SYNOPSIS

Study Title: A Phase 2b Multicenter, Randomized, Placebo-controlled, Dose-ranging Study to Evaluate the Efficacy and Safety of JNJ-77242113 for the Treatment of Moderate-to-Severe Plaque Psoriasis

Study Number: 77242113PSO2001

Study Phase: 2b

Name of Study Intervention: JNJ-77242113

Name of Sponsor/Company: Janssen Research & Development*

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Status:	Approved
Date:	27 October 2023
Prepared by:	Janssen Research & Development, LLC

Study Name: FRONTIER 1

EudraCT Number: 20021-003700-41
IND: 156446

Number of Study Centers and Countries/Territories:

This study was conducted at 60 centers that enrolled participants in 10 countries/territories (Poland, Germany, Spain, France, Great Britain, United States, Canada, Japan, Taiwan, and Korea).

Publications (if any): None

Study Period: 03 February 2022 to 16 December 2022

Rationale:

JNJ-77242113 is a peptide that binds directly to the interleukin-23 receptor (IL-23R) subunit and prevents IL-23 binding, thereby inhibiting proximal IL-23R signaling and downstream effector functions (eg, cytokine secretion). JNJ-77242113 has high potency in peripheral human cell based functional assays. Despite its low oral bioavailability (CCI), JNJ-77242113 has demonstrated systemic effects and is a promising candidate for further development in systemic, IL-23-driven diseases, such as plaque psoriasis.

Study 77242113PSO2001 (FRONTIER 1) was conducted to evaluate the clinical efficacy, safety, pharmacokinetics (PK), and immunogenicity of JNJ-77242113 in participants with moderate to severe plaque psoriasis.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the dose response of JNJ-77242113 at Week 16 in participants with moderate-to-severe plaque psoriasis	• Proportion of participants achieving Psoriasis Area and Severity Index (PASI) 75 (≥75% improvement from baseline in PASI) at Week 16
Secondary	
• To characterize additional efficacy of JNJ-77242113 versus placebo in participants with moderate-to-severe plaque psoriasis	• Change from baseline in PASI total score at Week 16 • Proportion of participants achieving PASI 90 (≥90% improvement from baseline in PASI) at Week 16 • Proportion of participants achieving PASI 100 (100% improvement from baseline in PASI) at Week 16 • Proportion of participants achieving an Investigator Global Assessment (IGA) score of cleared (0) or minimal (1) at Week 16 • Proportion of participants achieving an IGA score of cleared (0) at Week 16 • Change from baseline in body surface area (BSA) at Week 16
• To evaluate the effect of JNJ-77242113 treatment on patient-reported psoriasis severity versus placebo in participants with moderate-to-severe plaque psoriasis	• Change from baseline in Psoriasis Symptom and Sign Diary (PSSD) symptom score at Week 16 • Change from baseline in PSSD sign score at Week 16 • Proportion of participants achieving PSSD symptom score=0 at Week 16 among participants with a baseline symptom score ≥1 • Proportion of participants achieving PSSD sign score=0 at Week 16 among participants with a baseline sign score ≥1
• To evaluate the effect of JNJ-77242113 treatment on dermatology-specific health-related quality of life versus placebo in participants with moderate-to-severe plaque psoriasis	• Proportion of participants achieving a Dermatological Life Quality Index (DLQI) score of 0 or 1 at Week 16 among participants with baseline DLQI score >1
• To evaluate the effect of JNJ-77242113 treatment on general health-related quality of life versus placebo in participants with moderate-to-severe plaque psoriasis	• Change from baseline in domain scores of the Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29) at Week 16 • Proportion of participants who achieve at least a 5-point improvement from baseline in each PROMIS-29 domain at Week 16

• To assess the safety and tolerability of JNJ-77242113 in participants with moderate to severe plaque psoriasis	• Frequency and type of adverse events (AEs) and serious adverse events (SAEs)

Statistical Analyses:

The primary endpoint was the proportion of participants achieving PASI 75 at Week 16, defined as ≥75% improvement from baseline in PASI total score. This study is designed to enroll approximately 240 participants. Assuming a PASI 75 response rate of 6% and 80% in the placebo and JNJ-77242113 highest dose group, respectively, a sample size of approximately 40 participants in the placebo group and each of the JNJ-77242113 treatment groups provides an average power of at least 95% to detect a JNJ-77242113 dose-response signal for the primary endpoint using the Multiple Comparison Procedures with modeling techniques (MCP-Mod) method.

The sample size of 240 participants was also chosen to have at least a 90% power to detect a 35% difference between the JNJ-77242113 groups (n=40 each) and the placebo group (n=40) for the primary endpoint.

For the analysis of the primary endpoint, composite strategy (nonresponder imputation) was applied to address intercurrent event (ICE) 1 (discontinuation of study intervention due to lack of efficacy or due to an AE of worsening of psoriasis) and ICE 2 (initiation of a protocol-prohibited medication or therapy that could improve psoriasis); and treatment policy strategy (observed data) was applied to ICE 3 (discontinuation of study intervention due to other reasons). Participants with missing data after application of ICEs are also considered as nonresponders.

No adjustments for multiple comparisons were made for the secondary endpoints and nominal p-values were provided. For secondary binary endpoints, the same strategies for ICEs and the missing data as those for the primary endpoint are used. For continuous endpoints, zero was assigned to change from baseline or percent improvement for participants experiencing ICE 1 and ICE 2 while treatment policy strategy (observe data) was applied to ICE 3. The remaining missing data were handled by Mixed Models for Repeated Measures (MMRM) model under the assumption of missing at random.

For binary endpoints, comparisons between each of the JNJ-77242113 groups versus placebo were performed using a Cochran-Mantel-Haenszel (CMH) test stratified by the baseline weight (≤90 kg, >90 kg).

For continuous endpoints, treatment comparisons were performed using an MMRM model. The MMRM model had treatment group, baseline weight (≤90 kg, >90 kg), and baseline value for the corresponding efficacy endpoint as explanatory factors. The MMRM model also included visit, treatment group by visit interaction, baseline weight (≤90 kg, >90 kg) by visit interaction, and baseline value by visit interaction as additional explanatory factors.

Methodology:

Study 77242113PSO2001 was a Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging, parallel group, multicenter, interventional study that evaluated JNJ-77242113 in participants with moderate-to-severe plaque psoriasis. At Week 0, participants were randomized to 1 of 6 intervention groups: 5 dose groups of JNJ-77242113 (25 mg once daily [QD], 50 mg QD, 25 mg twice daily [BID], 100 mg QD, and 100 mg BID) or placebo.

The planned total sample size was approximately 240 participants (40 participants planned per group).

Eligible participants at Week 16 had the option to enroll in a 36-week long-term extension (LTE) study (77242113PSO2002 [FRONTIER 2]); all participants were to be treated with active study intervention in the LTE. The study design of the LTE is detailed in a separate protocol (77242113PSO2002) and results will be presented in a separate clinical study report (CSR).

Efficacy, safety, PK, immunogenicity, and biomarkers were assessed according to the Schedule of Activities. In addition, there were 4 optional substudy collections for participants who consented (where local regulations permitted): a pharmacogenomic blood sample, ex vivo cytokine release blood sample, skin biopsy, and photograph collection (lesional or lesional and full body). The results of the 4 optional substudies will not be presented in this CSR.

One planned database lock occurred at Week 16. Two interim analyses (IAs) occurred:

- when approximately 50% (n=120) of the participants reached Week 4, and
- when approximately 66% (n=160) of the participants reached Week 16.

The objective of the first IA was to evaluate futility, and the objective of the second IA was to plan the future development of JNJ-77242113. Futility was not met in the first IA and the results of both of the IAs did not impact the planned conduct of this study.

Safety monitoring was performed by an independent Data Monitoring Committee.

Number of Participants (Planned and Analyzed):

Of the 336 participants who were screened, a total of 255 participants were randomized into the study. All 255 randomized participants were treated and received at least 1 administration of study intervention.

Participants were randomized to 1 of 6 intervention groups. The number of participants in each treatment group at Week 0 were as follows:

- Placebo: 43 participants
- JNJ-77242113 25 mg QD: 43 participants
- JNJ-77242113 50 mg QD: 43 participants
- JNJ-77242113 25 mg BID group: 41 participants
- JNJ-77242113 100 mg QD group: 43 participants
- JNJ-77242113 100 mg BID group: 42 participants

Diagnosis and Main Criteria for Inclusion and Exclusion:

The target population consisted of adult participants with moderate to severe plaque psoriasis, defined by a PASI ≥12, IGA ≥3, and BSA ≥10%, who were candidates for phototherapy or systemic treatment. Participants were naïve to IL-23 inhibitors and must have discontinued IL-12/23 inhibitors, IL-17 inhibitors, and anti-tumor necrosis factor α biologic therapy at least 12 weeks or 5 half-lives, whichever is longer, prior to the first administration of study intervention. Participants must have discontinued immunosuppressants (eg, methotrexate, azathioprine, cyclosporine) for at least 4 weeks prior to the first dose of study intervention and must have discontinued topical therapies at least 2 weeks prior to the first dose of study intervention.

Study Interventions, Dose, and Mode of Administration:

JNJ-77242113 and placebo were both provided as yellow colored, film-coated tablets.

The unit dose strengths for JNJ-77242113 were 25 mg or 100 mg, taken on an empty stomach.

Duration of Study Intervention:

The total duration of this study was up to 24 weeks: a screening period of ≤4 weeks, a 16-week treatment period, and a 4-week safety follow-up period after the last study intervention administration for participants who were ineligible or decided to not enroll in the LTE study at Week 16.

SUMMARY OF RESULTS AND CONCLUSIONS:

Demographic and Other Baseline Characteristics:

Of the 336 participants who were screened, a total of 255 participants were randomized into the study from 60 centers across 10 countries/territories. The majority of participants were from Europe (49.4%), with the remainder from North America (33.3%) and Asia Pacific (17.3%).

All 255 randomized participants received at least 1 administration of study intervention.

A total of 24 participants (9.4%) discontinued study intervention prior to Week 16. The most common reason for discontinuation of study intervention was Withdrawal by Subject (3.1%). A higher percentage of participants discontinued from study intervention in the placebo group and the 25 mg QD group compared with the other JNJ-77242113 groups. The most common reason for discontinuation was Lack of Efficacy in the placebo group and Lost to Follow-up in the 25 mg QD group.

A participant who discontinued study intervention was not automatically discontinued from the study. A total of 24 participants (9.4%) discontinued study participation. The most common reason for discontinued study participation was Withdrawal by subject (5.9%). A higher percentage of participants discontinued study participation in the placebo group (16.3%) and the 25 mg QD group (16.3%) compared with the other JNJ-77242113 groups (range 2.4% to 9.5%).

Demographics and baseline characteristics were generally similar among groups. The mean age was 44.3 years, and the majority of participants were male (69.0%). This proportion was similar in all treatment groups, although the placebo group had the lowest percentage of males (58.1%). Most participants were white (74.5%). The weight and body mass index (BMI) were comparable across all groups, with a mean weight of 88.9 kg and a mean BMI of 29.9 kg/m^2.

Variability in the psoriasis disease characteristics at baseline were observed across treatment groups, but groups were mostly balanced. A slightly higher proportion of participants in the 25 mg QD group (30.2%) and the 100 mg BID group (28.6%) had an IGA score of 4 at baseline compared with the placebo group (11.6%) and other JNJ-77242113 treatment groups (range 16.3% to 19.5%).

The proportions of participants receiving previous therapies in each psoriasis medication category were generally comparable across treatment groups.

Exposure:

The median duration of exposure was 16.1 weeks in the combined JNJ-77242113 group and 16.0 weeks in the placebo group. The median daily dose of JNJ-77242113 was consistent with what was planned for each dose group.

Efficacy Results:

- A statistically significant dose-response signal was detected for the primary endpoint (PASI 75 response at Week 16) using MCP-Mod methodology.
- The proportion of participants achieving PASI 75 at Week 16 was statistically significantly higher in each of the groups treated with JNJ-77242113 compared with the placebo group (placebo 9.3%, JNJ-77242113: 25 mg QD: 37.2%; 50 mg QD: 58.1%; 25 mg BID: 51.2%; 100 mg QD: 65.1%; 100 mg BID: 78.6%).
- Efficacy of JNJ-77242113 was additionally shown versus placebo in statistically significantly higher proportions of participants achieving the following at Week 16:
  - Response rates for PASI 90, PASI 100, IGA score of cleared (0) or minimal (1), and IGA score of cleared (0) (highest responses in the 100 mg BID group for all endpoints).

  - PSSD symptom score of 0; PSSD sign score of 0 (with the exception of the JNJ-77242113 25 mg QD group); and clinically meaningful improvement (≥4-point improvement) in PSSD itch score.
  - DLQI score of 0 or 1 (highest percentage among participants with a baseline DLQI score >1 in the 100 mg QD group and 100 mg BID group).
- Clinical outcomes and patient-reported outcomes (PROs) evaluating regional psoriasis were more favorable in the JNJ-77242113 treatment groups than the placebo group at Week 16, though sample size was small.

Safety Results:

- JNJ-77242113 was well tolerated, as evidenced by the similar overall incidence of AEs and AEs that were considered as related across the treatment groups compared with placebo.
- Overall, there was no clear evidence of dose-dependent differences in AE incidence across the JNJ-77242113 dose groups.
- There were no deaths reported through the end of the study.
- There was a low overall incidence of SAEs, AEs leading to discontinuation of the study intervention, and severe AEs.
- The adverse events of special interest (AESIs) for JNJ-77242113 are active tuberculosis, malignancy, and potential Hy's Law cases; no AESIs were reported.
- The rates of abnormal hematology and chemistry laboratory test results were generally low and comparable between the treatment groups.

Pharmacokinetic Results:

- Following oral administration of JNJ-77242113 for 16 weeks, median plasma drug concentrations increased in a dose-related manner, with no apparent drug accumulation consistent with the study intervention’s short elimination half-life.
- The highest trough quartile had the greatest proportions of participants achieving PASI 75, PASI 90, PASI 100, and IGA score 0 or 1.

Immunogenicity Results:

- The incidence of antibodies to JNJ-77242113 through Week 16 was low (3.8%, 8/209), of low titer (1:50), and transient, with no clear association between positive antidrug antibodies (ADA) and dose level or length of time on treatment.
- All ADA-positive samples were negative for neutralizing antibodies (NAbs).
- There was no apparent correlation between ADA positivity and efficacy.

Conclusions:

- A statistically significant dose-response signal was detected for the primary endpoint and the highest response rate was seen in the 100 mg BID group. Therapy with JNJ-77242113 consistently resulted in greater clinical efficacy compared with the placebo group by Week 16, as evidenced by higher proportions of participants achieving responses in both clinical outcomes and PROs.
- Treatment with JNJ-77242113 was well tolerated, as evidenced by the similar overall incidence of AEs and related AEs across the treatment groups compared with placebo. Overall, there was no clear evidence of dose-dependent differences in AE incidence across the JNJ-77242113 dose groups.

- JNJ-77242113 median plasma drug concentrations increased in a dose-related manner with no apparent drug accumulation, consistent with its short elimination half-life.
- There was a low incidence of antibodies to JNJ-77242113, which were not dose related, of low titer, transient, and negative for NAbs.

A limitation of this study is that only 16 weeks of therapy was studied; future studies are needed to assess the benefits and risks of long-term therapy.

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