SYNOPSIS

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

Study Number: 77242113PSO2002

Study Phase: 2b

Name of Study Intervention: JNJ-77242113

Name of Sponsor/Company: Janssen Research & Development*

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Status:	Approved
Date:	24 June 2024
Prepared by:	Janssen Research & Development, LLC

Study Name: FRONTIER 2

IND: 156446

EudraCT Number: 2021-004320-16

Number of Study Centers and Countries/Territories: This study was conducted at 56 centers that enrolled participants in 10 countries.

Publications (if any): None

Study Period: 10 June 2022 to 29 September 2023

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, JNJ-77242113 has demonstrated systemic effects and is a promising candidate for further development in systemic, IL-23-driven diseases, such as plaque psoriasis.

This study, 77242113PSO2002 (FRONTIER 2), is the long-term extension (LTE) to Protocol 77242113PSO2001, a Phase 2b dose ranging study of JNJ-77242113 in adults with moderate-to-severe plaque psoriasis. The focus of the 77242113PSO2002 CSR is to present the long-term efficacy and safety data of JNJ-77242113 during 36 weeks of additional treatment after 16 weeks of treatment in Study 77242113PSO2001. Study 77242113PSO2001 occurred from Week 0 through Week 16 while Study 77242113PSO2002 occurred from Week 16 (LTE Week 0) through Week 56 (LTE Week 40). The following data are presented in this CSR:

- Efficacy data are presented for Week 52 (LTE Week 36). Efficacy data from both Studies 77242113PSO2001 and 77242113PSO2002 are also provided from Week 0 of Study 77242113PSO2001 through Week 52 (LTE Week 36) of Study 77242113PSO2002.

- Safety data are reported from Week 16 (LTE Week 0) through Week 56 (LTE Week 40) which includes 36 weeks of JNJ-77242113 treatment and a 4-week safety follow-up visit. Safety data from both Studies 77242113PSO2001 and 77242113PSO2002 are also provided from Week 0 of Study 77242113PSO2001 through Week 56 (LTE Week 40 of Study 77242113PSO2002).
- Pharmacokinetics data from both Studies 77242113PSO2001 and 77242113PSO2002 are presented from Week 1 of Study 77242113PSO2001 through Week 52 (LTE Week 36) of Study 77242113PSO2002.
- Cumulative immunogenicity data from both Studies 77242113PSO2001 and 77242113PSO2002 are presented from Week 1 of Study 77242113PSO2001 through Week 56 (LTE Week 40) of Study 77242113PSO2002.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate long-term clinical response of JNJ-77242113 treatment in participants with moderate-to-severe plaque psoriasis	Proportion of participants achieving Psoriasis Area and Severity Index (PASI) 75 (≥75% improvement in PASI from baseline of the originating* study) at Week 36
Secondary	
To evaluate long-term clinical response of JNJ-77242113 treatment in participants with moderate-to-severe plaque psoriasis	• Proportion of participants achieving PASI 90 (≥90% improvement in PASI from baseline of the originating study) at Week 36 • Proportion of participants achieving PASI 100 (100% improvement in PASI from baseline of the originating study) at Week 36 • Change from baseline of the originating study in PASI total score at Week 36 • Proportion of participants achieving an Investigator Global Assessment (IGA) score of cleared (0) or minimal (1) at Week 36
To evaluate the effect of JNJ-77242113 treatment on patient-reported psoriasis severity in participants with moderate-to-severe plaque psoriasis	• Change from baseline of originating study in Psoriasis Symptom and Sign Diary (PSSD) symptom score at Week 36 • Change from baseline of originating study in PSSD sign score at Week 36 • Proportion of participants achieving PSSD symptom score=0 at Week 36 among participants with a baseline (in the originating study) symptom score ≥1 • Proportion of participants achieving PSSD sign score=0 at Week 36 among participants with a baseline (in the originating study) sign score ≥1
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)

*Throughout table "originating study" refers to Protocol 77242113PSO2001, and Week 36 refers to Week 52 (LTE Week 36) of Study 77242113PSO2002.

Statistical Analyses:

Protocol 77242113PSO2002 is the LTE study of Protocol 77242113PSO2001, therefore there was no formal calculation of the sample size for Study 77242113PSO2002. The sample size of this LTE study was determined by the number of participants who enrolled in Study 77242113PSO2001 and were eligible to enter and choose to participate in this LTE study.

The primary efficacy endpoint was the proportion of participants achieving PASI 75 at LTE Week 36, defined as at least a 75% improvement in PASI from baseline of the originating study. For the primary analysis, composite strategy 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). Treatment policy strategy (observed data) was applied to ICE 3 (discontinuation of study intervention due to other reasons). All ICEs occurred prior to Week 52 (LTE Week 36). Participants with missing data after application of ICEs were also considered as non-responders.

No formal hypothesis testing was performed for the primary and secondary endpoints. The baseline data from the originating study (77242113PSO2001) was used to calculate the change-from-baseline-related endpoints.

For continuous endpoints, the change from baseline at each week was analyzed using a restricted maximum likelihood-based mixed model for repeated measures with fixed effects for treatment, visit, stratification factor of baseline weight category (≤ 90 kg, >90 kg), baseline value, baseline value by week interaction, baseline weight category by week interaction, and the treatment-by-week interaction. Least Square means (LSmeans) and their corresponding 95% confidence interval were provided, and no statistical testing was performed.

Methodology:

Study 77242113PSO2002 was a multicenter, LTE, double-blind, dose-ranging, parallel group, interventional study in participants with moderate-to-severe plaque psoriasis.

All eligible participants from Protocol 77242113PSO2001 were given the option to enroll in this LTE study, 77242113PSO2002.

All participants randomized to an active JNJ-77242113 dose regimen (25 mg QD, 50 mg QD, 100 mg QD, 25 mg BID, or 100 mg BID) in Protocol 77242113PSO2001 continued to receive the same dosing regimen of JNJ-77242113 in this study in a blinded manner. Participants randomized to placebo in Protocol 77242113PSO2001 received JNJ-77242113 100 mg QD starting at Week 16 (LTE Week 0) of Study 77242113PSO2002 through the end of the treatment period in this study.

Efficacy, safety, PK, immunogenicity, and biomarkers were assessed according to the Schedule of Activities.

One planned database lock occurred at Week 56 (LTE Week 40).

Safety monitoring was performed by an independent Data Monitoring Committee.

Number of Participants (planned and analyzed):

A total of 227 participants entered the study. All 227 participants were treated and received at least 1 administration of study intervention.

The number of participants in each treatment group at Week 16 (LTE Week 0) were as follows:

- 35 participants in the 25 mg QD group

- 39 participants in the 50 mg QD group
- 40 participants in the 25 mg BID group
- 40 participants in the 100 mg QD group
- 38 participants in the 100 mg BID group
- 35 participants in the placebo→100 mg QD group

Diagnosis and Main Criteria for Inclusion and Exclusion:

Participants had to have completed the Week 16 visit in the 77242113PSO2001 study and had to agree to discontinue all topical therapies that could affect psoriasis or the PASI or IGA evaluations, other than nonmedicated emollient and salicylic acid shampoos, prior to first administration of study intervention. Participants could not have received any biologic therapy or experimental therapy since completion of the originating study, 77242113PSO2001. In addition, participants could not have received any phototherapy or systemic treatment, except for systemic corticosteroids taken <2 weeks in duration since completion of the originating study, 77242113PSO2001, and within 4 weeks of the first administration of study intervention.

Study Interventions, Dose, Mode of Administration:

JNJ-77242113 and placebo were both provided as CCI [redacted].

The unit dose strengths for JNJ-77242113 were 25 mg, 50 mg, or 100 mg, taken on an empty stomach.

Duration of Study Intervention:

The total duration of this study is up to 40 weeks: a 36-week treatment period and a 4-week safety follow-up period after the last study intervention administration.

SUMMARY OF RESULTS AND CONCLUSIONS:

Demographic and Other Baseline Characteristics:

Demographics and other baseline characteristics are presented in the 77242113PSO2001 CSR. A total of 227 participants entered Study 77242113PSO2002. A total of 36 participants (15.9%) discontinued study intervention from Week 16 (LTE Week 0) through Week 52 (LTE Week 36).

Exposure:

The median duration of exposure was 52 weeks, and the median daily dose of JNJ-77242113 was consistent with what was planned for each dose group.

Efficacy Results:

The efficacy of JNJ-77242113 was generally maintained from Week 16 (LTE Week 0) through Week 52 (LTE Week 36) in measures of:

- Clinician-reported outcomes including PASI score, IGA score, and BSA.
- Patient-reported outcomes, including PSSD symptom and sign scores and DLQI.
- Regional psoriasis assessments, including psoriasis of the scalp, fingernails, hands and feet, and genitalia.

Safety Results:

From Week 0 of Study 77242113PSO2001 through Week 56 of Study 77242113PSO2002:

- JNJ-77242113 was well tolerated, as evidenced by the similar overall incidence of AEs and related AEs across the treatment groups.
- 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 AEs of severe intensity.
- The AESIs for JNJ-77242113 are active TB, malignancy, and potential Hy's Law cases. The only reported AESI was malignancy (basal cell carcinoma) in the 50 mg QD group.
- 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, median plasma drug concentrations increased in a dose-related manner and were generally consistent for each dose group through Week 52.
- The highest trough plasma concentration quartile of JNJ-77242113 had the greatest proportions of participants achieving PASI 90, PASI 100, and IGA score 0 or 1. The second to highest concentration quartile had the greatest proportion of participants achieving PASI 75.

Immunogenicity Results:

- The incidence of treatment-emergent antibodies to JNJ-77242113 through Week 52 was CCI CCI . ADAs were CCI with CCI being the most abundant and CCI observed in CCI . The CCI of ADA formation was observed with the CCI
- CCI .
- There was CCI has an CCI or C CCI .
- Participants CCI JNJ-77242113 showed CCI CCI with participants CCI JNJ-77242113. This observation should be CCI as there was CCI CCI JNJ-77242113 CCI or on any CCI after participants CCI CCI

Conclusions:

- Efficacy as measured by clinical outcomes and PROs was generally maintained from Week 16 through Week 52 (LTE Week 36) in Study 77242113PSO2002 in all JNJ-77242113 dose groups.
- Treatment with JNJ-77242113 was well tolerated, as evidenced by the low incidence of AEs with no clear evidence of dose dependencies in AE incidence across the JNJ-77242113 dose groups.

- Following oral administration of JNJ-77242113, median plasma drug concentrations increased in a dose-related manner and were generally consistent for each dose group through Week 52.
- The incidence of antibodies to JNJ-77242113 was CCI and they were CCI CCI CCI ; however, the sample size is too small to draw conclusions on the CCI

A limitation of the study is the relatively small sample size; future studies are needed to assess the benefits and risks of JNJ-77242113 in a larger population.

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