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Leading the BTK Field in Immune-Mediated Disease

Dolca Thomas, MD: Chief Medical Officer

Robust Homegrown Pipeline with Multiple Clinical Assets

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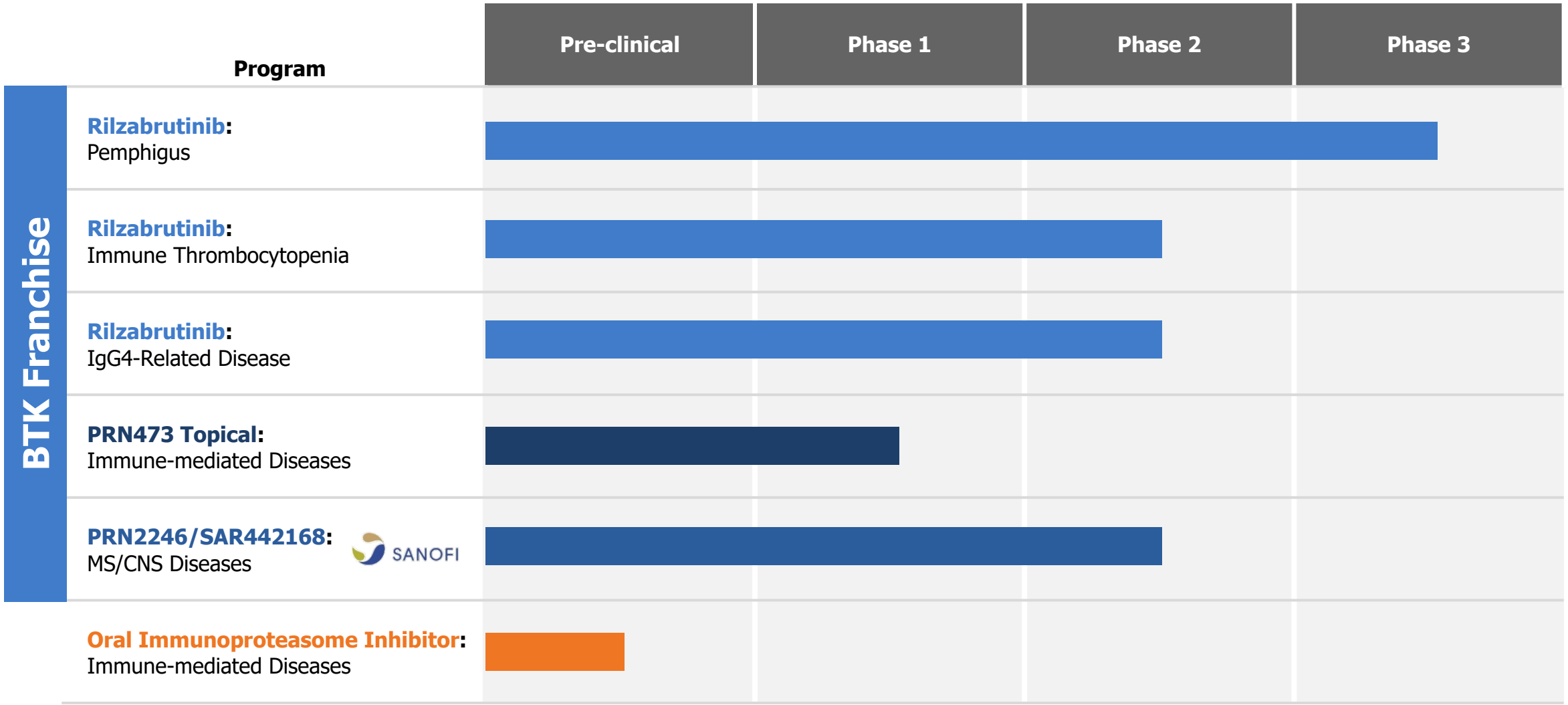

BTK Has a Broad Role in Multiple Immune-mediated Disease Processes[1-3]

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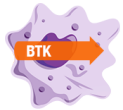
Mast cell / Eosinophil

IgE-mediated FcεR activation and degranulation

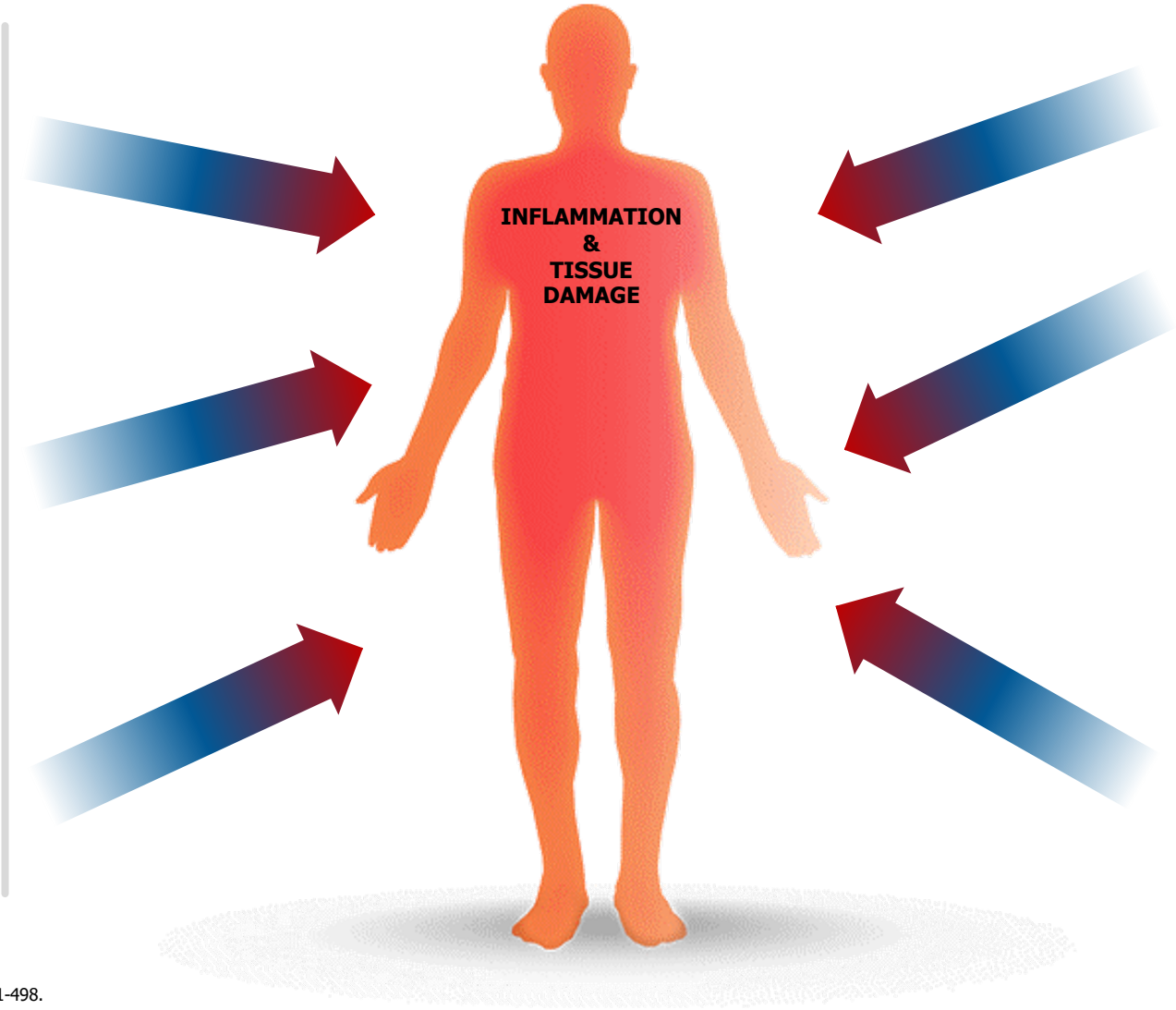


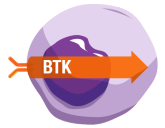
Macrophage

IgG-mediated FcγR activation, phagocytosis, inflammatory mediators

Neutrophil

Activation, adhesion, recruitment, oxidative burst





Autoreactive memory B cell

Long-lived plasma cell

Plasma cell differentiation and antibody production

Autoantibodies

(1) LeBien TW, Tedder TF. *Blood.* 2008;112(5):1570-1580.
(2) Elkon K, Casali P. *Nat Clin Pract Rheumatol.* 2008;4(9):491-498.
(3) Lacy P, Stow JL. *Blood.* 2011;118(1):9-18.

Pemphigus: Debilitating Autoimmune Skin-blistering Disease

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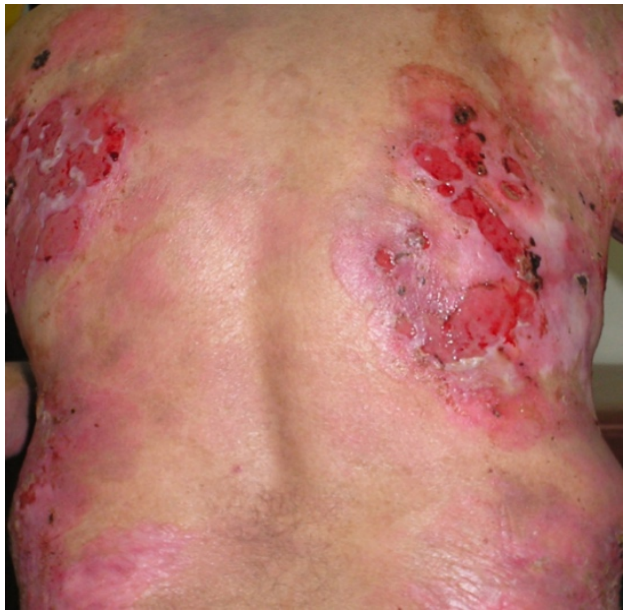
Rare disease affecting
~40K in the United States(1)
~170K Worldwide



- **Pemphigus patients are poorly managed due to their struggle with prednisone toxicities**
- **Driven by autoantibody** to desmogleins 1 and 3 with delamination of the skin layers and mucosal membranes
- **Standard of care is** high-dose CS (60-90mg/day), with high toxicity; Rituxan; other immunosuppressants
- **Considerable medical need** exists for oral, Corticosteroids-sparing, fast acting therapy that reduces autoantibody generation, and related target tissue inflammation

Source: Globaldata Database.
(1) Approximately 30K pemphigus vulgaris and 10K pemphigus foliaceus.

Phase 2: Believe-PV Study Design Part A and Part B

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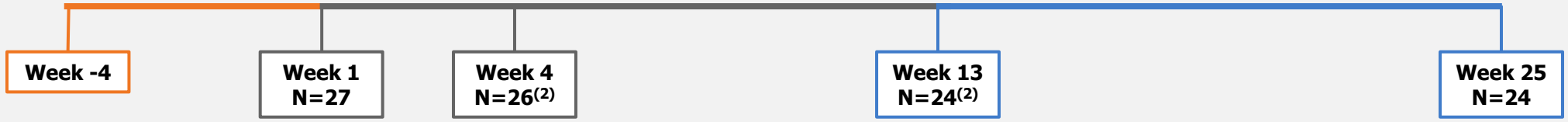
Part A

Oral PRN1008 ± low dose Corticosteroids (LDCS)[1]

Screening | Dosing | Post-treatment follow-up

Intra-patient escalating dose adjustment allowed

400 mg BID, 500 mg BID, 600 mg BID



Part B N=15

Oral PRN1008 ± low dose Corticosteroids (LDCS)[1]

Screening | Dosing | Post-treatment follow-up

Intra-patient escalating dose adjustment allowed

400 mg QD, 400 mg BID, 600 mg BID

Screening

Patient population:

- **Naïve or relapsing PV**
  - Newly diagnosed (mild-mod)[3]
  - Relapsed patients (mild-severe)[3]
- **Low dose corticosteroid[1] (≤0.5 mg/kg)**
- **Part B:** PDAI skin score 8 - 45 points

Dosing

Primary endpoint:

- Control of Disease Activity (CDA) within 4 weeks (Day 29) while on ≤0.5 mg/kg/day of corticosteroid[1] (LDCS)

Secondary endpoints:

- Complete remission (CR), PDAI, ABSIS, time to remission
- Minimization of prednisone usage
- Laboratory including change in anti-desmoglein autoantibody levels
- BTK white cell occupancies & pharmacokinetics

Follow up

- Follow up for 4 weeks off treatment in Part A
- Follow up for 12 weeks off treatment in Part B

Source: Part A Data on File from MDS/AAD presentation Feb 2019.

(1) Prednisone or equivalent.

(2) Three patients dropped out due to treatment-emergent adverse events unrelated to rilzabrutinib at Days 10, 43 and 44 are not included in this analysis.

(3) Shimizu, 2014 and Broulard, 2016 classification.

Phase 2 Part A: Rilzabrutinib Patient Demographics Broadly Reflect Newly Diagnosed and Relapsing Patients

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Rilzabrutinib Phase 2 Study Patient Demographics

Characteristics		Baseline N=27
Age	Mean, Year (SD, Range)	52 (9, 37-72)
Gender	Male, n (%)	12 (44)
	Female, n (%)	15 (56)
Disease Stage	Relapsing, n (%)	18 (67)
	Newly Diagnosed, n (%)	9 (33)
Duration of Disease	Mean, Year (SD, Range)	6 (7, 0-25)
Disease Severity(1)	PDAI <15 (mild-moderate)	11 (41)
	PDAI ≥15 (moderate-severe)	16 (59)
Antibody Profile	Positive, n (%)	26 (96)
	• Anti-dsg3 ± 1 Positive, n (%)	23 (85)
	• Anti-dsg1 Positive Only, n (%)	3 (11)
	Negative, n (%)	1 (4)
CS(2) Dose at Entry	Mean, mg/day (SD, Range)	14 (11, 0-30)
PDAI Score(3)	Mean, Points (SD, Range)	19 (11, 8-43)

Source: Presented at 2019 AAD annual meeting during Late-Breaking Research: Clinical Trials session.
(1) Moderate-severe included 6 patients with severe, relapsing disease per PDAI severity quartiles for relapsing disease of 9 and 25 (Shimizu 2014) vs. newly diagnosed disease of 15 and 45 (Boulard 2016).
(2) Corticosteroids.
(3) Pemphigus Disease Area Index Score total activity score.

Phase 2 Part A Data Aligns with Pemphigus Patient Needs

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Pemphigus Patient Needs	Rilzabrutinib Phase 2 Part A Results
Fast acting	**54% Control of Disease Activity** within 4 weeks of treatment
Fast complete remission	**25% Complete Remission** after 12 weeks of treatment
No/Low corticosteroids	Mean (SD) 12 mg (10 mg)/day (~1000 mg/12 weeks) Compared to 60 – 120 mg/day standard of care treatment
Convenient and well tolerated	**Oral Therapy**

N=27	Grade 1-2	Grade 3-4
Nausea	15%	0%
Abdominal Pain	11%	0%
Headache	11%	0%
Infection	7%	4%

Source: Presented at 2019 AAD annual meeting during Late-Breaking Research: Clinical Trials session.
"Control of Disease Activity," which is defined as new lesions have stopped appearing and current lesions have started to heal
"Complete Remission," which is defined as absence of new lesions and complete healing of existing lesions

Phase 2 Part B Data Confirms 400 mg BID Dose and Supports Phase 3 Trial Design

Pemphigus Patient Needs	Rilzabrutinib Phase 2 Part B Results
Fast acting	**60% Control of Disease Activity** within 4 weeks of treatment
Improved Response	**80% Control of Disease Activity** within 12 weeks of treatment
Fast complete remission	**40% Complete Remission** after 24 weeks of treatment

- 400 mg QD starting dose was determined to be less effective. Based on SMC recommendation all patients escalated to BID dosing
- Safety consistent with Part A(1)

Source: "FC04.08 TIP - 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" By Dr. Dedee Murrell et al. EADV October 10th, 2019.
Data cut off September 2019
"Control of Disease Activity," which is defined as new lesions have stopped appearing and current lesions have started to heal
"Complete Remission," which is defined as absence of new lesions and complete healing of existing lesions

PEGASUS Phase 3 Trial: Patient Relevant Endpoints in Broad Population

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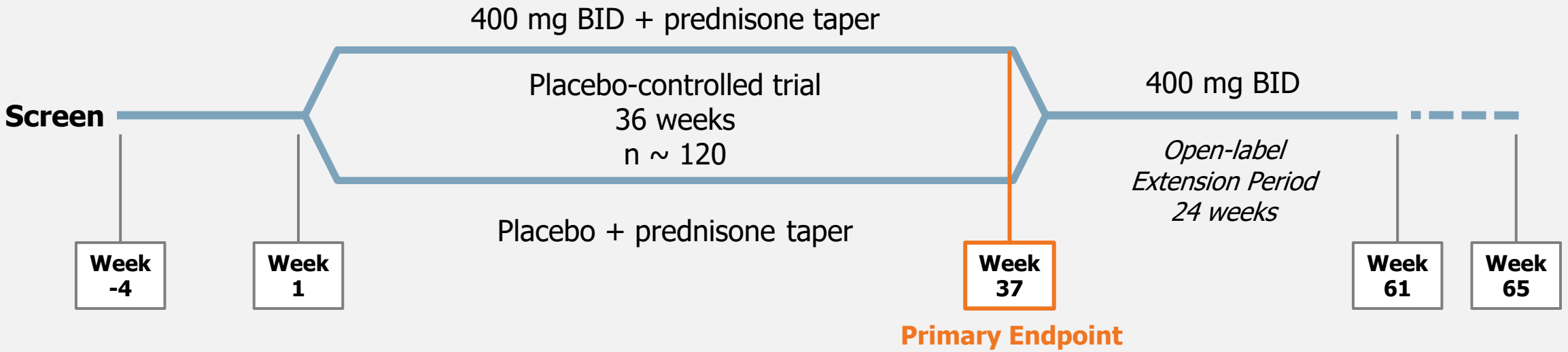
PEGASUS
ALIGNING THE STARS FOR PATIENTS WITH PEMPHIGUS

Population

Represents **~75%** of accessible patient population[(1)]



Endpoints

Primary

- Complete Remission on ≤5 mg prednisone for ≥8 weeks at Week 37

Secondary

- Cumulative prednisone use over 36-week treatment
- Time to Complete Remission
- Complete Remission with ≤10 mg prednisone for ≥8 weeks at Week 37

(1) Harman et al. 2017 British Journal of Dermatology (2017) 177, pp1170–1201.

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Thank you

bonding matters