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Phase 2 BELIEVE study part B: Efficacy and safety of rilzabrutinib for patients with pemphigus vulgaris

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Running head: Rilzabrutinib efficacy and safety in pemphigus vulgaris

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A. Neale was an employee of, received stock ownership from, and has a patent pending for rilzabrutinib from Principia Biopharma Inc, a Sanofi Company, at the time of the study.

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Author Contribution
Conception and design of the study: D.F.M., A.P., A.N., V.P.W., P.J.
Collection and assembly of data: D.F.M., A.P., A.N., F.C.
Data analysis and interpretation: D.F.M., A.P., A.N., P.A., F.C., V.P.W., P.J.
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Data sharing statement: Qualified researchers may request access to patient-level data and related documents (including, e.g., the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications). Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://www.clinicalstudydatarequest.com.

Prior presentation: Study results for BELIEVE part B were previously presented in part as a late-breaking oral presentation at the 2020 American Academy of Dermatology meeting.

***Journal of EADV* Letter to the Editor: Word/Table/Figure Counts**

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Pemphigus vulgaris (PV) is a potentially life-threatening, blistering autoimmune disease commonly treated with firstline corticosteroids (CS).[1,2] The oral, covalent Bruton tyrosine kinase (BTK) inhibitor rilzabrutinib[3] was validated in proof-of-concept BELIEVE part A phase 2 study (NCT02704429) at 400-600 mg bid doses (±CS) for 12 weeks (mean CS=0.18 mg/kg/day) plus 12 weeks follow-up in newly diagnosed/relapsing, mild-to-severe PV.[4] Part B expanded these findings in patients aged 18-80 years with biopsy-proven, newly diagnosed (≤six months from diagnosis) or relapsing PV, and Pemphigus Disease Area Index (PDAI) score 8-60.[5] Patients initially received oral rilzabrutinib 400 mg qd with optional dose escalation to 400 mg bid at/after week 2, and further to a maximum 600 mg bid dose at/after week 4. Treatment was given for 24 weeks plus 4 weeks off-treatment with allowed prednisone-equivalent CS ≤0.5 mg/kg/day (tapered per investigator discretion[6]). All patients provided written informed consent; study followed local regulatory bodies/IRB/IEC per Declaration of Helsinki/ICH Guidelines for GCP. Primary endpoints were Control of Disease Activity (CDA) within 4 weeks and safety (NCI-CTCAE, v≥4.0); secondary/exploratory endpoints/statistical analyses were as described for part A.[4,7,8]

Between 28March2018-10January2020 (data cut-off 5March2020), 15 patients with baseline median age 47 years (range, 30-64) were enrolled; 47% female and 6 newly diagnosed/9 relapsing PV (one patient >5 years). Mean time from diagnosis was 1.1 years (SD, 1.3). Mean baseline PDAI score was 15.5 overall (n=8 mild-to-moderate PDAI 8 to <15, n=7 moderate-to-severe PDAI ≥15; maximum 36).

Fourteen patients initiated rilzabrutinib 400 mg qd; 1 patient previously received and continued 400 mg bid. By study end, 1 patient maintained rilzabrutinib 400 mg qd, 8 dose escalated to 400 mg bid, and 6 to 600 mg bid. Mean duration of exposure was 163 days (SD, 35).

Median rilzabrutinib plasma concentration after dose 1 (2 hours) was 89.5 ng/mL (range, 36.3-608; n=14). Mean BTK occupancy was ≥83% with multiday dosing at steady state (~2-4 hours post-dose).

The primary endpoint CDA by week 4 was 60% (Fig. 1a), including 1 patient without CS use. Median time to first CDA was 29 days (95% CI, 14-43). Median time to first relapse in 7 CDA patients was 198 days (95% CI, 101 to not estimable). Six patients (40%) achieved complete healing of all lesions with absence of new lesions on CS <10 mg/day on at least one visit (i.e., complete response [CR][7,8]; 400 mg qd [n=1], 400 mg bid [n=3], and 600 mg bid [n=2]) at week 28. Median time to first CR was 124.5 days (range, 56-196); durations of CR at data cutoff were 1, 34, 60, 95, 120, and 153 days. Improvements in clinical outcomes were supported by reductions in PDAI scores, CS doses, and anti-desmoglein-3 levels over time (Fig. 1b/c), along with maintenance/increases in scores for ABQOL and SNAQ (suggesting no appetite suppression).

Thirteen patients experienced a treatment-emergent adverse event (TEAE; n=5 treatment-related [Table 1]). There were no thrombotic/neutropenia/bleeding/cardiac arrhythmia events, serious TEAEs, or deaths. Treatment-related TEAEs were all grade 1/2 and transient. One patient with chronic, relapsing pemphigus (PDAI 36 at baseline) and worsening disease failed to achieve CDA despite rilzabrutinib dose escalation, was hospitalized at week 9 to receive intravenous immunoglobulin/rituximab, and discontinued the study.

Part B confirmed and expanded on previous results with 12 weeks of rilzabrutinib (±CS) from part A.[4] Importantly, disease control was observed early and improved with continued treatment. Reduced CS use was accompanied by multiple indicators of clinical improvement.

Safety consistently showed grade 1/2 treatment-related TEAEs. Although results were limited by a small number of patients, rilzabrutinib (±CS) demonstrated a consistently favorable benefit-risk profile with broader rilzabrutinib doses and longer treatment in newly diagnosed/relapsing pemphigus patients.

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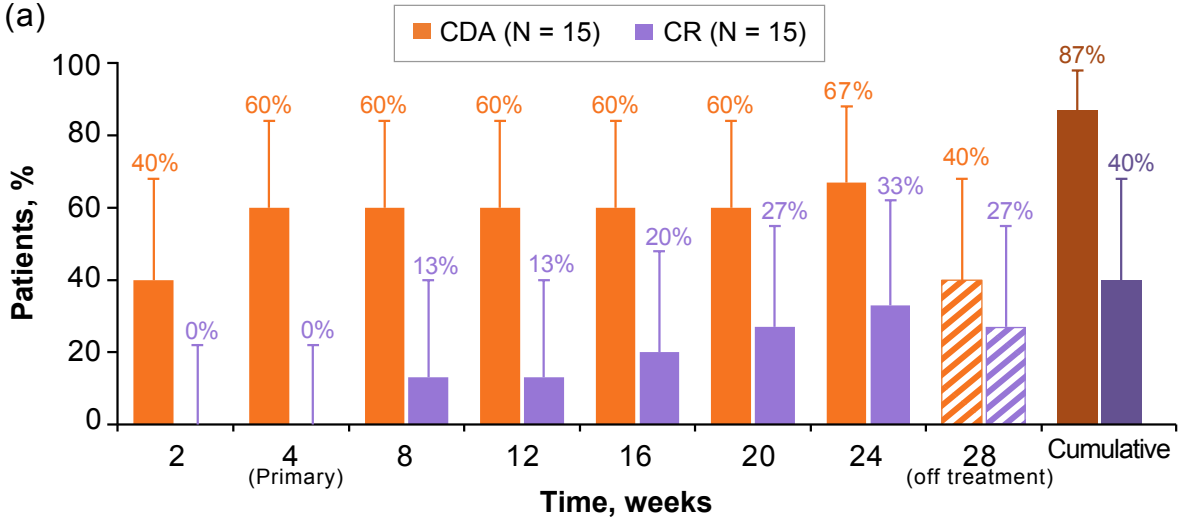
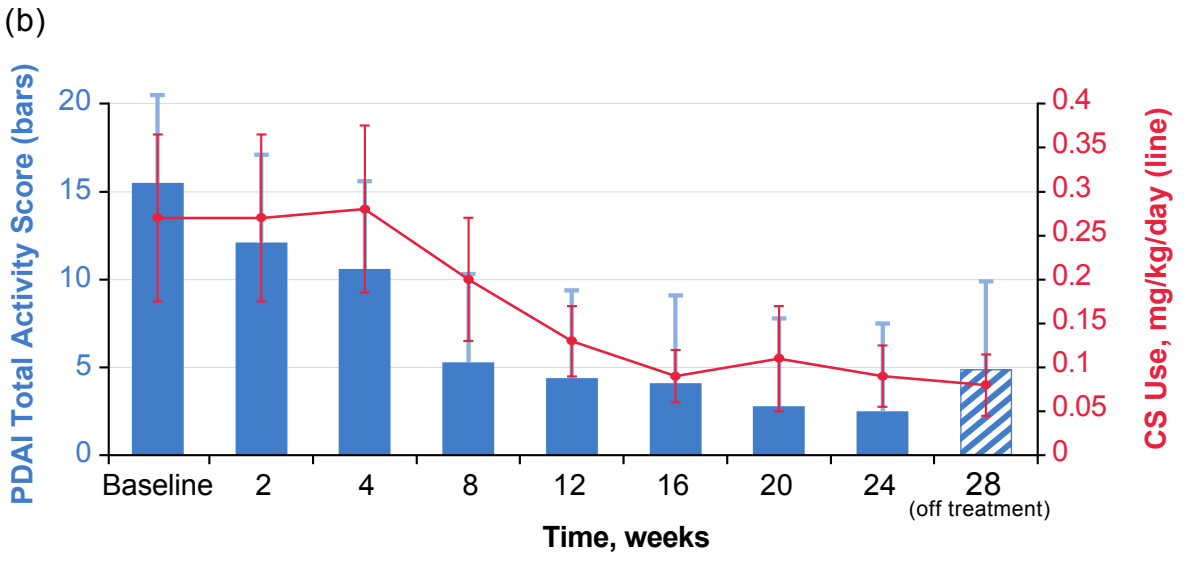
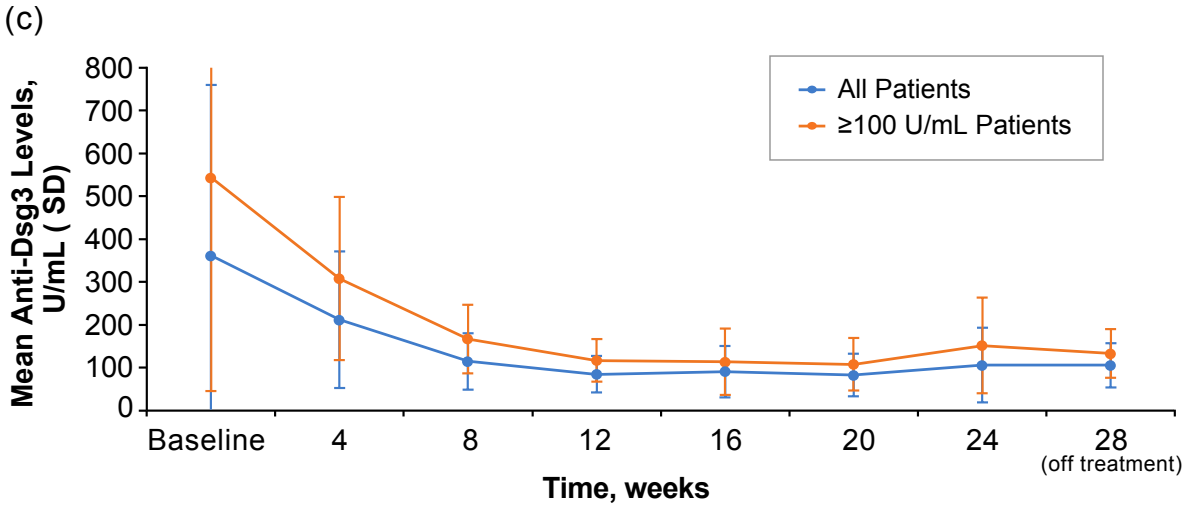
Figure Legend

Figure 1 Efficacy of rilzabrutinib over time based on Control of Disease Activity (CDA) and complete response (CR) (a), Pemphigus Disease Area Index (PDAI) and corticosteroid (CS) use (b), and anti-desmoglein-3 levels in all patients and patients with anti-desmoglein-3 levels ≥100 units/mL at baseline (c). Shown in (a) are the percentages of patients with CDA (orange) and CR (purple) by each timepoint of rilzabrutinib treatment (solids bars; week 2-24), off-treatment (dashed bars; week 28), and cumulatively over 28 weeks of the study (darker solid bars) (N=15). Numbers in figure bars represent percentages of patients; error bars represent 95% CIs. (b) Mean PDAI total activity scores (blue bars; left y-axis) and CS use (red line; right y-axis) are shown over time (N=15*). (c) Mean anti-desmoglein-3 levels (SD) in all patients (n=13) and in patients with ≥100 units/mL anti-desmoglein-3 levels at baseline (n=8); levels are shown from baseline through rilzabrutinib treatment (week 24) and off-treatment (week 28). The error bars indicate standard deviations. *Data for PDAI and CS use are missing for one patient beginning at week eight because of early study withdrawal due to progressive pemphigus.







All Patients, n	13	13	11	10	12	12	12	10
≥100 U, n	8	8	6	6	7	7	7	7

Table 1 Summary of treatment-related treatment-emergent adverse events (occurring in ≥1 patient; N=15 patients)

	Treatment-Related Treatment-Emergent Adverse Events*
Any treatment-emergent adverse event	**5 (33)**
Nausea	3 (20)
Abdominal distension	2 (13)
Abdominal pain upper	1 (7)
Amenorrhea	1 (7)
Asthenia	1 (7)
Change of bowel habit	1 (7)
Ear pain	1 (7)
Erythema nodosum	1 (7)
Gastrointestinal disorder	1 (7)
Hot flush	1 (7)
Muscle spasms	1 (7)
Nasopharyngitis†	1 (7)
Oliguria	1 (7)
Pain in extremity	1 (7)
Rash	1 (7)
Teeth brittle	1 (7)
Tracheitis†	1 (7)
Vision blurred	1 (7)

Values are number of patients (%).

*All treatment-related treatment-emergent adverse events were grade 1, except gastrointestinal disorder and rash, which were grade 2.

†One patient each reported treatment-related infection/infestations (grade 1 nasopharyngitis and tracheitis) that were managed/resolved without disrupting rilzabrutinib treatment. Not reported above, 5 patients showed infections/infestations that were not deemed related to rilzabrutinib treatment: 1 patient each with grade 1 dermatophytosis and upper respiratory tract infection; grade 2 pharyngitis streptococcal, sinusitis, and vaginal infection.