Efficacy and Safety of Emapalumab in Patients with Macrophage Activation Syndrome (MAS) in Systemic Lupus Erythematosus (SLE)

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CONCLUSIONS

- Emapalumab rapidly controlled MAS in SLE in 75% of patients with an initial inadequate response to high-dose glucocorticoid (GC) treatment
- No patients had MAS recurrence or died during the study
- The efficacy and safety profile of emapalumab in patients with MAS in SLE was similar to patients with MAS in Still's disease[1,2]
- Median GC dosing was reduced from 5.66 mg/kg/day at baseline to 0.80 mg/kg/day at Week 8
- Median time to any GC tapering (50% reduction from baseline or reduction to dose prior to MAS episode) was 7 days
- These data further support the role of interferon-gamma (IFNγ) as a pivotal cytokine in patients with MAS in SLE

INTRODUCTION

- MAS is a life-threatening complication of rheumatic diseases, including SLE, and is characterized by macrophage activation and systemic hyperinflammation[3]
- There is substantial preclinical evidence of IFNγ having a role in MAS in SLE, but clinical data confirming these observations is limited[3]
- Emapalumab, an anti-IFNγ antibody, binds free and receptor-bound IFNγ, providing rapid and targeted neutralization of IFNγ[4]
- Emapalumab has previously demonstrated sustained control of MAS in patients with Still's disease[1,2]
- Case studies have suggested that emapalumab may be efficacious in patients with MAS in SLE, including improvement or normalization of clinical manifestations and laboratory parameters[5,6]

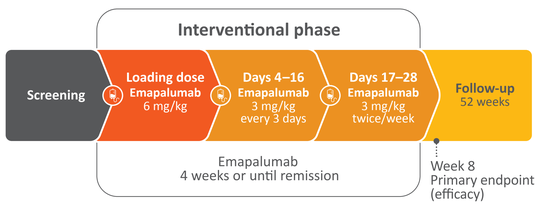
OBJECTIVE

- To investigate the efficacy and safety of emapalumab in the treatment of adults and children with MAS in SLE

METHODS

- An open-label, single-arm interventional study (NI-0501-14 [EMERALD; NCT05001737]) in patients with MAS in rheumatic diseases who had an inadequate response to high-dose intravenous (IV) GCs (**Figure 1**)
- Two cohorts were enrolled: MAS in Still's disease (Cohort 1) and MAS in SLE (Cohort 2)
  - Data from Cohort 2 alone is presented here

Figure 1: Study design[a]



[a]Emapalumab dose could be increased, or dosing interval could be shortened, at the investigator's discretion.

Inclusion criteria

- A confirmed diagnosis of SLE as per Systemic Lupus according to the International Collaborating Clinics (SLICC) 2012 criteria
- A diagnosis of active MAS where the patient was febrile, had a serum ferritin level >684 ng/mL, and any two of:
  - Platelet count ≤181 × 10^9/L
  - Aspartate aminotransferase (AST) levels >48 U/L
  - Triglycerides >156 mg/dL
  - Fibrinogen levels ≤360 mg/dL
- An inadequate response to high-dose IV GC treatment administered for at least 3 days as per local standard of care, including, but not limited to, pulses of 30 mg/kg methylprednisolone on 3 consecutive days
  - In cases of rapid worsening of the patient's condition and/or laboratory parameters, inclusion could occur <3 days after starting high-dose IV GCs

Exclusion criteria

- A diagnosis of primary hemophagocytic lymphohistiocytosis (HLH) or secondary HLH consequent to a neoplastic disease
- Patients treated with canakinumab, Janus kinase inhibitors, tumor necrosis factor α inhibitors, tocilizumab, or anakinra >4 mg/kg/day at the time of emapalumab initiation
- Treatment with etoposide for MAS within 1 month of study enrollment

Endpoints

- The primary endpoint was a complete response (CR) at Week 8 (Study Day 56 ± 5 days) according to an 8-component composite endpoint comprising the absence of MAS clinical signs and symptoms (visual analog scale [VAS] ≤1/10 cm) plus:
  - White blood cell and platelet counts above the lower limit of normal;
  - Lactate dehydrogenase, AST and alanine aminotransferase <1.5× the upper limit of normal;
  - Fibrinogen >100 mg/dL; and
  - Ferritin decreased by at least 80% from baseline (and <2000 ng/mL)
- Overall response was defined as CR or a partial response (VAS <4 cm and normalization of ≥3 MAS-related laboratory parameters)
- Other endpoints included GC tapering, survival, biomarkers (chemokine C-X-C motif ligand 9 [CXCL9], a specific biomarker primarily induced by IFNγ activity, and soluble CD25 [sCD25], a marker of T-cell activation) and safety
  - The lower limit of quantitation (LLOQ) for CXCL9 was 80 ng/L

Statistics

- No hypothesis test was performed because this cohort was not fully enrolled (n=8) because of difficulties in recruitment
- Time-to-event analyses were performed using the Kaplan–Meier method

RESULTS

Baseline characteristics

- Eight patients with an inadequate response to high-dose GCs were enrolled (5 [62.5%] females), with a median age of 16 years (range, 2–24) (**Table 1**)
- All patients had lung and/or hepatic involvement
- All patients received concomitant GCs and 1 patient received concomitant anakinra; no other treatments for SLE were co-administered

Table 1: Demographics and baseline characteristics

	N=8
Age, years, median (range)	16 (2–24)
Age ≥17 years, n (%)	4 (50)
Sex, female, n (%)	5 (62.5)
Lung and/or hepatic involvement, n (%)	8 (100)
Receiving dialysis or hemofiltration, n (%)	1 (12.5)
MAS clinical signs and symptoms (VAS), cm, median (range)	7.75 (3–9)

MAS, macrophage activation syndrome; VAS, visual analog score.

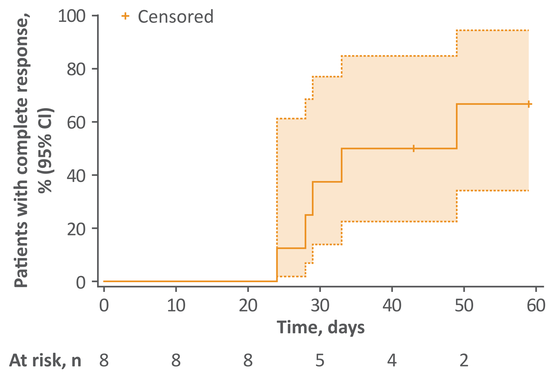
Treatment duration

- Median duration of emapalumab treatment was 16 days (range, 7–44)
- Seven (87.5%) patients completed the study

Response rates

- At Week 8, four (50%) patients had achieved a CR with a median time to first CR of 41 days (**Figure 2**)
- Seven (87.5%) patients achieved a CR at any time up to Day 56 (±3 days)
- Six (75%) patients achieved an overall response at Week 8 with a median time to first overall response of 26 days
- No recurrent MAS events were reported during 1 year of follow-up

Figure 2: Time to CR in patients with MAS in SLE administered emapalumab

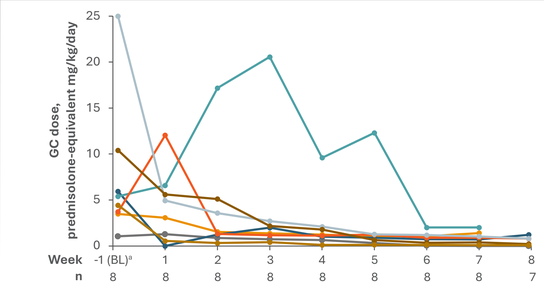


Patients censored at Study Day 59.
CI, confidence interval; CR, complete response; MAS, macrophage activation syndrome; SLE, systemic lupus erythematosus.

GC tapering

- Median GC dose reduced from 5.66 mg/kg/day at baseline to 0.80 mg/kg/day at Week 8 (**Figure 3**)
- Median time to any GC tapering (50% reduction from baseline or reduction to dose prior to MAS episode) was 7 days
- Median time to weekly average daily GC dose of ≤1 mg prednisolone-equivalent/kg/day was 38.5 days

Figure 3: GC dosing in individual patients with MAS in SLE administered emapalumab (N=8)



[a]Study Days -7 to -1 (week prior to first dose of emapalumab).
BL, baseline; GC, glucocorticoid; MAS, macrophage activation syndrome; SLE, systemic lupus erythematosus.

Biomarkers

- Median (range) CXCL9 levels were reduced from 623 ng/L (below LLOQ–9405; n=6) to 191 (40–471; n=5) at Day 4, 71 (40–104; n=4) at Day 7, and below LLOQ (range, below LLOQ–383; n=5) at Day 56
- Median sCD25 levels were reduced from 4954 ng/L (range, 2187–7907; n=6) to 2257 ng/L (range, 1294–3430; n=5) at Day 56

Safety

- No new safety concerns were identified
- Four serious adverse events were reported in 4 patients (**Table 3**)
- Infection adverse events (n=15) were reported by 7 patients (87.5%)
- One patient discontinued because of an adverse event (progressive decrease in prothrombin activity)
- No infusion-related reactions occurred
- No deaths occurred

Table 3: GC dosing in patients with MAS in SLE administered emapalumab

n (%)	N=8
TEAEs	8 (100)
TEAEs related to emapalumab	3 (37.5)
Serious TEAEs	4 (50.0)[a]
TEAEs leading to emapalumab withdrawal	1 (12.5)[b]
Infection TEAEs	7 (87.5)[c,d]

[a]Abscess limb, condition aggravated, prothrombin level decreased, and lupus nephritis (n=1 each).
[b]Progressive decrease in prothrombin activity. [c]URTI (n=3 events), cytomegalovirus infection (n=2 events), sinusitis (n=2 events), abscess limb (n=1 event), COVID-19 (n=1 event), cystitis (n=1 event), rotavirus infection (n=1 event), UTI (n=1 event), viral pharyngitis (n=1 event). [d]One EBV and one CMV infection event were considered unrelated to emapalumab; one CMV–EBV co-infection event as considered related to emapalumab.
All three patients were receiving antiviral prophylaxis during treatment.
EBV, Epstein-Barr virus; CMV, cytomegalovirus; MAS, macrophage activation syndrome; SLE, systemic lupus erythematosus; URTI, upper respiratory tract infection; UTI, urinary tract infection; TEAE, treatment-emergent adverse event.

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