Efficacy and Safety of Emapalumab in Patients with Macrophage Activation Syndrome in Still's disease

Results from a Pooled Analysis of Two Prospective Trials

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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]
- This analysis presents pooled efficacy and safety data from two prospective trials in patients with MAS in Still's disease administered emapalumab

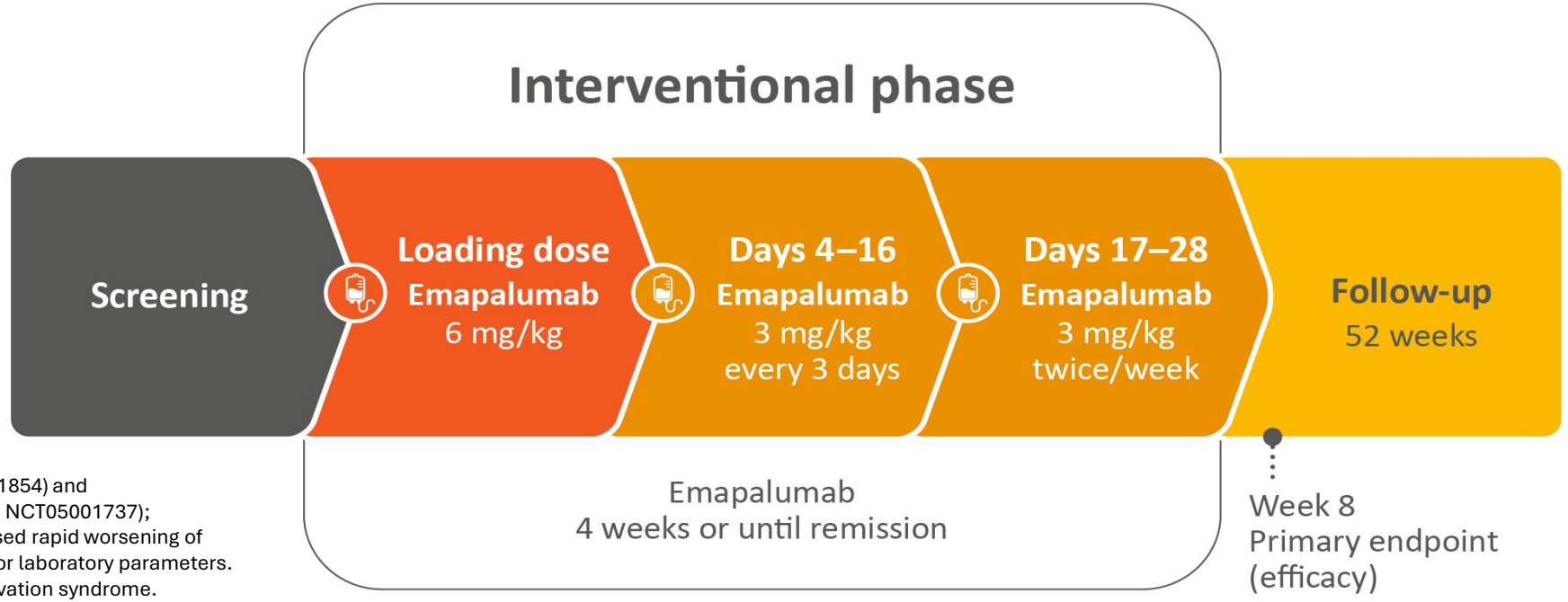
IFNγ, interferon gamma; MAS, macrophage activation syndrome.

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.

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[b]

- 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);
[b]Or investigator-assessed rapid worsening of clinical condition and/or laboratory parameters.
MAS, macrophage activation syndrome.

1. De Benedetti F, et al. *Ann Rheum Dis* 2023;82:857–865.

Methods: Inclusion and exclusion criteria

Inclusion criteria

- 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)
  - 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 could occur 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: 8-component composite endpoint

- 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 decreased by at least 80% from baseline and <2000 ng/mL

All 8 components must be met at Week 8
for the patient to be classified as achieving a completed response

ALT, alanine aminotransferase; AST, aspartate aminotransferase; 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 (9 months–64)	12 (9 months–64)
Age at diagnosis, years, median (range)	6 (1–16)	10 (1–64)	9 (1–64)
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 (%)			
Glucocorticoids	14 (100.0)	25 (100.0)	39 (100.0)
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; MAS, macrophage activation syndrome.

Pooled primary endpoint: Complete response at Week 8[a]

At Week 8[a] % (95% CI)	Definition	NI-0501-06 (N=14)	EMERALD (N=25)	Pooled (N=39)
Complete response	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 complete response definition at Week 8[a]

- First complete response was observed on Day 10

[a]Day 56 ± 5 days.
CI, confidence interval.

Pooled primary endpoint: Components of composite endpoint in patients without a complete response (n=18)

Patient	MAS activity score (VAS ≤1/10 cm)	WBC	PLAT	LDH	ALT	AST	Fibrinogen	Ferritin
1							—[a]	
2				●				
3				●				
4				●				
5				●				
6				●				
7				●				
8				●			—[b]	
9		●						
10				●				●
11				●		●		
12	● (VAS 4 cm)							
13	● (VAS 4 cm)							●
14	● (VAS 2 cm)		●	●				
15	● (VAS 3 cm)		●			●		●
16	● (VAS 4.5 cm)		●	●		●		●
17	No data at Week 8 efficacy assessment (death on Study Day 56)							
18	No data at Week 8 efficacy assessment (death on Study Day 24)							

● = Did not meet normalization threshold at Week 8

— = No evaluation during Week 8

[a]Normal value available at Week 6; [b]Normal value available at Study Days 48 and 62.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; LLN, lower limit of normal; MAS, macrophage activation syndrome; PLAT, platelet; ULN, upper limit of normal; VAS, visual analog scale; WBC, white blood cell.

Pooled post-hoc sensitivity analysis: Complete response at Week 8

At Week 8 % (95% CI[a])	Definition	NI-0501-06 (N=14)	EMERALD (N=25)	Pooled (N=39)
Complete response	• 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 a complete response at Week 8, when the LDH component was excluded

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

Pooled secondary endpoints: Overall response and MAS clinical activity score

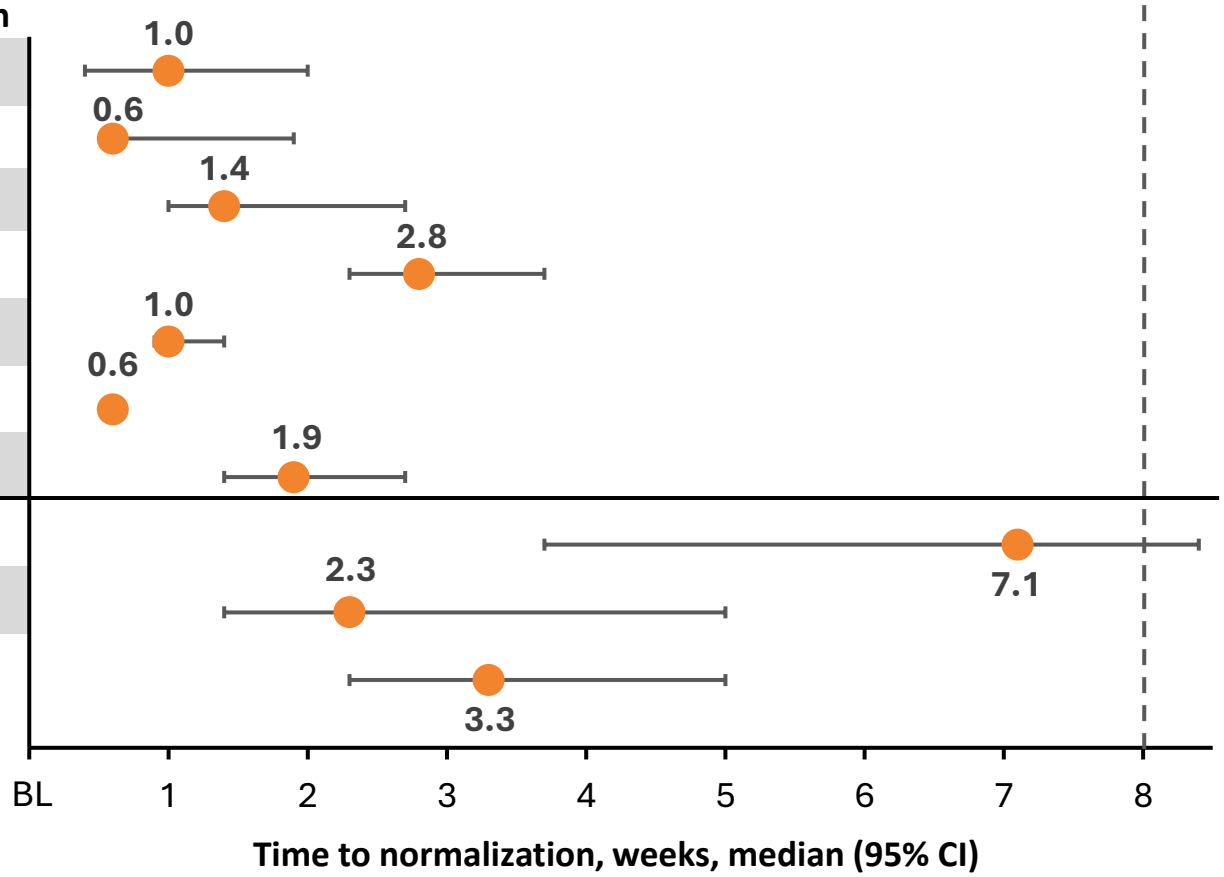
At Week 8	Definition	NI-0501-06 (N=14)	EMERALD (N=25)	Pooled (N=39)
Overall response,[a] % (95% CI)	Complete + partial response (VAS <4 cm AND normalization of ≥3 abnormal baseline laboratory parameters)	92.9 (66.1–99.8)	66.7 (44.7–84.4)	76.3 (59.8–88.6)
Time to first overall response, weeks, median (95% CI)		2.3 (1.4–3.0)	2.9 (1.4–8.4)	2.3 (1.4–5.0)
MAS clinical activity score, n (%)	VAS ≤1/10 cm	14 (100.0)	19 (66.7)	33 (84.6)
Time to MAS clinical activity score VAS ≤1/10 cm, weeks, median (95% CI)		3.0 (1.0–6.6)	4.0 (2.0–5.1)	3.3 (2.3–5.0)
Overall survival, n (%)	Survival at Week 8	14 (100.0)	23 (92.0)	37 (94.9)

33 (84.6%) patients achieved investigator-assessed MAS clinical activity score VAS ≤1/10 cm at any time up to Week 8

[a]At Day 56 ± 3 days; [b]Absence of MAS clinical signs and symptoms.
CI, confidence interval; MAS, macrophage activation syndrome; VAS, visual analog scale.

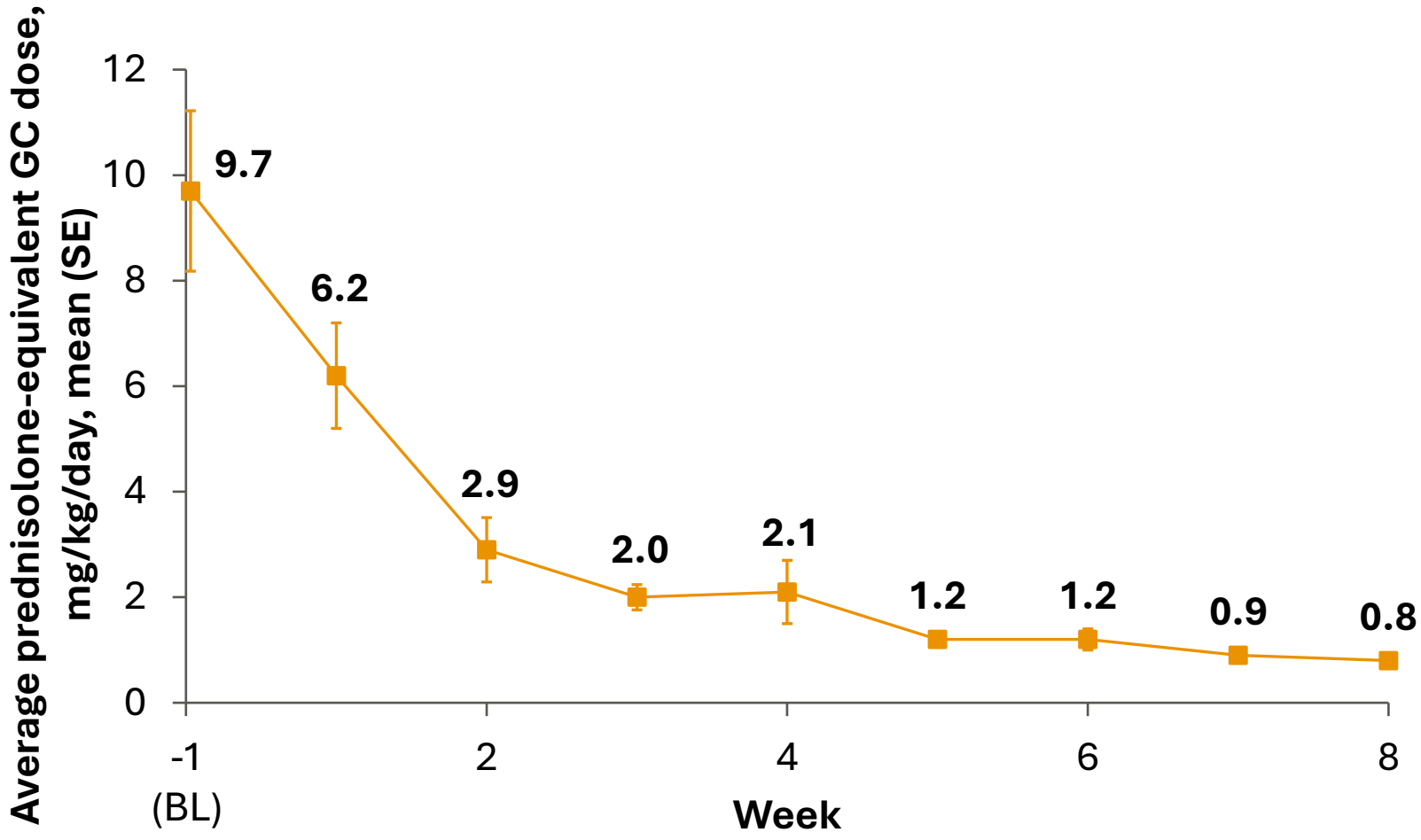
Pooled analysis of laboratory parameters and MAS signs and symptoms: Time to normalization[a]

	Abnormal at baseline, n	Normalised at Week 8, n
WBC 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 ≤1/10 cm	39	33



[a]n numbers represent patients with abnormal values at baseline.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; KM, Kaplan–Meier; LDH, lactate dehydrogenase; NE, not estimable; WBC, white blood cell.

Pooled results: Glucocorticoid tapering



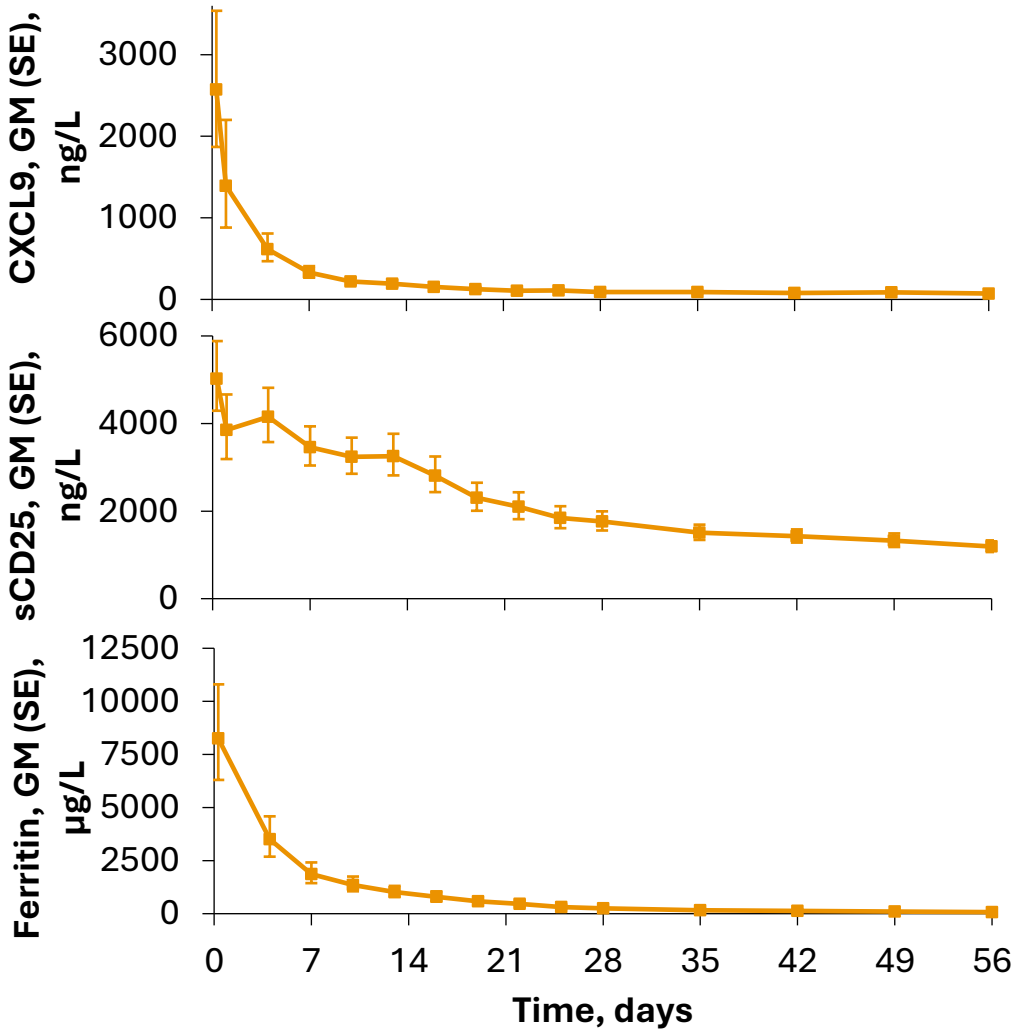
GCs were tapered by Week 8 to:

- ≤1 mg/kg/day in 28 (72%) patients
- ≤0.5 mg/kg/day in 17 (44%) patients

BL, baseline; GC, glucocorticoid; SE, standard error; 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, sCD25, and ferritin 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, chemokine C-X-C motif ligand 9; GM, geometric mean; IFNγ, interferon gamma; PK/PD, pharmacokinetics/pharmacodynamics; sCD25, soluble CD25; SE, standard error.
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 (%)	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[a]	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[b]	2 (14.3)	6 (24.0)	8 (20.5)
Infections	6 (42.9)	16 (64.0)	22 (56.4)
Viral test-positive events	2 (14.3)	2 (8.0)	4 (10.3)

- Safety profile was consistent with the established safety profile of emapalumab
- 4 patients experienced 6 serious adverse drug reactions
- Infectious events predominantly of viral origin and resolved spontaneously or with standard treatment
- 8 patients experienced 14 infusion-related reactions; none were serious or led to discontinuation of emapalumab infusion

[a]Both deaths occurred in adult patients; [b]Any adverse event occurring within 24 hours of infusion.
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[a] demonstrated:

- IFNγ was neutralized by emapalumab in all patients, as assessed by CXCL9
- The 8-component composite endpoint complete response 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 84.6% of patients[b]
- 72% of patients had clinically meaningful reductions in glucocorticoid dosing to ≤1 mg/kg/day at Week 8 from a mean daily dose at baseline of 9.7 mg/kg/day
- Safety profile was consistent with the established safety profile of emapalumab

[a]Or investigator-assessed rapid worsening of clinical condition and/or laboratory parameters; [b]MAS clinical activity score VAS ≤1/10 cm.
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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Country	NI-0501-06		EMERALD	
Belgium			Lien De Somer	
Canada			Deborah Levy	
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Czechia			Pavla Dolezalova	
France	Pierre Quartier		Pierre Quartier Bruno Fautrel	Gilles Kaplanski
Germany			Robert Biesen	Norbert Blank
Italy	Fabrizio De Bendetti Claudia Bracaglia	Manuela Pardeo Giulia Marucci	Fabrizio De Bendetti Giovanni Filocamo	Marco Gattorno
Japan			Masaaki Mori	Masaki Shimizu
The Netherlands			Sebastian Josef Vastet	
Poland			Bogdan Batko	
Spain	Jordi Anton Lopez		Jordi Anton Lopez	Inmaculada Calvo Penades
UK	Paul Brogan Despina Eleftheriou	Charalampia Papadopoulou	Paul Brogan	
USA	Grant Schulert		Melissa Elder	Alexei Grom

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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.
NA, not available.