These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor:	**Study Identifiers:**
Sanofi	UTN: U1111-1260-4263, NCT number : NCT03762265.
Drug substance(s):	**Study code:**
Rilzabrutinib	efc17092

Title of the study:

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial to Evaluate the Efficacy and Safety of Oral BTK Inhibitor Rilzabrutinib (PRN1008) in Moderate to Severe Pemphigus

Study center(s):

This study was conducted at 54 centers that screened participants in 17 countries.

Study period:

08 January 2019 to 17 December 2021

Study Status: Terminated, The Sponsor terminated the study on 08 October 2021 due to lack of efficacy in the Pemphigus population and not related to safety findings with rilzabrutinib.

Phase of development: Phase 3

Objectives:

Efficacy

- To evaluate the efficacy of rilzabrutinib in achieving durable complete remission (CR) on low to zero doses of oral corticosteroid (CS) and on the time course of quantitative disease activity scores
- To assess the ability of rilzabrutinib to reduce CS exposure and the adverse effects of CS
- To evaluate the time to specified clinical endpoints
- To assess the longer term durability of CR

Safety

- To evaluate the safety of rilzabrutinib
- To evaluate differences in potentially CS-related adverse events

PK/PD Objectives

- To evaluate the pharmacokinetics (PK) of rilzabrutinib
- To evaluate pharmacodynamic (PD) effects of rilzabrutinib on anti-desmoglein (anti-dsg) autoantibody titers (anti-dsg1 and anti-dsg3)

Long Term Extension Objective

- To evaluate the long-term safety and efficacy of rilzabrutinib

Methodology:

This was a randomized, phase 3, parallel-group, double-blind, placebo-controlled trial with 36 weeks of treatment during a Blinded Treatment Period followed by an Open-Label Extension Period of 24 weeks. After completing the Open-Label Extension Period, eligible participants continued in the Long Term Extension Period of 48 weeks. Participants had a 4-week follow-up visit after the participant's last dose of rilzabrutinib as detailed in the schema below. A total of 90 sites participated (initiated with or without participant).

Number of participants

Approximately 120 male or female participants with newly diagnosed or relapsing moderate to severe pemphigus (pemphigus vulgaris [PV] or pemphigus foliaceus [PF]) were planned to be enrolled with a targeted minimum of 90 participants with PV, and a target maximum of 22 participants with PF.

Diagnosis and criteria for inclusion:

Participants were included in the study if all of the following criteria were met.

I 01. Male or female patients, aged 18 to 80 years old with moderate to severe, newly diagnosed or relapsing PV or PF, with a clinical presentation and histopathology consistent with PV or PF.

I 02. Positive circulating anti-dsg1 or 3 autoantibody titer.

I 03. At Screening, PDAI score of at least 9 points for relapsing patients (diagnosed >6 months prior to Screening) or at least 15 points for newly diagnosed patients (diagnosed ≤6 months prior to Screening).

I 04. Adequate hematologic, hepatic, and renal function (including but not limited to absolute neutrophil count ≥1.5 × 10^9/L, hemoglobin [Hgb] >9 g/dL, platelet count ≥100 × 10^9/L, aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT] ≤1.5 × upper limit of normal [ULN], albumin ≥3 g/dL, creatinine ≤1.5 × ULN).

I 05. Female patients who are of reproductive potential must agree for the duration of the study to use an effective means of contraception (eg, hormonal contraception methods that inhibit ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner or condoms).

For females considered not to have reproductive potential:

Any woman of age ≥55 years with amenorrhea for >1 year, will be considered as having confirmed menopause and follicle-stimulating hormone (FSH) or pregnancy testing will not be needed. Postmenopausal females <55 years of age (defined as amenorrhea >1 year) must have menopause confirmed by elevated FSH levels at screening. Surgically sterile females do not require any further confirmation of menopause and will not be considered to have reproductive potential.

For participants in Germany, please see specific instructions in 16-1-1 protocol, Appendix 10 Section 12.10.

I 06. Able to provide written informed consent and agreeable to schedule of assessments.

Participants were excluded from the trial if they had any of the following criteria met:

E 01. Suspected paraneoplastic pemphigus and other forms of pemphigus that are not pemphigus vulgaris or pemphigus foliaceus.

E 02. Previous use of a Bruton tyrosine kinase (BTK) inhibitor.

E 03. Pregnant or lactating women.

E 04. Electrocardiogram (ECG) findings of QT corrected for heart rate (QTc) >450 msec (males) or >470 msec (females), poorly controlled atrial fibrillation (ie, symptomatic patients or a ventricular rate above 100 beats/min on ECG), or other clinically significant abnormalities.

E 05. A history of malignancy of any type within 5 years before Day 1, other than surgically excised non-melanoma skin cancers or in situ cervical cancer.

Prior/concomitant therapy

E 06. Use of immunologic response modifiers as concomitant medication and with the following washout periods: A) stop ***at least 2 weeks prior to Screening***: mycophenolate mofetil, azathioprine, methotrexate, cyclosporine, dapsone, intravenous immunoglobulin (IVIG), Kinaret (anakinra), Enbrel (etanercept), or any other immunosuppressant not mentioned in this exclusion criterion; B) ***12 weeks prior to Screening***: Remicade (infliximab), Humira (adalimumab), Simponi (golimumab), Orencia (abatercept), Actemra (tocilizumab), Cimzia (certolizumab), Cosentyx (secukinumab), plasmapheresis; C) ***6 months prior to Screening (or shorter if there is documented B cell reconstitution for anti-CD20 drugs):*** anti-CD20 drugs such as rituximab, ofatumumab, other long-acting biologics.

E 07. Use of proton pump inhibitor drugs such as omeprazole and esomeprazole within 3 days of Day 1 (it is acceptable to change patient to H2 receptor blocking drugs prior to Day 1).

E 08. Concomitant use of known strong-to-moderate inducers or inhibitors of CYP3A within 3 days or 5 half-lives (whichever is longer) of Day 1 (16-1-1-protocol, Appendix 7 Section 12.7).

E 09. Use of CYP3A-sensitive substrate drugs with a narrow therapeutic index within 3 days or 5 half-lives (whichever is longer) of Day 1 and for the remainder of the trial including, but not limited to alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus (topical and oral), or terfenadine.

E 10. Has received any investigational drug (or is currently using an investigational device) within the 30 days before Day 1, or at least 5 times the respective elimination half-life time (whichever is longer).

E 11. History of drug abuse within the previous 12 months.

E 12. Alcoholism or excessive alcohol use, defined as regular consumption of more than approximately 3 standard drinks per day.

Other exclusions

E 13. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate rilzabrutinib/placebo absorption.

E 14. Donation of a unit or more of blood or blood products within 4 weeks prior to Day 1.

E 15. History of solid organ transplant.

E 16. Positive at Screening for human immunodeficiency virus (HIV), hepatitis B (surface antigen and/or core antibodies), or hepatitis C (anti-HCV antibody confirmed with Hep C RNA).

E 17. Positive interferon-gamma release assay (IGRA) (eg, T-spot TB Test, QuantiFERON®-TB Gold, or QuantiFERON®-TB Gold Plus (QFT Plus), at Screening. Unless, the patient has latent tuberculosis (TB) and all of the following 3 conditions are true:

A) Chest X-ray does not show evidence suggestive of active TB disease.

B) There are no clinical signs and symptoms of pulmonary and/or extra-pulmonary TB disease.

C) Documented receipt of one of the following prophylactic treatment regimens:

i) Oral daily Isoniazid for 6 months

or

ii) Oral daily Rifampin (RIF) for 4 months

or

iii) Isoniazid and Rifapentine weekly for 3 months (3HP).

On a case-by-case basis, after discussion and approval by the Sponsor, a local TB test that is negative and is considered equivalent to 1 of the above tests may be used for eligibility. For example, if a QuantiFERON®-TB Gold, or QuantiFERON-TB Gold Plus (QFT Plus) is indeterminate for any reason and a local blood test or T-Spot TB test is negative, the patient may be enrolled using the local result upon approval of the Sponsor.

E 18. History of serious infections requiring intravenous therapy with the potential for recurrence or currently active moderate to severe infection at Screening (Grade 2 or higher).

E 19. Live vaccine within 28 days prior to Day 1 or plan to receive one during the trial.

E 20. Any other clinically significant disease, condition (including contraindication to CS and/or inability to follow CS dosing as outlined in the protocol [see Table 1 of 16-1-1 protocol for more details]), or medical history that, in the opinion of the Investigator, would interfere with patient safety, trial evaluations, and/or trial procedures. In areas endemic for Chagas disease, screening is recommended prior to enrollment.

For participants in Germany, please see specific instructions in 16-1-1 protocol, Appendix 10 Section 12.10.

Study Products

Investigational medicinal product(s): rilzabrutinib

Formulation/Form & composition: tablet

Route(s) of administration: oral

Dose regimen: Participants received oral administration of rilzabrutinib 400 mg twice daily (bid) or placebo bid during the Blinded Treatment Period.

All participants received active drug in the Open-Label Extension Period for 24 weeks. Patients who received placebo received active treatment with oral rilzabrutinib 400 mg bid. During the Long Term Extension Period participants continued to receive open-label oral rilzabrutinib 400 mg bid for 48 weeks.

Duration of study intervention

Blinded Treatment Period (Weeks 1 to 37)

Open-Label Extension Period (Weeks 37 to 61)

Long Term Extension (LTE) Period (Weeks 61 to 109)

Criteria for evaluation:

Primary Efficacy Endpoint

- The proportion of participants who are in CR from Week 29 to Week 37 with a CS dose of ≤10 mg/day

Key Secondary Efficacy Endpoints

- Cumulative CS dose from Baseline to Week 37
- Cumulative duration of CR with a CS dose ≤10 mg/day, from Baseline to Week 37
- Time to first CR with a CS dose ≤10 mg/day, from Baseline to Week 37

Other Secondary Endpoints

- The proportion of participants who are in CR from Week 29 to Week 37 with a CS dose of ≤5 mg/day
- The proportion of participants who have a Pemphigus Disease Area Index (PDAI) score <3 from Week 29 to Week 37 with a CS dose ≤10 mg/day
- Cumulative duration of CR with a CS dose ≤10 mg/day from Baseline to Weeks 61 and 109
- Cumulative duration of CR with a CS dose = 0 mg/day from Baseline to Weeks 61 and 109
- Glucocorticoid toxicity inde (GTI) score at Week 37
- Change in PDAI score from Baseline to Weeks 5, 13, 25, 37, 61, and 109
- Change in Autoimmune Bullous Disease Quality of Life (ABQOL) score from Baseline to Weeks 5, 13, 25, 37, 61, and 109
- Proportion of participants with ABQOL Score of zero at Weeks 5, 13, 25, 37, 61, and 109
- Change in EuroQOL-5 Dimension 5 Level (EQ-5D-5L) results (visual analog scale [VAS] results and individual dimension) scores from Baseline to Weeks 5, 13, 25, 37, 61, and 109
- Time to first CR with a CS dose ≤10 mg/day, from Baseline to Weeks 61 and 109
- Total number of disease relapses/flares from initial control of disease activity (CDA) to Week 37
- Time to initial relapse/flare from initial CDA to Week 37
- Proportion of participants with 3 or more new lesions within 1 month that do not heal spontaneously within 1 week, or with extension of established lesions, from Baseline to Week 37
- Proportion of participants with at least one disease relapse/flare from initial CDA to Week 37
- Cumulative duration of CR with a CS dose ≤10 mg/day, from Week 37 to Week 61
- Cumulative duration of CR with a CS dose = 0 mg/day, from Week 37 to Week 61

Safety

- Nature, frequency, and severity of adverse events, including serious adverse events, adverse events leading to discontinuation and possible corticosteroid-related adverse effects
- Change from Baseline in vital signs and clinical laboratory test results (including complete blood count and blood chemistry)

Pharmacokinetic Endpoints

- Plasma concentrations of rilzabrutinib at approximately the time of maximum concentration at Day 1 and at varied subsequent timepoints (refer to [16-1-1-protocol] Table 2 and Table 3)

Pharmacodynamic Endpoints

Change from Baseline in anti-dsg1 and anti-dsg3 autoantibody levels by enzyme-linked immunosorbent assay (ELISA) at Weeks 13, 25, 37, 49, 61, and 109

Long Term Extension Endpoints

- Nature, frequency, and severity of adverse events, including serious adverse events, adverse events leading to discontinuation and possible corticosteroid-related adverse effects during the LTE from Week 61 to Week 113
- Average daily dose of CS from Week 61 to Week 113
- Time to initial relapse/flare from initial CDA to Week 109

Statistical methods:

Efficacy Endpoints: The primary efficacy endpoint was the proportion of participants who are in CR from Week 29 to Week 37 with a prednisone dose of ≤ 10 mg/day in participants treated with PRN1008 compared with placebo.
Allow p_0 to represent the proportion of responders in the placebo group; p_1 will represent the proportion of responders in the PRN1008 group. The null and alternative hypotheses are:

H_0: $p_1 - p_0 = 0$

The proportion of participants who are in CR from Week 29 to Week 37 with a prednisone dose of ≤ 10 mg/day does not differ between the two treatment groups.

H_1: $p_1 - p_0 \neq 0$

The proportion of participants who are in CR from Week 29 to Week 37 with a prednisone dose of ≤ 10 mg/day differs between the two treatment groups.

The primary endpoint was analyzed using a CMH test, stratified by disease history. The observed number and proportion of participants meeting the primary endpoint as well as the proportion difference (PRN1008 – placebo), estimated standard error (SE), 95% CI and the associated p-value was reported. Descriptive summaries of participants who are in CR with a CS dose of ≤10 mg/day were provided by visit through Week 37.

Safety Endpoints: Safety was evaluated from reported TEAEs, changes in clinical laboratory values, changes in vital signs and physical exam results. All safety analyses were performed on the Safety population. All summaries of safety were presented for the blinded treatment portion of the study separately from the open-label portion of the study. The long-term extension period was separately reported. All safety and tolerability data summaries were reported by treatment group in double-blinded portion and overall. No statistical tests were performed for any of the safety assessments.

Summary Results

This clinical study report is being written as an abbreviated report, because the study did not meet its primary or key secondary endpoints. The Sponsor terminated the study on 08 October 2021 due to lack of efficacy in the Pemphigus population and not related to safety findings with rilzabrutinib.

Demographic and other baseline characteristics:

As of the study termination date of 08 October 2021, a total of 210 participants were screened and 131 participants were randomized and treated in the PRN1008-012 study. Demographic data are generally balanced between rilzabrutinib and placebo.

For participants in the Randomized Population, mean time from pemphigus diagnosis to enrollment in years standard deviation (SD) in the placebo and rilzabrutinib groups was 3.271 (4.3199) and 2.984 (4.2427), respectively. The number of newly diagnosed participants in the placebo and rilzabrutinib groups was 24 (36.4%) and 24 (36.9%), respectively. The number of relapsing participants in the placebo and rilzabrutinib groups was 42 (63.6%) and 41 (63.1%), respectively. Disease severity at screening was classified into moderate and severe. The placebo and rilzabrutinib groups presented with 62 (93.9%) and 59 (90.8%) participants with moderate severity, respectively; and 4 (6.1%) and 6 (9.2%) participants with severe severity, respectively.

Exposure:

During the blinded treatment period, participants treatment duration was measured in weeks. Placebo and rilzabrutinib groups, mean (SD) treatment duration in the blinded period was 31.44 (10.015) and 35.40 (3.829) weeks, respectively.

Efficacy Results:

This clinical study report is being written as an abbreviated report, because the study did not meet its primary or key secondary endpoints. The Sponsor terminated the study on 08 October 2021 due to lack of efficacy in the Pemphigus population and not related to safety findings with rilzabrutinib.

Therefore, the other and exploratory efficacy evaluations originally planned for the open label period and the long-term extension period were no longer considered to be relevant.

The primary efficacy endpoint for this study was to determine the proportion of participants who were in Complete Remission (CR) from Week 29 to Week 37 with a corticosteroids (CS) dose of ≤10 mg/day. Complete Remission (CR) was defined as the absence of new and established lesions and is intended to mean “no disease activity”.

The PV participants in the mITT population classified as responders, included 10 participants (18.2%) in the placebo group, and 13 participants (24.1%) in the rilzabrutinib group, with a total risk difference (SE) of 5.73 (7.535), (95% CI: -9.037, 20.500), (p= 0.4469). The proportion of participants in the PV patients in mITT population who achieved durable complete remission was greater in the rilzabrutinib group 13 participants (24.1%) compared to placebo group 10 participants (18.2%), respectively. The p-value for these analyses did not meet pre-specified significance level of 5%, and therefore, the study did not meet the primary endpoint. In the all mITT population, participants classified as responders, included 12 participants (18.2%) in the placebo group, and 17 participants (26.2%) in the rilzabrutinib group with a total risk difference (SE) of 8.13 (7.085), (95% CI: -5.752, 22.019). Similar results were seen comparing the PV mITT population results and the mITT population results.

The first key secondary endpoint was the analysis of the cumulative CS dose from baseline to Week 37 and results were compared across treatment groups.

Cumulative CS dose (mg) from baseline to Week 37 in the mITT population and in PV participants in the mITT population: In the mITT population the placebo group of 66 participants had a mean (SD) CS dose of 5392 mg (2993), minimum and maximum CS dose of 675 mg and 14897 mg. The rilzabrutinib group of 65 participants had a mean (SD) CS dose of 4860 mg (2545) with minimum and maximum CS dose of 1445 mg and 13805 mg.

Cumulative CS dose (mg) from baseline to Week 37 in the PV participants in the mITT population, placebo group of 55 participants had a mean (SD) CS dose of 5653 mg (3156), minimum and maximum CS dose of 675 mg and 14897 mg. The rilzabrutinib group of 54 participants had a mean (SD) CS dose of 5131 mg (2624) with minimum and maximum CS dose of 1576 mg and 13805 mg.

The second key secondary endpoint was the cumulative duration of CR with CS dose ≤10mg/day from Baseline to Week 37 analyzed using a zero-inflated negative binomial model with terms for treatment group and disease history. The mean (SD) duration of CR with CS dose ≤10mg/day for PV participants in the mITT population for the placebo group was 34.1 days (51.58), and for the rilzabrutinib group was 50.5 days (67.10). The mean (SD) duration of CR with CS dose ≤10mg/day for participants in the mITT population for the placebo group was 34.0 days (54.36), and for the rilzabrutinib group was 54.3 days (68.76), p=0.2628.

The third key secondary endpoint was the time to first CR with a CS dose ≤10 mg/day, from Baseline to Week 37. Based on the estimates, by Week 37 (Day 253), 50.72% of participants (95% CI: 37.049, 66.115), had events in the placebo group, and 52.46% of participants (95% CI: 39.543, 66.670), had events in the rilzabrutinib group.

Safety results:

The incidence of all treatment emergent adverse events (TEAEs) reported during the blinded treatment period was similar between the study intervention groups. Participants reporting at least one TEAE in the placebo group totaled 54 (81.8%) of 66 participants with 301 events. Participants reporting at least one TEAE in the rilzabrutinib group totaled 55 (84.6%) of 65 participants with 382 events. There were 14 participants (21.2%) in placebo group, 16 participants (24.6%) in rilzabrutinib group who experienced treatment-related TEAEs. A large majority of these TEAEs were deemed to be related to corticosteroids as per Investigator's judgment, 65.2% vs 75.4% in the placebo and rilzabrutinib groups respectively. Eight participants (12.1%) in placebo group, and 2 participants (3.1%) in rilzabrutinib group experienced TEAE leading to study discontinuation. There were 2 participants (3.0%) in placebo group, and 0 participants (0%) in rilzabrutinib group who experienced TEAEs leading to death. In addition, 10 placebo participants (15.2%) reported a total of 14 SAEs versus 6 rilzabrutinib participants (9.2%) for a total of 8 SAEs.

Treatment-Emergent Adverse Events with CTCAE grade reported in the blinded treatment period are presented in Table 17 of CSR body. A total of 5 (7.6%) participants with 9 events in the placebo group reported a Grade 3 TEAE. Seven (10.8%) participants with 13 events in the rilzabrutinib group reported a Grade 3 TEAE. Four (6.1%) participants with 4 events in the placebo group, and 1 (1.5%) participant with 2 events in the rilzabrutinib group reported a Grade 4 TEAE. Two Grade 5 TEAEs were reported in the placebo group and none were reported in the rilzabrutinib group.

In the OLE Period, 33 (64.7%) participants in the placebo/rilzabrutinib group reported 88 events; of which 11 (21.6%) participants had 15 events that were treatment-related TEAEs and 1 (2.0%) participant had 1 event that led to study discontinuation. No TEAEs reported from the placebo/rilzabrutinib group led to death of a participant. Additionally, 4 (7.8%) participants in this group reported 4 SAE events.

Thirty-five (57.4%) participants in the rilzabrutinib/rilzabrutinib group reported 96 events, of which 5 (8.2%) participants experienced 7 events that were treatment-related TEAEs, and 1 (1.6%) participant had an event that led to study discontinuation. No TEAEs reported from the rilzabrutinib/rilzabrutinib group led to death of a participant.

In the LTE Period, 18 (51.4%) of 35 participants in the placebo/rilzabrutinib group reported 47 events; of which none were treatment-related TEAEs, led to study discontinuation or resulted in death. Fourteen (41.2%) of 34 participants in the rilzabrutinib/rilzabrutinib group reported 37 TEAE events, of which 2 (5.9%) participants with 4 events were considered treatment-related TEAEs. No TEAEs from this group led to study discontinuation or resulted in death. One (2.9%) of 35 participants in the placebo/rilzabrutinib group and 2 (5.9%) of 34 participants in the rilzabrutinib/rilzabrutinib group reported an SAE in the LTE treatment period

Overall, the mean changes in clinical laboratory values and vital signs were similar across the study intervention groups in the blinded treatment period.

There were no clinically meaningful findings in the vital signs measurements, physical examination assessments, or other observations related to safety in this study. The assessments and observations were comparable across intervention groups for the blinded treatment period.

Pharmacokinetic results:

Plasma concentrations of rilzabrutinib (PRN1008) were evaluated in participants with PV and PF at pre-dose and 2 hours after the first dose, and at random timepoints relative to the previous dose at subsequent visits.

For PRN1008, mean (coefficient of variance, %CV) plasma concentrations at 2 hours after the first dose (a time point at which maximal concentrations are anticipated to be reached for PRN1008) of 400 mg rilzabrutinib in PV and PK participants are 273.13 (97%) ng/ml. Subsequent PK collections were not standardized with respect to the time since last dose, thus additional summary statistics could not be performed.

Pharmacodynamic results:

By Week 37, for anti-DSG1, plasma levels in 5 of 50 (10%) participants in the placebo group were below limit of quantification (LOQ) and 12 of 57 (21%) participants in the rilzabrutinib group were below LOQ with a mean (SD) of 59.5 units/mL (101.58) and 37.0 units/mL (68.28), respectively. By Week 37, for anti-DSG3, plasma levels in 3 of 50 (6%) participants in the placebo group and 7 of 57 (12%) participants in the rilzabrutinib group were below LOQ with a mean (SD) of 167.8 units/mL (293.78) and 176.5 units/mL (362.67), respectively.

Issue date: 29-Jun-2022