Emapalumab Treatment for Patients with Differing Presentations of Macrophage Activation Syndrome (MAS) Secondary to Still's Disease: Results from a Pooled Analysis of Two Prospective Trials

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CONCLUSIONS

- Emapalumab treatment was associated with consistent complete response rates of approximately 55–60% among patients with differing MAS presentations, who had an inadequate response to high-dose glucocorticoids (GCs), including patients with chronic relapsing disease
- Overall (complete + partial) response at Week 8 was high (72.7–100%) across all MAS subgroups
- The proportion of patients achieving a MAS clinical activity score visual analog scale (VAS) ≤1/10 cm was similar across MAS subgroups
- Baseline GC dosing was higher in patients with classic MAS or MAS diagnosis at onset compared with chronic relapsing MAS, but GCs were tapered from baseline to Week 8 across all MAS subgroups
- Emapalumab induced rapid and robust pharmacodynamic marker improvements across all MAS subtypes

INTRODUCTION

- MAS is a life-threatening complication of Still's disease, and is characterized by interferon gamma (IFNγ)-driven macrophage activation and systemic hyperinflammation[1–4]
- Emapalumab, an anti-IFNγ antibody, binds free and receptor-bound IFNγ, providing rapid and targeted neutralization of IFNγ[2]
- Emapalumab has demonstrated safety and efficacy in patients with MAS in Still's disease with an inadequate response to high-dose GCs in two clinical trials (NCT03311854 and NCT05001737)[5–7]
- Patients with Still's disease may present with MAS at any disease stage, including at the time of initial diagnosis of Still's disease[8–10]
- Some patients may have chronic relapsing MAS, which can be difficult to treat[11,12]

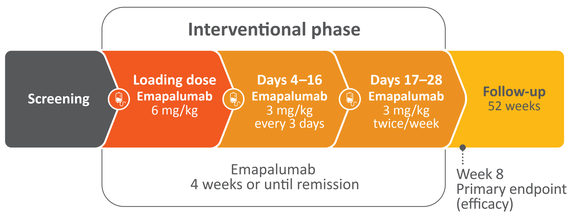
OBJECTIVE

- To compare outcomes for patients with MAS in Still's disease treated with emapalumab according to MAS presentation

METHODS

- Data were pooled from two prospective, open-label, single-arm interventional studies in patients with MAS in Still's disease who had an inadequate response to high-dose GCs with similar study designs (NCT03311854 [NI-0501-06] and NCT05001737 [NI-0501-14]; **Figure 1**)

Figure 1: Study design[a]



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

METHODS

Inclusion 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; and fibrinogen levels ≤360 mg/dL
- An inadequate response to high-dose intravenous (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 HLH consequent to a neoplastic disease
- Patients treated with canakinumab, Janus kinase inhibitors, tumor necrosis factor α inhibitors, tocilizumab, etoposide (for MAS) or anakinra >4 mg/kg/day at the time of emapalumab initiation

Endpoints

- The primary endpoint of the pooled analysis was a complete response at Week 8 according to an 8-component composite endpoint comprising the MAS clinical activity score (VAS ≤1/10 cm; absence of MAS clinical signs and symptoms) 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
  - Partial response was defined as VAS <4 cm and normalization of ≥3 of the abnormal baseline laboratory parameters

BASELINE CHARACTERISTICS

- 39 patients were enrolled (31 [79.5%] females), with a median age of 12 years (range, 9 months–64 years; **Table 1**)
- Five patients had classic MAS, defined as MAS occurring during the course of Still's disease, and 20 patients had MAS at Still's disease onset
- Chronic relapsing MAS was present in 14 patients
- 26 patients (66.7%) received concomitant anakinra during the study period, which may still need to be administered concomitantly with emapalumab to maintain control of the underlying Still's disease

Table 1: Demographics and baseline characteristics

	N=39
Age at diagnosis, years, median (range)	9 (9 months–64)
Age, years, median (range)	12 (9 months–64)
Sex, female, n (%)	31 (79.5)
Geographic region, n (%)	
North America	6 (15.4)
Europe/UK	30 (76.9)
Japan	2 (5.1)
China	1 (2.6)
Weight, kg, median (range)	45.0 (9.5–80.0)
MAS clinical activity score (VAS), cm, median (range)	6.5 (2.0–10.0)
Previous MAS episode, n (%)	14 (35.9)

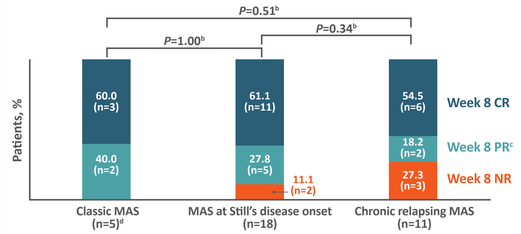
MAS, macrophage activation syndrome; VAS, visual analog scale.

RESULTS

Response rates

- Complete response rates at Week 8 (54.5–61.1%) were similar across MAS subgroups (**Figure 2**)
- Overall (complete + partial) response at Week 8 was high (72.7–100%) across all MAS subgroups (**Figure 2**)

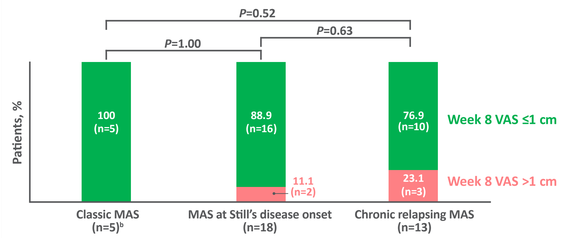
Figure 2: Response rates by MAS subgroup[a]



[a]Patients with a response assessment at Week 8. [b]Pairwise comparison of response (CR+PR) using Fisher's exact test. [c]VAS <4 cm and normalization of ≥3 abnormal baseline laboratory parameters included in the composite primary endpoint. [d]MAS occurring during the course of Still's disease.
CR, complete response; MAS, macrophage activation syndrome; NR, no response; PR, partial response; VAS, visual analog scale.

- MAS clinical activity score VAS ≤1 cm rates at Week 8 were similar across MAS subgroups (**Figures 3 and 4**)

Figure 3: MAS clinical activity score by MAS subgroup[a]



[a]Patients with a VAS assessment at Week 8; [b]MAS occurring during the course of Still's disease.
MAS, macrophage activation syndrome; VAS, visual analog scale.

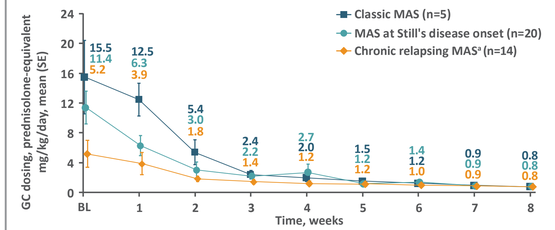
Figure 4: MAS clinical activity score over time in individual patients administered emapalumab

Empty cells = not assessed/data not available for this visit.
MAS, macrophage activation syndrome; SD, study day; VAS, visual analog scale.

Glucocorticoid tapering

- Baseline GC dosing was higher in patients with classic MAS or MAS at Still's disease onset compared with chronic relapsing MAS (**Figure 5**)
- Tapering of GC dosing from baseline to Week 8 were observed across all MAS subgroups (**Figure 5**)

Figure 5: Changes in GC dosing over time in patients with MAS in Still's disease administered emapalumab by MAS subgroup

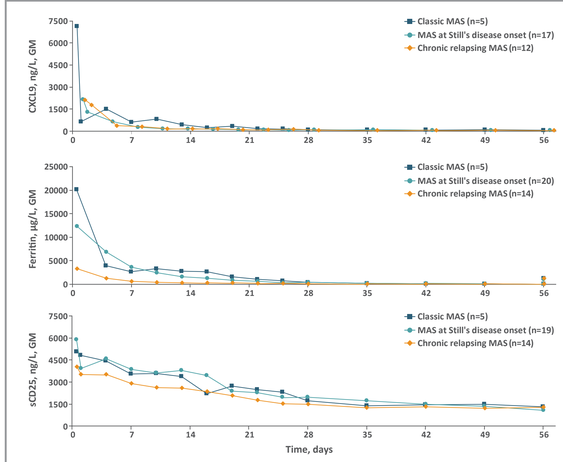


[a]One patient with chronic relapsing MAS could not be evaluated from Week 5 after their death.
BL, baseline; GC, glucocorticoid; MAS, macrophage activation syndrome; SE, standard error.

Pharmacodynamic markers

- Baseline levels of chemokine C-X-C motif ligand 9 (CXCL9; a specific biomarker primarily induced by IFNγ activity) and ferritin levels were highest in patients with classic MAS (**Figure 6**)
  - Patients with chronic relapsing MAS generally presented with lower CXCL9 and ferritin levels
- No differences in soluble CD25 levels (a marker of T-cell activation), were observed across MAS subtypes (**Figure 6**)
- Emapalumab induced rapid and robust pharmacodynamic marker improvements across all MAS subtypes (**Figure 6**)

Figure 6: Changes in pharmacodynamic markers in patients with MAS in Still's disease by MAS subgroup



CXCL9, chemokine C-X-C ligand 9; GM, geometric mean; MAS, macrophage activation syndrome; sCD25, soluble CD25.

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