2. SYNOPSIS

Name of Sponsor/Company: Provention Bio, Inc. **Name of Finished Product:** PRV-6527/JNJ-40346527 **Name of Active Ingredient:** PRV-6527/JNJ-40346527	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of Study:

A Phase 2a, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Study to Evaluate the Efficacy and Safety of Oral PRV-6527 (JNJ-40346527), an Inhibitor of Colony Stimulating Factor-1 Receptor, in Subjects with Moderately to Severely Active Crohn's Disease

Principal Investigator: Not applicable

Investigators:

58 investigators as listed in Appendix 16.1.4.

Study center(s):

58 sites in 7 countries: Austria, Germany, Hungary, Poland, Russia, Spain, and Ukraine.

Publications (reference):

None.

Studied period (years):	**Phase of development:**
Date first patient enrolled: 20 March 2018 Date last patient completed: 13 August 2019	2a

Objectives:

Primary:

- To evaluate the efficacy of PRV-6527 (JNJ-40346527) for 12 weeks in the treatment of moderately to severely active Crohn's disease (CD), as measured by the Crohn's Disease Activity Index (CDAI)

Secondary:

Clinical Outcomes

- Colonic and ileal mucosa, based upon the Simple Endoscopic Score for CD (SES-CD)
- Clinical symptoms, based upon the frequency of diarrheal stools and abdominal pain
- Clinical symptoms, based upon the PRO-2 portion of CDAI

Safety

- Safety and tolerability of PRV-6527 in subjects with active CD

Pharmacokinetics

- Trough plasma concentrations of PRV-6527 (C_{min}) and its active metabolites, M2 and M7 and their

sum, in subjects with active CD using a population pharmacokinetic (PK) approach

Pharmacodynamics

- Pharmacodynamic (PD) effects measured by fecal calprotectin and ultrasensitive C-reactive protein (CRP)

Exploratory:

- CDAI score independent of change in hematocrit, since PRV-6527 may cause anemia independent of its effects on CD.
- Clinical remission, clinical response, and endoscopic healing of the mucosa
- Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC)
- PK (C_{min}), PD, and biomarker response to PRV-6527, M2 and M7 and their sum
- Changes in histology using a modified Global Histology Activity Score (GHAS)
- Changes in M1 and M2 macrophages, and DC1 dendritic cells as assessed by immunohistochemistry (IHC)
- Changes in peripheral blood and gut tissue myeloid cells
- Effect of CDAI, SES-CD, and symptom endpoints on response and remission
- Effect of baseline CDAI, SES-CD, CRP and fecal calprotectin, and demography on efficacy
- Effect of presence or absence of CSF-1 and CD gene signature on efficacy
- Effect of C_{min} of PRV-6527 and its active M2 and M7 metabolites and their sum on efficacy

Methodology:

This was a Phase 2a, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in adult subjects with moderately to severely active CD. Approximately 90 subjects were planned to be randomized in a 2:1 ratio (approximately 60 in the PRV-6527 group and approximately 30 in the placebo group) to ensure approximately 75 evaluable subjects with at least one post-treatment CDAI score. Randomization was stratified by prior history of biologic treatment (bio-experienced) or not (bio-naïve) and by baseline CDAI score (<300 and ≥300).

Eligible subjects included males and females aged 18-75 years with moderately to severely active CD for at least 3 months, defined as CDAI score of ≥220 but ≤450 and SES-CD ≥6 (or ≥4 for ileal disease) based on centrally read video endoscopy during screening. Corticosteroid was allowed at a baseline dose of ≤20 mg/day prednisone or equivalent. Subjects who were bio-naïve or had previously received anti-tumor necrosis factor (TNF) and/or vedolizumab treatment could be eligible, but those who had been primary nonresponders to anti-IL-12/23 or anti-IL-23 agents were excluded.

The assigned treatment was given twice daily (BID) over 12 weeks, followed by a 4-week safety follow-up period. The total duration of the study was 16 weeks, excluding the screening period.

An independent Data Monitoring Committee (DMC) was commissioned for this study to monitor study progress and subject safety. If a substantial proportion of subjects (e.g., >50%) did not achieve target trough concentrations at Week 4 or the average trough levels were <50% of the target 160 ng/mL, and approximately 50% of subjects showed no increase in CSF-1 levels above baseline, the DMC could suggest increasing the dose to achieve the target level in a larger percentage of subjects. This did not occur, and the study proceeded as planned.

Number of patients (planned and analyzed):

Planned: 90

Analyzed: 93

Diagnosis and main criteria for inclusion:

- Subjects had moderate to severe CD with a CDAI score between 220 and 450 (inclusive) and a histologic diagnosis of CD for at least 3 months before screening. The histological diagnosis was confirmed locally from the screening colonoscopy if not previously documented at the site.
- Subjects had a SES-CD score ≥6 or ≥4 for ileal-only disease.
- Subjects who had had prior experience with anti-TNF, anti-integrin, or anti-MAdCAM 1 treatment could have been eligible if they had been primary nonresponders, secondary nonresponders, intolerant or allergic to anti-TNF agents (e.g., infliximab), or stopped such treatment for other reasons. Subjects who had had prior experience with anti-IL-12/23 (e.g., ustekinumab) or anti-IL-23 agents could have been eligible if they had been responders, secondary nonresponders, or stopped the treatment due to intolerance or reasons unrelated to efficacy. Primary nonresponders to anti-IL-12/23 or anti-23 were excluded.

Test product, dose and mode of administration, batch number:

PRV-6527 150 mg, taken orally BID

Batch numbers: ICTK02M, ICTK02N, 22067.19, 22067.20, 22067.21, 22067.22

Duration of treatment:

12 weeks

Reference therapy, dose and mode of administration, batch number:

Placebo, taken orally BID

Batch numbers: ICTK02M, ICTK02N, 22067.15, 22067.16, 22067.17, 22067.18

Criteria for evaluation:

Efficacy:

Ileocolonoscopy with biopsy was performed at screening and Week 12. Subjects recorded symptoms, including abdominal pain and stool quality and frequency, using an eDiary. The efficacy assessments included CDAI, PRO-2 score, SES-CD score, BSFS and stool frequency, numerical rating scale (NRS) for abdominal pain, PGIS, PGIC.

Blood samples were drawn at protocol-specified time points for biomarker analyses. PD biomarkers included fecal calprotectin, CRP, CSF-1, insulin-like growth factor 1 (IGF-1), serum type I C-telopeptide (sCTx-I) and serum procollagen 1N-terminal peptide (P1NP), CD gene signature and mRNA, peripheral blood mononuclear cells (PBMC) by fluorescence-activated cell sorting (FACS).

Histology and IHC analyses were conducted on mucosal biopsy samples. M1 and M2 macrophages and DC1 dendritic cells were enumerated with IHC.

Pharmacokinetics:

Plasma samples were collected for measurement of PRV-6527 and its metabolites M2 and M7 concentrations at Week 0 (pre-dose), Week 2 (pre-dose), Week 4 (pre-dose), Week 8 (random), Week 12 (random), and Week 16 (random).

Safety:

Adverse events, clinical laboratory tests (including liver function tests [LFTs]), electrocardiograms (ECGs), vital signs, and physical examinations.

Statistical methods:

Analyses were conducted using the Intent-to-Treat (ITT), Safety, and Per Protocol (PP) populations, as well as PK and PD populations.

Data were summarized using descriptive statistics. Continuous variables and respective changes from baseline were summarized by treatment and assessment time using the number of observations (N), mean, standard deviation (SD), coefficient of variation (CV), median and minimum and maximum. Pharmacokinetic exposure parameters were further summarized by geometric means and geometric coefficient of variation (GCV). Ordinal/categorical variables were summarized by frequency (number of observations) and proportions (%).

All tests were two-sided. P-values smaller than 0.05 were considered statistically significant. In addition to the inferential statistics, 95% confidence intervals (CIs) were constructed where appropriate.

The primary analyses included the continuous baseline CDAI score and prior treatment with biologic(s) to increase sensitivity of the tests and were retained in the respective models regardless of their significance or lack thereof. The primary endpoint was analyzed using analysis of covariance (ANCOVA), where the continuous baseline CDAI score and biologic experience (past treatment with a biologic agent) were included as covariates and treatment group was the main effect in the statistical model. Within-treatment effects and between-treatment differences (active – placebo) were estimated, and the respective 95% CIs were calculated. The modelling results were tabulated.

Secondary efficacy and PD analyses are described in the Statistical Analysis Plan (Appendix 16.1.9).

Trough concentrations of PRV-6527 and metabolites at Weeks 0, 2, 4 were summarized. All concentration data, including random samples, were listed.

Safety variables were reported descriptively.

SUMMARY – CONCLUSIONS

SUBJECTS DISPOSITION AND DEMOGRAPHICS

A total of 186 subjects were screened, and 93 of these subjects were randomized. Of the randomized subjects, 63 were assigned to the PRV-6527 group and 30 to the placebo group. All 93 subjects were included in the ITT, Safety, and PK populations. The PP1 population included 61 TNF-naïve subjects, and the PP2 population included 24 TNF-experienced subjects. The PD population included 70 subjects. Fourteen (15.1%) subjects discontinued study drug, including 10 (15.9%) who discontinued PRV-6527 and 4 (13.3%) who discontinued placebo.

Overall, the mean (SD) age was 38.3 (14.61) years. Nearly half of the subjects were female (48.4%). The mean (SD) BMI was 23.2 (4.19) kg/m^2. All subjects were white, and nearly all were not Hispanic or Latino (96.8%). The PRV-6527 and placebo groups were largely comparable in most demographic characteristics. The subjects in the PRV-6527 group were somewhat younger with lower BMI than those in the placebo group. Most subjects in both groups reported no nicotine or alcohol use. The mean (SD) duration of disease was 5.8 (5.98) years.

EFFICACY RESULTS:

In this study of subjects with moderately to severely active CD, the treatment groups were well balanced in past biologic use and clinical disease activities at baseline; however, the PRV-6527 group had higher levels of CRP, fecal calprotectin, and CSF-1, as well as GHAS scores, indicating more inflammation than the placebo group. The effect of PRV-6527 was compared with placebo, while subjects were receiving standard-of-care medications, including mesalamine, steroids, and immunomodulators.

There was substantial improvement in symptoms, which was similar in both groups. Treatment with PRV-6527 150 mg BID or placebo for 12 weeks led to mean (SD) changes of -128.0 (113.35) and -166.0 (93.65) in CDAI score from baseline to Week 12. The LS mean difference between the

PRV-6527 and placebo groups was 38.84 (95% CI: -5.34, 83.03), which was not statistically significant (p=0.0841). Thus, the primary endpoint was not met.

The PRV-6527 and placebo groups did not differ significantly in the endoscopic, clinical, patient-reported, histological exploratory endpoints.

Subgroup analyses based on past TNF therapy (TNF-naïve and TNF-experienced subjects) yielded results consistent with the ITT analyses.

It should be noted that the symptomatic improvements from baseline to Week 12 in the placebo group were much higher than expected, particularly in Eastern and Central European sites, in TNF-naïve subjects, and in subjects receiving more baseline CD medications such as steroids.

Despite this effect in the placebo group, there were significant improvements in objective and clinically relevant endpoints and biomarkers in the PRV-6527 group, suggesting that the drug had an effect in the disease process at the intestinal level:

- The CSF-1 level increased from Week 2 through Week 12 in the PRV-6527 group but not the placebo group, which indicates substantial engagement of PRV-6527 with the target, CSF-1R.
- Analyses of the peripheral and intestinal PD biomarkers and mRNA gene signatures confirmed the target engagement of PRV-6527 with CSF-1R, which reduced selective inflammatory myeloid cells both in peripheral circulation and in tissues; the CSF-1 colonic gene signature also decreased.
- These PD effects were associated with endoscopic (SES-CD), histologic (GHAS), and clinical improvements in the PRV-6527 group. However, the clinical benefits were similar to those in the placebo group.
- PRV-6527 exposure was correlated with CSF-1 levels, and the CSF-1 gene signature was correlated with the SES-CD score at baseline and at Week 12. These correlations support the finding that benefits in endoscopy (i.e., macroscopic inflammation) may be associated with a decrease in CSF-1 signaling by PRV-6527.

In summary, the objective effects of PRV-6527 may have been obscured by the high response rates to placebo in the study population.

SAFETY RESULTS:

PRV-6527 150 mg BID oral administration for 12 weeks was well tolerated. The overall incidence of treatment-emergent adverse events (TEAEs) was slightly higher in the PRV-6527 group (52.4%) than in the placebo group (43.3%).

No subject died. Treatment-emergent serious adverse events (SAEs) occurred in 3 (4.8%) subjects in the PRV-6527 group and 1 (3.3%) subject in the placebo group; none of the SAEs was considered related to the study drug. Four (6.3%) subjects in the PRV-6527 group discontinued study drug because of TEAEs, and none of these events were considered related to the study drug. Three (10.0%) subjects in the placebo group discontinued study drug because of TEAEs.

Overall, the incidence of any particular TEAE was low. None of the AE Preferred Terms occurred in more than 10% of the subjects in the PRV-6527 group. The most common TEAEs in the PRV-6527 group were CD (6 [9.5%] subjects), headache (5 [7.9] subjects), and pruritus and blood creatine phosphokinase increased (4 [6.3%] subjects each). In the placebo group, no specific TEAE occurred in more than 2 (6.7%) subjects.

No treatment-emergent adverse events of special interest (AESIs) (infections) or safety events of interest (pregnancy and overdose) occurred during the study.

In the PRV-6527 group, 7 (11.1%) subjects had potentially clinically important (PCI) hemoglobin abnormality, compared with none in the placebo group. This finding was not unexpected. The incidences of other PCI laboratory abnormalities were comparable between the two groups.

PRV-6527 is known to reduce macrophages, including Kupffer cells, in the liver, which is expected to

reduce clearance of enzymes by the liver. Therefore, the detection of minor elevations of these enzymes was not unexpected.

CONCLUSION:

Treatment of PRV-6527 150 BID orally for 12 weeks did not lead to significantly different efficacy results compared with placebo in subjects with moderate to severe CD who remained on standard-of-care medications including mesalamine, steroids, and immunomodulators, during the study. PRV-6527 was generally well tolerated with no unexpected safety signals detected.

The biomarker analyses demonstrated that PRV-6527 150 mg BID was sufficient to inhibit the CSF-1R target and increased CSF-1 levels and reduced selective inflammatory myeloid cells and CSF-1 gene signatures. These changes were associated with endoscopic (SES-CD), histologic (GHAS), and clinical (CDAI) improvements from baseline. However, the difference between the two treatment groups were not significant. It is possible that the effects of PRV-6527 were obscured by the unexpectedly high response rates in the placebo group in this patient population receiving standard of care. This effect may have been related to the enhanced standard of care during the study, including the background medications, in the predominantly biologic-naïve, high-disease-activity population in Central/Eastern Europe.

The totality of the data from this study support the role of CSF-1 in the pathophysiology of CD, as PRV-6527 150 mg BID, with confirmed target engagement to the CSF-1R, was associated with significant improvement from baseline to Week 12 in SES-CD and GHAS scores in no-steroid subjects within the PRV-6527 group and significant reductions compared with placebo in colonic CSF-1 gene signature and inflammatory cell populations, such as macrophages and DC1 dendritic cells.

Despite the limitations of the study (placebo effect, single dose-level, limited duration and sample size, and geography), the totality of the data confirmed a role of CSF-1R in the pathophysiology of Crohn's disease. PRV-6527 could potentially be a safe, oral, first-line therapy for patients with early CD.

Date of the report:

11 February 2020