

**Clinical trial results:****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****Summary**

EudraCT number	2017-003017-25
Trial protocol	HU AT ES PL DE
Global end of trial date	13 August 2019

Results information

Result version number	v1 (current)
This version publication date	19 November 2021
First version publication date	19 November 2021
Summary attachment (see zip file)	PRV-6527-CD2a_Clinical Study Report Synopsis v1.1 (PRV-6527-CD2a_Clinical Study Report Synopsis v1.1 [No date].pdf)

Trial information**Trial identification**

Sponsor protocol code	PRV-6527-CD2a
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03854305
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Provention Bio, Inc.
Sponsor organisation address	55 Broad Street, 2nd Floor, Red Bank, NJ, United States, 07701
Public contact	Gail M. Comer, MD, Provention Bio, Inc., +1 908 698 4612, gcomer@proventionbio.com
Scientific contact	Gail M. Comer, MD, Provention Bio, Inc., +1 908 698 4612, gcomer@proventionbio.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 August 2019
Global end of trial reached?	Yes
Global end of trial date	13 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

This trial was designed and monitored in compliance with the ethical principles of Good Clinical Practice as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

Each subject was required to give written consent according to local requirements after the Investigator or designee had fully explained the aims, methods, and potential benefits and risks of the study. The subject was given sufficient time to read the Informed Consent Form (ICF) and the opportunity to ask questions. The ICF(s) were signed before any study-related activity was initiated.

An independent Data Monitoring Committee (DMC) was established to monitor safety and benefit/risk throughout the trial. Additionally, the DMC reviewed PK data after at least the first 9 subjects completed their Week 4 visit to assure minimum threshold exposures were achieved. The DMC monitored data on an ongoing basis based upon enrollment and the emerging safety profile to ensure the continuing safety of the subjects enrolled in this study. The committee met at least quarterly to review unblinded safety data. The DMC made the recommendation for the continuation of the study without modifications.

Background therapy:

Mesalamine and low dose steroids.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	01 February 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	Ukraine: 34

Worldwide total number of subjects	93
EEA total number of subjects	38

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	90
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient enrolled on 20 March 2018; last patient completed on 13 Aug 2019. A total of 93 patients were enrolled at 54 sites in in 6 countries: Austria, Germany, Hungary, Poland, Russia, and Ukraine.

Pre-assignment

Screening details:

186 subjects were screened and 93 subjects were randomized; 93 screen failures were due to inclusion/exclusion criteria not met.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Every effort was made to retain the integrity of the blind. To maintain blinding, the study drug container had a label containing the study name, the container number, and other information. The study drugs were identical in appearance and were packaged in identical containers. The label did not identify the study drug in the container.

One subject with an SAE was unblinded by the investigator.

Arms

Are arms mutually exclusive?	Yes
Arm title	PRV-6527 150 mg

Arm description:

Experimental therapy arm: PRV-6527 150 mg (50 mg, 3 capsules), taken orally BID for 12 weeks.

Results are presented for the Intent-to-Treat (ITT) population, which included all 63 subjects who were randomized to the PRV-6527 150 mg arm. To note, the ITT, Safety, and PK populations contained the same data sets, as all randomized subjects received at least one dose of the study drug as assigned.

10 subjects in the PRV-6527 150 mg arm discontinued treatment due to: adverse event (3) or other reason (7).

Arm type	Experimental
Investigational medicinal product name	PRV-6527
Investigational medicinal product code	
Other name	JNJ-40346527
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

PRV-6527 was provided as 50 mg capsules. The dose was 150 mg (3 capsules) BID.

The study drug, PRV-6527 50 mg, was provided as free-base equivalent hard gelatin, size 3, gray opaque capsules for oral administration. All subjects were instructed to self-administer 6 capsules daily, 3 in the morning and 3 in the evening at approximately the same times each day with or without food. Subjects who were taking a histamine-2 receptor antagonist (H2RA) (e.g., ranitidine, famotidine, or nizatidine) or frequent antacids were instructed to take their dose of study drug BID always with food.

Arm title	Placebo
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Arm description:

Placebo arm: placebo capsules taken orally BID for 12 weeks.

Results are presented for the Intent-to-Treat (ITT) population, which included all 30 subjects who were randomized to the placebo arm. To note, the ITT, Safety, and PK populations contained the same data sets, as all randomized subjects received at least one dose of the study drug as assigned.

4 subjects in the placebo arm discontinued treatment due to: prohibited medication (1), adverse event (2), or other reason (1).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo was provided as 50 mg capsules. The dose was 3 capsules BID.

The placebo with a matching appearance consisted of lactose monohydrate in a gray-colored, hard, gelatin capsule.

All subjects were instructed to self-administer 6 capsules daily, 3 in the morning and 3 in the evening at approximately the same times each day with or without food. Subjects who were taking a histamine-2 receptor antagonist (H2RA) (e.g., ranitidine, famotidine, or nizatidine) or frequent antacids were instructed to take their dose of study drug BID always with food.

Number of subjects in period 1	PRV-6527 150 mg	Placebo
Started	63	30
Completed	53	26
Not completed	10	4
Early termination	10	4

Baseline characteristics

Reporting groups

Reporting group title	PRV-6527 150 mg
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Reporting group description:

Experimental therapy arm: PRV-6527 150 mg (50 mg, 3 capsules), taken orally BID for 12 weeks.

Results are presented for the Intent-to-Treat (ITT) population, which included all 63 subjects who were randomized to the PRV-6527 150 mg arm. To note, the ITT, Safety, and PK populations contained the same data sets, as all randomized subjects received at least one dose of the study drug as assigned.

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Reporting group title	Placebo
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Reporting group description:

Placebo arm: placebo capsules taken orally BID for 12 weeks.

Results are presented for the Intent-to-Treat (ITT) population, which included all 30 subjects who were randomized to the placebo arm. To note, the ITT, Safety, and PK populations contained the same data sets, as all randomized subjects received at least one dose of the study drug as assigned.

4 subjects in the placebo arm discontinued treatment due to: prohibited medication (1), adverse event (2), or other reason (1).

Reporting group values	PRV-6527 150 mg	Placebo	Total
Number of subjects	63	30	93
Age categorical			
Units: Subjects			
Adults (18-64 years)	61	29	90
From 65-84 years	2	1	3
Age continuous			
Overall, the mean (SD) age was 38.3 (14.61) years.			
Units: years			
arithmetic mean	37.0	41.1	-
standard deviation	± 14.95	± 13.67	-
Gender categorical			
Nearly half of the subjects were female (48.4%).			
Units: Subjects			
Female	28	17	45
Male	35	13	48
Ethnicity			
Nearly all subjects were not Hispanic or Latino (96.8%).			
Units: Subjects			
Hispanic or Latino	2	1	3
Not Hispanic or Latino	61	29	90
Race			
All subjects were white.			
Units: Subjects			
White	63	30	93
Use of nicotine products			
Most subjects in both groups reported no nicotine use (77.4%).			
Units: Subjects			

Never used	51	21	72
Ex-user	7	4	11
Current user	5	5	10
Alcohol consumption			
Most subjects in both groups reported no alcohol use (95.7%).			
Units: Subjects			
Never used	59	30	89
Ex-user	1	0	1
Current user	3	0	3
Extra-intestinal manifestations			
Approximately half of the subjects had extra-intestinal manifestations (50.5%). The most common extra-intestinal manifestations were arthritis/arthralgia (44.1%).			
Units: Subjects			
Yes	30	17	47
No	33	13	46
Prior Crohn's Disease-related Surgeries			
The majority of subjects had no previous CD-related surgeries (83.9%).			
Units: Subjects			
Yes	9	6	15
No	54	24	78
Weight			
Units: kg			
arithmetic mean	66.3	71.7	-
standard deviation	± 11.82	± 14.70	-
Weight			
Units: kg			
median	65.3	73.0	-
full range (min-max)	44.7 to 100.0	48.2 to 107.0	-
Body Mass Index			
The mean (SD) BMI was 23.2 (4.19) kg/m ² .			
Units: kg/m ²			
arithmetic mean	22.5	24.8	-
standard deviation	± 3.73	± 4.69	-
Body Mass Index			
Units: kg/m ²			
median	21.8	24.1	-
full range (min-max)	15.5 to 31.9	18.8 to 41.4	-
Duration of Crohn's Disease			
The mean (SD) duration of disease at baseline was 5.8 (5.98) years. The extent of the disease occurs most frequently in the ileum (65.6%) and rectum (55.9%).			
Units: years			
arithmetic mean	5.7	5.8	-
standard deviation	± 6.19	± 5.62	-
Duration of Crohn's Disease			
Units: years			
median	3.3	3.2	-
full range (min-max)	0.3 to 32.0	0.5 to 22.0	-

End points

End points reporting groups

Reporting group title	PRV-6527 150 mg
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Reporting group description:

Experimental therapy arm: PRV-6527 150 mg (50 mg, 3 capsules), taken orally BID for 12 weeks.

Results are presented for the Intent-to-Treat (ITT) population, which included all 63 subjects who were randomized to the PRV-6527 150 mg arm. To note, the ITT, Safety, and PK populations contained the same data sets, as all randomized subjects received at least one dose of the study drug as assigned.

10 subjects in the PRV-6527 150 mg arm discontinued treatment due to: adverse event (3) or other reason (7).

Reporting group title	Placebo
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Reporting group description:

Placebo arm: placebo capsules taken orally BID for 12 weeks.

Results are presented for the Intent-to-Treat (ITT) population, which included all 30 subjects who were randomized to the placebo arm. To note, the ITT, Safety, and PK populations contained the same data sets, as all randomized subjects received at least one dose of the study drug as assigned.

4 subjects in the placebo arm discontinued treatment due to: prohibited medication (1), adverse event (2), or other reason (1).

Primary: Change in Crohn's Disease Activity Index (CDAI) Scores from Baseline to Week 12

End point title	Change in Crohn's Disease Activity Index (CDAI) Scores from Baseline to Week 12
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End point description:

The primary endpoint of the study was the change in Crohn's Disease Activity Index (CDAI) score from baseline to Week 12, compared between the PRV-6527 and placebo groups. The CDAI was assessed by collecting information on 8 different Crohn's Disease-related variables (Best 1976): extra-intestinal manifestations, abdominal mass, weight, hematocrit, total number of liquid stools (Bristol Stool Form Scale type 6 or 7 stools), abdominal pain/cramping, use of antidiarrheal drug(s) and/or opiates, and general well-being. The last 4 variables were collected from the 7 most recent noncensored days as reported by the subject on the eDiary. Subjects were asked to complete the eDiary daily entry and bring the eDiary to each visit.

End point type	Primary
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End point timeframe:

Baseline to Week 12

End point values	PRV-6527 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	30		
Units: Change from baseline to Week 12				
arithmetic mean (standard deviation)	-128.0 (\pm 113.35)	-166.0 (\pm 93.65)		

Statistical analyses

Statistical analysis title	CDAI scores
Comparison groups	PRV-6527 150 mg v Placebo
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	= 0.0841
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	38.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.34
upper limit	83.03
Variability estimate	Standard error of the mean
Dispersion value	22.24

Notes:

[1] - Descriptive statistics

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events and special reporting situations, whether serious or nonserious, were reported from the time a signed and dated ICF was obtained until completion of the subject's last study-related procedure, which may include follow-up of safety.

Adverse event reporting additional description:

Treatment emergent adverse events were those that occurred after dosing of study drug through the study follow-up period. Events that occurred prior to study drug administration were considered baseline signs/symptoms.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	PRV-6527 150 mg
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Reporting group description:

Treatment-emergent adverse events (TEAEs) are presented for the Safety population, which includes all randomized subjects who received at least 1 dose of study drug. The Safety population includes all 63 subjects who were randomized to the PRV-6527 arm.

All treatment-emergent serious adverse events (SAEs) that occurred are reported. Non-serious TEAEs that occurred in 3 or more subjects in the active treatment group are reported.

No deaths occurred during the study.

Reporting group title	Placebo
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Reporting group description:

Treatment-emergent adverse events (TEAEs) are presented for the Safety population, which includes all randomized subjects who received at least 1 dose of study drug. The Safety population includes all 30 subjects who were randomized to the Placebo arm.

All treatment-emergent serious adverse events (SAEs) that occurred are reported. Non-serious TEAEs that occurred in 3 or more subjects in the active treatment group are reported.

No deaths occurred during the study.

Serious adverse events	PRV-6527 150 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 63 (4.76%)	1 / 30 (3.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	2 / 63 (3.17%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Cachexia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 63 (1.59%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	PRV-6527 150 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 63 (38.10%)	6 / 30 (20.00%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 63 (6.35%)	1 / 30 (3.33%)	
occurrences (all)	4	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 63 (4.76%)	1 / 30 (3.33%)	
occurrences (all)	3	1	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 63 (7.94%)	2 / 30 (6.67%)	
occurrences (all)	5	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 63 (4.76%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	5 / 63 (7.94%)	0 / 30 (0.00%)	
occurrences (all)	5	0	
Skin and subcutaneous tissue disorders			

Pruritus subjects affected / exposed occurrences (all)	4 / 63 (6.35%) 5	2 / 30 (6.67%) 2	
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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 March 2018	<ul style="list-style-type: none">- In Exclusion criterion #1, the condition of "tight stricture that prevents the passage of any colonoscope" was added to be excluded.- In Exclusion criterion #22 and in Section 9.2.1, the TB screening procedures were clarified. Only an indeterminate result was inconclusive and required repeat testing.- In Exclusion criterion #23, Hy's Law is specified as an indicator of hepatic impairment.- In Exclusion criterion #29, the history of substance abuse is added for exclusion.- The randomization method was revised from dynamic block central randomization to list-based block central randomization, as the list-based method was considered more appropriate for this study.- DMC was unblinded to both safety and efficacy data to better monitor the benefit/risk ratio for study subjects during the study.
19 November 2018	<ul style="list-style-type: none">- Prior biologic treatment remained a stratification factor but the required percentages (30% to 40% of all enrolled subjects being bio-naïve) were removed to facilitate patient recruitment. This did not affect any planned analyses.- The screening HIV test was changed from HIV antibody tests to antibody to p24 antigen (Ab-p24Ag) confirmed by HIV 1/2 Western blot as the replacement test is able to detect earlier infection.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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.

Notes: