A Phase III, Randomized, Double-Blind, Controlled Study (PEMPHIX) to Evaluate the Efficacy and Safety of Rituximab Versus Mycophenolate Mofetil in Patients With Pemphigus Vulgaris

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INTRODUCTION

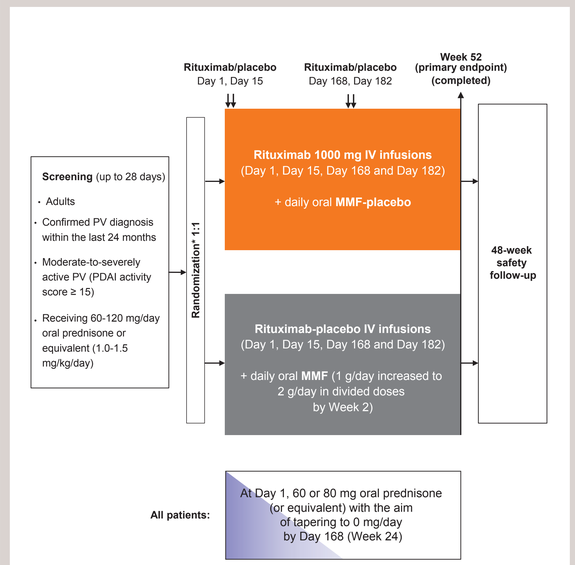
- The aims of pemphigus vulgaris (PV) treatment are to control the disease, limit recurrence, and minimize side effects associated with treatment
- Systemic corticosteroids (CS) are first-line treatment[1]
- Rituximab is an anti-CD20 monoclonal antibody approved to treat moderate to severe PV in the United States and Europe[2,3]
  - An independent analysis of the Ritux 3 study[4] demonstrated that at Month 24, rituximab plus a short course of CS was significantly more effective than a standard dose and duration of CS in achieving complete remission off CS for ≥ 2 months (CRoff ≥ 2 months) in patients with PV[5]
- Mycophenolate mofetil (MMF) is recommended in pemphigus treatment guidelines as a first-line CS-sparing agent and is commonly used, though its efficacy in PV has not been proven[1,6]

OBJECTIVE OF THE STUDY

- To compare the efficacy and safety of rituximab to mycophenolate mofetil in patients with moderate to severe PV

METHODS

Figure 1. Study Design



*At randomization, patients were stratified by duration of PV and geographic region.
CS, corticosteroid; MMF, mycophenolate mofetil; PDAI, Pemphigus Disease Area Index; PV, pemphigus vulgaris.

Study Endpoints

- **Primary efficacy endpoint:** At Week 52, the proportion of patients achieving sustained complete remission (CR) without experiencing treatment failure
  - Sustained CR was defined as Pemphigus Disease Area Index (PDAI) activity score of 0 and 0 mg/day prednisone or equivalent for at least 16 consecutive weeks (i.e., **sustained CRoff prednisone ≥ 16 weeks**), during the 52-week treatment period
- **Secondary efficacy endpoints (ranked):**
  - Cumulative oral CS dose (prednisone or equivalent) over the treatment period
  - Total number of disease flares during the treatment period
  - Time to sustained CR
  - Time to disease flare
  - Change in in health-related quality of life, as measured by the Dermatology Life Quality Index (DLQI) score, from baseline to Week 52
- Efficacy analyses were performed on the modified intent-to-treat (mITT) population, which excluded from the ITT population exploratory data in 10 patients for whom telemedicine was used to enable accessibility for study participation
- **Safety:** adverse events (AEs) and serious AEs (SAEs), AEs leading to study withdrawal, and CS-related AEs
  - Safety analyses were performed on the safety population (ITT population)

RESULTS

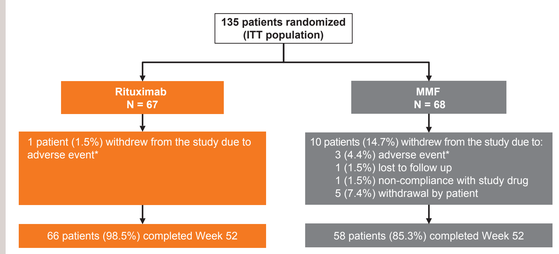
Patient Enrollment

- 135 patients were enrolled at 49 academic sites in 10 countries: United States, Canada, Argentina, Brazil, France, Germany, Israel, Italy, Spain, & Turkey
  - 52 (38.5%) from North America and 83 (61.5%) rest of world
- At screening, 113 patients had moderate PV (PDAI activity score 15-45) and 20 patients had severe PV (PDAI activity score > 45)[7]; there were 2 patients with PDAI activity score < 15 (major protocol deviation)

Patient Disposition

- 67 patients and 68 patients were randomized to rituximab and MMF, respectively. 66 patients (98.5%) in the rituximab arm and 58 (85.3%) in the MMF arm completed Week 52 (**Figure 2**)

Figure 2. Patient Disposition



Five patients treated via telemedicine were enrolled in each arm.
*Adverse Events leading to withdrawal: lumbar vertebral fracture (*1 rituximab patient*); pneumonia, influenza, and pulmonary embolism (*1 MMF patient*), urinary retention (*1 MMF patient*), small cell lung cancer (*1 MMF patient*).
ITT, intent-to-treat; MMF, mycophenolate mofetil.

Demographics and Baseline Characteristics

Table 1. Demographics and Baseline Characteristics

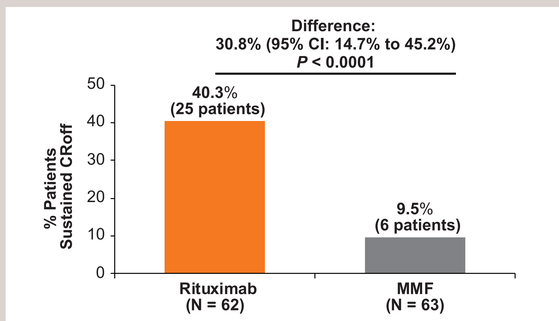
mITT population	Rituximab (N = 62)	MMF (N = 63)
Gender, n (%)		
Male	31 (50.0)	28 (44.4)
Female	31 (50.0)	35 (55.6)
Age, years		
Mean (SD)	50.2 (13.2)	46.9 (12.8)
Median (range)	50.0 (27-75)	46.0 (23-71)
Disease status*, n (%)		
Newly diagnosed	48 (77.4)	44 (69.8)
Established	14 (22.6)	19 (30.2)
PDAI activity score (0-25)†		
Screening		
Mean (SD)	31.7 (14.0)	30.3 (15.8)
Baseline		
Mean (SD)	24.9 (14.4)	23.4 (18.4)
DLQI (0-30)		
Mean (SD)	10.4 (8.1)	11.2 (8.9)

*Newly diagnosed = diagnosis of PV of < 6 months or no prior treatments for PV; established disease = PV for ≥ 6 months and received prior therapies for PV before study entry.
†During the screening period (up to 28 days), the daily corticosteroid dose was tapered, as directed by the investigator on the basis of disease activity and tolerability to reach a dosage of 60 or 80 mg/day by Day 1. Therefore, PDAI at screening/study entry may differ from PDAI at Baseline/Day 1.
DLQI, Dermatology Life Quality Index; mITT, modified intent-to-treat; MMF, mycophenolate mofetil; PDAI, Pemphigus Disease Area Index.

Primary Efficacy Endpoint at Week 52

- Rituximab was superior to MMF, in combination with a tapering course of oral prednisone (or equivalent):
  - At Week 52, a significantly higher proportion of patients in the rituximab arm achieved sustained CRoff prednisone ≥ 16 weeks than in the MMF arm (**Figure 3**)

Figure 3. Proportion of Patients Achieving Sustained CRoff Prednisone ≥ 16 Weeks at Week 52



CR, complete remission; MMF, mycophenolate mofetil.

Secondary Efficacy Endpoints

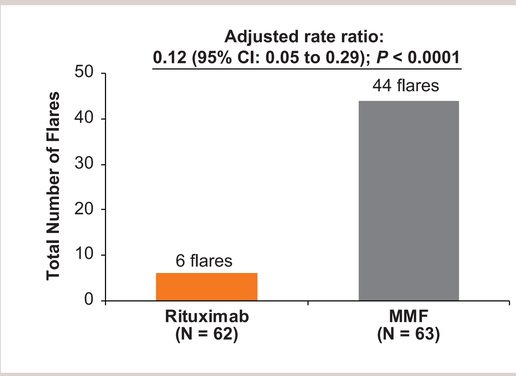
Corticosteroid Exposure

- Patients in the rituximab arm had a significantly lower cumulative oral CS dose (prednisone or prednisone equivalent) over the 52-week treatment than in the MMF arm
  - The median (min, max) cumulative dose was 2775 mg (450, 22180) in the rituximab arm compared to 4005 mg (900, 19920) in the MMF arm ($P = 0.0005$)

Disease Flare

- Total number of disease flares: significantly fewer number of flares occurred in patients treated with rituximab compared to MMF (6 vs. 44, $P < 0.0001$) (**Figure 4**)
- Number of patients with disease flare: fewer rituximab-treated patients experienced ≥ 1 disease flare, 5 rituximab patients (8.1%) vs. 26 MMF patients (41.3%)

Figure 4. Total Number of Disease Flares



Disease flare was defined as appearance of ≥ 3 new lesions a month that do not heal spontaneously within 1 week or by the extension of established lesions in a patient who has achieved disease control.
MMF, mycophenolate mofetil.

Time to Sustained CRoff ≥ 16 Weeks

- As less than 50% of patients had a sustained CRoff ≥ 16 weeks in both treatment arms, the median time to sustained CR was not estimable in either arm
- The likelihood of achieving sustained CR on rituximab was ~5 times greater than on MMF (hazard ratio [HR] = 4.83 [95% CI, 1.97 to 11.81], $P = 0.0003$)

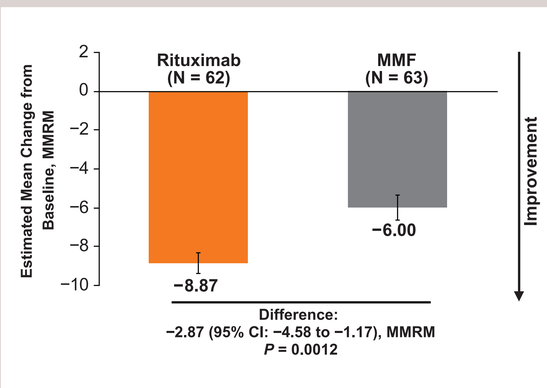
Time to First Flare

- As less than 50% of patients had a disease flare in both treatment arms, the median time to disease flare was not estimable in either arm
- The likelihood of experiencing flare was significantly lower in the rituximab group than in the MMF group, i.e. the likelihood of a flare on rituximab was ~7 times lower than on MMF (HR = 0.15 [95% CI, 0.06 to 0.39], $P < 0.0001$)

Dermatology Life Quality Index

- Significantly greater improvements in health-related quality of life from baseline at Week 52 (as measured by the DLQI) were observed in patients treated with rituximab compared to MMF (**Figure 5**)
- In a post-hoc analysis, 61.7% of patients in the rituximab arm had achieved a DLQI score of 0 (no impairment in health-related quality of life) at Week 52 compared to 25.0% of patients in the MMF arm

Figure 5. Change in DLQI Score From Baseline at Week 52



DLQI, Dermatology Life Quality Index; MMF, mycophenolate mofetil; MMRM, adjusted mixed models repeated measures.

Safety

Table 2. Adverse Events

	Rituximab (N = 62)	MMF (N = 63)
Patients with ≥ 1 AE, n (%)	57 (85.1)	60 (88.2)
Total number of AEs	352	301
Patients with ≥ 1 SAE, n (%)	15 (22.4)	10 (14.7)
Patients with ≥ 1 SAE related to the study drug*, n (%)	6 (9.0)	5 (7.4)
Patients withdrawn from study due to AE, n (%)	1 (1.5)	3 (4.4)
Death, n (%)	0	1 (1.5)†
Patients with IRR, n (%)	15 (22.4)‡	6 (8.8)¶
Patients with serious IRR, n (%)	3 (4.5)	1 (1.5)
Patients with infection, n (%)	42 (62.7)	37 (54.4)
Patients with serious infection, n (%)	6 (9.0)	4 (5.9)
Total number of serious infections	8	6
Patients with serious infection related to study drug*, n (%)	2 (3.0)	2 (2.9)
Total number of serious infections related to study drug	3	3
Opportunistic infection**, n (%)	0	0
Patients with Grade 3 or higher CS-related AEs*, n (%)	1 (1.5)	5 (7.4)
Total number of Grade 3 or higher CS-related AEs	1	6

*Related as assessed by the investigator.
†One patient in the MMF arm was diagnosed on Day 107 and died on Day 115 from small cell lung cancer related to the patient's 50-year smoking history and unrelated to MMF.
‡The most common IRR symptoms/Preferred Terms in the rituximab arm were dyspnoea (7.5%), erythema, hyperhidrosis, flushing/hot flush, hypotension and rash/rash pruritic (3.0% each).
¶IRRs reported from placebo infusion.
**Pneumocystis jirovecii pneumonia prophylaxis was performed according to local clinical practice guidelines and investigator judgment.
AE, adverse event; CS, corticosteroid; IRR, infusion-related reaction; MMF, mycophenolate mofetil; SAE, serious adverse event.

Adverse Events and Serious Adverse Events

- The most common AEs in ≥ 10% of rituximab-treated patients were IRR (15 patients, 22.4%), headache (10 patients, 14.9%), lymphopenia (8 patients, 11.9%) and upper respiratory tract infection (7 patients, 10.4%)
  - The most common AEs in ≥ 10% of MMF-treated patients were diarrhea (10 patients, 14.7%) and nasopharyngitis (8 patients, 11.8%)
- SAEs related to rituximab were IRR (*3 patients*), pneumonia and upper respiratory tract infection (*1 patient*), bursitis infective (*1 patient*) and abdominal pain (*1 patient*)
  - SAEs related to MMF were, in 1 patient each, pneumonia and influenza (*same patient*), herpes zoster, urinary retention, chronic obstructive pulmonary disease and skin ulcer

Infusion-Related Reactions

- IRRs in the rituximab arm occurred primarily at the 1st infusion and frequency decreased with subsequent infusions
  - 17.9% (1st infusion), 4.5% (2nd infusion), 3% (3rd infusion) and 3% (4th infusion)
- IRRs were Grade 1 or 2 in 11 of 15 patients
- 3 rituximab patients experienced serious (life-threatening) IRRs that led to discontinuation of infusions and withdrawal from treatment
  - 2 patients (1st infusion), 1 patient (2nd infusion)
  - All serious IRRs resolved with symptomatic treatment
- IRRs in PV patients were consistent with those seen in patients in other autoimmune indications, both in clinical trials and in the post-marketing setting

Infections

- All serious infections resolved and in the rituximab arm, none led to treatment withdrawal

Corticosteroid-Related Adverse Events

- More patients experienced Grade 3 or higher CS-related AEs in the MMF arm compared to the rituximab arm

CONCLUSIONS

- In patients with moderate to severe PV, the efficacy of rituximab was superior to MMF
  - The primary efficacy endpoint, sustained CRoff prednisone ≥ 16 weeks, was statistically significant in favor of rituximab
  - All ranked secondary efficacy endpoints were statistically significant in favor of rituximab
- The safety profile of rituximab was manageable with an acceptable tolerability, consistent with the known rituximab safety profile in the approved autoimmune indications
- Rituximab has a superior overall benefit-risk profile compared to MMF in patients with moderate to severe PV

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AUTHOR DISCLOSURES

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