Efficacy and Safety of Emapalumab for Treating Macrophage Activation Syndrome in Still's disease: A Pooled Analysis of Two Prospective Trials

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CONCLUSIONS

- Data from two pooled prospective studies in patients with macrophage activation syndrome (MAS) in Still's disease with an inadequate response to high-dose glucocorticoid (GC) treatment demonstrated:
  - The 8-component composite endpoint complete response (CR) rate was achieved by 53.8% of patients at Week 8
  - When excluding the lactate dehydrogenase (LDH) component from the CR definition, the CR rate was 69.2%
  - Emapalumab rapidly controlled signs and symptoms of MAS in >80% of patients with first MAS clinical activity score visual analog scale (VAS) ≤1 cm being observed as early as Day 6
  - GC dosing was reduced to ≤1 mg/kg/day in 72% of patients
  - Interferon-gamma (IFNγ) was neutralized by emapalumab in all patients, as assessed by chemokine C-X-C motif ligand 9 (CXCL9)
  - Adverse events (AE) were consistent with the established safety profile of emapalumab
- Emapalumab was the first and only treatment for MAS in Still's disease to be approved by the US Food and Drug Administration in June 2025

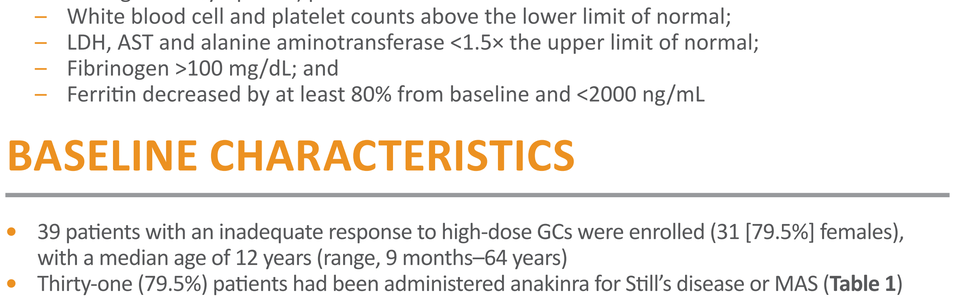
INTRODUCTION

- MAS is a potentially life-threatening complication of Still's disease when left untreated, and is characterized by IFNγ-driven macrophage hyperactivation[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 a clinical trial (NCT03311854; NI-0501-06)[5]
- Data are presented here from an expanded population of patients with MAS in Still's disease treated with emapalumab

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 [EMERALD]; **Figure 1**)
- Enrollment in EMERALD was extended to patients with adult-onset Still's disease after encouraging preliminary results in the NI-0501-06 study[5]

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 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 were also excluded

Endpoints

- The primary endpoint of the pooled analysis was a CR at Week 8 according to an 8-component composite endpoint comprising the MAS clinical activity score VAS ≤1 cm (absence of MAS clinical signs and symptoms) plus:
  - White blood cell and platelet counts above the lower limit of normal;
  - LDH, 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

BASELINE CHARACTERISTICS

- 39 patients with an inadequate response to high-dose GCs were enrolled (31 [79.5%] females), with a median age of 12 years (range, 9 months–64 years)
- Thirty-one (79.5%) patients had been administered anakinra for Still's disease or MAS (**Table 1**)

Table 1: Demographics and baseline characteristics

	NI-0501-06 (N=14)	EMERALD (N=25)	Pooled (N=39)
Age at diagnosis, years, median (range)	6 (1–16)	10 (1–64)	9 (1–64)
Age, years, median (range)	11 (2–25)	13 (9 months–64)	12 (9 months–64)
Sex, female, n (%)	10 (71.4)	21 (84.0)	31 (79.5)
Geographic region, n (%)			
North America	3 (21.4)	3 (12.0)	6 (15.4)
Europe/UK	11 (78.6)	19 (76.0)	30 (76.9)
Japan	0	2 (8.0)	2 (5.1)
China	0	1 (4.0)	1 (2.6)
Weight, kg, median (range)	45.5 (12.0–68.8)	45.0 (9.5–80.0)	45.0 (9.5–80.0)
Prior medications to control Still's disease or MAS, n (%)			
GCs	14 (100)	25 (100)	39 (100)
Anakinra	10 (71.4)	21 (84.0)	31 (79.5)
IVIg	4 (28.6)	0	4 (10.3)
Calcineurin inhibitors	9 (64.3)	15 (60.0)	24 (61.5)

GC, glucocorticoid; IVIg, intravenous immunoglobulin; MAS, macrophage activation syndrome.

RESULTS

Efficacy

- 21 (53.8%) patients achieved the 8-component CR definition at Week 8 (**Table 2**)
  - First CR was observed on Day 10; Kaplan–Meier estimate of median time to first CR was 7.1 weeks (**Figure 2**)
- In a post-hoc sensitivity analysis that excluded LDH from the primary endpoint, 27 (69.2%) patients achieved the CR at Week 8 (**Table 2**)
  - All 6 patients who achieved a CR after excluding LDH from the composite endpoint had an underlying cause of elevated LDH that was deemed unrelated to MAS
- 29/38 (76.3%) patients achieved an overall response (**Table 2**)
  - First overall response was observed on Day 4; median time to first overall response was 2.3 weeks (**Figure 2**)
- 32 (82.1%) patients achieved investigator-assessed MAS clinical activity score VAS ≤1 cm at any time up to Week 8 (**Table 2**)
  - In a time-to-event (Kaplan–Meier) analysis 86.4% achieved an event up to Week 8
  - First MAS clinical activity score VAS ≤1 cm was observed on Day 6; median time to first MAS clinical activity score ≤1 cm was 3.3 weeks (**Figure 2**)

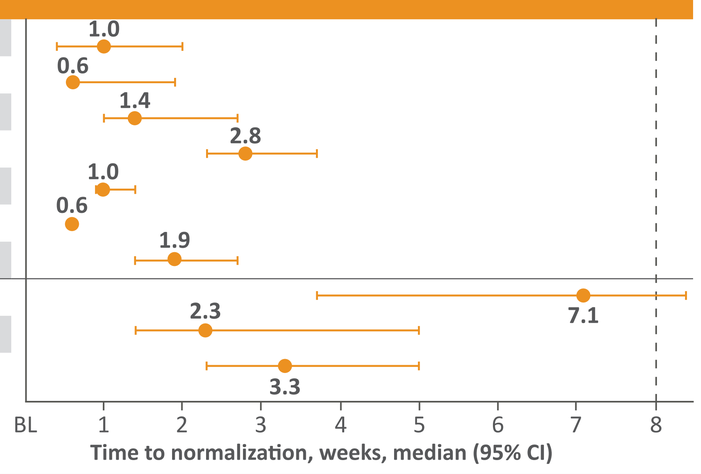
Table 2: Primary and secondary efficacy endpoint outcomes

At Week 8 % (95% CI)[a]	Definition	NI-0501-06 (N=14)	EMERALD (N=25)	Pooled (N=39)
CR (primary)[b]	Composite endpoint with 8 components	71.4 (41.9–91.6)	44.0 (24.4–65.1)	53.8 (37.2–69.9)
CR (post-hoc sensitivity analysis)[b]	Composite endpoint with 7 components (LDH excluded)	85.7 (57.2–98.2)	60.0 (38.7–78.9)	69.2 (52.4–83.0)
Overall response[c]	CR + PR (VAS <4 cm AND normalization of ≥3 of the abnormal baseline laboratory parameters)	92.9 (66.1–99.8)	66.7 (44.7–84.4)[d]	76.3 (59.8–88.6)[e]
MAS clinical activity score	VAS ≤1 cm	100[f]	76.0[g]	82.1[f]

[a]Two-sided 95% Clopper-Pearson CI. [b]Day 56 ± 5 days. [c]Day 56 ± 3 days. [d]n=24. [e]n=38. [f]Day 57. [g]Day 58.
CI, confidence interval; CR, complete response; LDH, lactate dehydrogenase; NE, not evaluable; PR, partial response; VAS, visual analog scale.

Figure 2: Time to normalization of laboratory parameters and MAS signs and symptoms

	Abnormal at baseline, n	Normalized at Week 8, n
White blood cell count	10	9
Platelet count	20	17
LDH	37	24
ALT	32	28
AST	26	24
Fibrinogen	7	6
Ferritin	39	33
Complete response	39	21
Overall response	39	29
MAS clinical activity score VAS ≤1/10 cm	39	33



ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; CI, confidence interval; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; VAS, visual analog scale.

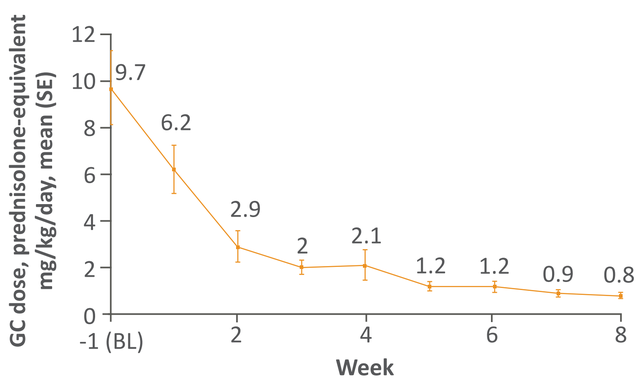
GC tapering

- Mean (standard deviation) GC dosing was tapered from 9.7 (9.5) mg/kg/day at baseline to 0.8 (0.6) mg/kg/day at Week 8 (**Figure 3**)
- At week 8, GCs had been tapered to ≤1 mg/kg/day in 28 (72%) patients and ≤0.5 mg/kg/day in 17 (44%) patients

Biomarkers

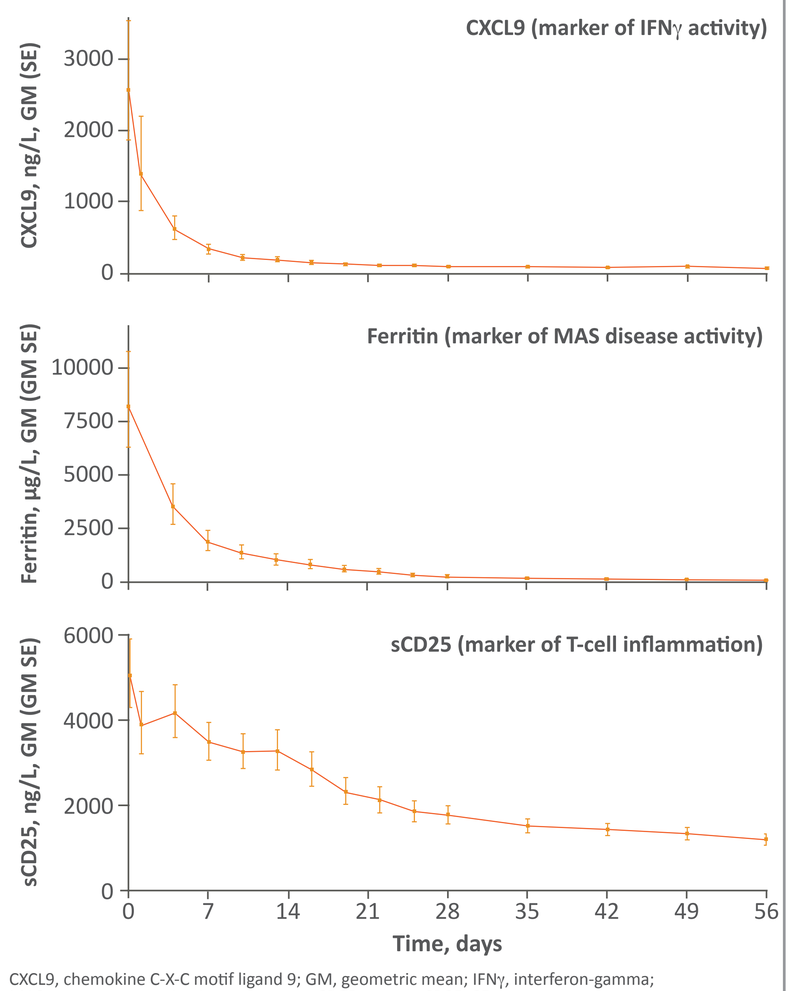
- Serum CXCL9 was used as a biomarker of IFNγ activity because:
  - Serum IFNγ levels do not reflect IFNγ activity
  - CXCL9 is primarily induced by IFNγ, stable, and easily measurable in blood[4,6,7]
- Baseline geometric mean (95% confidence interval) CXCL9, ferritin, and sCD25 levels were 2572 (1869–3539) ng/mL, 8248 (6299–10,800) µg/L and 5025 (4292–5883) ng/L, respectively (**Figure 4**)
- CXCL9, ferritin, and sCD25 levels rapidly reduced after initiating treatment with emapalumab (**Figure 4**)
  - At week 8, the respective values had reduced to 72 (62–84) ng/L (97% reduction from baseline), 74 (54–100) µg/L (99% reduction) and 1191 (1065–1332) ng/L (76% reduction)
- Clinical improvement generally paralleled IFNγ neutralization, i.e., reductions in serum CXCL9 levels

Figure 3: Changes in GC dosing over time



BL, baseline; GC, glucocorticoid; SE, standard error.

Figure 4: Pharmacodynamic effect of emapalumab



CXCL9, chemokine C-X-C motif ligand 9; GM, geometric mean; IFNγ, interferon-gamma; MAS, macrophage activation syndrome; sCD25, soluble CD25; SE, standard error.

Safety

- Adverse events were consistent with the established safety profile of emapalumab
- 4 patients reported 6 serious adverse drug reactions (**Table 3**)
  - Cytomegalovirus (CMV) infection, CMV infection reactivation, pneumonia, sepsis, multiple organ dysfunction, pulmonary arterial hypertension (n=1 each)
- Infection AEs were predominantly of viral origin and resolved spontaneously or with standard treatment (**Table 3**)
  - Infection AEs were reported in 71.4% (5/7) of patients without Herpes zoster viral prophylaxis compared with 53.1% (17/32) of patients who received Herpes zoster viral prophylaxis
- 8 patients experienced 14 infusion-related reactions (**Table 3**)
  - None were serious or led to discontinuation of emapalumab infusion
- Two deaths were reported in adult patients
  - Neither death was considered related to emapalumab

Table 3: Adverse events

n (%)	NI-0501-06 (N=14)	EMERALD (N=25)	Pooled (N=39)
Any TEAE	13 (92.9)	23 (92.0)	36 (92.3)
Related to emapalumab	4 (28.6)	12 (48.0)	16 (41.0)
Leading to emapalumab withdrawal	0	1 (4.0)	1 (2.6)
Leading to death	0	2 (8.0)	2 (5.1)
SAEs	6 (42.9)	7 (28.0)	13 (33.3)
Related to emapalumab	1 (7.1)	3 (12.0)	4 (10.3)
TEAEs leading to study withdrawal	0	1 (4.0)	1 (2.6)
IRRs	2 (14.3)	6 (24.0)	8 (20.5)
Infections	6 (42.9)	16 (64.0)	22 (56.4)

IRR, infusion-related reaction; SAE, serious adverse event; TEAE treatment-emergent adverse event.

References **1.** Fautrel B, et al. *Ann Rheum Dis* 2024;83:1614–1627; **2.** Jacqmin P, et al. *Br J Clin Pharmacol* 2022;88:2128–2139; **3.** Fajgenbaum DC, June CH. *N Engl J Med* 2020;383:2255–2273; **4.** De Benedetti F, et al. *Nat Rev Rheumatol* 2021;17:678–691; **5.** De Benedetti F, et al. *Ann Rheum Dis* 2023;82:857–865; **6.** Shakoory B, et al. *Arthritis Rheumatol* 2023;75:1714–1732; **7.** Kuo PT, et al. *Front Med (Lausanne)* 2018;5:257.

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