Clinical trial results:
An Open-Label, Phase 2, Pilot Study Investigating the Safety, Clinical Activity, Pharmacokinetics, and Pharmacodynamics of Oral Treatment with the BTK Inhibitor PRN1008 in Patients with Newly Diagnosed or Relapsing Pemphigus Vulgaris

Summary

EudraCT number	2015-003564-37
Trial protocol	GR HR
Global end of trial date	10 January 2020

Results information

Result version number	v1 (current)
This version publication date	24 January 2021
First version publication date	24 January 2021

Trial information

Trial identification

Sponsor protocol code	PRN1008-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02704429
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement , Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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	05 March 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical safety of rilzabrutinib in patients with pemphigus vulgaris (PV) over a 12-week (Part A) and 24-week (Part B) treatment period;
To evaluate the clinical activity of rilzabrutinib in patients with PV, per criteria in the European Academy of Dermatology and Venereology 2014 Pemphigus S2 Guideline (Hertl 2015).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject was participating, contact details and any information needed in the event of a medical emergency.
Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

No background therapy was permitted. The use of oral prednis(ol)one may have been permitted in some circumstances. For admission to the study, doses of oral prednis(ol)one in the 2 weeks prior to Day 1 may have been no higher than 0.5 mg/kg/day (inhaled and mucosal [for symptomatic treatment of oral lesions] CS were allowed). Where patients entered the study on LDCS, the regimen should have been maintained for the initial 2 weeks of rilzabrutinib therapy. At the Day 15 review, a good clinical response to rilzabrutinib should have allowed the tapering of the CS to commence using the Werth taper. At all times, the rescue criteria should have been followed. In some circumstances, CS should have been added or the dose increased, with or without cessation of rilzabrutinib.

Evidence for comparator: -

Actual start date of recruitment	22 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Greece: 16
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Israel: 7
Worldwide total number of subjects	42
EEA total number of subjects	22

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)	39
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 69 patients were screened for the study (52 patients in Part A and 18* patients in Part B). Of these, 41 unique patients were enrolled in the study (27 patients in Part A and 15* patients in Part B). *One patient who completed Part A of the study and later relapsed was enrolled in Part B.

Pre-assignment

Screening details:

Up to 28 days before dosing, patients signed an informed consent to screen and, after meeting eligibility criteria, received treatment. All patients who provided informed consent and had Screening assessments evaluated for study participation were part of the Screening population

Period 1

Period 1 title	Overall - Part A + Part B (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A

Arm description:

12 weeks of treatment, followed by 12 weeks of follow-up off treatment. The total duration of individual patient participation was approximately 28 weeks.

Arm type	Experimental
Investigational medicinal product name	PRN1008
Investigational medicinal product code	
Other name	rilzabrutinib
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received 400 mg twice a day (BID) rilzabrutinib treatment for 12 weeks with intrapatient dose adjustment allowed up to 600 mg BID.

Arm title	Part B

Arm description:

Total duration was 24 weeks of therapy, with a follow-up visit 4 weeks later. The total duration of individual patient participation was approximately 32 weeks.

Arm type	Experimental
Investigational medicinal product name	PRN1008
Investigational medicinal product code	
Other name	rilzabrutinib
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients initially received 400 mg once a day (QD) rilzabrutinib but were permitted to dose escalate to a maximum of 600 mg BID rilzabrutinib at the Investigator’s discretion.

Number of subjects in period 1	Part A	Part B
Started	27	15
Completed	24	14
Not completed	3	1
Adverse event, non-fatal	3	-
Worsening of pemphigus	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Part A
Reporting group description:	
12 weeks of treatment, followed by 12 weeks of follow-up off treatment. The total duration of individual patient participation was approximately 28 weeks.	
Reporting group title	Part B
Reporting group description:	
Total duration was 24 weeks of therapy, with a follow-up visit 4 weeks later. The total duration of individual patient participation was approximately 32 weeks.	

Reporting group values	Part A	Part B	Total
Number of subjects	27	15	42
Age categorical			
One patient who completed Part A of the study and later relapsed was enrolled in Part B. Therefore baseline results of one patient are repeated in Part B and total patient number is 15.			
Units: Subjects			
Adults (18-64 years)	24	15	39
From 65-84 years	3	0	3
Gender categorical			
One patient who completed Part A of the study and later relapsed was enrolled in Part B. Therefore baseline results of one patient are repeated in Part B and total patient number is 15.			
Units: Subjects			
Female	15	7	22
Male	12	8	20
Race (NIH/OMB)			
One patient who completed Part A of the study and later relapsed was enrolled in Part B. Therefore baseline results of one patient are repeated in Part B and total patient number is 15.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	2	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	22	8	30
More than one race	0	0	0
Unknown or Not Reported	4	5	9

End points

End points reporting groups

Reporting group title	Part A
Reporting group description:	
12 weeks of treatment, followed by 12 weeks of follow-up off treatment. The total duration of individual patient participation was approximately 28 weeks.	
Reporting group title	Part B
Reporting group description:	
Total duration was 24 weeks of therapy, with a follow-up visit 4 weeks later. The total duration of individual patient participation was approximately 32 weeks.	

Primary: Percentage of Participants With Treatment-emergent Adverse Events

End point title	Percentage of Participants With Treatment-emergent Adverse Events[1]
End point description:	
Treatment-emergent adverse events (TEAEs) including clinically significant changes in physical examination, laboratory tests, and vital signs. An AE was defined as any untoward medical occurrence in a participant who received study drug and did not necessarily had to have a causal relationship with the treatment. TEAEs were defined as AEs that developed or worsened or became serious during on-treatment phase that was defined as the time from the start of study drug up to study completion. Analysis was done in Safety Analysis population which included All patients who received at least 1 dose of rilzabrutinib.	
End point type	Primary
End point timeframe:	
Part A: until 24 weeks and Part B: until 28 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics has been presented for this endpoint.

End point values	Part A	Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	15		
Units: percentage				
number (not applicable)				
Any TEAE	74.1	86.7		
Any serious TEAE	11.1	0		
Any TEAE leading to treatment discontinuation	11.1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Are Able to Achieve Control of Disease Activity (CDA) Within 4 Weeks of Starting PRN1008 Treatment Without the Need for Doses of Prednisone or Prednisolone >0.5 mg/kg

End point title	Percentage of Participants Who Are Able to Achieve Control of

	Disease Activity (CDA) Within 4 Weeks of Starting PRN1008 Treatment Without the Need for Doses of Prednisone or Prednisolone >0.5 mg/kg[2]

End point description:

CDA was defined as the time at which new lesions cease to form and established lesions begin to heal. Analysis was done in Intent-to-Treat (ITT) population which included all patients who received at least 1 dose of rilzabrutinib.

End point type	Primary

End point timeframe:

4 weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics has been presented for this endpoint.

End point values	Part A	Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	15		
Units: percentage				
number (confidence interval 95%)				
Percentage of Participants Achieved CDA	51.9 (31.9 to 71.3)	60.0 (32.29 to 83.66)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Able to Achieve Control of Disease Activity (CDA) Without Corticosteroids Within 4 Weeks

End point title	Percentage of Participants Able to Achieve Control of Disease Activity (CDA) Without Corticosteroids Within 4 Weeks

End point description:

CDA was defined as the time at which new lesions cease to form and established lesions begin to heal. Analysis was done in ITT population which included all patients who received at least 1 dose of rilzabrutinib.

End point type	Secondary

End point timeframe:

4 weeks

End point values	Part A	Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	15		
Units: percentage				
number (confidence interval 95%)				
Participants Achieved CDA Without Corticosteroids	11.1 (2.4 to 29.2)	6.7 (0.17 to 31.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Able to Achieve a Complete Response (CR) Without Corticosteroids

End point title	Percentage of Participants Able to Achieve a Complete Response (CR) Without Corticosteroids

End point description:

CR was defined as complete healing of all lesions and the absence of new lesions. Analysis was done in ITT population which included all patients who received at least 1 dose of rilzabrutinib.

End point type	Secondary

End point timeframe:

Part A: 12 weeks treatment and Part B: 24 weeks treatment

End point values	Part A	Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	15		
Units: percentage				
number (not applicable)				
Participants Achieved CR without Corticosteroids	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Able to Achieve Complete Remission (CR) Without the Need for Doses of Prednisone or Prednisolone of Greater Than 0.5mg/kg

End point title	Percentage of Participants Able to Achieve Complete Remission (CR) Without the Need for Doses of Prednisone or Prednisolone of Greater Than 0.5mg/kg

End point description:

CR was defined as complete healing of all lesions and the absence of new lesions. Analysis was done in ITT population which included all patients who received at least 1 dose of rilzabrutinib.

End point type	Secondary

End point timeframe:

Part A: 12 weeks treatment and Part B: 24 weeks treatment

End point values	Part A	Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	15		
Units: percentage				
number (confidence interval 95%)				
Participants Achieved Complete Remission (CR)	14.8 (4.2 to 33.7)	33.3 (11.82 to 61.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Control of Disease Activity (CDA)

End point title	Time to Control of Disease Activity (CDA)

End point description:

CDA was defined as the time at which new lesions cease to form and established lesions begin to heal. Kaplan-Meier estimate median time is reported. Analysis was done in ITT population which included all patients who received at least 1 dose of rilzabrutinib.

End point type	Secondary

End point timeframe:

Part A: until 24 weeks and Part B: until 28 weeks

End point values	Part A	Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	15		
Units: Days				
median (confidence interval 80%)				
Time to CDA	33.0 (29.0 to 58.0)	29.0 (15.0 to 34.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to End of Consolidation Phase (ECP)

End point title	Time to End of Consolidation Phase (ECP)

End point description:

ECP was defined as the time at which no new lesions have developed for minimum of 2 weeks, and approximately 80% of existing lesions have healed. Kaplan-Meier estimate median time is reported. Here, '99999' signifies that the upper CI was not estimable due to the insufficient number of patients with an ECP response. Analysis was done in ITT population which included all patients who received at least 1 dose of rilzabrutinib.

End point type	Secondary

End point timeframe:

Part A: until 24 weeks and Part B: until 28 weeks

End point values	Part A	Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	15		
Units: Days				
median (confidence interval 80%)				
Time to End of Consolidation Phase (ECP)	170.0 (95.0 to 99999)	58.0 (48.0 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Complete Remission (CR)

End point title	Time to Complete Remission (CR)

End point description:

CR was defined as complete healing of all lesions and the absence of new lesions. Here, '99999' signifies that the upper CI was not estimable because no patients in Part A of the study achieved CR at or prior to the Week 13 visit and no patients in Part B of the study achieved CR at or prior to the Week 25 visit. Analysis was done in ITT population which included all patients who received at least 1 dose of rilzabrutinib.

End point type	Secondary

End point timeframe:

Part A: until 24 weeks and Part B: until 28 weeks

End point values	Part A	Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	15		
Units: Days				
median (confidence interval 80%)				
Time to CR	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Relapse After PRN1008 Treatment Discontinuation

End point title	Time to Relapse After PRN1008 Treatment Discontinuation

End point description:

Relapse was defined as appearance of ≥3 new lesions/month that do not heal spontaneously within 1 week, or by extension of established lesions, in a patient who has achieved disease control. Kaplan-Meier estimate median time is reported. Analysis was done in ITT population which included all patients who received at least 1 dose of rilzabrutinib.

End point type	Secondary

End point timeframe:

Part A: until 24 weeks and Part B: until 28 weeks

End point values	Part A	Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	15		
Units: Days				
median (full range (min-max))				
Relapse After PRN1008 Treatment Discontinuation	96.0 (27.0 to 99.0)	198.0 (41.0 to 209.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative Corticosteroid Usage

End point title	Cumulative Corticosteroid Usage

End point description:

Cumulative Corticosteroid Usage. Analysis was done in ITT population which included all patients who received at least 1 dose of rilzabrutinib.

End point type	Secondary

End point timeframe:

Part A: until 24 weeks and Part B: until 28 weeks

End point values	Part A	Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	15		
Units: mg				
arithmetic mean (standard deviation)				
Cumulative Corticosteroid Usage	983.43 (± 827.676)	2089.600 (± 1274.011)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline in Pemphigus Disease Area Index (PDAI) Total Activity Scores

End point title	Percentage Change From Baseline in Pemphigus Disease Area Index (PDAI) Total Activity Scores

End point description:

The PDAI questionnaire has 2 components including activity and damage. The activity component consists of skin, scalp and mucosa parts, and the damage component consists of skin and scalp parts. The total activity score was used for the summary of PDAI scores. PDAI total activity score = Total skin activity + Total scalp activity + Total mucosa activity. PDAI Total Activity Score ranged from 0 to 250 points representing disease activity (higher scores mean a worse outcome). Negative change in total activity score from baseline indicates improvement in pemphigus activity. Analysis was done in ITT population which included all patients who received at least 1 dose of rilzabrutinib.

End point type	Secondary

End point timeframe:

Part A: until 24 weeks and Part B: until 28 weeks

End point values	Part A	Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	14		
Units: percent				
arithmetic mean (standard deviation)				
End of treatment (n%)	-55.7 (± 40.91)	-78.60 (± 35.839)		
End of follow-up (n%)	-57.7 (± 38.45)	-59.68 (± 48.403)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) Total Activity Score

End point title	Change From Baseline in Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) Total Activity Score

End point description:

ABSIS Total Activity Score ranged from 0 to 206 points representing disease activity (higher scores mean a worse outcome). Negative change in total activity score from baseline indicates improvement in pemphigus activity. Analysis was done in ITT population which included all patients who received at least 1 dose of rilzabrutinib.

End point type	Secondary

End point timeframe:

Part A: until 24 weeks and Part B: until 28 weeks

End point values	Part A	Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	14		
Units: Not specified				
arithmetic mean (standard deviation)				
End of treatment	-8.18 (± 14.475)	-6.591 (± 4.7664)		
End of follow-up	-9.98 (± 18.369)	-5.705 (± 4.6248)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Autoimmune Bullous Diseases Quality of Life (ABQOL)

End point title	Change From Baseline in Autoimmune Bullous Diseases Quality of Life (ABQOL)

End point description:

ABQOL score ranged from 0 to 68 points representing disease activity (higher scores mean a worse outcome). Analysis was done in Intent-to-Treat (ITT) population which included all patients who received at least 1 dose of rilzabrutinib.

End point type	Secondary

End point timeframe:

Part A: until 24 weeks and Part B: until 28 weeks

End point values	Part A	Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	14		
Units: Not specified				
arithmetic mean (standard deviation)				
End of treatment	-3.7 (± 6.96)	-6.36 (± 9.394)		
End of follow-up	-2.9 (± 6.71)	-3.79 (± 9.569)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Treatment of Autoimmune Bullous Diseases Quality of Life (TABQOL) Scores

End point title	Change From Baseline in Treatment of Autoimmune Bullous Diseases Quality of Life (TABQOL) Scores

End point description:

TABQOL score ranged from 0 to 68 points representing disease activity (higher scores mean a worse

outcome). Analysis was done in ITT population which included all patients who received at least 1 dose of rilzabrutinib.

End point type	Secondary

End point timeframe:

Part A: until 24 weeks and Part B: until 28 weeks

End point values	Part A	Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	14		
Units: Not specified				
arithmetic mean (standard deviation)				
End of treatment	0 (± 6.73)	-2.00 (± 6.051)		
End of follow-up	-0.1 (± 5.92)	-2.14 (± 5.655)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Appetite (SNAQ Score)

End point title	Change From Baseline in Appetite (SNAQ Score)

End point description:

Simplified Nutritional Appetite Questionnaire (SNAQ) score ranged from 0 to 20 points representing disease activity (higher scores mean a better outcome). Analysis was done in ITT population which included all patients who received at least 1 dose of rilzabrutinib.

End point type	Secondary

End point timeframe:

Part A: until 24 weeks and Part B: until 28 weeks

End point values	Part A	Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	14		
Units: Not specified				
arithmetic mean (standard deviation)				
End of treatment	1.1 (± 2.45)	0.21 (± 2.082)		
End of follow-up	1.0 (± 2.84)	0.50 (± 2.103)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Part A: until 24 weeks
Part B: until 28 weeks

Adverse event reporting additional description:

Reported AEs and deaths are TEAEs that developed, worsened, or became serious during the treatment period. Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Part A

Reporting group description:

27 patients were enrolled in Part A population. 12 weeks of treatment, followed by 12 weeks of follow-up off treatment. The total duration of individual patient participation was approximately 28 weeks.

Reporting group title	Part B

Reporting group description:

15 patients were enrolled in Part B population. Total duration was 24 weeks of therapy, starting on Day 1 and ending on Study Day 169, with a follow-up visit 4 weeks later. The total duration of individual patient participation was approximately 32 weeks.

Serious adverse events	Part A	Part B	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 27 (11.11%)	0 / 15 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Pulmonary sequestration			
subjects affected / exposed	1 / 27 (3.70%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatic pseudocyst			
subjects affected / exposed	1 / 27 (3.70%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			

subjects affected / exposed	1 / 27 (3.70%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Part A	Part B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 27 (74.07%)	13 / 15 (86.67%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	2 / 27 (7.41%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Oedema peripheral			
subjects affected / exposed	1 / 27 (3.70%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Peripheral swelling			
subjects affected / exposed	2 / 27 (7.41%)	0 / 15 (0.00%)	
occurrences (all)	2	0	

Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 27 (7.41%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 27 (3.70%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 27 (7.41%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Terminal insomnia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Blood glucose increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
International normalised ratio increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 27 (7.41%)	2 / 15 (13.33%)	
occurrences (all)	2	2	

Dysgeusia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	4 / 27 (14.81%)	1 / 15 (6.67%)	
occurrences (all)	4	1	
Lethargy			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Migraine			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	2 / 27 (7.41%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Sciatica			
subjects affected / exposed	1 / 27 (3.70%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	2 / 27 (7.41%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Eye pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	1 / 27 (3.70%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Abdominal pain			
subjects affected / exposed	2 / 27 (7.41%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper			
subjects affected / exposed	3 / 27 (11.11%)	1 / 15 (6.67%)	
occurrences (all)	3	1	
Change of bowel habit			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	3 / 27 (11.11%)	0 / 15 (0.00%)	
occurrences (all)	3	0	
Dry mouth			
subjects affected / exposed	2 / 27 (7.41%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	6 / 27 (22.22%)	4 / 15 (26.67%)	
occurrences (all)	6	4	
Stomatitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Teeth brittle			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	2 / 27 (7.41%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Haematemesis			
subjects affected / exposed	1 / 27 (3.70%)	1 / 15 (6.67%)	
occurrences (all)	1	1	

Hepatobiliary disorders			
Non-alcoholic steatohepatitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Androgenetic alopecia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	2 / 27 (7.41%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Erythema nodosum			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	1 / 27 (3.70%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Rash erythematous			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	2 / 27 (7.41%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Back pain			
subjects affected / exposed	1 / 27 (3.70%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Muscle spasms			
subjects affected / exposed	2 / 27 (7.41%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 27 (3.70%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Musculoskeletal pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Osteoporosis			
subjects affected / exposed	1 / 27 (3.70%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	2 / 27 (7.41%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Infections and infestations			
Dermatophytosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 27 (3.70%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

Staphylococcal skin infection			
subjects affected / exposed	2 / 27 (7.41%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Tracheitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	2 / 27 (7.41%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Vaginal infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 27 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2015	Protocol v2: - Test was added to the Screening procedures. Added the inclusion criterion, "Anti Dsg 3 ELISA titre >20 RU/mL".
04 November 2015	Protocol v3.1: - Removed the inclusion criterion, "Anti Dsg-3 ELISA titre >20 RU/mL"; - Adjusted the washout period for strong to moderate inducers or inhibitors of CYP3A (exclusion criteria #8) and the use of CYP3A-sensitive substrate drugs (exclusion criteria #9) was changed from "14 days or 5 half-lives" to "7 days or 5 half-lives".
20 April 2016	Protocol v4: - Added exploratory objective, "To evaluate the relationship of PK and PD to each other and to efficacy and safety in the patient population."; - SNAQ appetite added as secondary endpoint; - Simplified inclusion criteria; - Anorexia nervosa and epilepsy added to exclusion criteria; - Adjusted the washout period for strong to moderate inducers or inhibitors of CYP3A (exclusion criterion #8) and the use of CYP3A-sensitive substrate drugs (exclusion criterion #9) was changed from "7 days or 5 half-lives" to "3 days or 5 half-lives"; - Serious infection added to exclusion criteria; - Live vaccine added to exclusion criteria; - Added that rilzabrutinib "should be taken with a glass of water"; - CPK and TSH (at each follow-up visit) added to laboratory assessments; - An SMC was implemented to periodically review patient safety; - Additional information added for the rationale for the selection of the starting dose; - Added concomitant medications, "Other immunosuppressive medications are not permitted except for low-dose CS and when rescue immunotherapy is triggered."; - Added prior therapy not permitted, "ofatumumab, any other anti-CD20 antibody, or any other long-acting biologic"; - Deleted body temperature from Schedule of Assessments. Body temperature was measured as part of the vital signs assessment. Anti-DSG antibodies removed from Screening assessments; - Added clinical assessment to evaluate treatment safety, "Detailed neurological examination including cranial nerve assessment and MRI of the brain".
12 May 2017	Protocol v4.1: - Added a list of seizure medications in exclusion criteria' - Revised protocol for inclusion of Part B of the study to primary objectives, study design and plan, dosing, study drug administration, secondary outcome measures, planned enrollment, inclusion criteria, exclusion criteria, study treatment and study treatment duration, intrapatient dose adjustment guidelines, etc. Allowed patients currently enrolled in PRN1008 005 (in active treatment) to be enrolled in Part B of the study. Modified protocol to allow for additional subgroup analysis and combining Part A and B data for analysis, where appropriate, and added an interim analysis report for Part A.

06 April 2018	Protocol v5.0: - Added a starting dose of 400 mg QD for patients in Part B of the study, with an exception for those continuing treatment from Part A of the study; - Modified Section 4.5.2 to clarify that proton pump inhibitors were not permitted during the study; - Modified Section 6.3.1 (Prior Therapy) to prohibit the use of intravenous gamma globulin within 4 weeks (rather than 12 weeks) of Day 1; - Added PDAI and ABSIS assessments to list of Screening assessments before the first dose of study drug; - Revised storage and handling requirements for study drug; - Revised exclusion criteria to allow patients who completed Part A (ie, not in active treatment) to be eligible for Screening in Part B.
30 July 2018	Protocol v6.0: - Removed body mass index requirement of >17.5 kg/m2 for Part B as an inclusion criterion.
19 March 2019	Protocol v7.0: - Revised exclusion criterion regarding patients with TB; - Added language to clarify that the disease under study was captured in efficacy endpoints and should not also be captured as an AE. Added more details for AE recording guidelines; - Revised language regarding the monitoring of treatment-related SAEs after study exit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported