SYNOPSIS

Study Title: Intervention Specific Appendix to Master Clinical Protocol PLATFORMPACRD2001: A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Platform Study Evaluating the Efficacy and Safety of Interventions in Participants with Moderately to Severely Active Crohn's Disease

Study Number: 67864238PACRD2001

Study Phase: 2a

Name of Study Intervention: JNJ-67864238

Name of Sponsor/Company: Janssen Research & Development*

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen Pharmaceutica NV; Janssen, Inc; Janssen Sciences Ireland UC; or Janssen Research & Development, LLC. The term "sponsor" is used to represent these various legal entities as identified on the Sponsor List.

Status:	Approved
Date:	27 June 2022
Prepared by:	Janssen Research & Development, LLC

Study Name: PRISM-SCARLET

EudraCT Number: 2019-003335-37

Number of Study Centers and Countries: The study was conducted at multiple sites in Eastern Europe (Poland, Russia, and Ukraine), the USA, Argentina, and Italy.

Publications (if any): None

Study Period: 23 September 2019 to 14 December 2021

Rationale: Targeting of the IL-23 pathway has shown to be effective in the treatment of Crohn's disease in clinical studies. JNJ-67864238 is an oral antagonist of IL-23R that was being developed for the treatment of moderately to severely active Crohn's disease. CCI [redacted]

Objectives and Endpoints:

Primary Objective: The primary objective was to evaluate the efficacy of JNJ-67864238 as measured by the change in the CDAI score from baseline at Week 12.

Secondary Objectives

- To investigate the safety and tolerability of JNJ-67864238 in participants with moderately to severely active Crohn's disease
- To evaluate the efficacy of JNJ-67864238 to reduce the SES-CD, induce clinical remission, clinical response, and endoscopic healing of the mucosa
- To evaluate the PK, PD, immunogenicity (if applicable), and biomarker response of JNJ-67864238

Primary Endpoint: The primary endpoint was the change from baseline in the CDAI score at Week 12.

Major Secondary Endpoints

- Change in the SES-CD from baseline
- Clinical response as measured by CDAI (≥100-point reduction from baseline in CDAI or CDAI <150)
- Clinical remission rate as measured by CDAI (CDAI <150)
- PRO-2 remission defined as AP mean daily score (AP component of the CDAI) at or below 1 AND SF mean daily score at or below 3, ie, AP ≤1 and SF ≤3
- Endoscopic response defined as at least a 50% improvement from baseline in the SES-CD
- Endoscopic remission defined as an SES-CD score ≤2

Methodology: This was a Phase 2a, randomized, double-blind, placebo-controlled study that evaluated the oral IL-23R antagonist JNJ-67864238 in participants with moderately to severely active Crohn's disease. Participants may have been intolerant or refractory to biologics or biologic nonfailures (Bio-IR or Bio-NF, respectively). The planned total sample size was 90 participants randomized to receive JNJ-67864238 CCI or placebo in a 3:2 ratio using permuted block randomization, stratified by baseline CDAI score (≤300, >300) and biological refractory status (Bio-IR, Bio-NF). The study duration was 12 weeks of treatment with a safety follow-up 4 weeks after the last dose of study intervention.

The IA was planned to take place when approximately 45 participants had completed their Week 12 assessments or had withdrawn from the study before Week 12. If the futility criteria were met, the decision to terminate enrollment was to be made based on a benefit-risk assessment of the totality of data, including overall efficacy assessments, analysis of PD/biomarker data, and a safety review by the external DMC. If the futility criteria were not met and the DMC had not raised any safety issue, enrollment was to continue until the planned sample size was reached. To augment decision-making, all available data at the IA, including from those participants without Week 12 assessments, were to be analyzed. An Interim Analysis Committee reviewed the unblinded interim data and formulated recommendations.

Diagnosis and Main Criteria for Inclusion and Exclusion: The target population consisted of adult men or women 18 to 75 years of age with moderately to severely active Crohn's disease of at least 3 months' duration, defined as a CDAI score ≥220 but ≤450 at Week 0, with a SES-CD score ≥3 by central endoscopy read OR an elevated CRP (>0.3 mg/dL or 3.0 mg/L) or elevated fecal calprotectin (>250 µg/g). Participants with a screening SES-CD score <3 who had an elevated CRP or elevated fecal calprotectin were to be limited to 20% of the participant population. Participants may have been Bio-IR or Bio-NF as defined below:

- Bio-IR Population: Those participants who have received infliximab, adalimumab, certolizumab pegol, vedolizumab, or ustekinumab at a dose approved for the treatment of Crohn's disease, and either did not respond initially, responded initially but then lost response, or were intolerant to the medication.
- Bio-NF Population: Those participants who have demonstrated an inadequate response to or have failed to tolerate conventional therapy such as corticosteroids or the immunomodulators 6-MP, AZA, or MTX. Participants who have demonstrated corticosteroid dependence (ie, an inability to successfully taper corticosteroids without a return of the symptoms of Crohn's disease) were also eligible. Bio-NF participants may also have received biologic therapy but only if it was discontinued for reasons other than lack of efficacy or intolerance (eg, a drug holiday).

Study Interventions, Dose, Mode of Administration, and Batch Numbers:

Intervention [a]	Bulk Lot Number	Packaged Lot Number	Initial Expiration at Packaged Release	Updated Expiration at End of Study
Placebo tablets for JNJ-67864238 300 mg oral tablets	4495931	T314262	25-Mar-24	25-Mar-24
JNJ-67864238 300 mg oral tablet	4494961	T314262	25-Mar-24	25-Mar-24
Placebo tablets for JNJ-67864238 300 mg oral tablets	3626201	4378441	20-Feb-20	20-Aug-21
JNJ-67864238 300 mg oral tablet	3626195	4378441	20-Feb-20	20-Aug-21
Placebo tablets for JNJ-67864238 300 mg oral tablets	3626201	4379372	21-Aug-20	21-Aug-21
JNJ-67864238 300 mg oral tablet	3684506-SUB-A	4379372	21-Aug-20	21-Aug-21
Placebo tablets for JNJ-67864238 300 mg oral tablets	3984930	4380602	2-Mar-22	2-Mar-22
JNJ-67864238 300 mg oral tablet	3830938	4380602	2-Mar-22	2-Mar-22
Placebo tablets for JNJ-67864238 300 mg oral tablets	3626201	4379373	21-Aug-20	21-Aug-21
JNJ-67864238 300 mg oral tablet	3684506-SUB-B	4379373	21-Aug-20	21-Aug-21
Placebo tablets for JNJ-67864238 300 mg oral tablets	3626201	4379571	21-Feb-21	21-Feb-22
JNJ-67864238 300 mg oral tablet	3792725	4379571	21-Feb-21	21-Feb-22
Placebo tablets for JNJ-67864238 300 mg oral tablets	3626201	4379573	21-Feb-21	21-Feb-22
JNJ-67864238 300 mg oral tablet	3792723	4379573	21-Feb-21	21-Feb-22

[a] The JNJ-67864238 300 mg and matching placebo oral tablets were manufactured by Catalent Pharma Solutions, USA. The JNJ-67864238 300 mg drug substance was manufactured by AmbioPharm, Inc., USA.

Duration of Study Intervention: Participants were to receive study intervention for 12 weeks followed by a safety follow-up visit 4 weeks after their last dose of study intervention.

Statistical Methods: The statistical hypothesis was that JNJ-67864238 is superior to placebo as measured by the reduction from baseline in the CDAI at Week 12 in participants with moderately to severely active Crohn's disease.

The primary efficacy analysis was based on the full analysis set, which included all participants randomized to JNJ-67864238 or placebo and who received at least 1 dose of study intervention. Safety analyses included all participants who received at least 1 dose of the study intervention. The primary endpoint was the change from baseline in CDAI scores at Week 12 based on an MMRM model that considered covariates of treatment, time, and treatment-by-time interaction.

An overall Type I error rate of 0.1 (2-sided) was used.

The hypothesis testing was conducted in a hierarchical manner with the test on the primary endpoint conducted first and the tests on major secondary endpoints conducted next. Within the major secondary endpoints, the gatekeeping approach in conjunction with graphical multiplicity control procedures were applied. As the IA will not lead to an early ISA completion due to success, multiplicity adjustment was not required. Nominal p-values were calculated for all comparisons.

There were no changes in the planned analyses for the study.

The planned IA included 42 participants who had either completed their Week 12 assessments or had terminated study participation before Week 12. The IAC completed the review of the futility analysis data and determined that futility criteria were met. As a result, study 67864238PACRD2001 was terminated on 03 November 2021. No safety concerns or trends were observed.

SUMMARY OF RESULTS AND CONCLUSIONS:

Number of Participants:

Number of Participants in Each Analysis Set; All Randomized Analysis Set (Study 67864238PACRD2001)

	Placebo	JNJ-67864238	Total
All randomized	18	30	48
Full analysis set	18 (100.0%)	30 (100.0%)	48 (100.0%)
Per protocol analysis set	17 (94.4%)	28 (93.3%)	45 (93.8%)
Safety analysis set	18 (100.0%)	30 (100.0%)	48 (100.0%)
Pharmacokinetics analysis set	0	30 (100.0%)	30 (62.5%)

[TSIDEM02.RTF] [JNJ-67864238\PACRD2001\DBR_FINAL_CRO\RE_FINAL_CRO\PROD\TSIDEM02.SAS] 28APR2022, 22:09

Demographic and Other Baseline Characteristics: Overall demographic characteristics were relatively balanced across treatment groups. A higher proportion of participants were male (56.3% [N=27/48]), most participants were from Eastern Europe (77.1% [N=37/48]), almost all participants were white (97.9% [N=47/48]), with a median age of 36.5 years. Demographics and baseline characteristics were generally well balanced across the Bio-IR and Bio-NF groups, with the exception of a higher proportion of males in the Bio-IR group.

A total of 37 of the 48 randomized participants completed the study. Seven participants discontinued or terminated early. An additional 4 participants enrolled at the time of the study termination, were terminated by the sponsor, and had completed at least 1 week and up to 8 weeks of treatment. A total of 35 of 48 participants completed the 12-week treatment duration.

Exposure: A total of 48 participants were randomized to JNJ-67864238 or placebo and received at least 1 dose of the study intervention through the final database lock. The majority of participants received study intervention through Week 12 (72.2% [N=13/18] and 63.3% [N=19/30] in the placebo and JNJ-67864238 groups, respectively) and completed study visits through the final safety follow-up visit (72.2% [N=13/18] and 76.7% [N=23/30] in the placebo and JNJ-67864238 groups, respectively).

Efficacy Results:

Interim Analysis and the Decision to Terminate 67864238PACRD2001: At the IA, the (0.1, 0.95) CIs for the change from baseline in the CDAI score and the SES-CD score at Week 12 were calculated to assess futility. Futility is declared if the change in CDAI score for the 95% upper bound <60 (TV) and the 10% lower bound <40 (MAV, placebo-active), and the change in the SES-CD score the 95% upper bound <1.6 (TV) and the 10% lower bound <0.4 (MAV). The (0.1, 0.95) CI for the change in the CDAI score is (-112.7, 19.5), which met the criteria for futility. The (0.1, 0.95) CI for the change in the SES-CD score is (-1.2, 3.1) which met 1 of the 2 criteria for futility as the lower bound of the CI is <0.4. Considering the totality of data including PK and PD/biomarkers, the decision was made at the IA to terminate the study for futility.

Primary Analysis: The primary analysis was the change in the CDAI score from baseline at Week 12. The median changes from baseline in CDAI scores at Week 12 were -161.0 and -117.0 in the placebo and JNJ-67864238 groups, respectively (p=0.288).

Secondary Endpoints: There was no differentiation at Week 12 in clinical response and clinical remission between the JNJ-67864238 and placebo groups, respectively. While not statistically significant, participants in the JNJ-67864238 group demonstrated a trend toward endoscopic response compared with the placebo group at Week 12 (26.7% [N=8/30] and 5.6% [N=1/18], respectively). While not statistically significant, there were also trends toward endoscopic remission and a reduction in the SES-CD score of ≥3 versus

baseline in the JNJ-67864238 group compared with the placebo group (16.7% [N=5/30] and 5.6% [N=1/18], and 30.0% [N=9/30] and 16.7% [N=3/18], respectively).

PRO-2 remission is defined as the AP mean daily score (AP component of the CDAI) at or below 1 AND the SF mean daily score at or below 3 (ie, AP ≤1 and SF ≤3). There was no differentiation at Week 12 in PRO-2 remission between the JNJ-67864238 and placebo groups.

Safety Results: An overall summary of treatment-emergent AEs through Week 12 is presented in the table below.

Overall Summary of Treatment-emergent Adverse Events Through Week 12; Safety Analysis Set (Study 67864238PACRD2001)

	Placebo	JNJ-67864238	Total
Analysis set: Safety	18	30	48
Participants with 1 or more:			
AEs	9 (50.0%)	15 (50.0%)	24 (50.0%)
Related AEs [a]	3 (16.7%)	3 (10.0%)	6 (12.5%)
AEs leading to death [b]	0	0	0
Serious AEs	1 (5.6%)	4 (13.3%)	5 (10.4%)
Related serious AEs	0	0	0
AEs leading to discontinuation of intervention	1 (5.6%)	4 (13.3%)	5 (10.4%)
Infections [c]	4 (22.2%)	3 (10.0%)	7 (14.6%)
Serious infections	0	2 (6.7%)	2 (4.2%)

Key: AE= adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to intervention.
[b] AEs leading to death are based on AE outcome of Fatal.
[c] Infections are based on the Investigator assessment.

[TSFAE01A.RTF] [JNJ-67864238\PACRD2001\DBR_FINAL_CRO\RE_FINAL_CRO\PROD\TSFAE01A.SAS] 16FEB2022, 18:21

Higher proportions of participants in the JNJ-67864238 group compared with the placebo group reported both SAEs and AEs leading to discontinuation of study intervention. No SAEs were related to study intervention. Serious infections (COVID-19) reported for 2 participants in the JNJ-67864238 group were not related to study intervention and the participants recovered by Week 12. Note that interpretation is limited by the small sample size.

The proportions of participants with 1 or more infections (as indicated by the investigator on the eCRF) were 22.2% (N=4/18) and 10.0% (N=3/30) in the placebo and JNJ-67864238 groups, respectively, with serious infections reported for no participants in the placebo group and 6.7% (N=2/30) of participants in the JNJ-67864238 group. No deaths and no AEs of special interest were reported. Three events of COVID-19 were reported, a nonserious event in the placebo group and 2 serious events in the JNJ-67864238 group; all participants recovered by Week 12.

Through Week 12, there were no clinically significant shifts in chemistry or hematology laboratory values, no significant trends in vital signs, and no clinically important ECG post-baseline values.

Pharmacokinetic Results: Plasma and fecal JNJ-67864238 concentrations in participants with Crohn's disease are consistent with PK data from healthy participants who received the same dose of JNJ-67864238 ([redacted]) in study PTG-200-01. No correlations were observed between plasma, fecal, or colon tissue JNJ-67864238 concentrations and clinical efficacy endpoints. However, due to the limited number of participants with PK data, no firm conclusions about correlation trends with efficacy endpoints can be made.

Biomarkers: Among participants who received JNJ-67864238, there were trends towards reduction in fecal calprotectin and CRP compared with participants who received placebo. However, these were not statistically significant and no correlation to exposure was observed.

Conclusions: Overall baseline demographic characteristics were well balanced across the JNJ-67864238 and the placebo groups, and the majority of participants in the total population and the JNJ-67864238 and placebo groups were receiving 1 or more concomitant medications for Crohn's disease at baseline. Based on the preplanned futility rules, the 67864238PACRD2001 study of JNJ-67864238 was terminated due to lack of efficacy without safety concerns at the IA. Similar proportions of participants in the placebo and JNJ-67864238 groups reported AEs, while higher proportions of participants in the JNJ-67864238 group reported both SAEs and AEs leading to discontinuation of study intervention. No deaths were reported and SAEs were low in both groups. Serious infections (COVID-19) reported for 2 participants in the JNJ-67864238 group were not related to study intervention and the participants recovered by Week 12. There were no notable or clinically significant changes in clinical laboratory assessments in the JNJ-67864238 and the placebo groups. No correlations were observed between plasma, fecal, or colon tissue JNJ-67864238 concentrations and clinical response endpoints. No notable study limitations were identified by the sponsor.

Disclaimer

Information in this posting shall not be considered to be a claim for any product, whether marketed or under development. In case of a marketed product, some of the information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.