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

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Disclosures – Dedee F. Murrell

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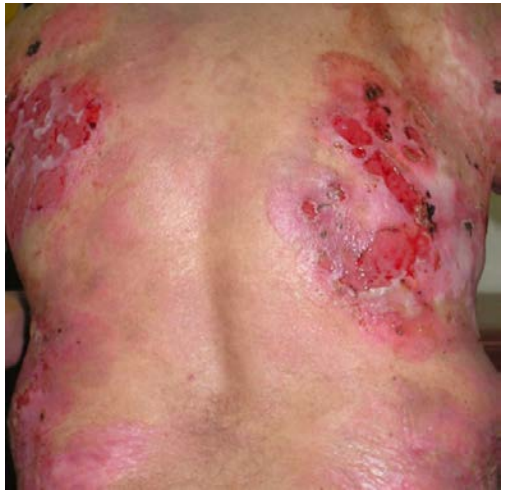
- Government affiliation: N/A
- Dermatology society involvement
  - International Board member, European Academy of Dermatology and Venereology (EADV)
  - Board of Directors, International Society of Dermatology; President of ASDR
- Editor or author of nonscientific publications: N/A
- Director, Premier Specialists: Clinical Trials Centre for Dermatology
- Consultancies: GSK, Novartis, Principia Biopharma, Roche
- Inventor/Co-inventor of the PDAI, ABQOL and TABQOL measures

Pemphigus is a Blistering Disease With Mortality Rate of ~5% in the Corticosteroid Era

Rare disease affecting

~40K in the US* and ~170K Worldwide

Driven by autoantibodies to desmogleins 1 & 3



Current Therapy Challenges

- **Standard of care is high-dose corticosteroids (CS)** in prednisone-equivalent doses of ≥ 1 mg/kg with high toxicity, and/or rituximab plus moderate to high initial doses of CS (≥ 0.5-1 mg/kg)
- **Even with rituximab, high unmet need remains due to CS toxicities**

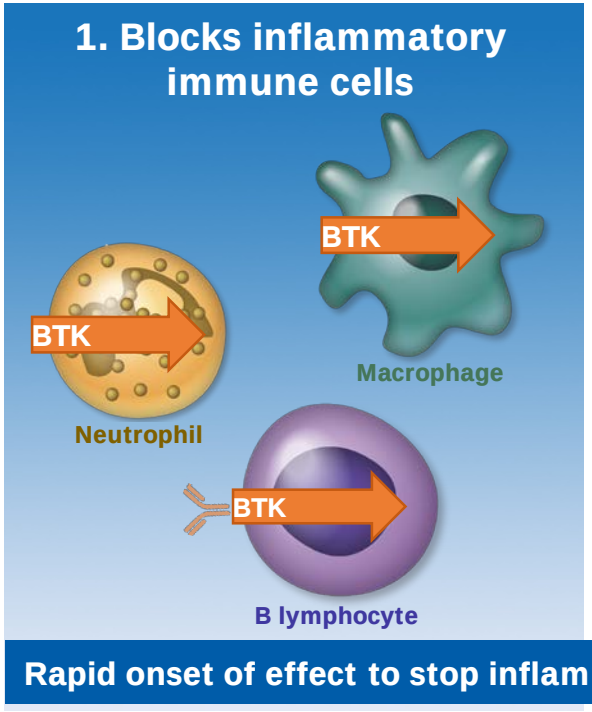
Considerable Unmet Medical Need

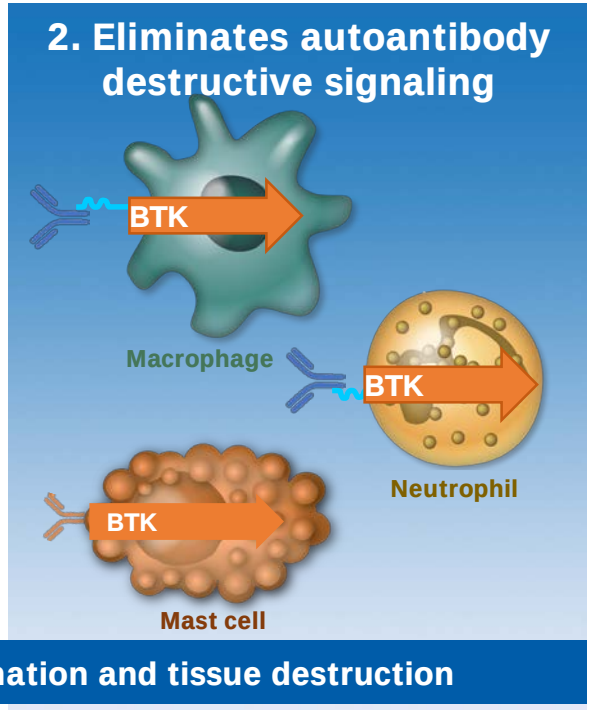
- Rapid onset
- Steroid sparing or steroid avoiding
- Safe for chronic administration
- Avoids long term B-cell depletion
- Efficacy in both newly diagnosed and relapsed patients
- Convenient administration

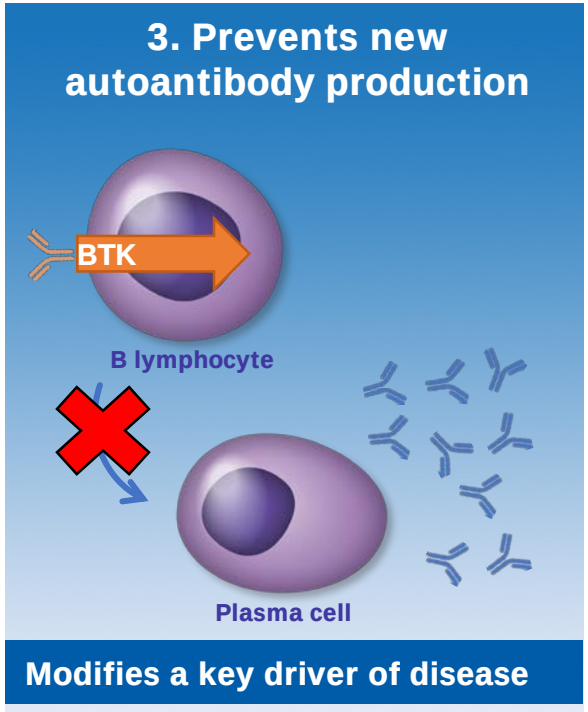
*Includes approximately 30K pemphigus vulgaris and 10K pemphigus foliaceus.

Murrell, et al. *J Am Acad Dermatol*. 2018; doi: 10.1016/j.jaad.2018.02.021. Epub ahead of print.

Bruton Tyrosine Kinase (BTK) Inhibition Shows Novel Mechanisms for Targeting Key Underlying Drivers of Immune-Mediated Disease



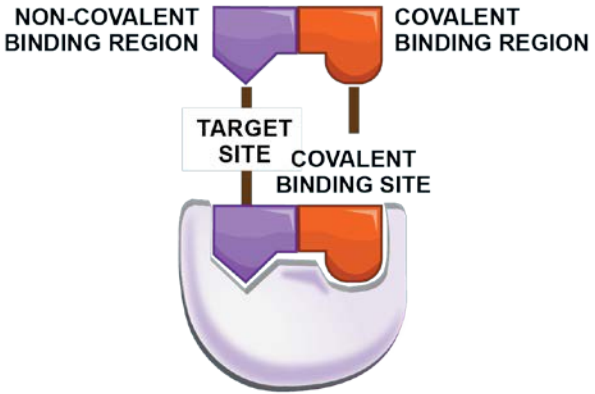


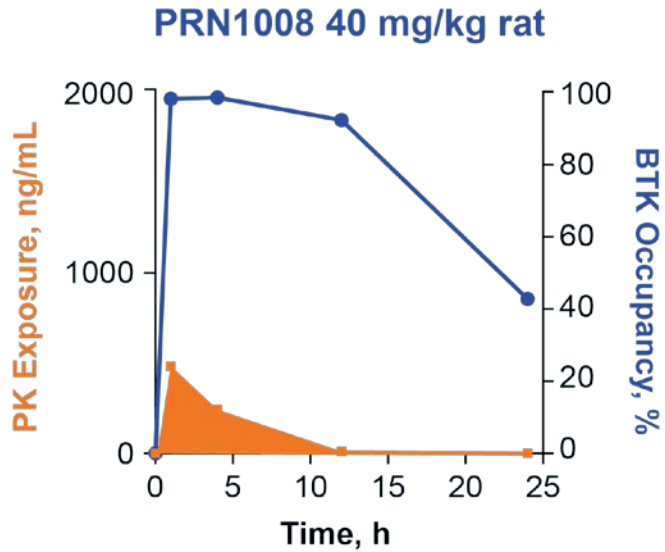


Rapid onset of effect to stop inflammation and tissue destruction

Modifies a key driver of disease

PRN1008 Is An Oral BTK Inhibitor Designed for Immunology Using Tailored Covalency™





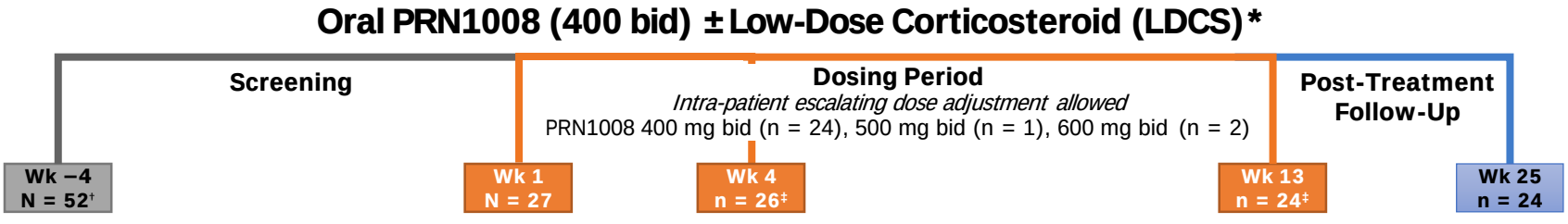
PRN1008 With Reversible Covalent Binding

PK/PD: Durable Inhibition With Low Drug Exposure

PD, pharmacodynamics; PK, pharmacokinetics.

1. Bradshaw JM, et al. *Nat Chem Biol.* 2015;11:525-531. 2. Data on file, Principia Biopharma Inc.

Phase 2 Part A: BELIEVE-PV Study Design

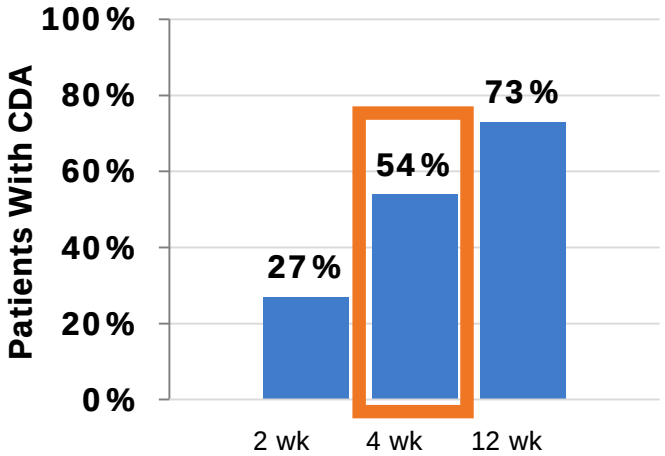


Screening 4 wk	Treatment Period	Follow-Up
Patient population ▪ **Naïve or relapsing PV** – Newly diagnosed (mild-mod)[1,2] – Relapsed patients (mild-severe)[1,2] ▪ **LDCS (≤ 0.5 mg/kg)*** ▪ **PDAI skin score 8 to 45 points**	**Primary end point** ▪ Control of Disease Activity (CDA) within 4 wk (day 29) while on LDCS at ≤ 0.5 mg/kg/day **Secondary end points** ▪ Complete remission (CR), PDAI, ABSIS, time to remission ▪ Minimization of prednisone usage ▪ Laboratory including change in anti-desmoglein autoantibody levels ▪ BTK white blood cell occupancies and PK	▪ Follow-up for 12 wk off treatment

*Prednisone or equivalent.
†Most common reasons for screen failure were unwilling to consent to study procedures/visits (n = 6), positive viral (n = 6) or TB screening (n = 5), and failed diagnostic confirmation (n = 4).
‡Excluded 3 patients who dropped out due to treatment-emergent adverse events (AEs) unrelated to PRN1008 at days 10, 43 and 44.
ABSIS, autoimmune bullous skin disorder intensity score; bid, twice daily; CDA, control of disease activity; mod; moderate; PDAI, pemphigus disease area index; PV, pemphigus vulgaris.
1. Shimizu T, et al. *J Dermatol.* 2014;41:969-973. 2. Boulard C, et al. *Br J Dermatol.* 2016;175:142-149.

Phase 2 Part A: BELIEVE-PV Efficacy and Safety Results

Primary End Point: Control of Disease Activity (CDA) within 4 wk on LDCS* (n = 26)



- 54% CDA at 4 wk was further increased to 73% at 12 wk

Treatment-Related TEAEs

(≥ 10% Patients; N = 27)

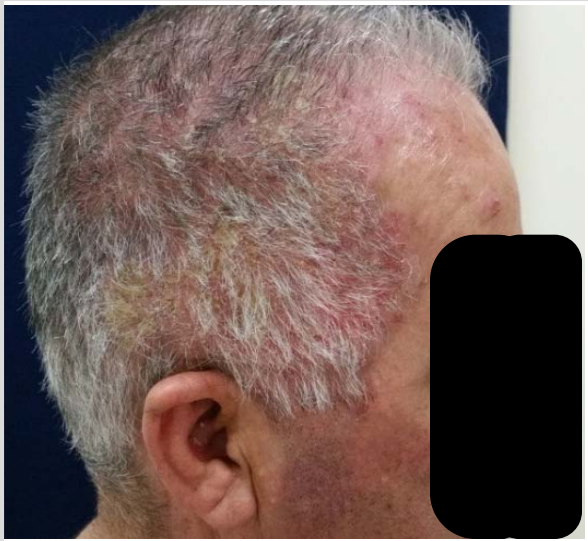
TEAEs, n (%)	Grade 1-2	Grade 3-4
Nausea	4 (15)	0
Upper abdominal pain	3 (11)	0
Headache	3 (11)	0
Infection†	2 (7)	1 (4)

- **Safety**: favorable tolerability and risk/benefit profile
- **Other efficacy results**
  - CR achieved in 25% of patients with 12 wk of therapy
  - ~70% Median reduction in PDAI scores
  - 65% Median reduction in autoantibody levels at wk 12
  - Low CS usage (average 12 mg/day) vs usual care of CS (≥ average 0.5 mg/kg/day) ± rituximab

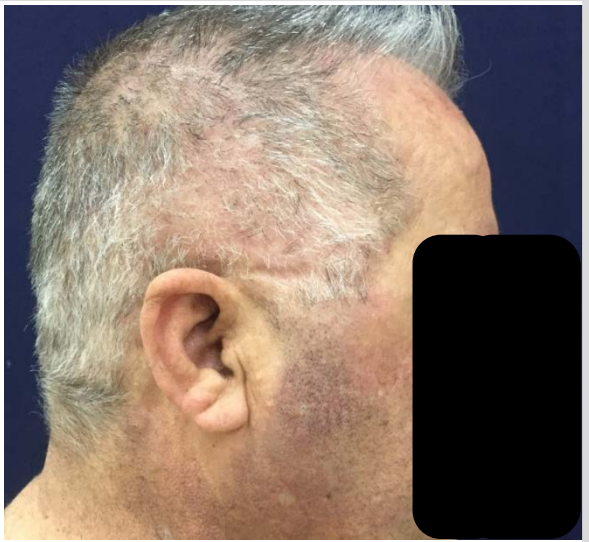
*Mean (SD) prednisone dose over 12 wk was 12 (± 10) mg/day.
†One SAE occurred with localized patch of leg cellulitis and a high fever (culture negative), PRN1008 at 400 mg bid was resumed for a further 2 mo without event recurrence; 2 other infections were transient upper respiratory tract infections.
LDCS, low-dose corticosteroid; TEAE, treatment-emergent adverse event.
Murrell DF, et al. AAD 2019:abstract 10086.

Pemphigus Vulgaris Patient Improvement After 12 Weeks of PRN1008 and Low-Dose Corticosteroid Treatment (< 0.5 mg/kg/d)

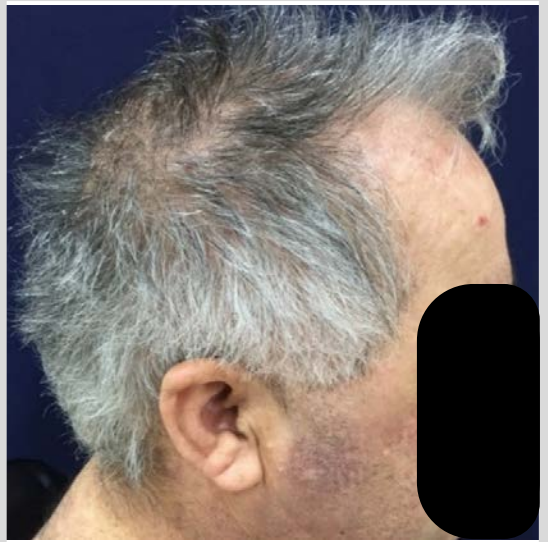
Screening



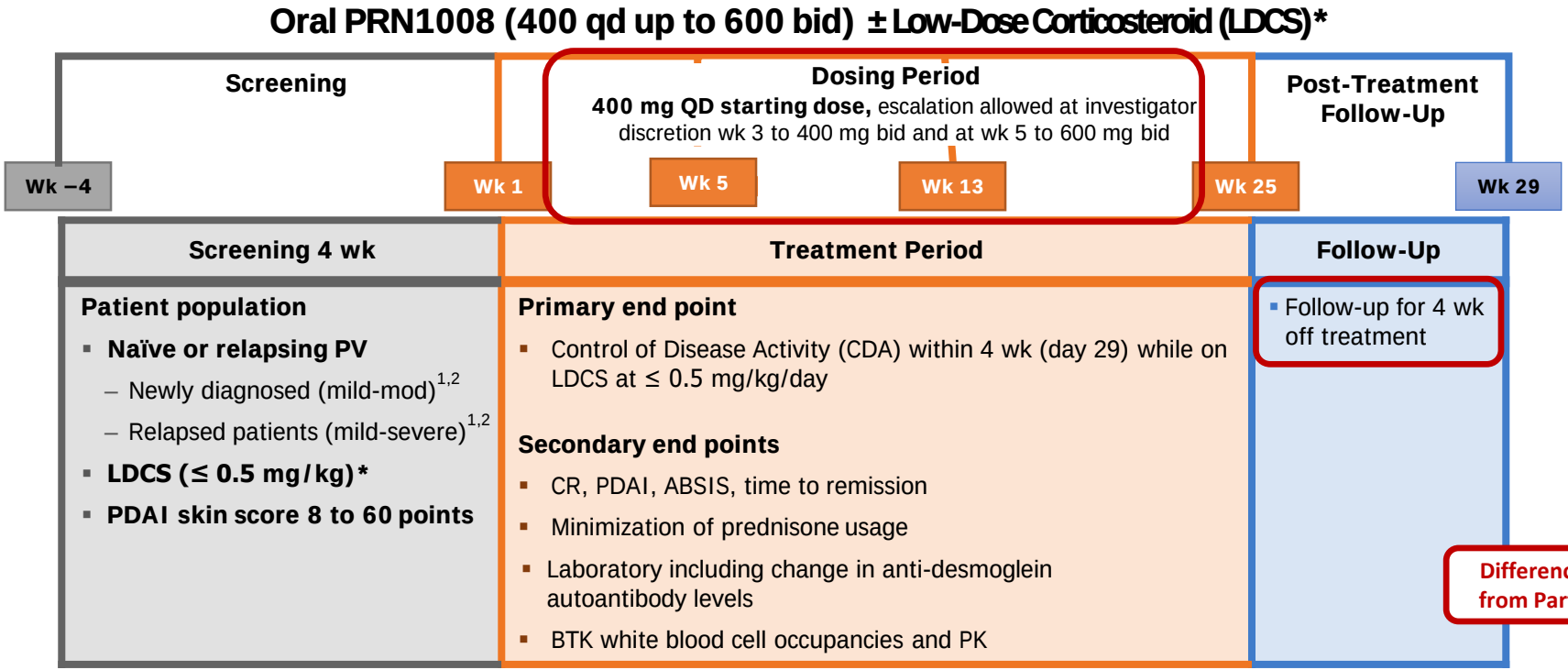
Wk 4



Wk 12



Phase 2 Part B: BELIEVE-PV Study Design



*Prednisone or equivalent.
†Most common reasons for screen failure were were positive viral (n = 2) and tuberculosis screening (n = 1).
‡Excluded 1 patient because of worsening of pemphigus at wk 5.
1. Shimizu T, et al. *J Dermatol.* 2014;41:969-973. 2. Boulard C, et al. *Br J Dermatol.* 2016;175:142-149.

Overall Phase 2 Data Support Phase 3 Study Design

Part B (n = 15) preliminary data confirm outcomes observed in Part A (n = 27)

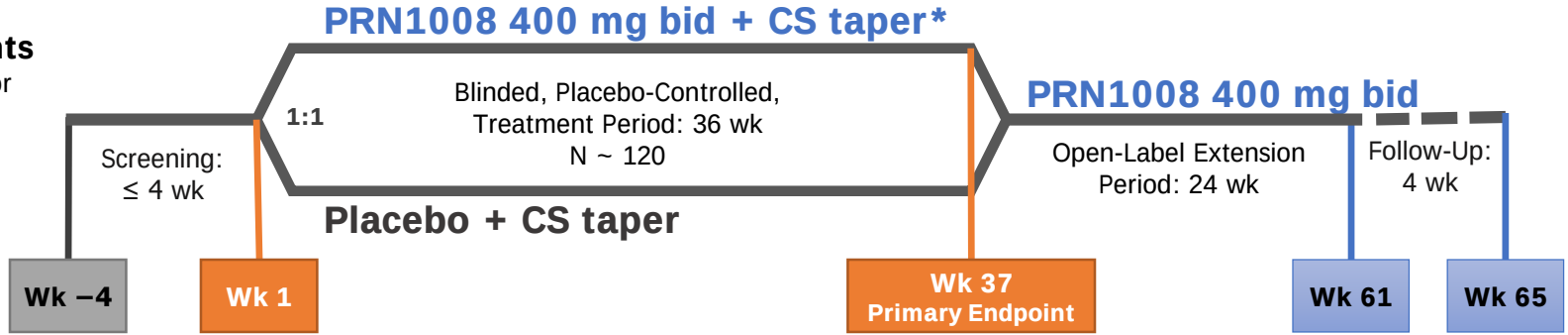
- Safety profile and risk benefit remain favorable and similar (no SAEs)
- Efficacy endpoint benefit (CDA) was similar in part A and B
- Minimally effective dose of 400 mg bid was determined
- Complete remission rate improved from 25% (3 months - part A) to at least 40% with longer treatment (6 months - part B) in patients ongoing and completed
- 9 of 15 patients (60%) achieved a PDAI score of 0 or 1

Detailed phase 2 Part B results will be presented at an upcoming medical conference

Phase 3: PEGASUS Multicenter, Double-Blind, Randomized, Pivotal Study

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 5-7 d as needed, and rituximab allowed during the treatment period at/after wk 5 after a second or subsequent, clinically significant, qualifying relapse.
ABQOL, autoimmune bullous diseases quality of life assessment; CR, complete remission; CS, corticosteroid.

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PEGASUS Key Inclusion/Exclusion Criteria

Key Inclusion Criteria

- Age, 18 to 80 years
- Moderate to severe, newly diagnosed or relapsing PV or PF
- Positive anti-desmoglein-1 and/or -3 autoantibody titer
- Adequate laboratory results for hematologic, hepatic, and renal function
- Contraception use if woman of reproductive age

Key Exclusion Criteria

- Previous/concomitant use of BTK inhibitor; immunologic response modifiers; investigational drug/device; CYP3A inducer, inhibitor, or substrate; and live vaccine
- Pregnant/lactating women
- Positive for HIV, hepatitis A or B, or active/latent tuberculosis
- History of any malignancy other than surgically excised non-melanoma skin or in situ cervical cancers ≤ 5 y before d 1
- Any clinically significant abnormalities, history of serious infection, or drug abuse/alcoholism

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Summary of PRN1008 in Pemphigus

- BELIEVE phase 2A study results to date have shown favorable tolerability and risk/benefit profile in patients with PV
  - Phase 2B has completed enrollment and will be submitted to an upcoming scientific conference
- PEGASUS pivotal phase 3 study shows encouraging and on-target enrollment in patients with PV/PF (planned: N = 120)
  - Study start date: Jan 2019
  - Estimated primary completion date: Dec 2021 (study completion: 1H 2022)

Thank You!

- Patients, families, caregivers, and co-investigators who are participating in BELIEVE and PEGASUS studies globally
- Principia Biopharma for sponsoring the study

For more information on PEGASUS (clinicaltrials.gov NCT03762265)

Email: clinicaltrials@principiabio.com

PEMPHIGUS VULGARIS SUPPORT GROUP

ippf International Pemphigus & Pemphigoid Foundation

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