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The PLUTO Study: Intravenous Belimumab in Children with Systemic Lupus Erythematosus

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Introduction

- Belimumab is a human monoclonal antibody that binds to and blocks the biological actions of BAFF, a B-cell activating factor[1]
- Belimumab is approved for the treatment of adults with active systemic lupus erythematosus (SLE), as an add-on to standard of care (SoC).[2,3] In April 2019 the Food and Drug Administration also approved belimumab for use in paediatric patients with childhood-onset SLE (cSLE)[4]
- This study (PLUTO) is the first double-blind, placebo-controlled clinical trial specifically designed to evaluate belimumab for treatment of children and adolescents with active cSLE

Objective

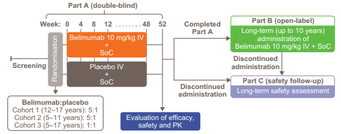
- To evaluate the efficacy, safety and pharmacokinetics (PK) of intravenous (IV) belimumab compared with placebo, plus SoC, in cSLE

Methods

Study design and participants

- PLUTO is a Phase 2, randomised, placebo-controlled trial (**Figure 1**)
  - Here we report results from the 52-week double-blind treatment period (PLUTO Part A; BEL114055; NCT01649765) of this ongoing trial

Figure 1. PLUTO study design



- Twenty nine centres, most belonging to the PRINTO/PRCSG networks, recruited patients in 10 countries from North, Central and South America, Europe and Japan, from September 2012 to January 2017
- Patients were randomised to receive belimumab 10 mg/kg intravenously (IV) or placebo every 4 weeks, plus SoC, for 48 weeks, with a final evaluation at Week 52 (**Figure 1**)
- Children 5–17 years of age with clinically active SLE disease according to American College of Rheumatology (ACR) criteria were included (**Table 1**)

Table 1. Key inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• 5–17 years of age • Diagnosis of SLE by ACR criteria • ANA positive and/or anti-dsDNA positive • Active SLE disease (SELENA-SLEDAI ≥6) • Receiving stable SLE therapy	• Active CNS lupus or severe nephritis • High-dose steroids (>1.5 mg/kg/day) or steroid injections during the 60 days before baseline

ANA, antinuclear antibodies; CNS, central nervous system; dsDNA, double-stranded deoxyribonucleic acid; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment Trial-Systemic Lupus Erythematosus Disease Activity Index

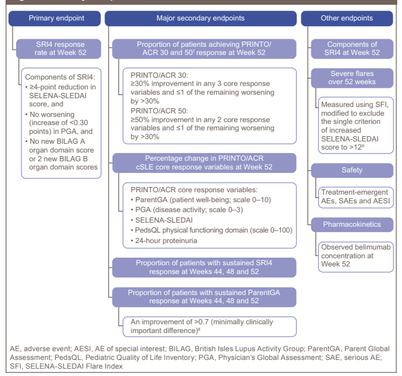
Endpoints

- The primary efficacy endpoint was the SLE Responder Index 4 (SRI4) response rate at Week 52[5,6] (**Figure 2**)
- Major secondary efficacy and other endpoints are listed in **Figure 2**

Statistics

- Analyses were conducted on the intent-to-treat population, comprising patients who were randomised and received at least one dose of study agent
- A logistic regression model was used to estimate the odds of achieving a response for belimumab versus placebo, with odds ratio (OR) and 95% confidence intervals (CI) calculated. The analysis was descriptive and no p-values were calculated

Figure 2. Study endpoints



AE, adverse event; AESI, AE of special interest; BILAG, British Isles Lupus Activity Group; ParentGA, Parent Global Assessment; PedsQL, Pediatric Quality of Life Inventory; PGA, Physician's Global Assessment; SAE, serious AE; SFI, SELENA-SLEDAI Flare Index

Results

Patient disposition and baseline characteristics

- A total of 93 patients were randomised (placebo, n=40; belimumab, n=53) (**Figure 3**)
- Baseline demographics and disease characteristics were similar between treatment groups (**Table 2**)

Efficacy

- There were more SRI4 responders among patients receiving belimumab compared with placebo (**Figure 4**)
  - In addition, response results for the three individual SRI4 components numerically favoured belimumab over placebo (**Figure 4**)
- A higher proportion of patients receiving belimumab achieved PRINTO/ACR 30 and 50 responses at Week 52 compared with placebo (**Figure 5**)
- SRI4 response was sustained in 23 (43.4%) belimumab and 16 (41.0%) placebo patients during Weeks 44–52 (OR 1.08 [95% CI 0.46, 2.52])
- Sustained (Weeks 44–52) improvement of the ParentGA was present in 26 (59.1%) belimumab and 12 (33.3%) placebo patients (OR 3.49 [95% CI 1.23, 9.91])
- The percent improvement in three of the five PRINTO/ACR cSLE core response variables was greater in the belimumab group versus placebo; there was no difference between groups in the PedsQL physical functioning domain and SELENA-SLEDAI (**Figure 6**)
- Severe flares were 62% less frequent with belimumab compared with placebo (**Figure 7**)

Pharmacokinetics

- At Week 52, the geometric mean (95% CI) belimumab trough concentration was 56.18 (45.20, 69.84) µg/mL
- Belimumab exposures for the overall paediatric population, and both age groups, were similar to adult exposures at the 10 mg/kg dose level in Phase 3 trials;[10] younger patients had slightly lower exposures than older patients, consistent with lower body mass index

Safety

- Although the overall incidence of adverse events was similar in both study groups, fewer patients in the belimumab group experienced a serious adverse event compared with placebo (**Table 3**)

Results (continued)

Figure 3. Patient disposition

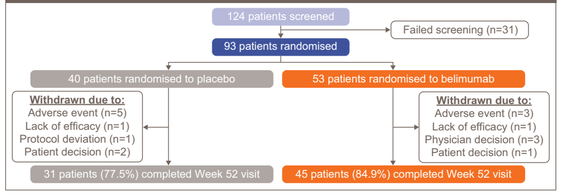


Table 2. Baseline demographics and disease characteristics

	Placebo (n=40)	Belimumab 10 mg/kg IV (n=53)
Age, years, median (IQR)	15.0 (14.00, 16.00)	14.0 (12.00, 15.00)
Age 5–11 years, n (%)	3 (7.5)	10 (18.9)
Age 12–17 years, n (%)	37 (92.5)	43 (81.1)
Female, n (%)	39 (97.5)	49 (92.5)
Disease duration, years, median (IQR)	1.97 (1.30, 3.57)	1.48 (0.79, 2.46)
SELENA-SLEDAI, median (IQR)	10.0 (8.00, 12.00)	10.0 (8.00, 12.00)
BILAG 1A or 2B domain score, n (%)	29 (72.5)	37 (69.8)
PGA (scale 0–3), median (IQR)	1.3 (1.07, 1.73)	1.4 (1.05, 1.50)
ParentGA (scale 0–10), median (IQR)	5.0 (3.00, 6.50)	4.5 (2.50, 6.50)
Proteinuria*, mg/mg, median (IQR)	0.12 (0.07, 0.29)	0.13 (0.08, 0.21)
PedsQL physical functioning domain (scale 0–100), median (IQR)	64.1 (45.31, 79.69)	59.4 (43.75, 78.13)
Medication, n (%)		
Any systemic corticosteroid	38 (95.0)	50 (94.3)
Corticosteroid dose, mg/day, median (IQR)	10.00 (7.50, 16.25)	7.50 (5.00, 10.00)
Any immunosuppressant	27 (67.5)	33 (62.3)
Anti-malarial	31 (77.5)	44 (83.0)
NSAID	12 (30.0)	11 (20.8)

*Urinary protein/creatinine ratio
IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug

Figure 4. SRI4 response (primary endpoint) and components of SRI4 at Week 52

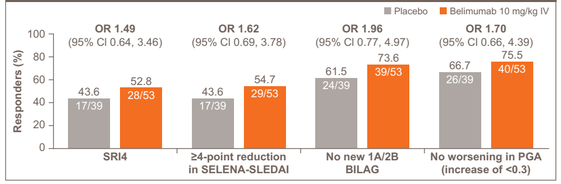


Figure 5. PRINTO/ACR responders at Week 52

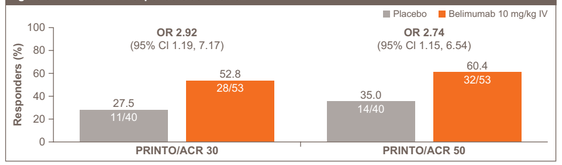


Figure 6. Percentage improvement from baseline in PRINTO/ACR cSLE core response variables at Week 52

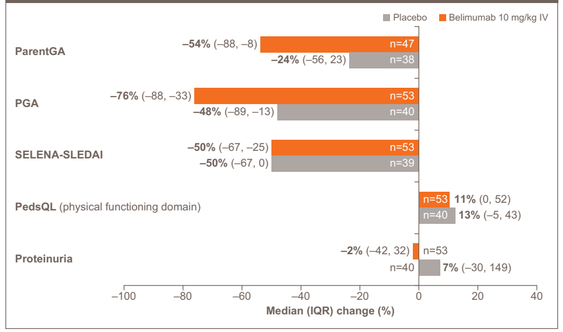


Figure 7. Severe flares over 52 weeks (modified SFI)

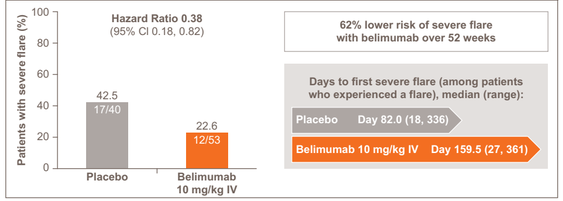


Table 3. Summary of adverse events

n (%)	Placebo (n=40)	Belimumab 10 mg/kg IV (n=53)
AEs by system organ class, any*	**33 (82.5)**	**42 (79.2)**
Infections and infestations	28 (70.0)	30 (56.6)
Gastrointestinal disorders	16 (40.0)	18 (34.0)
Musculoskeletal and connective tissue disorders	13 (32.5)	11 (20.8)
Nervous system disorders	11 (27.5)	12 (22.6)
Skin and subcutaneous tissue disorders	9 (22.5)	10 (18.9)
General disorders and administration site conditions	9 (22.5)	9 (17.0)
SAEs by system organ class and preferred term, any†	**14 (35.0)**	**9 (17.0)**
Infections and infestations	5 (12.5)	4 (7.5)
Renal and urinary disorders	3 (7.5)	2 (3.8)
Psychiatric disorders‡	3 (7.5)	0
Deaths§	**1 (2.5)**	**0**
AEs of special interest		
All post-infusion systemic reactions	3 (7.5)	4 (7.5)
All infections of special interest	3 (7.5)	7 (13.2)
Depression/suicide/self-injury	4 (10)	1 (1.9)

*AEs by system organ class that occurred in >20% of patients in either treatment group are listed; †SAEs by system organ class that occurred in >5% of patients in either treatment group are listed; ‡Includes major depression, suicidal ideation and suicide attempt; §acute pancreatitis

Conclusions

- At Week 52, compared with placebo, numerically higher proportions of patients receiving belimumab were SRI4 and PRINTO/ACR responders
- Patients in the belimumab group had a lower risk of experiencing a severe flare compared with placebo
- Belimumab was well tolerated and no new safety concerns were identified
- The benefit:risk profile of IV belimumab plus SoC in paediatric patients with cSLE appears favourable and consistent with that of the adult population,[11–13] confirming that the 10 mg/kg IV dose used in adults is appropriate for children

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Disclosures

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