BELIEVE-PV Phase II Part B Study: Extended Treatment With PRN1008 (Rilzabrutinib) For Patients With Pemphigus

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Disclosures

- Boards/officer of public or academic organization
  - Chair, Department of Dermatology, St George Hospital, Sydney, Australia
  - Professor of Dermatology, UNSW, Australia
- Dermatology society involvement: EADV International Board member, ISD Board of Directors, and President of ASDR
- Director, Premier Specialists: Clinical Trials Centre for Dermatology
- Inventor/Co-inventor of the PDAI, ABQOL and TABQOL measures
- Grants/research funding for institution: 3M Pharmaceuticals; AbbVie; Anacor Pharmaceuticals, Inc; CSL Behring; Janssen-Ortho Inc; MedImmune; Mölnlycke; Novartis Pharmaceuticals Corporation; Pfizer; Roche Laboratories; Samumed, LLC; Schering-Plough; Shire; XOMA (US) LLC; and for investigator: Galderma Laboratories, LP and Merck Serono
- Consulting/fees for institution: Almirall, Amgen, Castle Creek Pharmaceuticals, Merck Serono, Principia Biopharma Inc
- Equipment (uncompensated): Delfin Technology
- Honoraria/advisory board for institution: Abbott Laboratories and Amicus Therapeutics; and for investigator: Eli Lilly and Company, Novartis Pharmaceuticals Corporation, Roche Laboratories, Shire
- Honoraria/speaker for institution: Abbott Laboratories; Ascent Pharmaceuticals; CSL Behring; Pierre Fabre Dermo-Cosmétique US; Schering-Plough Corporation
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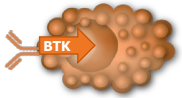
Bruton Tyrosine Kinase (BTK) Has a Broad Role in Multiple Immune-Mediated Disease Processes[1-3]



Mast cell / Eosinophil

IgE-mediated FcεR activation and degranulation

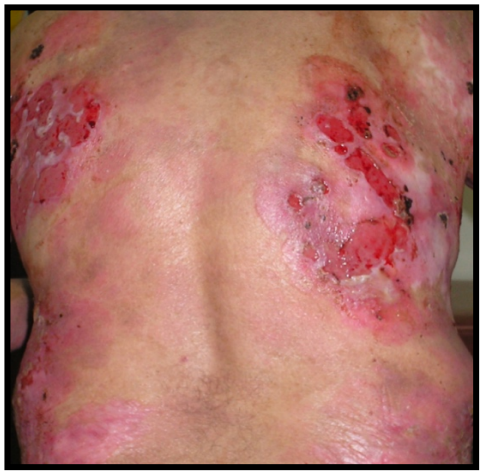
Macrophage

IgG-mediated FcγR activation, phagocytosis, inflammatory mediators

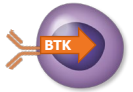
Neutrophil

Activation, adhesion, recruitment, oxidative burst

Innate



PEMPHIGUS



Autoreactive memory B cell

Long-lived plasma cell

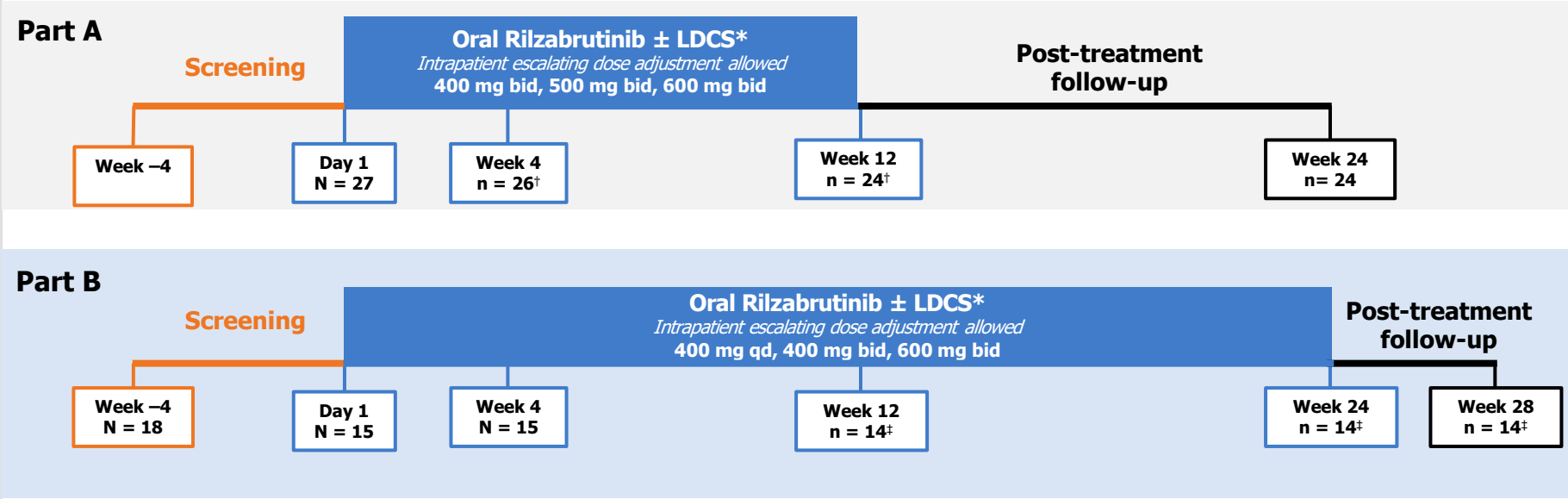
Plasma cell differentiation and antibody production

Autoantibodies

Adaptive

1. LeBien TW and Tedder TF. *Blood.* 2008;112:1570-1580. 2. Elkon K and Casali P. *Nat Clin Pract Rheumatol.* 2008;4:491-498. 3. Lacy P and Stow JL. *Blood.* 2011;118:9-18.

Phase 2 Part B: Rilzabrutinib Intrapatient Dose Escalation; 24 Wk Treatment



Primary endpoint

- Control of Disease Activity (CDA) within 4 weeks (day 29) while on CS ≤ 0.5 mg/kg/day

Secondary endpoints

- Complete remission (CR)
- PDAI
- Minimization of CS usage

*Prednisolone or equivalent.
†3 patients dropped out due to TEAEs unrelated to rilzabrutinib at days 10, 43, and 44.
‡1 patient discontinued at week 9 due to worsening of pemphigus that started during screening after stopping MMF, which continued resulting in hospitalization at week 9.

Part B Demographic Characteristics Were Generally Similar to Part A

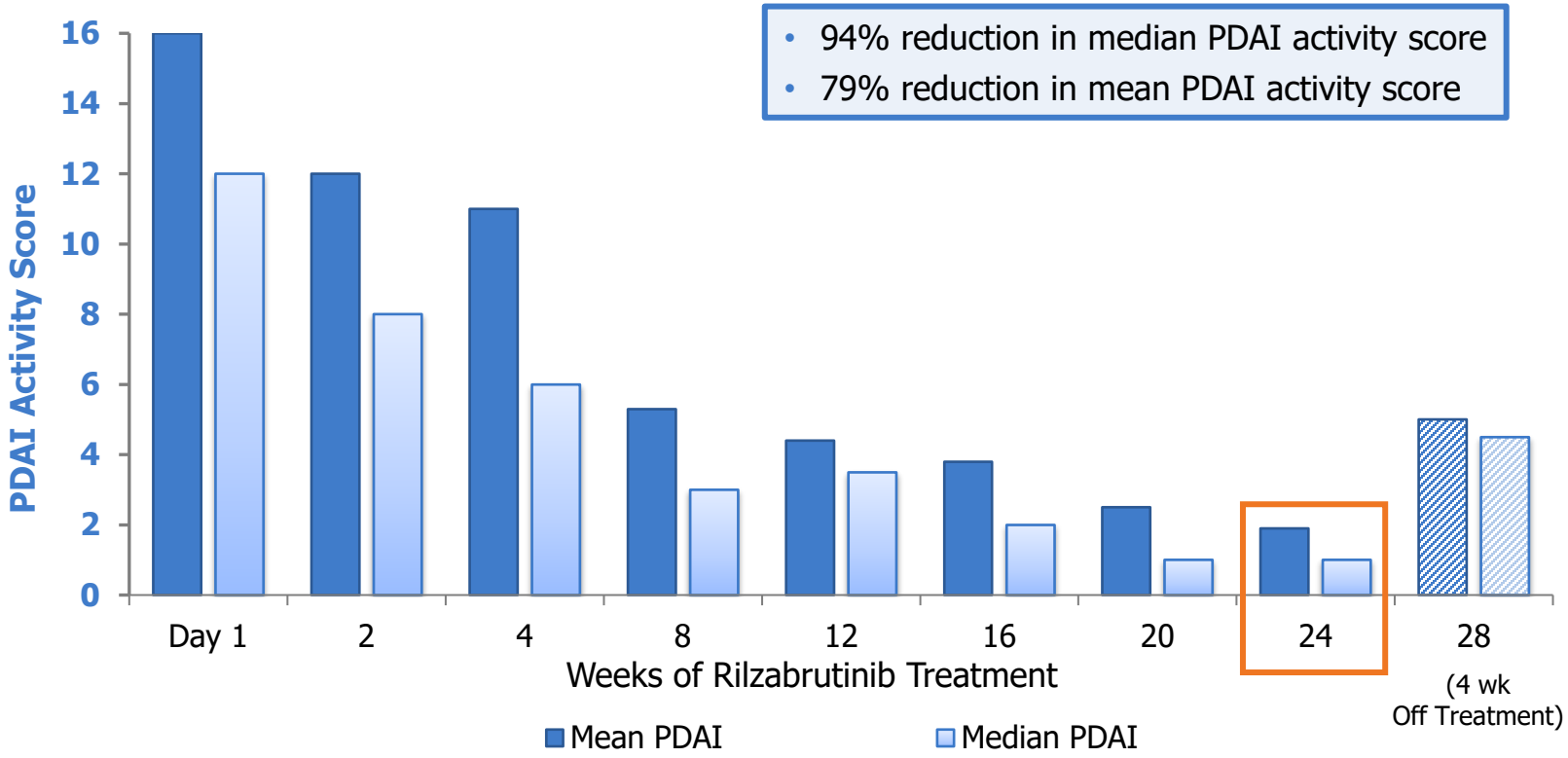
Characteristics		Part A (N = 27)	Part B (N = 15)
Mean age, y (SD, range)		52 (9, 37-72)	46 (9.5, 30-64)
Gender, n (%)	Male	12 (44)	8 (53)
	Female	15 (56)	7 (47)
Pemphigus type, n (%)	Pemphigus vulgaris	23 (85)	13 (88)
	Pemphigus foliaceus	3 (11)	1 (7)
	Neither	1 (4)	1 (7)
Pemphigus history, n (%)	Newly diagnosed	9 (33)	6 (40)
	Relapsed	18 (67)	9 (60)
Mean time from pemphigus diagnosis, y (mean, range)		6 (7, 0-25)	1.14 (1.35, 0-5.3)
Mean PDAI score, points (SD, range)		19 (11, 8-43)	15.5 (7.5, 8-36)
Disease severity*, n (%)	PDAI < 15 (mild-moderate)	11 (41)	8 (53)
	PDAI ≥ 15 (moderate-severe)	16 (59)	7 (47)
Antibody profile, n (%)	Positive	26 (96)	14 (93)
	• Anti-dsg-3 ± 1 positive	23 (85)	13 (87)
	• Anti-dsg-1 positive only	3 (11)	1 (7)
	Negative, n (%)	1 (4)	1 (7)
Mean CS dose at entry, mg/d (SD, range)		14 (11, 0-30)	21 (14, 0-50)

CS, corticosteroid; PDAI, Pemphigus Disease Area Index.

*Moderate-severe included patients with severe, relapsing disease per PDAI severity quartiles for relapsing disease[1] vs. mild-moderate in newly diagnosed disease[2].

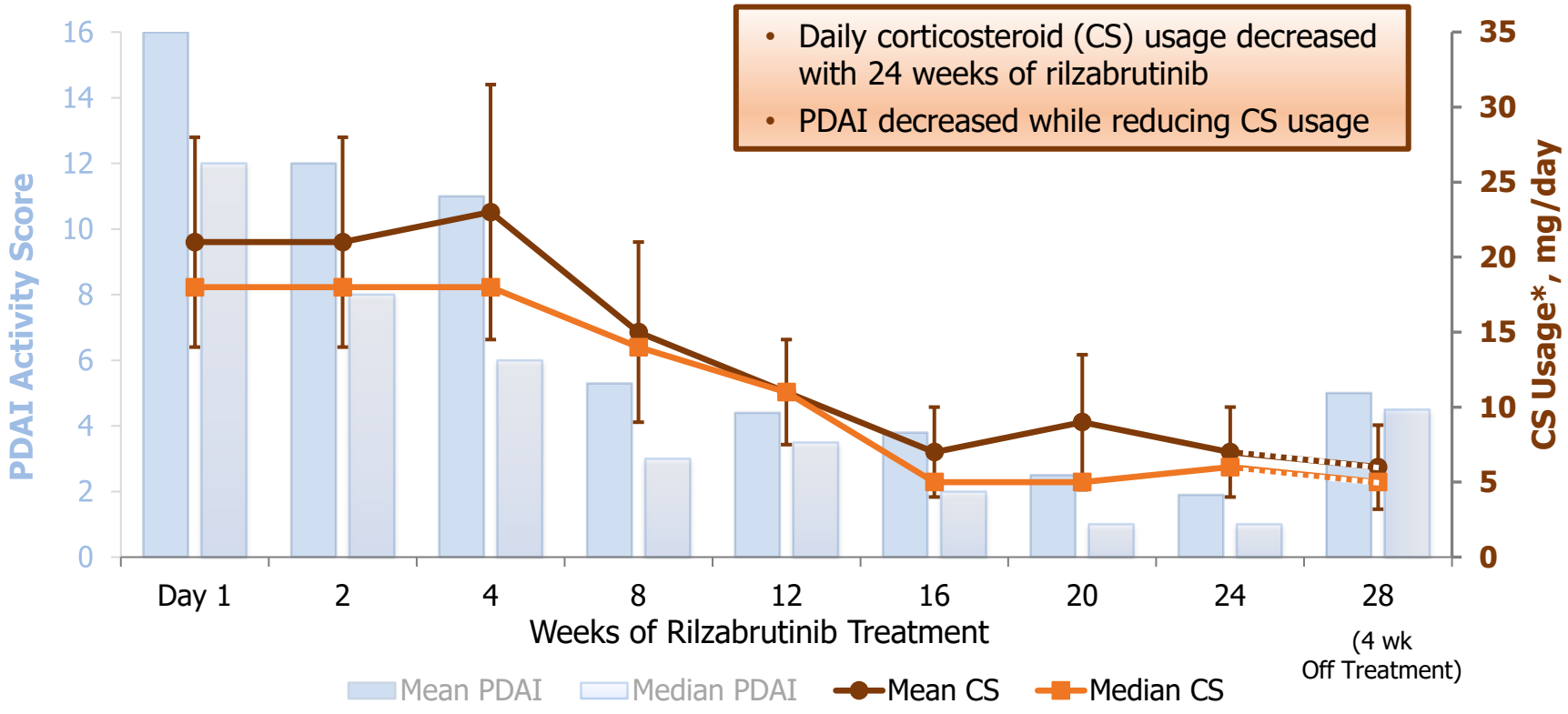
1. Shimizu T, et al. *J Dermatol.* 2014;41:969-973. 2. Boulard C, et al. *Br J Dermatol.* 2016;175:142-149.

Part B: 67% (10/15) of Patients Improved to PDAI 1 or 0 by 24 Weeks



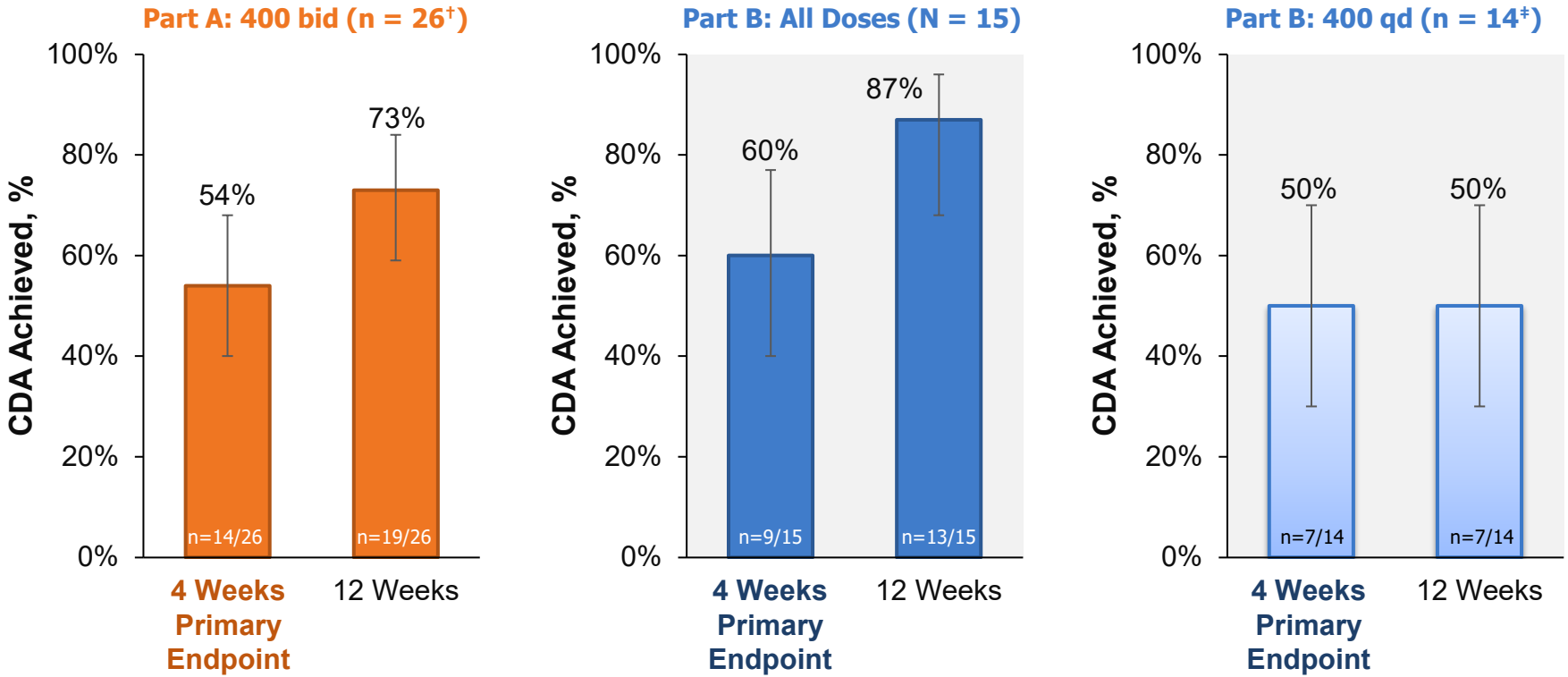
Note: 1 patient dropped out of study after 8 weeks due to worsening pemphigus and was not included in PDAI score/CS usage calculation after 8 weeks.

Part B: Rilzabrutinib Treatment Decreased Both PDAI and CS Usage



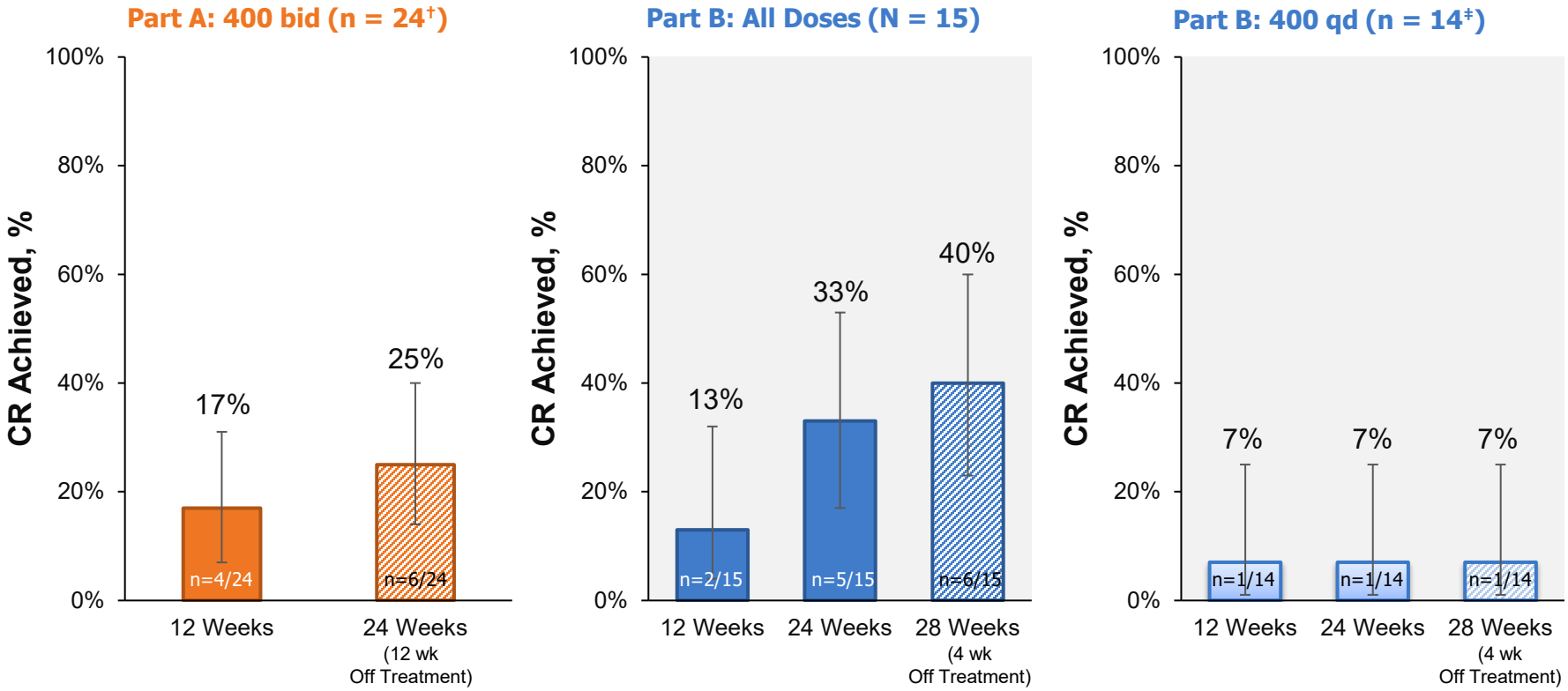
Note: 1 patient dropped out of study after 8 weeks due to worsening pemphigus and was not included in PDAI score/CS usage calculation after 8 weeks.

Rilzabrutinib Control of Disease Activity* was Rapid and Independent of Dose



LDCS was ≤ 0.5 mg/kg/day.
*CDA was defined as new lesions that have stopped appearing and current lesions that have started to heal.
†Excluded 1 patient who dropped out on day 10 due to treatment unrelated AE. ‡Excluded 1 patient who initiated 400 bid.
Error bars represent 80% CI calculated by Clopper Pearson Method.

Rilzabrutinib bid Dosing Led to Rapid and Improved Complete Remission*



LDCS was ≤ 0.5 mg/kg/day.
*CR was defined as absence of new lesions and complete healing of existing lesions.
†Excluded 3 patients due to a treatment-unrelated AEs after 10, 43, and 44 days. ‡Excluded 1 patient who initiated 400 bid.

Part B: All Treatment-Related, TEAEs Were Mild-Moderate and Transient

Treatment-Related TEAEs ≥ 10% by Preferred Term (N = 15), n (%)	Grade 1/2	Grade 3/4
Nausea	4 (27)	0 (0)
Abdominal distension	2 (13)	0 (0)
Dizziness	2 (13)	0 (0)

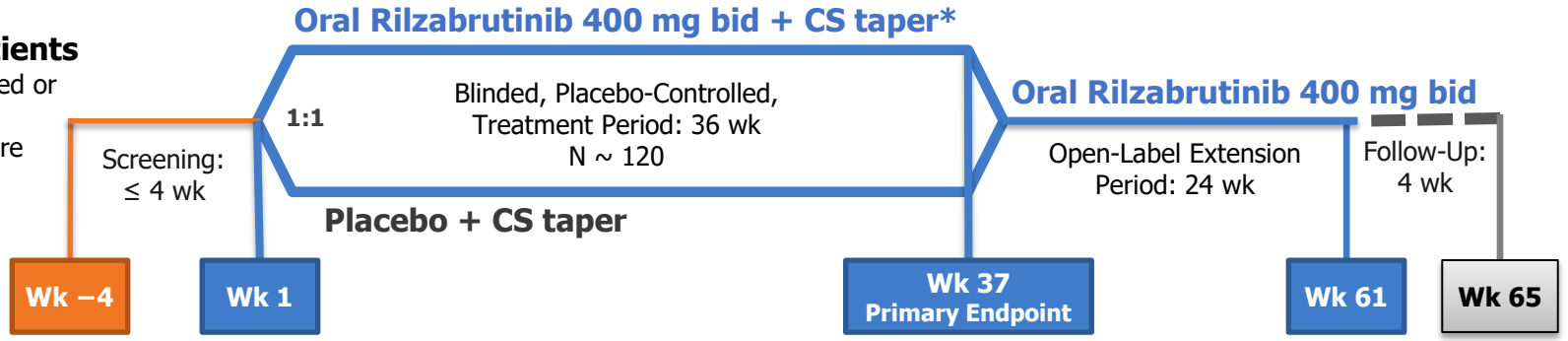
- Part B TEAEs were consistent with results previously reported in Part A
- In Part B, 2 of 15 patients reported a mild related infection (1 event each)
  - Grade 1 nasopharyngitis
  - Grade 1 tracheitis

Conclusions

- Rilzabrutinib delivered high CDA rates with a rapid onset independent of dose
  - 60% @ 4 weeks and 87% @ 12 weeks of treatment
- Longer treatment led to rapid and improved CR rates
  - 40% @ 28 weeks in Part B vs 25% @ 24 weeks in Part A
- 67% patients showed near-clear/clear skin (PDAI 1 or 0)
- Rilzabrutinib decreased PDAI with clinically-meaningful reduction in CS usage
- Rilzabrutinib was well tolerated, all treatment-related AEs were mild-moderate (grade 1 and 2 nausea, abdominal distension, and dizziness)
- 400 mg bid dose is the minimally effective dose based on improved efficacy
- Part A and B results were consistent, and support the phase 3 design and dose

Phase 3: PEGASUS Multicenter, Double-Blind, Randomized, Pivotal Study is Currently Enrolling Patients Globally

PV or PF Patients
- Newly diagnosed or relapsing
- Moderate-severe



Primary endpoint
- Proportion of patients in CR from wk ≤ 29 to 37 with CS dose ≤ 5 mg/d

Endpoints and Quality of Life Measurements
- Cumulative CS use and clinical impact over first 36 wk of treatment
- Change in EuroQOL-5 dimension 5-level score from baseline to wk 5, 13, 25, and 61
- Change in ABQOL from baseline to wk 5, 13, 25, and 61

clinicaltrials.gov: NCT03762265; EudraCT: 2018-002261-19.
*CS up-titration by 50%-100% allowed every 5-7d as needed, and rituximab allowed during the treatment period at/after wk 5 after a second or subsequent, clinically significant, qualifying relapse.

PEGASUS

Managing Pemphigus Patients in the COVID-19 Pandemic

- New guidance for the current COVID-19 environment[1-3]
- Current recommendations: steroids or steroid-sparing agents
- Phase 3 PEGASUS study with rilzabrutinib continues to enroll
  - Oral dosing; feasibility in outpatient setting
  - Short half-life and reversible
- PEGASUS clinical trial logistics
  - Provision for tele-dermatology, remote visits and dosing (country-dependent)

1. Shakshouk H, et al. *J Am Acad Dermatol.* 2020 Apr 2. doi:10.1016/j.jaad.2020.04.005. Epub ahead of print. 2. Murrell DF, et al. *J Am Acad Dermatol.* 2020;82:575-585.
3. IPPF guidance for patients: http://www.pemphigus.org/information-for-pemphigus-and-pemphigoid-patients-related-to-coronavirus-disease-covid-19/. Accessed Apr 22, 2020.

Thank You!

- We would like to thank our patients, families, caregivers, and co-investigators who are participating in BELIEVE and PEGASUS studies globally

Email: clinicaltrials@principiabio.com

For more information on PEGASUS

(clinicaltrials.gov: NCT03762265)

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