Clinical endpoint analysis of the Believe-PV phase 2 study of PRN1008 in pemphigus

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Introduction

Pemphigus, which is characterized by intraepidermal blisters in skin and/or mucosae, is known to be driven by autoantibodies to epidermal proteins and is responsive acutely to the anti-inflammatory effects of intravenous immunoglobulin and high dose corticosteroids (CS), typically in doses of 1-1.5mg/kg/day, and more chronically to B-cell depletion by anti-CD20 therapy[1]. Bruton's tyrosine kinase (BTK) is an essential signaling element of the B cell receptor, critical for B cell activation and antibody induction. BTK also regulates antibody-mediated activation of macrophages, and other immune cells via Fc-receptor signaling[2].

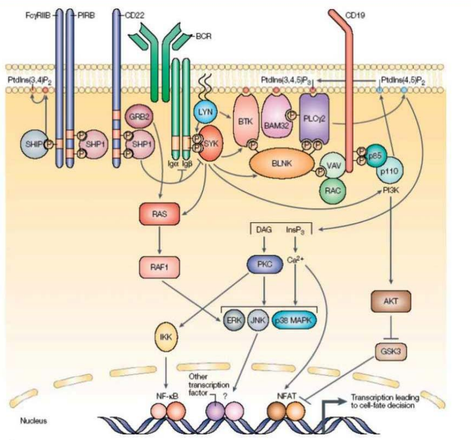

Figure 1[3]. BTK signaling pathway through the B-cell and FcγR

Principia Biopharma has developed a novel, small molecule inhibitor of non T cell white blood cell signaling (via B-cell receptor, FcγR, FcεR signaling of the BTK pathway). PRN1008 is an oral, reversible covalent small molecule with a high degree of affinity for BTK, and is more durably selective for BTK vs. related TEC kinases. This "reversible covalent selectivity" offers the potential to provide potent efficacy while minimizing adverse effects of off-target pharmacology[4].

In a healthy volunteer program of 114 subjects treated for up to 11 days, excellent tolerability was observed and a dose of 400 mg bid was shown to provide optimal BTK target engagement. This dose was chosen as the "full BTK occupancy dose" for initial study in the Believe-PV Phase 2 study.

Interim data from 12 pemphigus patients in the Believe-PV study reported in September 2017 suggested that PRN1008 has the ability to induce control of disease activity and/or achieve clinical remission in a high proportion of patients on a background of dose corticosteroids.

Methods and Materials

This open-label, Phase 2 study enrolled patients with newly diagnosed or chronic, relapsing pemphigus, on a dose of prednisolone/equivalent corticosteroid (CS) from 0-0.5mg/kg/day, and with a pemphigus disease activity index (PDAI) of 8-45. Anti-desmoglein confirmation of pemphigus vulgaris (PV) or pemphigus foliaceous (PF) was not required. Other immunosuppressives were not allowed as concomitant treatment. Maximum doses were 400 mg (n=19), 500 mg (n=1) and 600 mg (n=1) twice daily. Treatment duration was 12 weeks, with a further 12 weeks follow-up. The primary endpoint was control of disease activity (CDA) at 4 weeks on ≤0.5mg/kg/day of CS. This analysis examines the timing of a variety of potential endpoints and CS targets that could be used as the primary endpoint in a larger, placebo-controlled clinical trial.

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Results

The patient population studied reflected the expected population of pemphigus patients presenting with newly diagnosed or relapsing, chronic disease (Table 1). Two patients were autoantibody negative, and two were only anti-dsg1 positive, suggesting a diagnosis of PF. Newly diagnosed patients had a higher mean entry dose of CS of 18mg than relapsed patients with 12mg.

Of 21 patients, 18 had at least 4 weeks of follow-up and are included in the efficacy analysis.

Mean PDAI scores fell by 79% over 12 weeks associated with an improvement in quality of life (all patients, Figure 2).

CDA, defined as the absence of new lesions and the start of healing of old lesions, had been achieved by 11/18 (61%) patients by 4 weeks, 10 of whom were on zero or low dose CS. 13/18 (72%) had achieved CDA by 12 weeks, 11 of whom were on zero or low dose CS (patients with a clinical response, Figure 3).

Complete remission (CR), defined as complete healing of all lesions on any dose of CS, was achieved in 3 patients at 12 weeks, and 1 patient at 21 weeks. At the time of achieving CR, CS doses for the 4 patients were 20mg, 8mg, 2.5mg and 1mg.

The mean CS dose at study entry was 13mg and this dropped to 9mg at the end of 12 weeks of therapy. Five patients achieved clinical responses on 0- 5mg/day of CS (Figure 4).

Baseline Variables

Age (mean & range)	53 (37-72)
% female	52%
Chronic/New PV disease presentation (N/N)	16/5
Autoantibody negative	2 (10%)
Anti-dsg3 positive	7 (33%)
Anti-dsg1 positive	2 (10%)
Both anti-dsg3 & 1 positive	9 (43%)
Years since PV diagnosis (mean ± SD)	5 ± 6
PDAI total activity score (points, mean ± SD)	21 ± 6
Prednisolone dose at baseline (mg, mean ± SD)	13 ± 9

Table 1. Baseline characteristics of 21 patients enrolled at time of data analysis

Safety Summary

All 21 subjects enrolled were included in the safety analysis.

- One SAE of "cellulitis" resulted in 3 days of dose-interruption with therapy resumed safely for 2 further months.
- No clinically significant changes in vital signs or laboratory parameters have been observed.
- Few Grade 1/2 adverse events related to therapy have been reported (Table 2).

PRN1008-related TEAEs	Term	Freq. (N, %)
Grade 1/2 ≥10%	Headache	2 (10%)
	Dry mouth	2 (10%)
	Upper respiratory infection	2 (10%)

Table 2. PRN1008 related TEAEs reported by more than one patient

1. Murrell, D.F. *Dermatol Clin*. 2011 Jul;29(3):xv-xvi
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3. Niiro, H. and Clarke, E.A. *Nat Rev Immunol* 2002;2002:945–6
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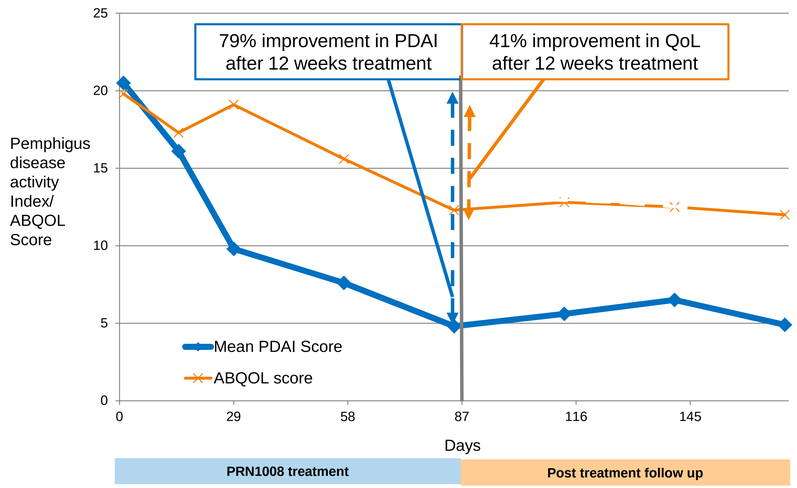

Figure 2. Change in mean PDAI and ABQOL scores over time

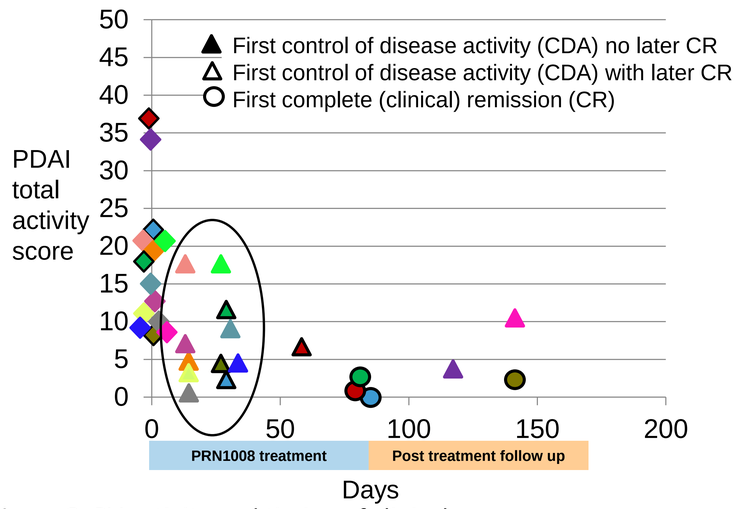

Figure 3. PV activity and timing of clinical responses

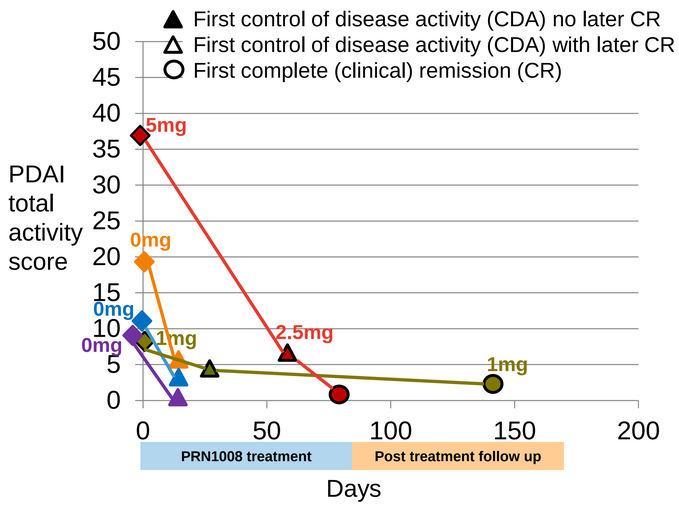

Figure 4. Clinical response profiles for patients on 0-5mg daily of CS

Conclusions

Although early responses in the majority of patients during 12 weeks of treatment are encouraging, treatment with PRN1008 for at least 6 months is potentially needed to assess the true rates of complete clinical response on minimal or no other immunosuppressive therapy. The low doses of CS at the time of CR in the current study suggest that CS maintenance doses of 5mg or less are achievable with PRN1008 monotherapy. A primary endpoint at ≥6 months of CR on 5mg of CS or less for ≥2 months is appropriate for a larger, randomized controlled trial.