anti-Drug Antibodies (ADA) through Week 52:

- ADA: 9.6% (199/2,083 participants)
- NAb: None detected (0/199 ADA-positive participants)

Overall ADA Titer Distribution:

- 59.8% (119/199) had the lowest titer of 1:50
- 37.2% (74/199) had titers between 100 and <1,000
- 3.0% (6/199) had titers ≥1,000
- Highest titer observed: 1:6,400 (in 1 participant)

Effect on Pharmacokinetics:

- Applicant reported that among ADA-positive participants, C_{max} increased by 1.2-fold and AUC by 1.3-fold compared to ADA-negative participants
- Applicant did not consider these changes to be clinically relevant

(Assessor comment: Given the nature of the drug, it is plausible that ADA could result in extension of the drug half-life. However, considering the competitive antagonist MOA of the drug, it does not appear that this phenomenon would result in decreased effectiveness.)

Effect on Efficacy:

- No clinically meaningful impact on efficacy endpoints was noted by the Applicant
- Applicant indicated that across trials, ADA development and titer levels did not reduce treatment effectiveness

Effect on Safety:

- No apparent relationship was observed by the Applicant between ADA incidence and hypersensitivity reactions
- Applicant reported that higher ADA titers were not associated with trend toward increased adverse events

Key Immunogenicity Conclusions:

1. ADA incidence (9.6%)
2. Predominantly low titers
3. No neutralizing antibodies detected
4. Applicant did not correlate immunogenicity with any clinically meaningful impact on pharmacokinetics, efficacy, or safety
5. Overall, the Applicant found that immunogenicity had no observed impact on the benefit/risk balance of icotrokinra

Immunogenicity Assessment Conclusion:

In summary, the immunogenicity assessment of icotrokinra (JNJ-77242113) for NDA 220149 reveals that while both the ADA and NAb assays employed by (b) (4) and (b) (4) laboratories demonstrate generally adequate validation for Phase 3 clinical trial support, several notable issues were observed. The ADA assays showed acceptable performance across most validation parameters, with minor concerns regarding precision at (b) (4) and limited evaluation of potential serum contaminants (particularly bilirubin) at both sites. The NAb assays exhibited several issues including inadequately justified control concentrations at (b) (4) (particularly the psoriasis LPC selection) and concerning susceptibility to hemolysis-induced false positivity at both laboratories and inadequate drug tolerance. Despite the analytical limitations, overall risk to patient safety appears manageable, as the assays' deficiencies tend toward increased clinical vigilance rather than under-detection of immunogenicity. The cross-validation studies demonstrating 100% concordance between JJIM, (b) (4), and (b) (4) laboratories provide support regarding the comparability of results across testing sites.

Therefore, the assays are deemed acceptable for their intended purpose of monitoring immunogenicity in icotrokinra-treated patients.

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Clinical Inspection Summary

Date	1/23/2026
From	Stephanie Coquia, MD, Reviewer 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	Kathleen Butler, MD, Clinical Reviewer Mary Kim, MD, Clinical Team Leader Tina Whang, Regulatory Project Manager Division of Dermatology and Dentistry (DDD)
NDA #	220149
Applicant	Janssen Biotech Inc.
Drug	Icotrokinra
NME (Yes/No)	Yes
Therapeutic Classification	Interleukin (IL)-23 receptor antagonist peptide
Proposed Indication	For the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy
Consultation Request Date	8/29/2025
Summary Goal Date	2/2/2026
Action Goal Date	3/17/2026
PDUFA Date	3/18/2026

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Janssen Biotech Inc., submitted clinical data from Studies 77242113PSO3001 LEAD (NCT06095115), 77242113PSO3002 ADVANCE 1 (NCT06143878), and 77242113PSO3004 ADVANCE 2 (NCT06220604) to support a New Drug Application (NDA 220149) for icotrokinra. The proposed indication is for the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy.

Three clinical investigators (Drs. Toth, Brzewski, and Weyergraf) were inspected.

At Dr. Weyergraf's site, Subject (b) (6) (icotrokinra arm) experienced a mild adverse event (AE, common cold) that was entered into the eCRF 7 months late and was not included in the 120-day safety update report (SUR). This was previously communicated to the Division on January 5, 2026. Additionally, Subject (b) (6) (placebo to icotrokinra arm) was discontinued after an elevated PHQ-9 score (15, moderately severe depression) while on icotrokinra. This was reported as a study discontinuation but not recorded as a separate

AE. OSI recommends the review division include these events in their safety analysis. Otherwise, inspections did not find significant concerns regarding the conduct of the clinical trials or GCP or regulatory compliance. Overall, the data generated by the clinical sites and submitted by the Applicant appear acceptable in support of the proposed indication.

II. BACKGROUND

Janssen Biotech Inc. seeks approval of an NDA for icotrokinra for the above proposed indication. In support of the NDA, the Applicant submitted clinical data from Studies 77242113PSO3001 LEAD, 77242113PSO3002 ADVANCE 1, and 77242113PSO3004 ADVANCE 2. The following is a summary of the study protocols and key study information relevant to the clinical inspections.

Study Designs

LEAD was a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter interventional study with randomized withdrawal and retreatment in participants with moderate to severe plaque psoriasis.

ADVANCE 1 and **2** were phase 3, randomized, double-blind, active comparator- and placebo-controlled, parallel-group, multicenter, interventional studies in adults with moderate to severe plaque psoriasis. Deucravacitinib was the active comparator in these trials.

Objectives and Endpoints

The **primary objective** for all three studies was to evaluate the efficacy of icotrokinra compared with placebo in participants with moderate to severe plaque psoriasis.

The **co-primary endpoints** for all three studies were:

- Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (minimal) and a ≥ 2 -grade improvement from baseline at Week 16
- Psoriasis Area and Severity Index (PASI) 90 at Week 16: 90% improvement in PASI score from baseline at Week 16

Key Eligibility Criteria

- Age:
 - LEAD: ≥ 12 years of age
 - ADVANCE 1 and 2: ≥ 18 years of age (or age of legal consent)
- Weight (LEAD only): For those < 18 years of age, body weight ≥ 40 kg
- Diagnosis of plaque psoriasis, with or without psoriatic arthritis, for at least 26 weeks
- Total body surface area (BSA) $\geq 10\%$ at screening and baseline
- Total PASI ≥ 12 at screening and baseline

- Total IGA ≥ 3 at screening and baseline
- Candidate for systemic treatment or phototherapy
- None of the following:
 - Contraindications, hypersensitivities, allergies, or intolerance to deucravacitinib (ADVANCE 1 and 2), icotrokinra, or their components
 - Nonplaque form of psoriasis
 - Current drug-induced psoriasis
 - Previous receipt of icotrokinra or deucravacitinib (ADVANCE 1 and 2)
 - No response or clinically significant AE related to agents directly targeting IL-23 or tyrosine kinase 2 (TYK2) inhibitor (ADVANCE 1 and 2)
 - Patient Health Questionnaire-9 (PHQ-9) ≥ 15 or with suicidal ideation/self-injurious behavior (LEAD)
 - Prohibited medications, including biologics and systemic immunomodulators (without the associated washout, if applicable)
 - Chest imaging suggestive of malignancy or active infection, including TB
 - Positive testing for Hepatitis B or C, HIV, or TB
 - Chronic, serious, or recurrent infectious disease or malignancy

Study Conduct

For LEAD, 138 sites enrolled at least 1 subject. The study was initiated October 12, 2023, and was on-going at the time of NDA submission; efficacy data was submitted through Week 52, and safety data was submitted through April 3, 2025.

For ADVANCE 1, 149 sites enrolled at least 1 subject. The study was initiated January 17, 2024, and was on-going at the time of NDA submission; efficacy data was submitted through Week 24, and safety data was submitted through April 3, 2025.

For ADVANCE 2, 114 sites enrolled at least 1 subject. The study was initiated March 9, 2024, and was on-going at the time of NDA submission; efficacy data was submitted through Week 24, and safety data was submitted through January 6, 2025.

For all three studies, the data cut-off date for the 120-day SUR was July 24, 2025.

III. RESULTS

1. Dr. Ansgar J. Weyergraf (Site BR4-DE10032, ADVANCE 1)

Hasestrasse 17

Bramsche, Lower Saxony, 49565 Germany

Inspection Dates: October 20-24, 2025

This investigator was inspected as a BIMO Review-based inspection for Study 77242113PSO3002 ADVANCE 1. This was the investigator's first FDA inspection.

The site screened 15 subjects and enrolled and randomized 14 subjects. One subject was discontinued by the clinical investigator (see below), therefore, 13 subjects completed the study.

The subject records of all enrolled subjects were reviewed and included: informed consent forms (ICFs), electronic case report forms (eCRFs), chest x-ray and laboratory reports, electrocardiograms (ECGs), medical records from outside institutions, and documentation of eligibility, investigational product (IP) dispensing, study assessments, AEs, protocol deviations, and subject follow-up.

Study- and site-related documents and records reviewed included: the protocol, signed investigator agreements, financial disclosures, the study delegation log, ethics committee (EC) and sponsor correspondence, and documentation related to IP management, training, and monitoring.

The source data for the three IGA component scores, total IGA scores, 16 component PASI scores, and total PASI scores at baseline and Week 16 were compared to the submitted data for all subjects without discrepancies identified.

Subject (b) (6) (placebo to icotrokinra arm) was discontinued on (b) (6), after an elevated PHQ-9 score (15, moderately severe depression) at study Visit 9/Week 24 (b) (6) while on icotrokinra. Follow-up was conducted, and the clinical investigator elected to discontinue the subject from the study as a precaution. This was reported as a study discontinuation but not recorded as a separate AE.

Reviewer Comment: We recommend the review division include this event (PHQ-9 score =15) in the safety analysis.

There were two mild AEs that were reported late:

- Subject (b) (6) (deucravacitinib to icotrokinra arm): Experienced a common cold on (b) (6) (while taking icotrokinra). Entered into the eCRF on May 27, 2025 (b) (6)
- Subject (b) (6) (icotrokinra arm): Experienced a common cold on (b) (6) (b) (6). Entered into the eCRF on September 26, 2025 (b) (6)

Both AEs were not included in the original submission, however, Subject (b) (6)'s AE was included in the eCRF on May 27, 2025, before the 120-day SUR July 24, 2025, cutoff.

Reviewer comments:

- *The primary review team was informed of the AEs listed above via email on January 5, 2026.*
- *Subject (b) (6)'s AE was entered into the eCRF on September 26, 2025, after the data cut-off for inclusion in the 120-day SUR (July 24, 2025), and we recommend*

the review division consider this event in their safety analysis.

There was no underreporting of significant protocol deviations identified.

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

2. Dr. Pawel Brzewski (Site BR5-PL10009 LEAD and Site CB4-PL0009 ADVANCE 2)

Ulica Zbozowa 2/25

Cracow, Malopolskie, 30-002 Poland

Inspection Dates: November 10-14, 2025

This investigator was inspected as a BIMO Review-based inspection for Studies 77242113PSO3001 LEAD and 77242113PSO3004 ADVANCE 2. This was the investigator's first FDA inspection.

The site screened 15 subjects and enrolled and randomized 12 subjects for LEAD. One subject withdrew early due to lack of efficacy. For ADVANCE 2, the site screened, enrolled, and randomized 16 subjects and received three subjects from terminated site CB4-PL10015 (Subjects [REDACTED] (b) (6)). Two subjects from the site withdrew (one due to lack of efficacy and another for pregnancy planning).

The subject records of all enrolled subjects at the site and of the three transferred were reviewed and included: ICFs, medical records, study notes, and documentation of eligibility review, randomization, IP dosing, concomitant medications, AE reporting, IGA and PASI assessments, and questionnaires.

Study- and site-related documents and records reviewed included: signed investigator agreements, financial disclosure forms, the protocol, training records, enrollment logs, IP accountability records, and documentation of EC oversight and monitoring by the sponsor.

For both studies LEAD and ADVANCE 2, the source data for the IGA and PASI scores at baseline and Week 16 for all subjects were compared to the submitted data without discrepancies identified. There was no underreporting of significant protocol deviations identified.

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

3. Dr. Darryl P Toth (Site BR5-CA10022 LEAD and Site BR4-CA10022 ADVANCE 1)

6160 Tecumseh Rd E Suite 201

Windsor, N8T 1E6

Inspection Dates: December 2-11, 2025

This investigator was inspected as a BIMO Review-based inspection for Studies 77242113PSO3001 LEAD and 77242113PSO3002 ADVANCE 1. This investigator was last inspected in 2018.

The site screened 27 and enrolled and randomized 24 subjects for LEAD. Two subjects withdrew early due to lack of efficacy. For ADVANCE 1, the site screened 23 and enrolled and randomized 18 subjects. One subject withdrew early due to lack of efficacy. The subject records of all enrolled subjects at the site were reviewed and included: ICFs, medical records, x-ray reports, visit notes, and documentation of eligibility review, randomization, IP dosing, concomitant medications, AE reporting, IGA and PASI assessments, and questionnaires.

Study- and site-related documents and records reviewed included: the clinical study contract, financial disclosure forms, the protocol, enrollment logs, laboratory certifications, training records, IP accountability records, and documentation of investigational review board (IRB) oversight and monitoring by the sponsor.

For both studies LEAD and ADVANCE 1, the source data for the IGA and PASI scores at baseline and Week 16 for all subjects were compared to the submitted data without discrepancies identified. There was no underreporting of significant protocol deviations or AEs identified.

Based on the results of the inspection, the data generated at Dr. Toth'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

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Review Division/Cross Discipline Team Lead/Mary Kim
Review Division/Clinical Reviewer/Kathleen Butler
OSI/Office Director/David Burrow
OSI/GCP Program Analysts/Yolanda Patague

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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: January 22, 2026

To: Tina Whang, PharmD
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)

Laurie Buonaccorsi, PharmD
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Jessica Chung, PharmD, MS
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Eunice Chung-Davies, PharmD, MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): ICOTYDE (icotrokinra)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 220149

Applicant: Janssen Biotech, Inc.

1 INTRODUCTION

On July 18, 2025, Janssen Biotech, Inc. submitted for the Agency's review an original New Drug Application (NDA) 220149 for ICOTYDE (icotrokinra) tablets. The proposed indication is for the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy.

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 July 30, 2025, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ICOTYDE (icotrokinra) tablets.

2 MATERIAL REVIEWED

- Draft ICOTYDE (icotrokinra) tablets PPI received on July 18, 2025, and received by DMPP and OPDP on January 13, 2026.
- Draft ICOTYDE (icotrokinra) tablets Prescribing Information (PI) received on July 18, 2025, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 13, 2026.

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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/s/

JESSICA M CHUNG
01/22/2026 10:57:32 AM

EUNICE H CHUNG-DAVIES
01/22/2026 11:38:45 AM

LAURIE J BUONACCORSI
01/22/2026 12:27:58 PM

BARBARA A FULLER
01/22/2026 12:31:23 PM

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

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

Memorandum

Date: January 22, 2026

To: Tina Whang, Regulatory Project Manager, Division of Dermatology and Dentistry (DDD)

Kathleen Butler, DDD

Matthew White, Associate Director for Labeling, DDD

From: Eunice Chung-Davies, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for icotrokinra tablets

NDA/BLA: NDA 220149

Background:

In response to DDD's consult request dated July 30, 2025, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for icotrokinra tablets.

PI/PPI:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on January 13, 2026, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed PPI, 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 submitted by the sponsor to the electronic document room on December 23, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Eunice Chung-Davies at 301-796-4006 or Eunice.Chung-Davies@fda.hhs.gov.

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/s/

EUNICE H CHUNG-DAVIES
01/22/2026 09:26:25 AM

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)

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

Date of This Review:	December 31, 2025
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 220149
Product Name, Dosage Form, and Strength:	Icotyde (icotrokinra) tablet, 200 mg
Applicant Name:	Janssen Biotech, Inc (Janssen)
FDA Received Date:	December 23, 2025
TTT ID #:	2025-15581-1
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Janssen Biotech, Inc submitted revised container label and carton labeling received on December 23, 2025 for Icotyde. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container label and carton labeling for Icotyde (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

Janssen Biotech, Inc implemented all of our recommendations and we have no additional recommendations at this time.

^a Hakeem, S. Label and Labeling Review for Icotyde (NDA 220149). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 OCT 27. TTT ID: 2025-15581.

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/s/

VALERIE S VAUGHAN
12/31/2025 09:33:14 AM

YEVGENIYA M KOGAN
12/31/2025 09:49:36 AM

Division of Gastroenterology Consult Memo

Date: December 23, 2025

To: Kathleen Butler, MD, Medical Officer, Division of Dermatology and Dental (DDD)
Mary Kim, MD, Lead Physician, DDD

From: Jaime Wolfe, MD, Medical Officer, Division of Gastroenterology (DG)

Through: Irena Lavine, MD, Acting Lead Physician, DG
Juli Tomaino, MD, MS, Deputy Division Director, DG

Subject: Evaluation of a potential safety risk of gastrointestinal bleeding with icotrokinra

Drug Product(s):	Name	Application	Application Holder/Sponsor ¹
	Icotrokinra	NDA 220149	Janssen Biotech, Inc.

Proposed Product Indication:	Icotrokinra is an orally administered cyclic peptide under development for the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy.
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Date Requested: July 18, 2025

I. Consultation Request

The Division of Dermatology and Dental (DDD) requests the Division of Gastroenterology (DG) consultation to evaluate potential safety risks of gastrointestinal (GI) bleeding with use of icotrokinra in patients with moderate to severe plaque psoriasis, including two deaths attributed to upper GI bleeding and two serious adverse events (SAEs; perforated gastric ulcer with peritonitis and rectal hemorrhage), all of which occurred on study drug.

Specifically, the DG team was asked to provide input on the following:

1. Is this observation within the expected rate of fatal or serious upper GI bleed in this study population size, and specifically are there any concerns with 2 deaths and 1 SAE all occurring on active drug vs no cases on placebo?

¹ In the body of this review, the terms "Sponsor" and "Applicant" will refer to Janssen Biotech, Inc., unless otherwise indicated.

2. Could you please comment on the risk factors these cases had for upper GI bleed vs known risk factors in this population for UGI bleed? In particular, the Sponsor attributes increased risk of upper GI bleed from psychiatric medications in the fatal case of the 49-year old male was not aligned with review of the adverse effect profile of those drugs (which seem primarily to be associated with nausea and vomiting).
3. Any further investigations or monitoring recommended for UGI bleed or GI adverse events?

Materials reviewed for this consultation include:

Scientific literature, Applicant's submission (SDN 1) dated July 18, 2025, safety reports submitted through the FDA Adverse Event Reporting System (FAERS), labeling and/or safety data and other select documents from the NDA submissions for approved IL-23 receptor antagonists.

II. Background

Icotrokinra (JNJ-77242113) is a first-in-class, orally administered peptide that selectively binds to the IL-23 receptor (IL-23R) to competitively antagonize the binding of IL-23.² Icotrokinra is a new molecular entity (NME) in development for the treatment of moderate-to-severe plaque psoriasis, psoriatic arthritis, moderately to severely active ulcerative colitis, and moderately to severely active Crohn's disease.

This consult is being conducted as part of a New Drug Application (NDA) for icotrokinra for the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy. DDD has requested that DG evaluate the risk factors for GI bleeding in the three cases (two deaths and one SAE) who experienced upper GI bleeding and received the study drug. Of note, the 120-day safety update (submitted by the Applicant on November 12, 2025) included an additional SAE of lower GI bleeding (PT: rectal hemorrhage, reported with the nonserious adverse events [AEs] of diverticulum and hemorrhoids).

IL-23 antagonists have been used to treat a variety of chronic inflammatory diseases. Presently, there are several IL-23 antagonists administered via subcutaneous or intravenous routes that are approved for the treatment of plaque psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease. There is no known association between IL-23 antagonists and GI bleeding, and there is not a plausible biologic explanation to suspect that the drug may have caused the events.

Nonclinical data

Per discussion with the DDD clinical team, the nonclinical studies did not indicate signs of gastrointestinal toxicity in rats and monkeys with a 60-fold margin over human exposure.

Clinical data

² From Applicant, NDA 220149 *Clinical Overview*.

The safety and tolerability of icotrokinra has been evaluated in four phase 3, adequate and well-controlled, randomized trials in subjects with plaque psoriasis:³

1. PSO3001- Multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of icotrokinra 200 mg once daily; includes adults and adolescents (≥ 12 years to < 18 years and weighing ≥ 40 kg) with a total BSA $\geq 10\%$, total PASI ≥ 12 , and total IGA ≥ 3 who were candidates for phototherapy or systemic treatment. Screened: 837, randomized 684 (618 adults and 66 adolescents).
2. PSO3002- Multicenter, randomized, double-blind, placebo- and comparator-controlled (deucravacitinib 6 mg) trial to evaluate the efficacy and safety of icotrokinra vs. deucravacitinib vs. placebo to demonstrate superiority to deucravacitinib; adults only with a total body surface area (BSA) $\geq 10\%$, total Psoriasis Area and Severity Index (PASI) ≥ 12 , and total Investigator's Global Assessment (IGA) ≥ 3 who were candidates for phototherapy or systemic treatment. Planned: 750, screened 986, randomized 774.
3. PSO3003- Multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of icotrokinra 200 mg once daily dose; includes adults and adolescents (≥ 12 years to < 18 years and weighing ≥ 40 kg); inclusion of subjects with plaque psoriasis with at least moderate special area (scalp, genital, and/or hand/foot) involvement defined as overall BSA $\geq 1\%$, IGA score ≥ 2 , and at least one of the following: scalp-specific Investigator's Global Assessment [ss-IGA] ≥ 3 , and/or Physician Global Assessment of hands and/or feet [hf-PGA] ≥ 3). Planned 300, screened 366, randomized 311.
4. PSO3004- Multicenter, randomized, double-blind, placebo- and comparator controlled (deucravacitinib 6 mg) trial to evaluate the efficacy and safety of icotrokinra vs. deucravacitinib vs. placebo to demonstrate superiority to deucravacitinib; adults only with PASI ≥ 12 , IGA ≥ 3 , and BSA $\geq 10\%$, who were candidates for phototherapy or systemic treatment. Planned 675, screened 917, randomized 731.

Overall, 2,367 subjects ≥ 12 years of age with plaque psoriasis were exposed to icotrokinra; 1,849 (78.1%) were exposed for at least 6 months, and 648 (27.4%) were exposed for at least 1 year in pooled PSO3001, PSO3002, PSO3003, and PSO3004. A total of 72 adolescent subjects, ≥ 12 to < 18 years of age, were exposed to icotrokinra.⁴

Icotrokinra is not approved or marketed in any country.

III. Case Narratives and Assessments

There were two deaths attributed to upper gastrointestinal bleeding and one SAE of acute gastric ulcer perforation with peritonitis reported in the controlled clinical trials in subjects that received

³ From NDA 220149 Clinical Filing Review, Dr. Kathleen Butler, September 12, 2025.

⁴ From NDA 220149, Summary of Clinical Safety, Section 1.2.

icotrokinra. In addition, the 120-day safety update included an SAE of lower gastrointestinal bleeding (PT: rectal hemorrhage).

Based on the narratives provided in the initial NDA submission, it was not clear that these events could be reasonably attributed to risk factors related to the patients' medical and/or lifestyle history (e.g., concomitant medications, alcohol intake). Therefore, the team sent an information request (IR) to the Applicant on October 17, 2025, to submit the following information:

1. A summary table of the proportion of subjects who experienced the gastrointestinal-related adverse events specified below. Provide the data for the icotrokinra groups by dose vs. placebo that have been reported for the psoriasis and psoriatic arthritis development programs for icotrokinra. If data are available from the ulcerative colitis and Crohn's disease programs, provide a similar table.

- Gastritis
- Peptic ulcer disease
- Gastrointestinal bleed/hemorrhage
- Hematemesis/blood in vomit
- Melena/tarry stool/black stool
- Bloody stool
- Gastrointestinal ulcer
- Gastrointestinal perforation
- Mallory-Weiss tear
- Peritonitis
- Thrombocytopenia

2. Additional medical history for subjects (b) (6)

including the following or lack thereof:

- History of gastrointestinal disease and/or risks factors for gastrointestinal bleeding, including: gastritis; gastric and/or intestinal ulcer; gastrointestinal bleeding (e.g., hematemesis, melena); chronic vomiting; chronic abdominal pain; thrombocytopenia; anemia; *Helicobacter pylori*
- History of endoscopy (upper and colonoscopy) including indication for Procedure
- History of non-steroidal anti-inflammatory (NSAID), corticosteroid, and/or acetylsalicylic acid use
- Autopsy report

Applicant's IR response, received October 24, 2025

1. The Applicant indicated that the icotrokinra clinical development program includes studies in healthy volunteers (phase 1), subjects with plaque psoriasis (PsO; phase 2

and 3), ulcerative colitis (UC; phase 2), and psoriatic arthritis (phase 3). Across seven placebo-controlled studies in subjects with PsO (phase 2 and 3) and UC (phase 2) through Week 16 (with 1,762 icotrokinra-treated subjects and 698 placebo-treated subjects), a total of 7/1,762 (0.4%) subjects who received icotrokinra and 1/698 (0.1%) subjects who received placebo reported at least one of the adverse events (12 PTs above) identified for this query. Of these 7 subjects treated with icotrokinra, the reported AEs included gastritis (6), hematemesis (1), and the 1 subject who received placebo reported the AE of peptic ulcer (1).

The Applicant reported that no cases of the following selected AEs were reported in subjects who received icotrokinra through Week 16: peptic ulcer, gastrointestinal hemorrhage, melaena, feces discolored, hematochezia, gastrointestinal ulcer, gastrointestinal perforation, Mallory-Weiss syndrome, peritonitis, or thrombocytopenia. Furthermore, none of the selected AEs were identified at higher doses (300 mg, 400 mg, or 1,000 mg); thus no dose-response relationship was identified.

Reviewer Comment:

Although the placebo sample size is small (as compared to the icotrokinra sample size), there is not an imbalance in the number of subjects who reported at least one of the specified GI related AEs between the icotrokinra and placebo arms in the seven placebo-controlled studies in subjects with psoriasis and UC. Of note, based on the results reported by the Applicant in response to the IR, there were no occurrences of serious GI events, including GI bleeding, gastrointestinal ulcer, or gastrointestinal perforation, across the placebo-controlled trials in the icotrokinra development programs other than the 2 deaths and 1 SAE of gastric ulcer perforation that are the focus of this consult. We note that the analyses included in this response from the Applicant do not include data from the 120-day safety update.

2. Based on the information provided in the NDA submission and the IR above, the four cases of GI bleeding are summarized below:

Case 1. (b) (6) **(Death)**

A 49-year-old male with a history of parkinsonism, obesity, hypertension, bipolar disorder, intellectual disability, and abnormal ECG Q wave who experienced a fatal event associated with hematemesis on Study Day 17. The subject developed an SAE of tremor on Study Day 3; due to worsening tremor the study drug was discontinued on Study Day 12, with some improvement in neurological symptoms. The subject was hospitalized on Study Day 17 for the SAE of hematemesis. According to the CSR, the subject reportedly *“woke up oriented and talking, had breakfast and a juice in the middle of the morning, but had little acceptance of the lunch meal. At 3:00 PM, after the afternoon snack, the first dark colored emetic episode occurred, followed by two more dark colored, jet emetic episodes. The [participant] suffered two*

cardiorespiratory arrests, evolving to death (Source: CIOMS).” An autopsy report was not able to be obtained, however, a death certificate identified the cause of death as “Part I: A: Upper digestive hemorrhage, B: Gastroesophageal varices rupture. Part II: psoriasis - Parkinson's disease.”⁵

No known history of alcohol or smoking. Concomitant medications included benserazide hydrochloride/levodopa, lithium carbonate, aripiprazole, primidone, and losartan. Family history included intestinal cancer in his older brother. No reported subject history of gastritis, gastric/intestinal ulcer, GI bleeding, chronic vomiting, chronic abdominal pain, thrombocytopenia, anemia, or *Helicobacter pylori* infection. The investigator did not report a history of endoscopy or use of NSAIDs, acetylsalicylic acid, or corticosteroids.

Reviewer Comment:

The subject’s cause of death was determined to be bleeding from ruptured gastroesophageal varices. It is unlikely that the variceal bleeding was related to icotrokinra use as gastroesophageal varices typically develop over a longer period of time compared to the subject’s short duration of exposure to the study drug (12 days). Mortality during the acute variceal bleeding episode is high and ranges from 16% to 24% (Reverter, 2014). Rupture of gastroesophageal varices is generally due to portal hypertension, and not likely to be precipitated by mucosal irritation from icotrokinra use. Additionally, review of the subject’s concomitant medications does not indicate that they appear to increase the risk of GI bleeding in this subject (e.g., no known history of peptic ulcer disease). The subject’s cause of death was likely unrelated to icotrokinra use.

Case 2. (b) (6) (Death)

A 72-year-old male with a history of hypertension, obesity, former tobacco use, current alcohol use, and varicose veins who experienced a fatal event associated with gastrointestinal hemorrhage on Study Day 385. According to the CSR, *“It was reported that the participant had nausea for two days, followed by vomiting since the previous night, including episodes of black vomit; this was accompanied by loss of consciousness and sudden cardiac arrest; chest compressions were initiated initially but had ceased by the time of arrival of emergency medical services (Source: CIOMS).”*

Concomitant medications at study entry included acetylsalicylic acid (75 mg daily for four years) and the subject was reported to be using an anticoagulant (drug not specified) at the time of death. The subject had a history of concomitant alcohol use

⁵ From the Applicant, “Response to FDA IR,” October 17, 2025.

(50 mL liquor and 1 can beer per week since (b) (6)), former cigarette use (7 packs of cigarettes/week for 23 years; 23 pack years), and a history of gastrointestinal problems (not otherwise specified). Per the investigator, the subject did not report a medical history of gastritis, gastric and/or intestinal ulcer, gastrointestinal bleeding (e.g., hematemesis, melena), chronic vomiting, chronic abdominal pain, thrombocytopenia, anemia, or *Helicobacter pylori*, nor a history of endoscopy or NSAID or corticosteroid use. A primary care physician for the subject could not be contacted to inquire about additional medical records or history not previously disclosed. An autopsy was not performed.

Reviewer Comment:

The subject's use of acetylsalicylic acid, alcohol, and tobacco are known risk factors for the development of peptic ulcer disease (Csordas, 2013; Peterson, 1986). Gastric ulcers have also been associated with obesity and coronary artery disease (Garrow, 2009). Due to these confounding factors that were present in this subject, causality of death to icotrokinra is not established.

Case 3. (b) (6) (SAE)

A 68-year-old male with a history of obesity, and current cigarette and alcohol use who experienced an SAE of gastric ulcer perforation on Study Day 271. Study drug was discontinued on the day of the event and the subject was discharged from the hospital on Study Day 295. No concomitant medications. Per the investigator, the subject did not report a medical history of gastritis, gastric and/or intestinal ulcer, gastrointestinal bleeding (e.g., hematemesis, melena), chronic vomiting, chronic abdominal pain, thrombocytopenia, anemia, or *Helicobacter pylori*. The investigator did not report a history of endoscopy or NSAID or corticosteroid use.

Reviewer Comment:

This case of SAE of peptic ulcer with perforation represented an incidence of 1/1864 (0.05%) total subjects across the four clinical trials in the phase 3 psoriasis program, which is lower than the incidence of GI ulcer with perforation in the general population.⁶ We also note the presence of multiple confounding factors for gastric ulcer, including obesity and cigarette and alcohol use, which prevent the establishment of causality to icotrokinra use.

Case 4. (b) (6) (SAE)

A 65-year-old white female with a history of ureteric dilatation (left renal ectasia), hysterectomy (b) (6), bariatric surgery due to obesity (b) (6), and *Helicobacter pylori* infection (b) (6) who experienced lower GI bleeding (PT: rectal hemorrhage) on

⁶ The incidence of the peptic ulcer disease has been reported in the literature to be 1.5-3%, with 2%-14% of the ulcers leading to perforation and acute illness (Chung KT and Shelat V. Perforated peptic ulcer-an update. World J Gastrointest Surg. 2017 Jan 27;9(1):1-12).

Study Day 503, reported along with the nonserious AEs of diverticulum and hemorrhoids. The subject reported one bowel movement with soft, dark brown/black stool on the same day (Study Day 503). On Study Day 507, the subject was admitted to the hospital following an “episodic vegetive episode with abundant dark brown/black stool containing clots.” No reported abdominal pain, vomiting, or other associated symptoms. The subject’s hemoglobin was 8.90, leukocyte count was 81010 and platelet count was 20600 (units and normal ranges not provided). Upper endoscopy and contract [sic] enhanced abdominal computed tomography scan did not identify a source of bleeding.

On the same day, the subject had another episode of dark stool and blood count showed a hemoglobin of 7.50 (units not provided); colonoscopy showed diverticulosis and two internal hemorrhoids reported as nonserious adverse events of diverticulum (reported term: diverticulosis) and hemorrhoids. Icotrokinra was continued. The event of rectal hemorrhage was reported as resolved on Study Day 508. On Study Day 510, the subject’s hemoglobin had improved to 10.9 (units not provided), and the subject was discharged from the hospital on Study Day 512 with a hemoglobin of 10.3

No concomitant medications at the time of study entry, however, the subject used acetylsalicylic acid from Study Day 55-62.

Reviewer Comment:

The clinical history of painless, large-volume, dark brown/black stool is consistent with colonic diverticular bleeding, particularly if the bleeding source is located on the right side of the colon. A diagnosis of colonic diverticular bleeding in this subject, however, is presumptive given that no active bleeding or stigmata of recent GI bleeding were noted on colonoscopy, and no active bleeding was seen on CT.

It is unlikely that hemorrhoids were the source of bleeding as it would have been associated with hematochezia (i.e., as opposed to brown/black stool), and more profuse bleeding that would lead to a decrease in the subject’s hemoglobin.

We also note the subject’s history of *Helicobacter pylori* infection, a risk factor for peptic ulcer disease. However, upper endoscopy at the time of the event did not reveal an ulcer or other source of bleeding.

Given the identification of colonic diverticulosis as a possible source of GI bleeding, causality of the event to icotrokinra is not established.

IV. DG Responses to Consultation Questions from DDD

DDD requests DG input regarding the potential GI-related safety risk of upper gastrointestinal bleeding with the use of IL23R antagonist, icotrokinra, based on the occurrence of two deaths attributed to upper gastrointestinal bleeding and one SAE of acute gastric ulcer perforation with peritonitis that were reported in the controlled clinical trials in subjects that received icotrokinra. In addition, the recently submitted 120 day safety update included an SAE of lower gastrointestinal bleeding (PT: rectal hemorrhage).

We have the following responses to the questions from DDD:

Question 1: Is this observation within the expected rate of fatal or serious upper GI bleed in this study population size, and specifically are there any concerns with 2 deaths and 1 SAE all occurring on active drug vs no cases on placebo?

Death from upper GI bleeding has been reported in the literature to occur with an annual incidence of approximately 80 to 150 per 100,000 population, with an estimated mortality rate of 2% to 10% (Stanley, 2019). Based on the pooled safety population of 1864 subjects across the four clinical trials of the phase 3 program in patients with psoriasis (1296 subjects who received icotrokinra and 568 subjects who received placebo), the two fatalities that were attributed to upper GI bleeding and the SAE of acute perforated ulcer with peritonitis represented 2/1864 (0.11%) subjects and 1/1864 (0.05%) subject, respectively. Therefore, the rate of GI bleeding identified in the icotrokinra PsO development program is consistent with the expected rate in the general population of the same size; however, the rate of fatal GI bleeding exceeds the expected rate in the general population of the same size.

Review of the literature does not indicate an increased risk of GI bleeding in the intended treatment population (i.e., adults with psoriasis). It is concerning that all 4 cases of these serious GI events occurred in subjects that received icotrokinra, and not placebo. We also acknowledge our discussion with our dermatological colleagues that these serious GI events are not commonly reported in clinical trials in patients with psoriasis.

Question 2: Could you please comment on the risk factors these cases had for UGI bleed vs. known risk factors in this population for UGI bleed? In particular, the Sponsor attributes increased risk of UGI from psychiatric medications in the fatal case of the 49-year old male was not aligned with review of the adverse effect profile of those drugs (which seem primarily to be associated with nausea and vomiting).

Known risk factors for upper GI bleeding were present in each of the cases, resulting in potential confounding (refer to Section III, Case Narratives, for a detailed discussion). However, icotrokinra cannot be excluded as contributing to GI adverse reactions with serious outcomes given the imbalance observed in these events between the drug and placebo arms of the trials.

We do not agree with the Applicant's assessment of the 49-year old male who died from esophageal variceal bleeding, attributing the increased risk of upper GI bleeding to psychiatric medications. This subject was receiving concomitant medications that included benserazide hydrochloride/levodopa, lithium carbonate, aripiprazole, primidone, and losartan. Levodopa has been associated with an increased risk of GI bleeding in patients who have a history of peptic ulcer disease (Gandhi, 2023); however, this subject did not have a known history of peptic ulcer disease. Although cases of thrombocytopenia have been reported in patients with Parkinson's disease who are treated with levodopa (Shahrestani, 2022), this subject did not have thrombocytopenia at the time that could have contributed to his GI bleeding. Review of the literature and prescription drug labels for the subject's other concomitant medications did not indicate that these medications are associated with an increased risk of severe GI bleeding. Therefore, we do not attribute this subject's fatal upper GI bleeding to concomitant psychiatric medications, but rather to bleeding from gastroesophageal varices.

Question 3: Any further investigations or monitoring recommended for UGI bleed or GI adverse events?

We do not recommend any further investigations or monitoring for upper GI bleeding or GI adverse events at this time. There was no trend in the risk factor(s) in the affected subjects that indicate a specific increased risk with icotrokinra use, and the affected subjects had coexisting conditions or concomitant medications that could have contributed to the GI bleeding events. Therefore, it is challenging to provide specific recommendations regarding how and/or in whom to monitor for these potential risks.

V. Overall Summary and Recommendations:

There remains uncertainty as to whether icotrokinra increases the risk of GI bleeding or other serious GI adverse events (e.g., ulcer perforation) as multiple confounding factors were present in each of the cases, and furthermore, there is no known pharmacologic mechanism associated with icotrokinra or other IL-23 antagonists that would support an increased risk of GI bleeding. However, there is some basis to believe that there is a causal relationship as these events only occurred in subjects that received icotrokinra, and the subject population (i.e., patients with psoriasis) is not considered to be at risk for GI bleeding or other serious GI adverse events.

Per the FDA guidance for industry - *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2006),⁷ “[f]or serious adverse events that are unusual in the absence of drug therapy (e.g., liver failure, agranulocytosis, rhabdomyolysis, idiopathic thrombocytopenic purpura, intussusception), there is a basis to believe there is a causal relationship between the event and the drug at a very low rate of occurrence. Therefore, these events are generally listed in the adverse reactions section even if there are only one or two reported events, unless it is clear that a causal relationship can be

⁷ We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

excluded.” We therefore recommend that the events of upper gastrointestinal bleeding (1 case of esophageal variceal bleeding; fatal, 1 case of nonspecific hematemesis; fatal), lower gastrointestinal bleeding (1 case of rectal bleeding), and gastric ulcer perforation (1 case) be included in the USPI in the ADVERSE REACTIONS, Clinical Trials Experience subsection as low frequency, serious adverse reactions.

We present the following language for your consideration for inclusion in Section 6.1 of the USPI, under (b) (4)

(b) (4)

During discussions with DDD, they communicated that it is unusual to have SAEs, including death, in clinical trials of PSO. They felt that it would be important to communicate these ARs beyond Section 6.1 of the PI. DDD drafted the following proposal and requested feedback from DG:

(b) (4)

DG defers to DDD as to whether a W&P is needed. We have the following suggestions if DDD recommends proceeding with a W&P:

- *Consider discussing the two fatal cases and the timing of the events in relation to study drug.*
- *Suggest HCPs and patients monitor for new onset or worsening GI symptoms in patients with known risk factors for GI bleeding and instruct patients to seek immediate medical attention for these symptoms.*
- *If a serious GI event is suspected, discontinue drug, and refer patients for additional evaluation, as clinically indicated.*

Labeling negotiations are ongoing at the time that this consult was finalized. DG is continuing to collaborate with DDD on finalizing labeling language.

References:

Csordas A, Bernhard D, 2013, The biology behind the atherothrombotic effects of cigarette smoke, *Nat Rev Cardiol*, 10:219–30.

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/s/

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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
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Division of Pediatrics and Maternal Health Review

Date: December 16, 2025 **Date consulted:** July 23, 2025

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, Division Director
Division of Pediatrics and Maternal Health

To: Division of Dermatology and Dentistry (DDD)

Drug: Icotyde (icotrokinra)

NDA: 220149

Applicant: Janssen Biotech, Inc.

Subject: Pregnancy and Lactation Labeling

Indication: For the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy.

Materials

Reviewed:

- DPMH consult request, dated 7/23/2025. DARRTS Reference ID: 56330267.
- Applicant's background package and proposed labeling for NDA 220149, Sequence Number (SN) 0001, dated 7/18/2025.

- Applicant's response to DPMH Information Request (IR) dated 10/14/2025, SN 0015, submitted 10/29/2025.

Consult Question: PLLR Labeling Review - "Please review the labeling (PI * carton/container) and propose any labeling change(s), attend meetings, and participate in the Priority Review of the original NDA."

I. INTRODUCTION AND BACKGROUND

On July 18, 2025, the Applicant, Janssen Biotech, Inc., submitted a 505(b)(1) Original New Drug Application for Icotyde (icotrokinra), a first-in-class interleukin-23 (IL-23) receptor antagonist peptide, for the treatment of moderate-to-severe plaque psoriasis (PsO) in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy. The Division of Dermatology and Dentistry consulted the Division of Pediatrics and Maternal Health (DPMH) on July 23, 2025, to assist with the Pregnancy and Lactation subsections of labeling.

Relevant Regulatory History

- Icotrokinra was submitted under Investigational New Drug (IND) 156446 on December 1, 2021.
- On March 4, 2025, the Applicant notified DDD of their intent to utilize the Rare Disease Priority Review Voucher, PRV NDA 217026, for NDA 220149 icotrokinra.

Psoriasis and Pregnancy^{1,2,3,4,5}

Psoriasis is a chronic inflammatory skin disease that affects about 3% of the global population. Although it can occur at any age, the incidence rate of psoriasis is highest in the age groups between 15 to 39 years and 50 to 69 years. Women and men are equally affected by psoriasis, and, among the female population, about 75% of patients develop the disease before reaching 40 years of age. Therefore, psoriasis commonly occurs in women of reproductive age. Pregnancy may impact the severity of the disease. Psoriasis improves in pregnancy in 40% to 60% of patients, worsens in 10% to 20%, and remains stable in the remainder. In the postpartum period, psoriasis severity remains the same or worsens in most patients. Topical treatment with emollients or moisturizers and a low- or medium-potency topical corticosteroid is the first-line intervention for pregnant patients with limited psoriasis. Ultraviolet B (UVB) phototherapy is the

¹ Xie W, Huang H, Ji L, Zhang Z. Maternal and neonatal outcomes in pregnant women with psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Rheumatology (Oxford)*. 2021 Sep 1;60(9):4018-4028. doi: 10.1093/rheumatology/keab357. PMID: 33878171.

² Rahmati S, et al. Impact of maternal psoriasis on adverse maternal and neonatal outcomes: a systematic review and meta-analysis. *BMC Pregnancy Childbirth*. 2023 Sep 30;23(1):703. doi: 10.1186/s12884-023-06006-5. PMID: 37777747; PMCID: PMC10543305.

³ D'Agostino M, Potestio L, Megna M. Psoriasis, pregnancy, and lactation: clinical implications and treatments. *Expert Rev Clin Immunol*. 2025 Jul;21(7):841-853. doi: 10.1080/1744666X.2025.2514606. Epub 2025 Jun 2. PMID: 40444497.

⁴ Feldman, SR. Psoriasis: Epidemiology, clinical manifestations, and diagnosis. In: UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed 11/10/2025)

⁵ Pomeranz, MK and Strober, BE. Management of psoriasis in pregnancy. In: UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed 11/10/2025)

preferred treatment for pregnant patients with more severe symptoms. The effect of maternal psoriasis on pregnancy outcomes remains uncertain.

II. REVIEW

PREGNANCY

Nonclinical Experience

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

In the Embryofetal Development (EFD) study conducted in rats, there were no adverse effects on embryofetal development observed at any doses tested, resulting in a NOAEL of 1000 mg/kg/day (297-times the maximum recommended human dose (MRHD) based on AUC). In the EFD study conducted in rabbits, pregnancy losses and an increased incidence of fetal skeletal malformation (fused ribs) were observed at 500 mg/kg/day (157-times the MRHD based on AUC), resulting in a NOAEL of 200 mg/kg/day (27-times the MRHD based on AUC). In a pre- and postnatal development (PPND) study, icotrokinra was administered orally to pregnant rats from implantation through weaning at doses up to 200 mg/kg/day (127-times the MRHD based on AUC). There were no maternal or reproductive developmental effects observed, and, thus, the NOAEL for maternal toxicity in F₀ rats and pre- and postnatal developmental toxicity for F₁ rats was 200 mg/kg/day.

The reader is referred to the full nonclinical review by Yen-Ming Chan, Ph.D.

Reviewer comment:

There were no adverse effects observed in the rat. Although skeletal malformations and pregnancy losses were observed in the rabbits, these adverse effects occurred at a dose exposure greater than 100 times the clinical exposure at the maximum recommended human dose. No adverse effects were observed with icotrokinra when administered orally up to 297-times and 27-times the exposure at the MRHD in rats and rabbits, respectively. Therefore, there were no specific safety signals identified at clinical exposures in the EFD studies.

Review of Applicant's Pharmacovigilance Database^{6,7}

The Applicant reported 5 pregnancy cases with maternal exposure during the icotrokinra clinical development program. The birth outcomes included two live births, one elective abortion, and two unknown outcomes. The details of the pregnancy cases are provided below:

- A 27-year-old female with a past medical history significant for plaque psoriasis and hypertension, a past obstetrical history including one induced abortion and one "normal outcome", and a social history significant for alcohol and tobacco use, received the first dose of icotrokinra 50 mg once daily on (b) (6) (Study Day 1). Concomitant medication at the start of the study was amlodipine. On (b) (6) (Study Day 309), the participant had a positive urine pregnancy test and received the last dose of icotrokinra the same day, ultimately discontinuing participation in the study due to

⁶ NDA 220149, Module 2.7.4, Summary of Clinical Safety and 5.3.5.3 Safety Narratives.

⁷ NDA 220149, Applicant's response to DPMH IR, dated 10/14/2025.

pregnancy. The participant's last menstrual period was (b) (6) (Study Day 280). On (b) (6), she delivered a full term, "healthy male infant via caesarean section", weighing "approximately 7 pounds". The birth outcome was reported as normal. No further details were provided.

- A 40-year-old female with a past medical history significant for plaque psoriasis and mastocytosis, a past obstetrical history significant for one "normal birth", and a social history significant for tobacco use, received the first dose of icotrokinra on (b) (6) (Study Day 1). On (b) (6) (Study Day 56), she received the last dose of icotrokinra, permanently discontinuing the study medication due to pregnancy. The participant's last menstrual period was (b) (6). On (b) (6) (study Day 134), her ultrasound, amniocentesis, blood test, and urine test were normal. Expected date of delivery was (b) (6). Concomitant medications during study included paracetamol and ibuprofen. Concomitant medications during pregnancy included progesterone, iron, folic acid and a prenatal vitamin. On (b) (6) (Study Day 275), the participant had a spontaneous vaginal delivery of a "healthy male newborn", weighing 2.78 kg. No further details were provided.
- A 50-year-old female with a past medical history significant for plaque psoriasis, uterine leiomyoma, intervertebral disc herniation, renal cyst, and chronic cervicitis, received the first dose of icotrokinra on (b) (6) (Study Day 1). She was re-randomized to placebo on (b) (6) (Study Day 168; Week 24). She was not taking any concomitant medications at the start of the study. On (b) (6), she had positive urine and serum pregnancy tests, as well as an ultrasound that showed an intrauterine early pregnancy and "possibility of embryonic dysplasia". Her last menstrual period was on (b) (6) (Study Day 164). The participant's last dose of the placebo was on (b) (6). On (b) (6) (Study Day 201), the participant underwent an elective abortion. No further details were provided.

Reviewer comment:

Whether icotrokinra exposure during early pregnancy occurred in this pregnancy case is uncertain. The participant transitioned from icotrokinra to placebo four days after her last menstrual period (LMP). Based on icotrokinra's elimination half-life of 12 hours, the drug likely cleared the participant's circulation in approximately 2.5 days (5x half-life), and thus, likely cleared systemic circulation approximately 1 week after the LMP. Therefore, it is possible that icotrokinra exposure occurred before conception and embryonic development, and thus, may not be associated with the embryonic dysplasia seen on ultrasound. If early pregnancy exposure occurred, the participant's age confounds the relationship between icotrokinra exposure and the adverse pregnancy outcome.

- A 34-year-old female with a past medical history significant for plaque psoriasis and herpes simplex (b) (6), and a social history significant for alcohol use, received the first dose of icotrokinra on (b) (6) (Study Day 1). Concomitant medication at study entry was acyclovir. Other medication exposures during study included ambroxol hydrochloride (oral), xylometazoline hydrochloride (nasal), and aluminum

hydroxide/magnesium hydroxide (oral). On (b) (6), she received her last dose of icotrokinra, and treatment was discontinued due to pregnancy. The participant's expected delivery date and pregnancy outcome were not reported. No further details were provided.

- A 37-year-old female with a past medical history significant for plaque psoriasis, cholelithiasis, cholecystectomy in (b) (6), and anxiety, and a social history significant for tobacco use, received the first dose of icotrokinra on (b) (6) (Study Day 1). No concomitant medications were reported. On (b) (6) she received her last dose of icotrokinra, and treatment was discontinued due to pregnancy. The participant's expected date of delivery was (b) (6). The pregnancy outcome was not reported. No further details were provided.

Reviewer comment:

Icotrokinra exposure during early pregnancy occurred in four of the five pregnancy cases, including the two cases resulting in healthy newborns with no reported congenital anomalies, and the two cases in which the pregnancy outcomes are unknown. There are insufficient pregnancy data from the clinical development program to inform the safety of icotrokinra use in pregnancy.

Review of Literature

Applicant's review:

The Applicant did not perform a literature search.

DPMH review:

DPMH conducted a search of published human studies in PubMed and Embase, using the search terms "icotrokinra" 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", "adverse pregnancy outcomes", "prematurity" and "low birth weight". No relevant publications were found.

In addition, DPMH conducted a search for icotrokinra in Micromedex⁸, Reprotox⁹, TERIS¹⁰, Shepard's¹¹, and Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*¹². No information was found.

LACTATION

Nonclinical Experience

In the PPND study conducted in rats, although icotrokinra was not directly measured in rat milk, it was detected in the plasma of the nursing rat pups on PND4 and PND12.

⁸ Truven Health Analytics information, <http://www.micromedexsolutions.com> Accessed 10/7/2025.

⁹ Reprotox Website: www.Reprotox.org. Accessed 10/7/2025.

¹⁰ TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 10/7/2025.

¹¹ Shepard's database. Truven Health Analytics. Micromedex Solutions. Accessed 10/7/2025.

¹² 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.

The reader is referred to the full nonclinical review by Yen-Ming Chan, Ph.D.

Reviewer comment:

According to the nonclinical team, the presence of icotrokinra in the pups' sera during the lactation period could result from either placental transfer, transfer in milk, or both. There were no adverse effects observed in the nursing pups.

Review of Applicant's Pharmacovigilance Database⁷

The Applicant reported one case of icotrokinra exposure in a lactating woman during the icotrokinra clinical development program.

- A 29-year-old female who gave birth prior to enrolling in the study was randomized on (b) (6) (Study Day 1) to icotrokinra 200 mg QD and took the first dose of icotrokinra on the same day. On the night of Study Day 1, the participant breastfed her baby. The participant discontinued icotrokinra without taking any additional doses and the reason for discontinuation was reported as “withdrawal by subject [participant wanted to breastfeed her baby]”. The investigator confirmed there were no adverse events reported, and that the infant was healthy. The participant discontinued from study participation on (b) (6) (Day 8).

Reviewer comment:

This one case is insufficient to draw any meaningful safety conclusions about the effects of icotrokinra on lactation or its potential effects on the breastfed infant. There are no available data on the presence of icotrokinra in human breast milk. Icotrokinra has a 12-hour half-life and moderate protein binding (48% free fraction available). These physicochemical properties suggest that icotrokinra will be transferred into human breast milk; however, icotrokinra's molecular weight (1898.17 g/mol), its limited solubility at physiologic pH, and its potential for degradation as a small peptide suggest decreased transfer. Nonetheless, physicochemical characteristics alone are not sufficient to determine the transfer of a drug into breastmilk.

Review of Literature

Applicant's review:

The Applicant did not perform a literature search.

DPMH review:

DPMH conducted a search of published human studies in PubMed and Embase, using the search terms “icotrokinra” and “lactating”, “lactation”, “human milk”, “breastfeeding”, “breastfed”, “neonates”, and “infants”. No relevant publications were found.

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

¹³ 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.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

In a Fertility and Early Embryonic Development (FEED) study, icotrokinra did not adversely impact fertility in female rats at oral doses up to 70 mg/kg/day (335-times the MRHD based on AUC comparison). In a 6-month toxicity study, icotrokinra did not adversely impact fertility in male rats at oral doses up to 20 mg/kg/day (114-times the MRHD based on AUC comparison).

The reader is referred to the full nonclinical review by Yen-Ming Chan, Ph.D.

Review of Applicant's Pharmacovigilance Database⁷

The Applicant performed a review of their safety database using Standardized MedDRA Query (SMQ) "fertility disorders", identifying two participants on icotrokinra reporting adverse events (AE). The Applicant summarized the two events as follows:

- A 55-year-old participant reported an adverse event of hypogonadism, which was reported by the investigator as being due to low testosterone levels from being postmenopausal and reported as not related to study medication by the investigator. No further details were provided.
- A 17-year-old participant with a medical history of Cushing's syndrome reported an AE of PCOS (Day 120) reported as not related to study medication by the investigator. The participant was diagnosed with Cushing's syndrome in (b) (6), before entering the study.

With respect to the first case, the Applicant concluded the AE was related to menopause and did not consider this AE related to the impact of icotrokinra on fertility. With respect to the second case, the Applicant concluded that, although PCOS is a chronic condition that could affect female fertility, there is "no known biologically plausible mechanism. nor any evidence from preclinical or clinical trials, by which icotrokinra would promote the development of PCOS. Accordingly, PCOS is considered to be not related to icotrokinra."

Reviewer comment:

DPMH agrees with the Applicant's conclusion that neither of the identified cases suggest icotrokinra affects human fertility.

Review of Literature

Applicant's review:

The Applicant did not perform a literature search.

DPMH review:

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

In addition, DPMH conducted a search for icotrokinra in Micromedex, Reprotox, and TERIS. No relevant publications or additional information on the effects of icotrokinra on human fertility were found in the literature search

III. DISCUSSION AND CONCLUSIONS

Pregnancy

The animal reproduction studies did not identify a specific safety signal indicating an increased risk for embryo-fetal toxicity at clinical exposures. Animal reproduction data do not suggest a serious risk of developmental toxicity during pregnancy. Human data on icotrokinra exposure during pregnancy are insufficient to allow an assessment of a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

Psoriasis affects a significant number of women of reproductive age, and consequently, co-occurrence of psoriasis and pregnancy is not rare. However, since emollients, moisturizers, low to medium potency topical corticosteroids, and phototherapy are the preferred treatments during pregnancy, icotrokinra would not be used as first-line treatment in pregnant women. Although animal reproduction data do not suggest a serious risk of developmental toxicity during pregnancy, animal findings do not always predict findings in humans, therefore, there is a need to collect data in humans exposed. It is anticipated that icotrokinra may be used in a small population of pregnant patients. Thus, to obtain safety information related to the use of icotrokinra in pregnancy, DPMH recommends issuing a postmarketing requirement (PMR) for a descriptive pregnancy safety study. Together with the DPSS interim reports, DPMH recommends that the applicant submit reports of icotrokinra utilization rates in females of reproductive potential (females aged 15 to 50 years) calculated yearly and cumulatively from the time of initial approval. If there appears to be substantial use of icotrokinra in females of reproductive potential, then this would be considered new safety information that could result in the Agency considering revisiting the proposed PMR to include a pregnancy registry study and/or claims database study.

Lactation

There are no available data on the presence of icotrokinra in human breast milk, the effects of icotrokinra on the breastfed infant or the effects on milk production. In the PPND study, the presence of icotrokinra in the plasma of newborn pups suggests transfer into rat milk. When a drug is present in animal milk, it is likely the drug will be present in human milk. Based on the lack of available clinical data and the anticipated use of icotrokinra in females of reproductive potential, which includes lactating females, DPMH recommends issuing a postmarketing requirement (PMR) for a clinical lactation study. The data obtained from a clinical lactation study would be helpful in determining the amount of icotrokinra in human breastmilk. If a clinical lactation study demonstrates a clinically important amount of icotrokinra in breast milk, further study to examine systemic exposure in the breastfed infant may be needed.

Females and Males of Reproductive Potential

There are no available human data to suggest icotrokinra adversely affects female or male 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 that would require pregnancy testing or contraceptive use during treatment with icotrokinra. Therefore, DPMH recommends omitting labeling subsection 8.3 Females and Males of Reproductive Potential.

POSTMARKETING REQUIREMENTS (PMR) SUGGESTED LANGUAGE

- **Descriptive Pregnancy Safety Study:** Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Icotyde (icotrokinra) during pregnancy to assess risk of pregnancy and maternal complications, and adverse effects on the developing fetus, neonate, and infant. Assess infant outcomes through at least the first year of life. The minimum number of patients will be specified in the protocol.
- **Lactation Study:** Perform a lactation study in lactating women who have received icotrokinra to measure concentrations of icotrokinra 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, 8.2 and section 17 of labeling for compliance with the PLLR. DPMH discussed our labeling recommendations with the Division of Dermatology and Dentistry on 11/18/2025. DPMH recommendations are below and reflect the discussions with DDD. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)

APPENDIX A –

Drug Characteristics¹⁴

Drug Class	An interleukin-23 (IL-23) receptor antagonist peptide
Proposed Mechanism of Action	A peptide that selectively binds to the IL-23 receptor (IL-23R) with (b) (4) antagonizes the binding of IL-23 (b) (4) inhibition of the IL-23/IL-23R-dependent release of proinflammatory cytokines.
Proposed Dosage form and administration	200 mg tablets Recommended dosage is 200 mg orally once daily.
Molecular weight	1898.17 g/mol
Elimination Half-life	12 hours
% protein bound	52%
(b) (4)	

¹⁴ NDA 220149, draft Annotated Labeling with DDD review team edits, review ongoing.

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/s/

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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:	October 27, 2025
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 220149
Product Name, Dosage Form, and Strength:	Icotyde (icotrokinra) tablet, 200 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Janssen Biotech, Inc. (Janssen)
FDA Received Date:	July 18, 2025
TTT ID #:	2025-15581
DMEPA 1 Safety Evaluator:	Susan Hakeem, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 INTRODUCTION

As part of the approval process for Icotyde (icotrokinra) tablet, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Icotyde Prescribing Information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Icotyde (icotrokinra) is a proposed 505(b)(1) drug product.

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
Previous DMEPA Reviews	C

3 CONCLUSION

We evaluated the proposed Icotyde Patient Information and determined that it is acceptable from a medication error perspective.

However, the proposed Icotyde Prescribing Information (PI), 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 the Division of Dermatology and Dentistry (DDD) in Section 4 and for Janssen Biotech, Inc. (Janssen) in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

Table 2. Identified Issues and Recommendations for the Division of Dermatology and Dentistry (DDD)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	As currently presented, the proprietary name is denoted by the placeholder “Trade name”.	We reference our September 18, 2025, Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Icotyde, was found conditionally acceptable.	We recommend replacing the placeholder “Trade name” with the conditionally acceptable proprietary name, Icotyde, throughout the PI.

5 RECOMMENDATIONS FOR JANSSEN BIOTECH, INC. (JANSSEN)

Table 3. Identified Issues and Recommendations for Janssen Biotech, Inc. (Janssen) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	As currently presented, the graphic at the beginning of the proprietary name looks  (b) (4) which may lead to misinterpretation of the proprietary name, as  (b) (4)	The use of graphics should not distract the reader from critical information or add to label clutter. When such items are included, the graphic design should not compete with, interrupt, or distort critical information. <i>See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).</i> ^a	We recommend deleting or relocating and decreasing the prominence of the graphic at the beginning of the proprietary name.

^a Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors>.

Table 3. Identified Issues and Recommendations for Janssen Biotech, Inc. (Janssen) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Sample Carton Labeling			
1.	As currently presented on the principal display panel, it is not immediately clear that the designated strength is per blister unit (i.e., 200 mg is per tablet).	Failure to clearly express the product strength “200 mg per tablet” may lead to misinterpretation that all 7 tablets equal 200 mg.	We recommend revising the strength statement “200 mg” to state “200 mg per tablet” to make it clear that the designated strength is per unit so there is no confusion as to how much product is contained in a single unit as compared to the total contents of the entire blister card.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Icotyde received on July 18, 2025 from Janssen Biotech, Inc. (Janssen).

Table 4. Relevant Product Information for Icotyde	
Initial Approval Date	N/A
Active Ingredient	icotrokinra
Indication	Treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy.
Dosage Form	tablet
Strength	200 mg
Route of Administration	Oral
Dose and Frequency	200 mg orally once daily
How Supplied	Bottles of 30 tablets (NDC 57894-201-30), with a silica gel desiccant and a child -resistant closure.
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) [see USP Controlled Room Temperature]. Store in original package to protect from moisture. Do not discard desiccant. Keep out of reach of children.
Container Closure	White, 75 mL high-density polyethylene (HDPE) bottle with child-resistant (b) (4) closure with induction seal liner (b) (4) and silica gel desiccant (b) (4)

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,^b along with postmarket medication error data, we reviewed the following Icotyde labels and labeling submitted by Janssen Biotech, Inc. (Janssen).

- Prescribing Information and Patient Information received on July 18, 2025, available from <\\CDSESUB1\EVSPROD\nda220149\0001\m1\us\114-labeling\draft\labeling\uspi-draft-labeling-text-pdf.pdf>.
- Annotated Prescribing Information and Patient Information received on July 18, 2025, available from <\\CDSESUB1\EVSPROD\nda220149\0001\m1\us\114-labeling\draft\annotated\uspi-annotated-draft-labeling-text-pdf.pdf>.
- Container label received on July 18, 2025.
- Carton labeling received on July 18, 2025.
- Professional Sample Foil Backing received on July 18, 2025.
- Professional Sample Carton Labeling received on July 18, 2025.

B.2 Container Label and Carton Labeling Images

Container Label:



^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX C. PREVIOUS DMEPA REVIEWS

On October 1, 2025, we searched for previous DMEPA reviews relevant to this current review using the terms, NDA 220149. Our search identified zero previous reviews.

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

/s/

SUSAN HAKEEM
10/27/2025 09:02:37 AM

VALERIE S VAUGHAN
10/27/2025 09:43:49 AM



Memorandum

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

Date: October 22, 2025

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Associate Director, Cardiac Safety IRT, DCN

To: Tina Whang, RPM
DDD

Subject: QT Consult to NDA 220149 (SDN 001)

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

This memo responds to your consult to us dated 8/26/2025 regarding the Applicant's QTc assessment report and proposed label language. We reviewed the following materials:

- NDA submission (NDA 220149/SDN 001; [link](#));
- Previous IRT reviews for IND 156446 dated [04/03/2025](#); [09/24/2024](#); and [08/08/2024](#)
- C-QT analysis report (NDA 220149/SDN 007; [link](#));
- QT evaluation report check list (NDA 220149/SDN 007; [link](#)); and
- Proposed label (NDA 220149/SDN 001; [link](#)).

1 Responses for the Division

Consult Request: DDD requests QT-IRT review of the submitted document for NDA and proposed labeling language

IRT's response: We previously reviewed the Applicant's QTc assessment, which includes clinical study PN-235-01 and an integrated nonclinical risk assessment, and concluded that the QTc assessment supported an absence of QTc prolongation for icotrokinra (IRT review dated [08/08/2024](#)). While the highest dose (single dose of 1000 mg; 9.9 ng/mL) provides a mean C_{max} that is approximately 4- to 4.8-fold the mean C_{max} for the therapeutic dose for psoriasis (200 mg QD; range of 2.1–2.5 ng/mL), we could not determine whether these data could serve as a substitute for a TQT study because body weight and potentially renal function (major route of elimination) impact icotrokinra's pharmacokinetics. The renal impairment study was pending at that time.

The Applicant evaluated the impact of renal impairment on icotrokinra's pharmacokinetics and showed that renal impairment does not cause significant increase in Cmax. We therefore agreed that the highest dose in Study PN-235-01 covered high clinical exposure scenario and that the QTc assessment supports excluding a ≥ 10 msec mean increase in QTc (IRT review dated [04/03/2025](#)).

In this NDA, the Applicant has resubmitted the concentration-QTc analysis report that we already reviewed (IRT review dated [08/08/2024](#)). We have no additional comments on the report.

Below are our proposed changes to the label submitted by the Applicant. 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 [5 times the maximum](#) recommended dose of TRADENAME ^{(b) (4)} clinically [significant](#) ^{(b) (4)} -QTc interval prolongation was not observed.

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](#)).

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

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/s/

ELIFORD N KITABI
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10/22/2025 08:57:46 AM

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