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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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 clinical remission 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)
  - No new severe or serious safety concerns were identified

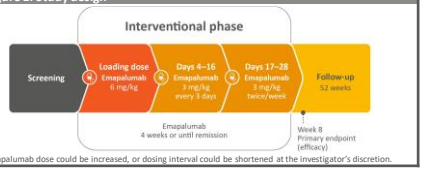
INTRODUCTION

- MAS is a potentially life-threatening complication of Still's disease when left untreated, 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; 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 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

METHODS (CONTINUED)

Inclusion criteria (continued)

- 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 absence of MAS clinical signs and symptoms (visual analog scale [VAS] ≤1 cm) 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, whichever is lower)

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
- 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**)
- 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
- 32 (82.1%) patients achieved investigator-assessed clinical MAS remission (absence of MAS clinical signs and symptoms; 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 clinical remission was observed on Day 6; median time to first clinical remission was 3.3 weeks

Table 2: Primary and secondary efficacy endpoint outcomes

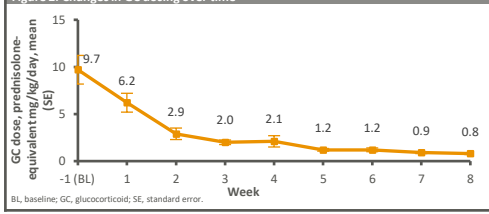
At Week 8 % (95% CI)[a]	Definition	NI-0501-06 (N=14)	EMERALD (N=25)	Pooled (N=39)
CR (primary)[b]	Composite endpoint with 8 components	71.4 (41.9–91.6)	44.0 (24.4–65.1)	53.8 (37.2–69.9)
CR (post-hoc sensitivity analysis)[b]	Composite endpoint with 7 components (LDH excluded)	85.7 (57.2–98.2)	60.0 (38.7–78.9)	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]
Clinical remission	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.

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 2**)
- At week 8, glucocorticoids had been tapered to ≤1 mg/kg/day in 28 (72%) patients and ≤0.5 mg/kg/day in 17 (44%) patients

Figure 2: Changes in GC dosing over time

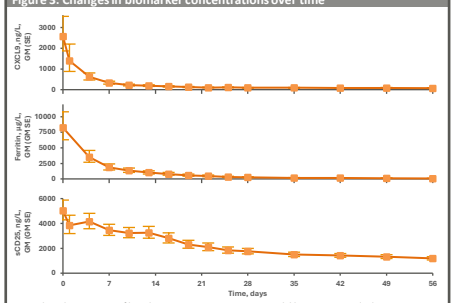


BL, baseline; GC, glucocorticoid; SE, standard error.

Biomarkers

- CXCL9, ferritin, and soluble CD25 levels rapidly reduced after initiating treatment with emapalumab (**Figure 3**)
- Clinical improvement generally paralleled IFNγ neutralization, i.e., reductions in serum CXCL9 levels

Figure 3: Changes in biomarker concentrations over time



CXCL9, chemokine C-X-C motif ligand 9; GM, geometric mean; sCD25, soluble CD25; SE, standard error.

Safety

- No new severe or serious safety concerns were identified
- 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)
- Infectious events were predominantly of viral origin and resolved spontaneously or with standard treatment (**Table 3**)
- 8 patients experienced 14 infusion-related reactions (**Table 3**)
  - None were serious or led to discontinuation of emapalumab infusion

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.

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Acknowledgements We thank the patients and families who participated in this study. The authors also wish to acknowledge Stefan Duscha, PhD from Sobi (Basel, Switzerland) for publication coordination and Blair Hesp, PhD CMPP of Kainic Medical Communications Ltd. (Dunedin, New Zealand) for medical writing and editorial support, funded by Sobi, based on the authors' input and direction, and in accordance with Good Publication Practice (GPP) 2022 guidelines (https://www.ismpp.org/gpp-2022).
Disclosures **A. Grom:** Consultant to Novartis, Sobi, Kiniksa; Research grants/Contracts from NIH, Novartis, Sobi, sJIA Foundation; Royalties from Up-to-Date. **U. Ullman, A Mahmood and J. Blomkvist** are employees of Sobi. **B.D. Jamieson** is an employee of Sobi, Inc. **F. De Benedetti:** Consultant and research grants from Sobi, Novartis, Elixiron, Apollo, Sanofi, Abbvie, Kiniksa.