

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

220149Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 156446

MEETING MINUTES

Janssen Research & Development, LLC
Attention: Jenna Giacchi
Associate Director, Global Regulatory Affairs, Immunology
Welsh and McKean Roads, P.O. Box 776
Spring House, PA 19477

Dear Jenna Giacchi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for JNJ-77242113.

We also refer to the video conference between representatives of your firm and the FDA on December 9, 2024. The purpose of the meeting was to discuss the proposed content and format of the planned NDA for JNJ-77242113 tablet for the treatment of adult and pediatric patients 12 years of age and older with moderate to severe plaque psoriasis.

A copy of the official minutes of the video conference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-3921.

Sincerely,

{See appended electronic signature page}

Craig Johnson, PharmD
Regulatory Project Manager
Division of Regulatory Operations for
Dermatology and Dentistry
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Date and Time: December 9, 2024; 9:30 – 10:30 a.m. EST
Meeting Location: Virtual
Application Number: IND 156446
Product Name: JNJ-77242113 tablet
Indication: Treatment of adult and pediatric patients 12 years of age and older with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Sponsor Name: Janssen Research and Development
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair: Jill Lindstrom, MD, FAAD, Director, Division of Dermatology and Dentistry
Meeting Recorder: Craig Johnson, PharmD, Regulatory Project Manager

FDA ATTENDEES

Jill Lindstrom, MD, FAAD, Director, Division of Dermatology and Dentistry (DDD)
Gary Chiang, MD, MPH, Clinical Reviewer, DDD
Melinda McCord, MD, Clinical Team Leader, DDD
Kathleen Fritsch, PhD, Master Statistician, Division of Biometrics III (DB III)
Matthew Guerra, PhD, Senior Biometrics Reviewer, DB III
Daeyoung Lim, PhD, Staff Fellow, DBIII
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Inflammation and Immune Pharmacology (DIIP)
Dipak S. Pisal, MS, PhD, Office of Clinical Pharmacology, (DIIP)
Craig Johnson, PharmD, Regulatory Project Manager, Division of Regulatory Operations for Dermatology and Dentistry, (DRO – DD) Office of Regulatory Operations

SPONSOR ATTENDEES

Norm Bohidar, PhD, Vice President, Head of Biostatistics, Immunology
Lisa Carey, MA, MS, Associate Director, Portfolio Lead Statistical Programming
Cynthia Deklotz, MD, Senior Director, Clinical Development
Jenna Giacchi, MS, Associate Director, North American Regulatory Leader

David Gordon, MB ChB, Vice President, Global Head of Development Immunology
Meka Harris, MS, Manager, Global Regulatory Affairs
Luis Humberto Anaya Velarde, MD, Director Global Medical Safety
Dana Leeds, PhD, Director, Global Regulatory Leader
Shu Li, PhD, Senior Director, Biostatistics
Quinn McCarthy, Manager, Global Regulatory Affairs
Paul Newbold, PhD, Executive Director, Compound Development Team Leader
Fabio Nunes, MD, Vice President, Clinical Development Dermatology
Liza O'Dowd, MD, Vice President, Head Global Regulatory Affairs Immunology & GRPI

1.0 BACKGROUND

The purpose of this meeting is to discuss the proposed content and format of the planned NDA for JNJ-77242113 for the treatment of adult and pediatric patients 12 years of age and older with moderate to severe plaque psoriasis.

FDA sent Preliminary Comments to Janssen Research and Development on December 5, 2024.

2.0 DISCUSSION

2.1. Category/Discipline A

Question 1:

Does the Agency agree that the nonclinical data package (including pharmacokinetics) is sufficient to support registration of JNJ-77242113 for the intended indication?

FDA Response to Question 1:

Yes, we agree that your nonclinical program appears reasonable to support registration of JNJ-77242113 for the intended indication.

2.2. Clinical Pharmacology

Question 2:

Does the Agency agree with the proposed content and analyses to be provided within the Summary of Clinical Pharmacology (Module 2.7.2), ISI (Module 5.3.5.3), and SBAAM (Module 2.7.1)?

FDA Response to Question 2:

The proposed content seems reasonable. However, it is premature to agree on the overall content and analyses as some of the studies are still ongoing. The adequacy

of the data will be a review issue. We would also like to refer you to the discussion at the EOP2 meeting minutes. It is expected that the final to be marketed formulation is used in the pivotal phase 3 trials. If you have used any other formulations PK bridging studies may be needed. In addition to the proposed E-R analysis for efficacy, you should also include E-R analysis for safety.

General Clinical Pharmacology Comments:

Following information is generally obtained during drug development to characterize the human PK and performance of a drug product. It includes, but is not limited to:

- Identification of major metabolites and active metabolites, if any, and the metabolic pathway (if applicable)
- In vivo mass balance study (if applicable)
- In vivo interconversion between isomers (if applicable)
- Bioavailability of each active component
- Single dose and multiple dose PK
- Dose-proportionality over the intended therapeutic dose range
- Accumulation potential
- Drug-drug interaction potential
- Drug interaction potential with acid reducing agents (if applicable)
- Effects of intrinsic factors (e.g., age, sex, race, renal impairment and hepatic impairment, etc.) on the PK of the drug
- Effects of extrinsic factors (e.g., concomitant administration of inducer or inhibitor of metabolic enzymes, food) on the PK of the drug
- If the final to-be-marketed product is different from that of the clinical trial product due to changes in formulation, manufacturing process, or manufacturing site, bridging studies may be needed
- Assessment of QT/QTc prolongation potential of the drug and its metabolites

2.3. Clinical Development

Question 3:

Does the Agency agree with the proposal for analysis and presentation of efficacy data in the Summary of Clinical Efficacy (Module 2.7.3)?

FDA Response to Question 3:

You proposed to submit a comprehensive analysis of safety and efficacy for four phase 3 clinical trials conducted in subjects with moderate-to-severe plaque psoriasis (3001, 3002, 3003, and 3004) who are 12 years and older and are candidates for systemic therapy or phototherapy. In addition, dose selection will be supported by your phase 2 dose-ranging studies (2001 and 2002). Efficacy between JNJ-77242113 and placebo will be limited to the first 16 weeks of each study, after which the placebo subjects cross over to JNJ-77242113. In two of the four clinical trials, comparison between JNJ-77242113 and deucravacitinib will be conducted through 24 weeks. You will also provide analyses up to Week 52 for durability of

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

response through a randomized withdrawal design (3001). You also state that you do not plan to pool phase 3 efficacy data for estimating efficacy rates in the phase 3 population. Your proposal appears reasonable.

Question 4:

The Sponsor proposes not to submit a separate ISE in Module 5. Does the Agency agree?

FDA Response to Question 4:

Because you are conducting a development program with four phase 3 studies, we recommend submitting a more detailed and comprehensive analysis in the Integrated Summary of Efficacy (ISE) and a more compact summary in the Summary of Clinical Efficacy (SCE). If you believe your SCE is sufficiently detailed to cover the contents of an ISE, then, size permitting, you may choose not to submit a separate ISE. However, such an approach is generally feasible only for relatively simple drug development programs and may not be feasible for your development program. Refer to guidance for industry, *Integrated Summary of Effectiveness*¹.

2.4. Safety

Question 5:

Does the FDA agree that the proposed safety database is adequate to support registration?

FDA Response to Question 5:

You are proposing to submit safety data from one phase 2 trial and four phase 3 plaque psoriasis clinical trials as the basis of your safety profile of JNJ-77242113, which amounts to an estimated total of 2,400 subjects exposed, including approximately 70 adolescent subjects with moderate-to-severe plaque psoriasis. You estimate that approximately 533 subjects will be exposed to 200 mg QD for 1 year at the time of NDA submission. We agree that your proposed safety population appears reasonable for review and safety analysis.

Question 6:

Does the Agency agree that the proposed safety analyses and proposed data display formats are adequate to assess the safety of JNJ-77242113 in the treatment of psoriasis?

¹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/integrated-summary-effectiveness>

FDA Response to Question 6:

You plan to provide a safety analysis based on the phase 2 trial and four phase 3 clinical trials. In general, we agree with your pooling based on the following:

- A summary of the safety data from each of the individual phase 2 and phase 3 psoriasis studies.
- Summaries of pooled safety data from the 4 phase 3 psoriasis studies.
- Selected subgroup analyses of the pooled safety data from the 4 phase 3 psoriasis studies, including subgroups defined by age for adolescents and those ≥ 65 years of age.
- Additional supportive safety data from other completed studies will be provided in the SCS.
- Phase 2 studies will not be pooled due to different dosage regimens studied.

Cumulative safety data from the studies will be analyzed over 3 analysis periods:

1. Placebo-controlled period through Week 16 (all 4 Phase 3 studies),
2. Deucravacitinib Active Comparator-controlled period through Week 24 (PSO3002 and PSO3004 studies), and
3. Reporting Period through the safety data cutoff dates (all 4 Phase 3 studies).

In addition to your above pooling strategies, we ask that you submit additional pooled safety analyses. Your Integrated Summary of Safety (ISS) should include safety analyses for the analysis sets described in the following table:

Analysis Set	Analysis Period	Pooled Studies	Treatment Groups
Placebo-Controlled Set #1 (Overall Moderate to Severe Plaque Psoriasis)	Weeks 0 to 16	PSO3001, PSO3002 and PSO3004	1. JNJ-77242113 200 mg QD 2. Placebo
Placebo-Controlled Set #2 (All Plaque Psoriasis)	Weeks 0 to 16	PSO3001, PSO3002, PSO3003, and PSO3004	1. JNJ-77242113 200 mg QD 2. Placebo
Active Comparator- Controlled #1 (Short-term)	Weeks 0 to 16	PSO3002 and PSO3004	1. JNJ-77242113 200 mg 2. Deucravacitinib 6 mg QD 3. Placebo
Active Comparator- Controlled #2 (Longer- term)	Weeks 0 to 24	PSO3002 and PSO3004	1. JNJ-77242113 200 mg 2. Deucravacitinib 6 mg QD
Long-term (52 weeks)	Weeks 0 to 52	PSO3001 and PSO3003	1. JNJ-77242113 200 mg QD
All JNJ-77242113 Exposed	Weeks 0 to Safety Data Cutoff	PSO3001, PSO3002, PSO3003, and PSO3004	1. JNJ-77242113 200 mg QD

We note that the phase 3 trials have unequal randomization ratios and sample sizes. We recommend that appropriate statistical approaches for integrating safety data across these trials be considered to account for differences in trial design (e.g., study-size adjusted rates). Crude pooling of AEs across trials to compare treatment arms may cause difficulty in interpreting safety signals (e.g., Simpson's paradox).

For discussion about the impact of improper pooling on interpretation of study findings which may lead to Simpson's paradox in reporting adverse events, we refer you to the following articles:

- Crowe, B., Chuang-Stein, C., Lettis, S., & Brueckner, A. (2016). Reporting adverse drug reactions in product labels. *Therapeutic Innovation & Regulatory Science*, 50(4), 455-463.
- Chuang-Stein, C., & Beltangady, M. (2011). Reporting cumulative proportion of subjects with an adverse event based on data from multiple studies. *Pharmaceutical Statistics*, 10(1), 3-7.

Meeting Discussion:

The Sponsor agreed to provide the pooled safety analyses presented in the table above. For the Long-term (52 weeks) and All JNJ-77242113 Exposed analysis sets, the Sponsor proposed to display additional treatment groups as described in their response to the Agency's preliminary comments. The Agency responded that their proposal regarding the treatment groups is reasonable.

The Sponsor acknowledged the Agency's comments regarding the pooling of trials with different designs (i.e., unequal randomization ratios and sample sizes). The Sponsor proposed to provide rates (i.e., proportions) for treatment-emergent adverse events (AEs) in $\geq 1\%$ in any treatment group by SOC and PTs for the first three Agency-requested analysis sets specified in the table above (i.e. Placebo-Controlled Sets #1 and #2 and Active Comparator-Controlled Set #1) using 1) crude pooling and 2) study size-adjustment (Crowe et al). The Agency responded that the study size-adjusted rates should be provided for all AE related tables.

For the Active Comparator-Controlled #2 analysis set, the Sponsor proposed to provide only the crude pooling rates as the randomization ratios for JNJ-77242113 and deucravacitinib are the same for Trials PSO3002 and PSO3004. The Agency stated that their proposal appears reasonable for this analysis set.

In the Sponsor response to the Agency's preliminary comments, the Sponsor stated that they plan to present risk difference (95% CIs) for select events contingent on sufficient number of events (proportion of participants with one or more SAEs, DCAEs, severe AEs, and other events of interest) for analysis sets #1 through #4 in the table above (i.e. Placebo-Controlled Sets #1 and #2 and Active Comparator-Controlled Sets #1 and #2). In addition, the Sponsor stated that the risk difference (and 95% CIs) between JNJ-77242113 and comparators (placebo or deucravacitinib) will be study-size adjusted. The

Agency stated that their proposal appears reasonable; however, the Agency reiterated the request for the Sponsor to submit the statistical analysis plan for the ISS/SCS.

Question 7:

Does the Agency agree with the proposal to provide a comprehensive safety analysis with supportive documentation and additional integrated analyses in the ISS?

FDA Response to Question 7:

You plan to include the key data necessary to support the safety profile of JNJ-77242113 in the summary of clinical safety (SCS) and the “full and integrated analysis of safety data for JNJ-77242113 within the framework of the CTD.”

Your proposal appears reasonable. However, your phase 3 trials are ongoing, and you have provided limited information regarding your planned safety analyses. Therefore, we cannot fully comment on the scope of the data analyses needed to support the safety of your 200mg daily dose. We recommend that you submit the statistical analysis plan (SAP) for the ISS/SCS for Agency review.

In addition, with regard to the analysis of the safety data, we have the following comments:

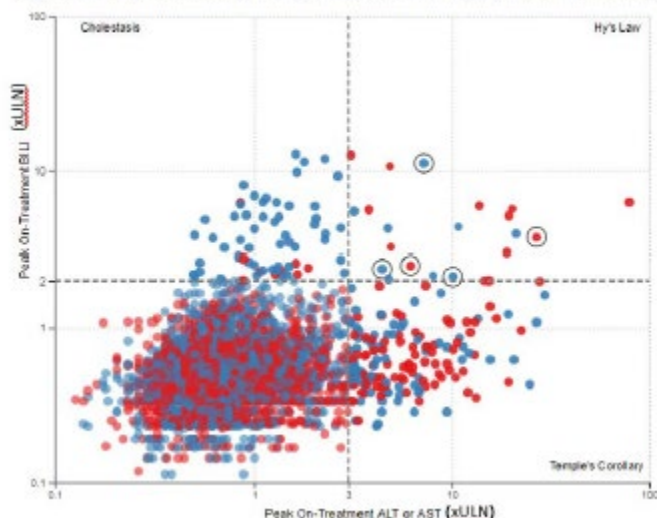
- Provide a tabulation of treatment-emergent adverse events (TEAEs) $\geq 1\%$ in any treatment arm, treatment related TEAEs (adverse reactions [AR] with possible or probable causality) $\geq 1\%$ in any treatment arm, adverse events (AEs) leading to discontinuation, and serious adverse events (SAEs) from Baseline to Week 16 and from Baseline to Week 24 (see table in *FDA Response to Question 6*). In addition, provide both percentages and exposure adjusted incidence rates (EAIRs) of TEAEs, adverse reactions (ARs), serious adverse events (SAEs) and AEs leading to discontinuation from Baseline to Week 52 and from Baseline to Safety Data Cutoff. See *FDA Response to Question 6*.
- We recommend that you pool related preferred terms in your tables (e.g., pool upper respiratory tract infection with nasopharyngitis, viral upper respiratory tract infection etc.)
- Provide shift tables for key laboratory values (hepatic enzymes and hematology results) in addition to vital signs from Baseline to end of treatment for both outside the normal range and outside the range that is considered clinically significant. Provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate.

- As we consider liver safety as an important topic of special interest, provide the following plots and summary tables for phase 3 trials for Weeks 0-16 and 0 to 52.

Hepatocellular Drug-induced Liver Injury (DILI) Screening Plot

(Bilirubin x ALT or AST): Each patient is plotted based on their maximum concurrent TB (y-axis) and transaminase (ALT or AST, whichever is higher), where concurrent is defined as TB elevation occurring on or within 30 days after the maximum ALT or AST elevation. Dashed lines represent TB and transaminase cut-offs of 2x ULN and 3x ULN (default), respectively. A potential Hy's Law case is defined as having a maximum postbaseline total bilirubin equal to or exceeding 2 x ULN within 30 days after maximum postbaseline ALT or AST equal to or exceeding 3x ULN, without findings of cholestasis (defined as ALP < 2 x ULN).

Figure X. Hepatocellular Drug-Induced Liver Injury Case Screening Plot



- Cholestatic Drug-induced Liver Injury Screening Plot (Bilirubin x ALP): Each patient is plotted based on their maximum concurrent TB (y-axis) and ALP (x-axis), where concurrent is defined as TB elevation on or within 30 days after the ALP elevation. Dashed lines represent TB and ALP cutoffs of 2x ULN and 3x ULN, respectively. A potential cholestatic liver injury case is defined as having a maximum postbaseline total bilirubin equal to or exceeding 2 x ULN within 30 days after maximum postbaseline ALP equal to or exceeding 3 x ULN).

Provide summary table for each plot above:

Table X. Number of Patients with Potential Hepatocellular DILI in Active Group versus Comparator by Treatment Group

Quadrant	Active (N=XXX) n (%)	Comparator (N=XXX) n (%)
Jaundice with $\geq 3x$ ULN elevation in AST or ALT (right upper)		
Jaundice without $\geq 3x$ ULN elevation in AST or ALT (left upper)		
Temple's corollary (right lower)		
Total		

Table X. Number of Patients with Potential Cholestatic DILI in Active Group versus Comparator by Treatment Group.

Quadrant	Active (N=XXX) n (%)	Comparator (N=XXX) n (%)
Jaundice with $\geq 3x$ ULN elevation in ALP (right upper)		
Jaundice without $\geq 3x$ ULN elevation in ALP (left upper)		
$\geq 3x$ ULN elevation in ALP without jaundice (right lower)		
Total		

Meeting Discussion

Your proposal for Shift tables for key laboratory values are reasonable. In response to questions regarding Hy's law, we agree with your interpretation and approach.

Question 8:

Does the Agency agree with the proposed plan for providing narratives and CRFs?

FDA Response to Question 8:

Your proposal for providing narratives and CRFs are reasonable.

Question 9:

Does the Agency agree with the proposed plan and data cutoff for the 120-Day Safety Update?

FDA Response to Question 9:

At initial filing, you propose to include safety data with the following cutoffs:

- Week 52 of Study PSO3001
- Week 52 of Study PSO3003
- Week 44 of Study PSO3002
- Week 24 of Study PSO3004

You propose to include safety data for the 120-Day safety update to the cutoff date of July 2025. At this timepoint “all Phase 3 studies will have data through at least Week 52.” In your initial submission of the NDA, we expect that your application will be substantially complete with adequate data to support the long-term safety of your novel product up to Week 52.

In the 120-day safety update report (SUR), per section 505(i) of the act, you should update the NDA application with new safety information learned about the product that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. Provide narratives in the SUR for all subjects who died, developed SAEs, pregnancies and AEs of special interest.

Your proposal otherwise appears reasonable.

Question 10:

- Does the Agency agree that the Sponsor’s proposed data package, if supportive, would be adequate (b) (4) (b) (4)?
- Does the Agency agree with the Sponsor’s proposed decision analytic/quantitative benefit-risk assessment of LTBI management detailed description of the model, specifically, (1) the model structure, and (2) the assumptions and planned parameters?

FDA Response to Question 10:

- 10a. You intend to submit (b) (4) (b) (4) (b) (4) in subjects with moderate-to-severe plaque psoriasis. Your proposal is to conduct a decision analytic/quantitative benefit-risk model-based assessment of alternative strategies for TB screening and treatment of LTBI (b) (4) (b) (4) at the time of NDA filing. We look forward in reviewing your proposal; however, the assessment

of mandatory testing for LTBI will be based on the data and scientific rationale during the NDA review. No agreement can be provided at this stage.

10b. Based on previous discussions and agreements with the Agency regarding treatment of LTBI during clinical trials, we reserve the evaluation of your proposal for the NDA review and subsequent labeling based on the data you provide.

2.5. Regulatory

Question 11:

Does the Agency agree with the proposed dossier content (TOC) and proposed studies to provide financial disclosure?

FDA Response to Question 11:

The proposed table of contents appears reasonable.

In Module 1.3.4, you propose to provide Financial Certification and/or Disclosure for investigators who participated in the phase 3 trials PSO3001, PSO3002, PSO3003, and PSO3004 as the covered trials. This plan is acceptable.

Question 12:

Does the Agency agree with the proposed plan for submission of programs, datasets, and BIMO?

FDA Response to Question 12:

For the clinical studies to be included in your submission, in addition to what you have proposed, we request the following:

- a. You stated that tabulation and analysis datasets will be provided in SAS XPORT format with .xpt extension, data definition files, and reviewer's guides in support of study reports corresponding to studies included in the submission. We note that the analysis datasets should include all variables needed for conducting the analyses included in the study report.
- b. Include dataset documentation (define.html, define.xml, or both) for tabulation and analysis datasets. The analysis dataset documentation should include sufficient detail, such as the definition or description of each variable in the dataset, algorithms for derived variables (including source variables used), and descriptions for the codes used in factor variables.
- c. Include all protocols (including protocol amendments) and statistical analysis plans.

- d. Include an annotated case report form. If any data is collected via electronic data capture rather than directly on the CRF, include annotated screen shots of the electronic data capture system.

Additional comments:

- Labeling for your proposed product is required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, provide a review of available information for your product and the moiety regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., from published literature, pharmacovigilance database, etc.) In addition,
 - a. Provide narratives for all pregnancies that occurred during the development program
 - b. Provide summary table or tables that include
 - Pregnancy outcomes:
 - gestational age of stillbirths and miscarriage and whether congenital anomalies were described
 - gestational age of live births with a table describing type and numbers of cases of adverse infant outcomes that were observed, including congenital anomalies, preterm birth, small for-gestational age and other adverse pregnancy outcomes.
 - Perinatal complications (the number and type), such as gestational diabetes, preeclampsia, postpartum hemorrhage, pregnancy-induced hypertension, etc.
 - Adverse effects on breastfed infants exposed to your product via lactation reported in the pharmacovigilance database and the number of cases for each type of reported adverse event. Please provide the case report forms for any lactation cases that were reported as fatal.
 - Adverse events (the number and type) related to male and female fertility in the pharmacovigilance database.
- Submit the coding dictionary used for mapping investigator verbatim terms to preferred terms. The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim). The Agency can provide recommendations regarding the pooling of certain preferred terms (e.g., viral upper respiratory tract infection and upper respiratory tract infection) to enhance your safety analysis if you submit your coding dictionary prior to completion of the safety analysis for your NDA.

- 476 • As part of our review of your original drug, the Agency will conduct a
477 comprehensive assessment of the benefits and risks of your drug product. The
478 information needed to complete this analysis is described in the guidance for
479 industry *Benefit-Risk Assessment for New Drug and Biological Products (October*
480 *2023)*.
481 [https://fda.sharepoint.com/sites/CDER-](https://fda.sharepoint.com/sites/CDER-CFGD/_layouts/15/viewer.aspx?sourcedoc={75dee45a-0b42-4073-8e26-5ca75ec8c340})
482 [CFGD/_layouts/15/viewer.aspx?sourcedoc={75dee45a-0b42-4073-8e26-](https://fda.sharepoint.com/sites/CDER-CFGD/_layouts/15/viewer.aspx?sourcedoc={75dee45a-0b42-4073-8e26-5ca75ec8c340})
483 [5ca75ec8c340}](https://fda.sharepoint.com/sites/CDER-CFGD/_layouts/15/viewer.aspx?sourcedoc={75dee45a-0b42-4073-8e26-5ca75ec8c340})
484
485 • For any clinical outcome assessment (COA) tool intended to support regulatory
486 decision-making and labeling claims, provide the following:
487
488 a. Exact copies of the instrument(s) as they were administered during the
489 clinical trial (e.g., copy of paper version, electronic screen shots) and any
490 associated training materials and user manuals.
491
492 b. Conceptual framework of the instrument(s), where applicable. This
493 includes a description of the items comprising each of the instrument's
494 domains.
495
496 c. Evidence of content validity and other measurement properties (e.g.,
497 reliability, construct validity, ability to detect change) obtained for the
498 specific context of use, including final qualitative and quantitative summary
499 reports if available. Literature related to the development history would be
500 acceptable; however, submit copies of publications.
501
502 d. Proposed scoring algorithm(s) with rationale and corresponding
503 information on how the instruments' scores were analyzed as part of an
504 endpoint, including what constitutes meaningful within-patient score
505 changes.
506
507 e. Strategy for handling missing data
508
509 f. Information regarding translation and cultural adaptation for the target
510 patient population(s), if applicable. Refer to the ISPOR principles for the
511 translation and cultural validation process2.
512

513 We recommend that you compile this information into an evidence dossier for the
514 target COAs for your NDA submission.
515

516
517 **Question 13:**

518 Does the Agency agree that data generated from foreign sites not conducted under
519 an IND are acceptable for inclusion in the planned NDA to support approval of JNJ-
520 77242113 for the treatment of psoriasis?

FDA Response to Question 13:

You may submit data generated from foreign sites not conducted under an IND to support your marketing application. However, the studies that you rely on should be conducted in accordance with good clinical practice (GCP), including review and approval by an independent ethics committee (IEC) and informed consent from subjects (21CFR 312.120). We also recommend that this data is clearly labeled as supportive clinical data.

3.0 ADMINISTRATIVE LANGUAGE**DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.² In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.³

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information⁴ and Pregnancy and Lactation Labeling Final Rule⁵ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential*:

² <https://www.fda.gov/media/86340/download>

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁴ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁵ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

Labeling for Human Prescription Drug and Biological Products – Content and Format.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h⁶ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁷. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.⁸

REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to include information in their submission cover letters that identifies uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products*.⁹ For questions or clarification, contact cdarmedicalpolicy-realworldvidence@fda.hhs.gov.

⁶ <https://www.fda.gov/media/84223/download>

⁷ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

⁸ <https://www.fda.gov/media/85061/download>

⁹ <https://www.fda.gov/media/124795/download>

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items that were identify during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

Janssen Research and Developments response to our preliminary meeting comments attached.

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/

CRAIG H JOHNSON
12/23/2024 10:22:18 AM



IND 156446

MEETING MINUTES

Janssen Research & Development, LLC.
Attention: Andrew Elias Ph.D.
Associate Director, Global Regulatory Affairs, Immunology
Welsh and McKean Roads
P.O. Box 776
Spring House, PA 19477

Dear Dr. Elias:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for JNJ-77242113.

We also refer to the teleconference between representatives of your firm and the FDA on June 21, 2023. The purpose of the meeting was to discuss the development plan of JNJ-77242113.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Craig Johnson, Regulatory Project Manager at 301-796-3921.

Sincerely,

{See appended electronic signature page}

Shari L. Targum, MD, MPH, FACP, FACC
Acting Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

1. Meeting Minutes
2. Janssen Research & Development response document



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2
Meeting Date and Time: June 21, 2023, 11:00 a.m. – 12:00 p.m. EST
Meeting Location: Virtual
Application Number: IND 156446
Product Name: JNJ-77242113
Indication: plaque psoriasis
Sponsor Name: Janssen Research and Development
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair: Dr. Shari Targum MD, MPH, FACP, FACC
Meeting Recorder: Dr. Craig Johnson, PharmD

FDA ATTENDEES

Shari Targum MD, MPH, FACP, FACC, Acting Director, Division of Dermatology and Dentistry (DDD)
Nikolay Nikolov, MD, Acting Deputy Office Director, Office of Immunology and Inflammation (OI)
Jill Lindstrom, MD, FAAD, Senior Physician, OI
David Kettl MD, FAAP, Clinical Team Leader, DDD
Shera Schreiber, MD, Clinical Reviewer, DDD
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Inflammation and Immune Pharmacology (DIIP)
Shukal Bala, PhD, Clinical Microbiology, Division of Anti-Infectives, Office of Infectious Diseases
Dapeng Hu, Statistical Reviewer, Division of Biometrics III, Office of Biostatistics
Kathleen Fritsch, PhD, Biometrics Reviewer, Division of Biometrics III
Baoqing Ma, PhD, Senior Pharmaceutical Quality Assessor, Division of New Drug Product II
Craig Johnson PharmD, Regulatory Health Project Manager, Division of Regulatory Operations for Dermatology and Dentistry

1.0 BACKGROUND

Purpose of meeting

To discuss the development plan of JNJ-77242113 for the treatment of plaque psoriasis in adolescent and adult patients.

FDA sent Preliminary Comments to Janssen Research and Development on June 16, 2023.

2.1. Nonclinical

Question 1:

Does the Agency agree that the outlined nonclinical safety pharmacology and toxicology studies are sufficient to support further development and registration of JNJ-77242113 for the proposed indication?

FDA Response to Question 1:

We acknowledge that you plan to conduct a peri- and postnatal development study in SD rats and a 6-month carcinogenicity study in transgenic rasH2 mice. We also note that a completed male fertility study in SD rats (Study# TOX14805) has not been submitted to the IND. Submit the male fertility study to the IND for review prior to the initiation of phase 3 clinical trials. Overall, your nonclinical program appears reasonable to support further development and registration of your product.

2.2. Clinical Pharmacology

Question 2:

Does the Agency agree that the proposed clinical pharmacology program is adequate to support registration of JNJ-77242113 for the proposed indication?

FDA Response to Question 2:

It is premature to answer this question at this point. We note that there are some (b) (4) and the fate of these is not clear.

Provide additional information to support your request for waiver for Mass Balance, Renal Impairment and Hepatic Impairment studies. The adequacy of the data will be a review issue.

You need to submit a separate waiver request for QT/QTc prolongation assessment for JNJ-77242113 (TQT study), with a scientific justification.

Adequate sample size and PK samples for subjects with different degrees of renal and hepatic impairment should be included in the popPK analysis from the data collected in pivotal phase 2 and phase 3 studies. The final determination of any dose

adjustment for patients with organ impairment and the necessity of a dedicated study will be determined after we review the PK data and model results.

Meeting Discussion

The Agency stated that they have not had a chance to review all the data from animal studies in support of a waiver of Mass balance study. However, the totality of evidence does seem to support the Sponsor's position to not conduct a dedicated mass balance study. Ultimately, this will be a review issue at the time of NDA submission.

With regards to DDI, the Agency advised the Sponsor to fully address the DDI potential of their product especially with transporters. The Agency further advised the Sponsor to address the DDI potential with the 200 mg QD dose and the adequacy of the data will be a review issue at the time of NDA submission.

Question 3:

Does the Agency agree with the Sponsor's proposal for characterizing ADA samples for neutralization potential in the Phase 3 studies?

FDA Response to Question 3:

No, we do not agree. You need to collect ADA samples in all pivotal studies and also need to characterize ADA samples for neutralization potential in all clinical studies including pivotal phase 2, and phase 3 studies. For more information, refer to FDA guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (available at <https://www.fda.gov/media/85017/download>). In addition, for more information on the immunogenicity assay development, refer to the FDA guidance for industry *Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection* (available at <https://www.fda.gov/media/119788/download>).

2.3. Clinical

Question 4:

Does the Agency agree that the clinical development program is adequate to support registration of JNJ-77242113 for the proposed indication?

FDA Response to Question 4:

In your phase 3 clinical development program, you propose enrolling approximately 1,650 subjects with active plaque psoriasis across the following 3 randomized, double-blind, placebo-controlled trials:

- Study 77242113PSO3001: "A Phase 3, randomized, placebo-controlled, double-blind, parallel, multicenter, interventional study in adult and adolescent subjects with moderate to severe plaque psoriasis with randomized withdrawal and

retreatment in adult subjects.” This study will include at least 60 adolescent subjects who will not undergo randomized withdrawal and retreatment.

- Study 77242113PSO3002: “A Phase 3, randomized, double-blind, parallel, placebo- and active comparator-controlled, multicenter, interventional study in subjects with moderate to severe plaque psoriasis.” This study will not include adolescents.
- Study 77242113PSO3003: “A Phase 3, multicenter, randomized, double-blind, parallel, placebo-controlled, interventional study to evaluate the efficacy and safety of JNJ-77242113 in adult and adolescent subjects with at least moderate severity plaque psoriasis affecting special areas or subject with lower BSA ($\geq 5\%$ to $< 10\%$) moderate to severe plaque psoriasis.” Subjects must have failed at least one topical therapy. This study will allow for enrollment of adolescents with no minimum enrollment number required.

The three study designs are intended to support the indication of the treatment of adult and adolescent patients 12 years of age and older with plaque psoriasis who are candidates for systemic therapy. However, we do not agree that the proposed clinical development program is adequate to support registration of your investigational product for the proposed indication. See *FDA responses to Questions 5, 6, and 7*, below.

Question 5:

Does the Agency agree that the design of Study 77242113PSO3001 is adequate to support the proposed indication?

FDA Response to Question 5:

For Study 77242113PSO3001, you propose conducting a multicenter, randomized, double-blind, placebo-controlled study with randomized withdrawal and retreatment in approximately 540 adult and 60 adolescent subjects with moderate to severe plaque psoriasis for a 163-week study period. The study will be further divided into a 5-week screening period, a 16-week placebo-controlled period, and a randomized withdrawal period for adult subjects from Week 24 to Week 52; from Week 52 to Week 156, all subjects will be treated with open-label JNJ-77242113. All subjects will have a 2-week safety follow-up period after discontinuation of study intervention or at the end of the treatment period.

At Week 0, subjects will be randomized in a 2:1 ratio to receive either JNJ-77242113 200 mg QD or placebo. Subjects randomized to placebo will transition to JNJ-77242113 at Week 16 and remain on treatment through Week 156. Among subjects initially randomized to JNJ-77242113, any adult subjects who fail to achieve a PASI 75 at Week 24 will remain on JNJ-77242113 through Week 156. Adult subjects who achieve PASI 75 response at Week 24 will be re-randomized to continue JNJ-

77242113 or transition to placebo through Week 52. Subjects re-randomized to placebo who experience $\geq 50\%$ loss of PASI improvement achieved at Week 24 will be retreated with JNJ-77242113. At Week 52, all subjects re-randomized to placebo at Week 24 will be transitioned to open-label therapy with JNJ-77242113 through Week 156. Adolescent patients will not participate in the randomized withdrawal and will remain on JNJ-77242113 through Week 156.

The co-primary endpoints for Study 77242113PSO3001 will be IGA score of 0 or 1 with a ≥ 2 -grade improvement from baseline at Week 16 and PASI 75 at Week 16. Safety will be evaluated via the assessment of adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (active TB, malignancy, potential Hy's Law cases), discontinuation of study intervention due to AEs, changes in laboratory assessments, changes in vital signs, and changes in weight.

We have the following comments regarding the proposed study protocol:

1. Study Endpoints

- a. The proposed co-primary endpoints of IGA score of 0 or 1 with a ≥ 2 -grade improvement from baseline, and achieving PASI 75, both evaluated at Week 16, are acceptable.
- b. You propose numerous secondary endpoints, including many that have been designated as key secondary endpoints. Secondary endpoints intended for labeling should be limited in number, clinically meaningful and adjusted for multiplicity. This comment applies to Studies 77242113PSO3002 and 77242113PSO3003 as well.
- c. Since you have defined co-primary endpoints of IGA score of 0 or 1 with a ≥ 2 -grade improvement from baseline and PASI 75, we recommend defining eligibility for the randomized withdrawal on the JNJ-77242113 arm in terms of achieving IGA response OR PASI 75 response and tracking the maintenance of response for each corresponding endpoint (i.e., maintenance of IGA response among Week 24 IGA responders, and maintenance of PASI 75 response among PASI 75 responders). We recommend defining retreatment criteria based on the IGA scale, rather than $\geq 50\%$ loss of PASI improvement achieved at Week 24. We recommend that the definitions of response, relapse, and rebound be based on IGA and PASI 75 so that the same endpoints are used throughout the various periods of the trial.

Meeting Discussion

Primary Endpoint

The sponsor presented a new endpoint which differs from that in the briefing document. They propose to change the PASI response to PASI 90 in place of PASI 75. They stated this may help their marketing efforts since primary endpoints are the first ones listed in the label and marketing materials. The Agency had no objection to the new

primary endpoint of PASI 90, as long as statistically appropriate analyses are included and powering the trials allows achievement of objectives. Results of PASI 75, PASI 90, and PASI 100 have been described in labeling. In general, we recommend that your studies include assessment of PASI 75, PASI 90, and PASI 100 under appropriate multiplicity control.

The sponsor requested to keep the randomized withdrawal criterion to loss of PASI 75 response, and not parallel to the primary endpoint of PASI 90. The Agency noted that additional discussion on this point is needed, and additional comments could be added to the meeting minutes.

Post-Meeting Comment

Since you have modified your proposal to include co-primary endpoints of IGA score of 0 or 1 with a ≥ 2 -grade improvement from baseline, and achieving PASI 90, the Agency reiterates the recommendation to define eligibility for the randomized withdrawal on the JNJ-77242113 arm in terms of achieving response on either primary endpoint (now IGA response OR PASI 90 response) and tracking the maintenance of response for each corresponding endpoint (i.e., maintenance of IGA response among Week 24 IGA responders, and maintenance of PASI 90 response among PASI 90 responders). We recommend defining retreatment criteria based on the IGA scale, rather than $\geq 50\%$ loss of PASI improvement achieved at Week 24. We recommend that the definitions of response, relapse, and rebound be based on IGA and PASI 90 so that the same endpoints are used throughout the various periods of the trial.

- d. Submit copies of all assessment tools you intend to use and provide evidence to support content validity, psychometric properties, and performance of the instruments (i.e., reliability, validity, and ability to detect change). Additionally, provide support for any differences between the ones you propose to use and those used in prior labeling for other products. This comment applies to Studies 77242113PSO3002 and 77242113PSO3003 as well.

2. Dosing Regimen

- You propose administering JNJ-77242113 at a dose of 200 mg once daily, which has not been evaluated previously in clinical trials. In the absence of clinical data to support the safety and efficacy of this dosing regimen, we are unable to comment on its acceptability for your phase 3 program. Refer to FDA response to Question 8.

3. Safety Monitoring

- a. Include active assessment for neuropsychiatric adverse events. Your phase 3 protocol should include a plan to screen subjects for previous history of treatment for depression and to prospectively monitor for the onset or worsening of depressive symptoms and of suicidal ideation and behavior

during the proposed study. Assessments to monitor prospectively for the onset or worsening of psychiatric symptoms ideally should be conducted at least monthly for the duration of the trial.

b. Examples of widely used instruments for depression screening include the Patient Health Questionnaire (PHQ-9) and the Quick Inventory of Depressive Symptomatology (QIDS-SR-16). For prospectively monitoring suicidal ideation and behavior (which is in addition to depression screening), a scale that maps to Columbia Classification Algorithm of Suicide Assessment (C-CASA) criteria like the Columbia Suicide Severity Rating Scale (C-SSRS) is appropriate. For the instruments that you select for depression and suicidality screening and symptoms monitoring over the course of the study, you should provide score thresholds that would exclude a candidate from the study at screening or that would trigger an action for an enrolled patient such as referral for mental health treatment or withdrawal from the study. You should provide research literature on the selected instruments to justify the thresholds proposed. This comment applies to Studies 77242113PSO3002 and 77242113PSO3003 as well.

c. Your proposal of performing 12-lead ECGs at baseline, Week 16, and Week 52, is acceptable. Your cardiovascular assessment should also include documentation and adjudication of thrombotic events, cerebrovascular events and Major Adverse Cardiovascular Events (MACE). Major adverse cardiovascular events include non-fatal myocardial infarction (MI), non-fatal stroke, and cardiovascular death. Extended MACE includes the following events: non-fatal MI, non-fatal stroke, cardiovascular death, unstable angina documented by a hospitalization or emergency department visit, and coronary revascularization (percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG)).

Other cardiovascular events include unstable angina documented by a hospitalization, coronary revascularization, transient ischemic attack, venous and peripheral arterial vascular thrombotic events, congestive heart failure, cardiac arrhythmia – no evidence of ischemia, and other serious non-MACE cardiovascular events such as syncope of a cardiovascular origin and severe/accelerated hypertension leading to hospitalization.

4. To capture all possible MACE and thrombotic events, examine all preferred terms (PT) and Standardized MedDRA Queries (SMQs) under:
- Ischemic Heart Disease SMQ /Myocardial Infarction SMQ/ Other Ischemic Heart Disease SMQ)
 - Cardiac Arrhythmias SMQ
 - Cardiac Failure SMQ
 - Embolic and Thrombotic Events SMQ (including Embolic and Thrombotic Events, Vessel Type Unspecified and Mixed Arterial and Venous SMQ)
 - Shock SMQ

- Torsade de pointes/QT prolongation SMQ
 - Cerebrovascular Disorders SMQ
 - Central Nervous System Haemorrhages and Cerebrovascular Accidents SMQ
 - Vasculitis SMQ
 - Cardiomyopathy SMQ
 - Hemodynamic Edema, effusions, and fluid overload SMQ
 - Hypertension SMQ
 - Pulmonary Hypertension SMQ
 - Renovascular Disorders SMQ
5. Review all of the following SOC's for possible cardiac events, thrombotic and MACE, since cardiac events may be found in several SOC's:
- Vascular Disorders
 - Cardiac Disorders
 - Nervous System Disorders
 - Respiratory, Thoracic, and Mediastinal Disorders
 - General Disorders and Administration Site Conditions
 - Injury, Poisoning, and Procedural Complications
 - Investigations
 - Musculoskeletal and Connective Tissue Disorders
 - Surgical and Medical Procedures
6. Have all possible cardiovascular events (rather than only MACE) reviewed by a DMC with expertise in cardiovascular adverse events.
7. Have all TIAs reviewed by the DMC (rather than only those resulting in hospitalization).
8. Evaluate possible thrombotic events alone and MACE alone during the uncontrolled period of the global psoriasis studies. This comment applies to Studies 77242113PSO3002 and 742113PSO3003 as well.

Question 6:

- a) Does the Agency agree that the design of Study 77242113PSO3002 is adequate to support the proposed indication?
- b) If highly statistically persuasive and consistent results are obtained in a single proposed active comparator study, 77242113PSO3002, does the Agency agree that the active comparator data can be described in Section 14 of the USPI?

FDA Response to Question 6:

- a) For Study 77242113PSO3002, you propose conducting a phase 3, randomized, double-blind, active comparator- and placebo-controlled, parallel, multicenter,

interventional study in approximately 750 adult subjects with moderate to severe plaque psoriasis. Subjects will be randomized in a 2:1:2 ratio to receive JNJ-77242113, placebo or deucravacitinib. The study will include a 5-week screening period and a 16-week placebo-controlled period which will run concurrently with a 24-week active comparator-controlled period.

At Week 16, subjects randomized to placebo will switch to JNJ-77242113 200 mg once daily through Week 156. At Week 24, subjects randomized to deucravacitinib will switch to JNJ-77242113 200 mg once daily through Week 156. All subjects will have a 2-week safety follow-up period after discontinuation of study intervention or at the end of the treatment period.

The proposed co-primary endpoints are the same as those for Study 77242113PSO3001, described above. Safety monitoring is also proposed to mirror that of Study 77242113PSO3001.

Safety Monitoring:

Since you plan to administer deucravacitinib as an active comparator, safety monitoring should include monitoring for adverse events observed in the deucravacitinib development program (e.g., infections, hypersensitivity reactions, elevated creatine phosphokinase, decreased glomerular filtration rate, lipid elevations).

- b) The inclusion of a comparative claim in the Clinical Studies Section of the prescribing information will be data driven and a review issue. To support comparative labeling claims, we generally require replication of study findings from two adequate and well-controlled clinical trials. Refer to the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

Meeting Discussion

The Agency noted that different randomization strategies may be acceptable, but the full protocol will have to be reviewed. In general, two replicative trials in which the active control is used optimally under labeled conditions are recommended to allow superiority claims in labeling.

Question 7:

Does the Agency agree that the design of Study 77242113PSO3003 is adequate to support the proposed indication and description of study results in Section 14 of the USPI?

FDA Response to Question 7:

No, we do not agree. For Study 77242113PSO3003, you propose conducting a phase 3, randomized, double-blind, placebo-controlled, multicenter study in adult and adolescent subjects with at least moderate severity plaque psoriasis affecting specific areas (scalp, genital, or palmoplantar psoriasis) or subjects with lower BSA ($\geq 5\%$ to $< 10\%$) moderate to severe plaque psoriasis who have failed at least one topical therapy.

You propose enrolling approximately 300 subjects in a 2:1 randomization ratio to receive either JNJ-77242113 200 mg QD or placebo with approximately 75 subjects in each of the 3 special areas and approximately 75 subjects with lower BSA moderate to severe plaque psoriasis.

The study will be comprised of a 5-week screening period, a 16-week placebo-controlled period, a 140-week open label JNJ-77242113-treatment period, and a 2-week safety follow-up period. Subjects randomized to JNJ-77242113 will take JNJ-77242113 from Week 0 through Week 156, and subjects initially randomized to placebo will receive placebo through Week 16 and then switch to JNJ-77242113 from Week 16 to Week 156.

The proposed primary endpoint for this study is IGA (overall) score of 0 or 1 and ≥ 2 -grade improvement from baseline at Week 16. Treatment groups will be stratified by population (special area [with the order of baseline hf-PGA ≥ 3 , sPGA-G ≥ 3 , and ss-IGA ≥ 3] and other), geographic region, and BSA category ($< 10\%$, $\geq 10\%$).

We have the following comments regarding the proposed study protocol:

- It appears that you propose an indication that encompasses mild, moderate and severe plaque psoriasis. Although the first two studies (77242113PSO3001 and 77242113PSO3002) aim to enroll subjects with moderate to severe plaque psoriasis, Study 77242113PSO3003 appears to target patients with milder disease (i.e., BSA $\geq 5\%$ to $< 10\%$). Based on the mechanism of action of your product and in the absence of safety data from your previous clinical trials, the use of JNJ-77242113 may not be justified in patients with mild plaque psoriasis. Therefore, to justify the risks of study participation and to augment the safety database for special site populations, we recommend that the subjects you enroll with BSA involvement $< 10\%$ have at least moderate psoriasis of one of the prespecified special areas (i.e, scalp, genital or palmoplantar).
- You essentially propose to evaluate 4 separate subpopulations in Study 77242113PSO3003. Although this “basket trial” approach may be theoretically acceptable, your proposed safety databases would not be adequate to support efficacy claims for each of the psoriasis subpopulations. Although you also plan to evaluate the special area psoriasis subpopulations in Studies 77242113PSO3001 and 77242113PSO3002, the sample size of each

subpopulation may not be adequate to appropriately characterize the safety and efficacy in these subpopulations.

Meeting Discussion

The sponsor requested clarification for the study population and eligible population for the differing grades of disease severity.

The Agency noted that there is not a consistent definition to differentiate severity characteristics, and we are concerned that the level of safety data has not adequately characterized the risk profile of the proposed treatment.

We agree to the criteria for moderate to severe psoriasis in “special areas.”

The safety database appears adequate for the primary indications. The population for “special areas” appears to be small compared to other programs. Safety may be supported by the larger trials, but we cannot predict that the safety experience expected by the sponsor will be confirmed as development proceeds. The Agency noted again that the safety experience to date is limited, and we await confirmation by further clinical trial data.

Question 8:

Does the Agency agree that the available data support the selection of 200 mg QD dose of JNJ-77242113 for further development in the proposed plaque psoriasis Phase 3 program?

FDA Response to Question 8:

You propose administering JNJ-77242113 at a dose of 200 mg once daily, which has not been evaluated previously in clinical trials. Whether this dose is optimized for your development program cannot be determined based on the available data.

Meeting Discussion

The Sponsor inquired on the adequacy of the 200 mg QD dose for the phase 3 trials based on their experience in the phase 2 dose ranging study. The Agency responded that based on dose/exposure-response data from the phase 2 dose ranging study, the 200 mg QD dose appears reasonable. However, the Agency also stated that the 200 mg QD dose was not studied in phase 2 dose ranging study and 100 mg BID dose was studied. Furthermore, the safety data from phase 2 dose ranging study is rather limited and there would be a potential for the 200 mg QD dose to produce a higher C_{max}, and the safety of this is not known. In conclusion, the Agency stated that, ultimately, the dose selection would be at the sponsor’s discretion and the adequacy of the dose will be assessed during the NDA review.

Question 9:

Does the Agency agree with the statistical analysis approach for the Phase 3 studies with JNJ-77242113?

FDA Response to Question 9:

Overall, your proposed analysis approach appears to be reasonable. However, we have the following comments:

1. You propose that proportion-based endpoints will be analyzed using the Cochran-Mantel-Haenszel (CMH) method adjusted for randomization stratification factors. It is unclear how p-values (e.g., CMH test, Wald test using CMH weights) and the 95% confidence intervals (e.g., stratified Newcombe confidence interval, Wald confidence interval using CMH weights) will be reported. We recommend aligning the testing and estimation methodology to minimize inconsistency in results. The protocol and/or Statistical Analysis Plan (SAP) should provide more details on these statistical measures.
2. You propose that for the 77242113PSO3002 study, (b) (4) While it may be possible to design your development program to support a comparative superiority claim in labeling (see *FDA response to Question 6b* above), trials that (b) (4) would not be appropriate for inclusion in labeling. Therefore, we do not recommend (b) (4) as it may not provide regulatory utility.
3. For the 77242113PSO3003 study, power calculations for the key secondary endpoints for special areas are based on data from clinical trials of other drug products. The effect size observed in the data from other drug products may not accurately reflect the effect size expected for JNJ-77242113. The study may be underpowered if power is based on incorrect effect size estimates.

Upon submission of the SAP, additional comments may be provided for further consideration.

2.4. Safety**Question 10:**

Does the Agency agree that the proposed safety database is adequate to support initial registration for JNJ-77242113 in plaque psoriasis?

FDA Response to Question 10:

You propose that at the time of initial BLA submission, approximately 1295 patients will have received the investigational product at the proposed dose level (either 100 mg BID or 200 mg QD) for 6 months and that approximately 527 will have received the investigational product at the proposed dose level for at least one year. Your proposal appears reasonable for an indication of moderate to severe psoriasis. However, as stated in the *FDA response to Question 7* above, the proposed safety

database for specific subsets or subtypes is unlikely to be adequate to support an indication of mild psoriasis or special area psoriasis.

The number of subjects needed to demonstrate safety may be substantially higher than the number of subjects needed to demonstrate efficacy and as such will greatly depend on the safety data collected from previous trials and any safety signal detected. Refer to the guideline for industry *The Extent of Population Exposure to Assess Clinical Safety: for Drugs Intended for Long term Treatment of Non-Life-Threatening Conditions*. Ultimately, the adequacy of the safety database will be review issue.

Question 11:

Does the Agency agree that the Sponsor's proposed strategy for the management of LTBI in the Phase 3 program would support the proposed labelling strategy?

FDA Response to Question 11:

For your phase 3 Studies 77242113PSO3001 and 77242113PSO3003, you propose mandatory screening for LTBI and allowing for optional treatment as required by local regulatory or IRB requirements at specific sites for subjects who test positive. You state that appropriate documentation of LTBI status at baseline will allow for differentiation of de novo infections versus LTBI reactivations

(b) (4)

(b) (4)

(b) (4)

Although your proposal for monitoring and addressing LTBI during your phase 3 studies appears reasonable, we do not agree

(b) (4)

(b) (4)

The number of cases of LTBI identified in your phase 3 studies is unlikely to be sufficiently large

(b) (4)

We have the following additional recommendations regarding your LTBI management strategy:

1. You propose measuring some of the inflammatory mediators relevant to the pathophysiology of psoriasis such as IL-23, IL-17A, IL-17F, IL-22, and beta-defensin-2. Although this is appropriate, we also recommend that you measure some of the other cytokines and chemokines, such as TNF- α , IL-6, IL-12, IFN- γ , and CXCL13 that are considered important in conferring protection against *M. tuberculosis* infection and/or granuloma formation.
2. The methods to be used for measuring inflammatory mediators were not specified. Also, it is unclear if testing will be performed in a central laboratory or at the site laboratories. It is recommended that the same method be used, and

testing be performed in a central laboratory. We encourage you to ensure that the laboratory used for all immunological measurements is a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory.

3. Due to the possibility of intra-subject variability, 2 baseline measurements for assessing inflammatory mediators should be considered.
4. Given the low baseline prevalence of LTBI in developed countries, it is unclear whether the lack of occurrence of reactivation of LTBI in the proposed clinical trials would rule out the potential of JNJ-77242113 to increase the risk for TB reactivation. Consider measuring the effect of treatment with JNJ-77242113 on reactivation of latent TB *in vitro* and/or in animal models of latent TB.
5. Given the significant morbidity and mortality associated with tuberculosis reactivation, we recommend that LTBI patients are well informed of the risks and benefits of LTBI treatment so they can make an informed treatment decision. If you intend to make treatment for LTBI optional in the aforementioned studies, the informed consent document (ICD) should clearly describe the risks of deferred treatment to subjects.

Meeting Discussion

The sponsor inquired whether

(b) (4)

(b) (4) The Agency noted that studies examining this issue would likely involve a low rate of reactivation, and the international TB prevalence is variable. It is unlikely that rare events could be excluded in the population expected to be tested, and testing will likely be included in labeling given the variable incidence and prevalence of TB globally.

2.5. Other

Question 12:

Does the Agency agree with the Sponsor's Diversity Plan for the JNJ-77242113 Phase 3 plaque psoriasis studies?

FDA Response to Question 12:

We have the following comments regarding your proposed Diversity Plan:

1. In Section 1 (Overview of the Disease/Condition)
 - For ease of evaluation, provide a table of epidemiologic (prevalence) and demographic information; provide your sources for this information.
2. In Section 2 (Scope of Medical Product Development Programs):
 - When available, provide data regarding differences in PK, PD, and pharmacogenomics associated with racial/ethnic populations.
3. In Section 3 (Goals for Enrollment of Underrepresented Racial and Ethnic Participants):

- You propose to enroll “a range of approximately 20% to 35% of participants with skin of color (self-identified as non-white or white + Hispanic) in the United States in each of the three Phase 3 psoriasis studies.” This goal does not adequately specify enrollment targets for specific racial/ethnic groups (e.g., Non-Hispanic Black or African Americans, Hispanic/Latino, Non-Hispanic Asian and Pacific Islanders, Non-Hispanic American Indian and Alaska Natives). You should revise the plan so that the target enrollment goals for these underrepresented minorities reflect the diverse US population. For ease of evaluation, please provide your target enrollment goals per population category in tabular format.
 - You should expand your Diversity Plan to include sex and age group demographics, as these demographics will be mandated in future Diversity Action Plans
4. In Section 4 (Specific Plan of Action to enroll and Retain Diverse Participants):
- Include a plan for the use of data to characterize safety, efficacy, and optimal dosage in these participants.
 - Provide further details on which patient advocacy groups and organizations will be contacted for this development program to facilitate enrollment of underrepresented populations.
 - Provide specific details on the methodology for assessment of retainment metrics.

3.0 ADMINISTRATIVE LANGUAGE

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include

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an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.¹ In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.²

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.³

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cdere-data@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page⁴ that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards

¹ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

² <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

³ <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

⁴ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.3 eCTD Sample Submission pg. 44) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.⁵

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of

⁵ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled

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Study Data Standards Resources⁶.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

6.0 ATTACHMENTS AND HANDOUTS

Janssen Research and Development response to FDA Preliminary Meeting Comments

⁶ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

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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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