Efficacy and Safety of Emapalumab in Children and Adults with Macrophage Activation Syndrome (MAS) in Still's disease

Results from a Phase 3 Study and a Pooled Analysis of Two Prospective Trials

Alexei A. Grom,[1] Uwe Ullman,[2] Adnan Mahmood,[3] Josefin Blomkvist,[3] Brian D. Jamieson,[4] Fabrizio De Benedetti[5]

[1]Cincinnati Children's Hospital, Division of Rheumatology, Cincinnati, OH, USA; [2]Sobi, Basel, Switzerland; [3]Sobi, Stockholm, Sweden; [4]Sobi, Inc., Morrisville, NC, USA; [5]Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy

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Disclosures

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Background

- MAS is a life-threatening complication of Still's disease, and is characterized by 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 a clinical trial (NCT03311854)[5]
- Data are presented here from an expanded population of patients with MAS in Still's disease treated with emapalumab

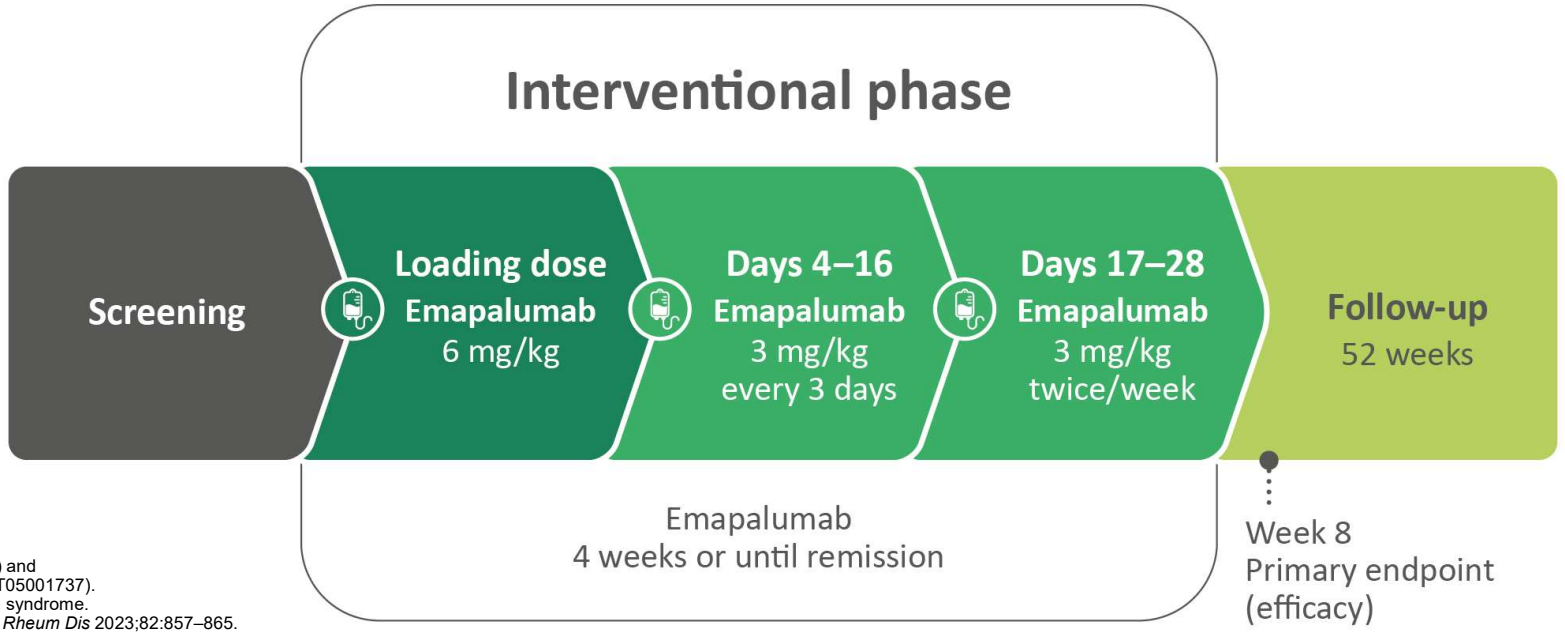
IFNγ, interferon gamma; MAS, macrophage activation syndrome.

1. Fautrel B, et al. *Ann Rheum Dis* 2024 [Epub ahead of print]. doi: 10.1136/ard-2024-225851; 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.

Study design

Data were pooled from two prospective, open-label, single-arm interventional studies[a] in patients with MAS in Still's disease who had an inadequate response to high-dose glucocorticoids

- Enrollment in EMERALD was extended to patients with adult-onset Still's disease after encouraging preliminary results in the NI-0501-06 (NCT03311854) study[1]



[a]NI-0501-06 (NCT03311854) and NI-0501-14 (EMERALD; NCT05001737).
MAS, macrophage activation syndrome.
1. De Benedetti F, et al. *Ann Rheum Dis* 2023;82:857–865.

Methods: Inclusion and exclusion criteria

Inclusion criteria

- High presumption or confirmed diagnosis of Still's disease
- A diagnosis of active MAS confirmed by the treating rheumatologist, having ascertained the following:
  - Febrile patient presenting with ferritin >684 ng/mL, **and**
  - Any two of: platelet count ≤181 × 10^9/L; AST levels >48 U/L; triglycerides >156 mg/dL; fibrinogen levels ≤360 mg/dL
- An inadequate response to high-dose IV glucocorticoid treatment administered for ≥3 days as per local standard of care[a]

Exclusion criteria

- Diagnosis of pHLH or HLH consequent to a neoplastic disease
- Patients treated with canakinumab, JAK inhibitors, TNFα inhibitors, tocilizumab, etoposide (for MAS) or anakinra >4 mg/kg/day at the time of emapalumab initiation

[a]Including, but not limited to, pulses of 30 mg/kg methylprednisolone on 3 consecutive days; in case of rapid worsening of the patient's condition and/or lab parameters, inclusion may occur within less than 3 days from starting high-dose IV glucocorticoids.
AST, aspartate aminotransferase; HLH, hemophagocytic lymphohistiocytosis; IV, intravenous; JAK, Janus kinase; MAS, macrophage activation syndrome; pHLH, primary hemophagocytic lymphohistiocytosis; TNFα, tumor necrosis factor alpha.
De Benedetti F, et al. *Ann Rheum Dis* 2023;82:857–865.

Methods: Composite endpoint with 8 component

- Absence of MAS clinical signs and symptoms (VAS <1 cm)

- WBC and platelet counts >LLN
- LDH, AST and ALT <1.5× ULN
- Fibrinogen >100 mg/dL
- Ferritin ≤80% from values at screening or baseline[a] or <2000 ng/mL[b]

All 8 components must be met for the patient to be classified as achieving a CR[a]

[a]Whichever is higher. [b]Whichever is lower.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CR, complete response; LDH, lactate dehydrogenase; LLN, lower limit of normal; MAS, macrophage activation syndrome; ULN, upper limit of normal; VAS, visual analog scale; WBC, white blood cell.

Pooled results: Demographics and baseline characteristics

	NI-0501-06 (N=14)	EMERALD (N=25)	Pooled (N=39)
Age, years, median (range)	11 (2–25)	13 (0.9–64)	12 (0.9–64)
Age at diagnosis, years, median (range)	6 (1–16)	10 (0.9–64)	9 (0.9–64)
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)
Biologic-experienced,[a,b] n (%)	9 (64.3)	21 (84.0)	30 (76.9)
Prior medications to control MAS, n (%)			
Glucocorticoids	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)

[a]Administered a biologic within a period equivalent to 5 half-lives of that biologic prior to first infusion of emapalumab; [b]>60% of patients received biologics to treat the underlying Still's disease.
IVIg, intravenous immunoglobulin.

Pooled primary endpoint: CR at Week 8[a]

At Week 8[a] % (95% CI)	Definition	NI-0501-06 (N=14)	EMERALD (N=25)	Pooled (N=39)
CR	• Composite endpoint with 8 components	**71.4 (41.9–91.6)**	**44.0 (24.4–65.1)**	**53.8 (37.2–69.9)**

21 (53.8%) patients achieved the full 8-component CR definition at Week 8[a]

[a]Day 56 ± 5 days.
CI, confidence interval; CR, complete response.

Pooled post-hoc sensitivity analysis: CR at Week 8

At Week 8 % (95% CI[a])	Definition	NI-0501-06 (N=14)	EMERALD (N=25)	Pooled (N=39)
CR	• Composite endpoint with 7 components • LDH component excluded	**85.7 (57.2–98.2)**	**60.0 (38.7–78.9)**	**69.2 (52.4–83.0)**

27 (69.2%) patients achieved the CR at Week 8

[a]Two-sided 95% Clopper-Pearson CI.
CI, confidence interval; CR, complete response; LDH, lactate dehydrogenase.

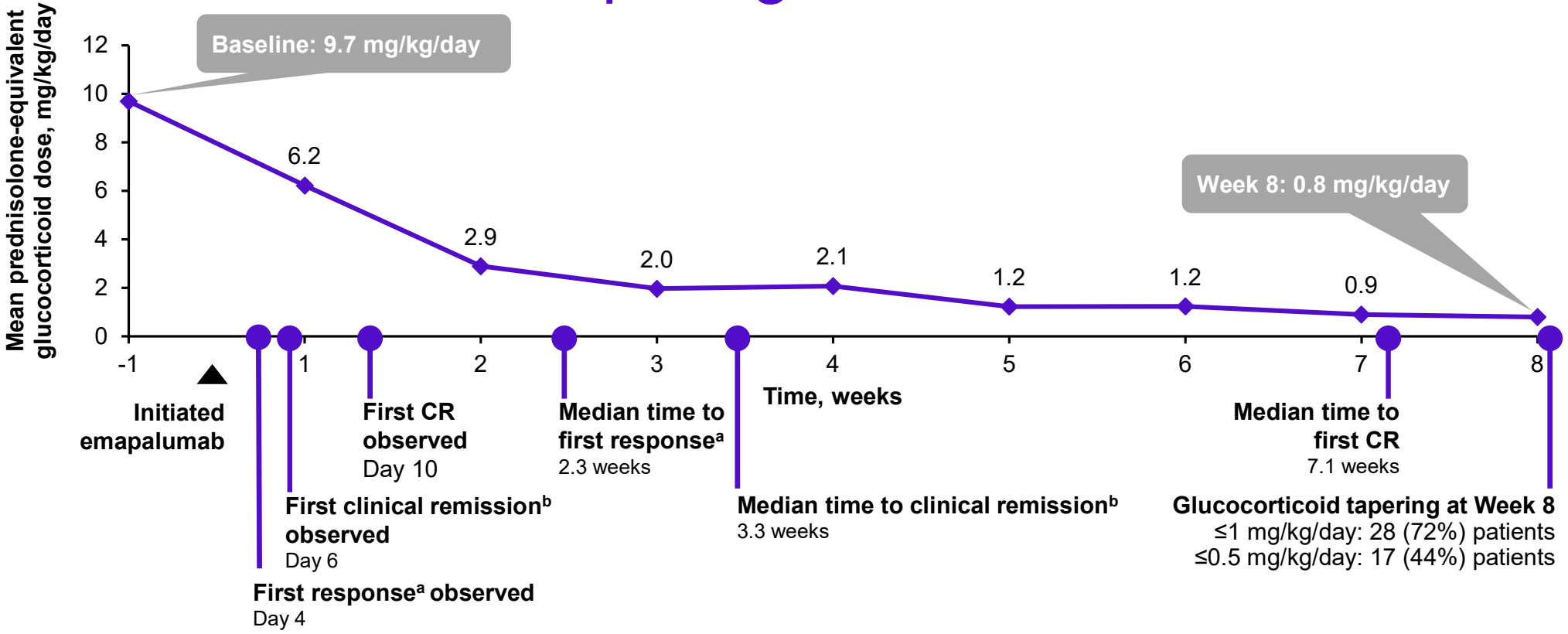
Pooled secondary endpoints: Overall response and clinical remission

At Week 8	Definition	NI-0501-06 (N=14)	EMERALD (N=25)	Pooled (N=39)
Overall response,[a] % (95% CI)	CR + PR (VAS <4 cm AND normalization of at least 3 of the abnormal baseline laboratory parameters)	92.9 (66.1–99.8)	66.7 (44.7–84.4)	76.3 (59.8–88.6)
Overall survival, n (%)	Survival at week 8	14 (100)	23 (92.0)	37 (94.9)

32 (82.1%) patients achieved investigator-assessed clinical MAS remission (absence of MAS clinical signs and symptoms; VAS ≤1) at any time

[a]At Day 56 ± 3 days.
CI, confidence interval; CR, complete response; MAS, macrophage activation syndrome; PR, partial response; VAS, visual analog scale.

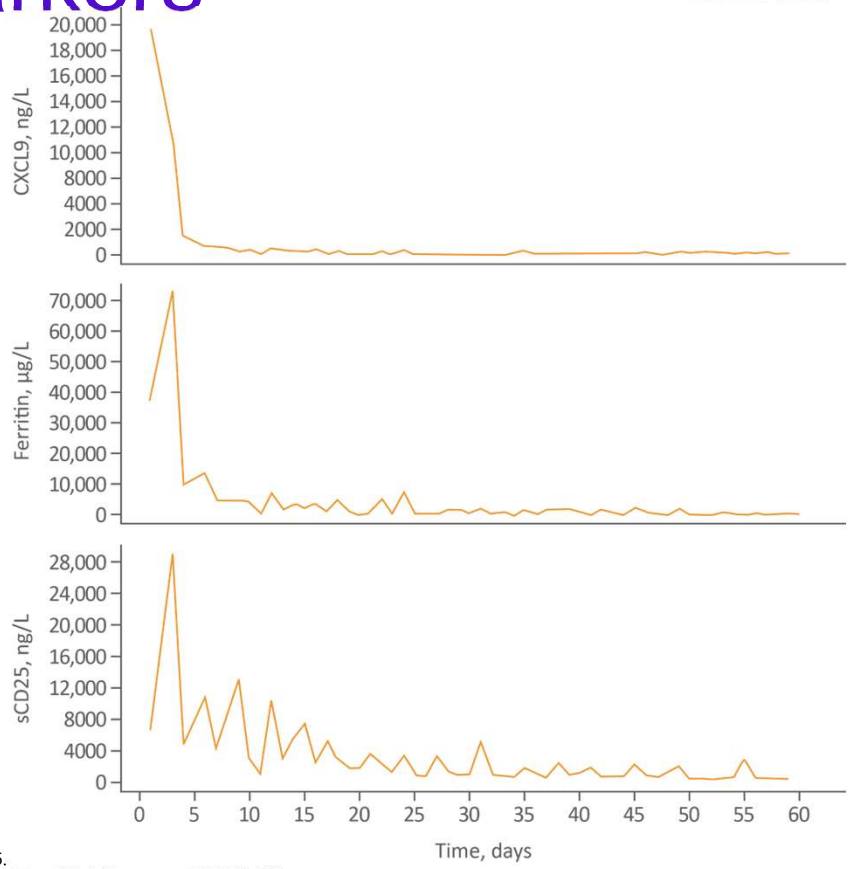
Pooled results: Glucocorticoid tapering



[a]PR or CR; [b]Physician global assessment; resolved clinical signs and symptoms, as determined by investigator-assessed VAS ≤1 cm.
CR, complete response; PR, partial response; VAS, visual analog score.

Pooled results: Emapalumab PK/PD and laboratory markers

- Serum CXCL9 was used as a biomarker of IFNγ activity because:
  - Serum IFNγ[a] levels do not reflect IFNγ activity
  - CXCL9 is primarily induced by IFNγ, stable, and easily measurable in blood[1–3]
- CXCL9, ferritin, and sCD25 levels rapidly reduced after initiating treatment with emapalumab
- Clinical improvement generally paralleled IFNγ neutralization, i.e., reductions in serum CXCL9 levels



[a]Both free and emapalumab-bound.
CXCL9/10, chemokine C-X-C motif ligand 9/10; IFNγ, interferon gamma; PK/PD, pharmacokinetics/pharmacodynamics; sCD25, soluble CD25.
1. Shakoory B, et al. *Arthritis Rheumatol* 2023;75:1714–1732; 2. De Benedetti F, et al. *Nat Rev Rheumatol* 2021;17:678–691; 3. Kuo PT, et al. *Front Med (Lausanne)* 2018;5:257.

Pooled safety

n (%) E	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)

- No new safety concerns were identified
- 6 serious adverse drug reactions were reported in 4 patients
- 14 infusion-related reactions occurred in 8 patients; none were serious or led to discontinuation of emapalumab infusion
- Infectious events predominantly of viral origin and resolved spontaneously or with standard treatment

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

Summary

Data from two pooled prospective studies in patients with MAS in Still's disease with an inadequate response to high-dose glucocorticoid treatment demonstrated:

- The 8-component composite endpoint CR rate was achieved by 53.6% of patients at Week 8
  - When excluding LDH, the CR rate was 69.2%
- Emapalumab rapidly controlled signs and symptoms of MAS in >80% of patients[a]
- 72% of patients had clinically meaningful reductions in glucocorticoid dosing to ≤1 mg/kg/day
- IFNγ was neutralized by emapalumab in all patients, as assessed by CXCL9
- No new safety concerns were identified

[a]VAS <1 cm.
CR, complete response; CXCL9, chemokine C-X-C motif ligand 9; IFNγ, interferon gamma; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; VAS, visual analog scale.

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The Netherlands			Sebastian Josef Vastet	
Poland			Bogdan Batko	
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The authors also wish to acknowledge the contribution of the study participants and their families

Back up

Pooled results: Demographics and baseline characteristics

	NI-0501-06 (N=14)	EMERALD (N=25)	Pooled (N=39)
Lung and/or hepatic involvement,[a] n (%)	NA	17 (68.0)	NA

[a]Lung and hepatic involvement at baseline were not collected in NI-0501-06.