Baseline Pharmacodynamic Markers and Response to Emapalumab in Children and Adults with Macrophage Activation Syndrome (MAS) in Still's Disease: Results from a Pooled Analysis of Two Prospective Trials

Edward M. Behrens,[1] Sebastiaan J. Vastert,[2] Jordi Antón,[3] Pierre Quartier,[4,5] Bruno Fautrel,[6–8] Paul Brogan,[9,10] Melissa Elder,[11] Francesca Minoia,[12] Pavla Dolezalova,[13] Robert Biesen,[14] Masaki Shimizu,[15] Uwe Ullmann,[16*] Adnan Mahmood,[17*] Andrew Danquah,[16*] Elena Burillo,[16] Steve Mallett,[16*] Brian D. Jamieson,[18] Alexei A. Grom,[19] Fabrizio De Benedetti[20]

[1]Division of Rheumatology, The Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Pediatric Rheumatology & Immunology, University Medical Center Utrecht, Wilhelmina Children's Hospital, Utrecht, The Netherlands; [3]Hospital Sant Joan de Déu, Division of Pediatric Rheumatology, University of Barcelona, Barcelona, Spain; [4]Université Paris-Cité, Paris, France; [5]RAISE reference centre, Pediatric Immuno-Hematology and Rheumatology Unit, Necker Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France; [6]Department of Rheumatology, Pitié-Salpêtriere Hospital, Assistance Publique-Hôpitaux de Paris, Sorbonne University, Paris, France; [7]CRI-IMIDIATE Clinical Research Network and ERN Rita, CEREMAIA Reference Center, Paris, France; [8]Pierre Louis Institute of Epidemiology and Public Health, INSERM UMR-S 1136, Paris, France; [9]Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK; [10]University College London Great Ormond Street Institute of Child Health, London, UK; [11]College of Medicine, University of Florida, Gainesville, FL, USA; [12]Pediatric Immuno-Rheumatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [13]Paediatric Rheumatology and Autoinflammatory Diseases Unit, General University Hospital, Prague, Czechia; [14]Department of Rheumatology and Clinical Immunology, Charité Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität, Berlin, Germany; [15]Department of Pediatrics and Developmental Biology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan; [16]Sobi, Basel, Switzerland; [17]Sobi, Stockholm, Sweden; [18]Sobi, Inc., Morrisville, NC, USA; [19]Cincinnati Children's Hospital, Division of Rheumatology, Cincinnati, OH, USA; [20]Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy. *At time of study conduct.

CONCLUSIONS

- Emapalumab treatment rapidly controlled signs and symptoms of MAS in 82.1% of patients with Still's disease
- Emapalumab enabled reductions in key inflammatory pharmacodynamic markers by inhibiting interferon-gamma (IFNγ) activity in patients with MAS in Still's disease
- Patients with a complete or partial response to emapalumab treatment at Week 8 had higher levels of pharmacodynamic biomarkers associated with MAS at baseline

INTRODUCTION

- 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 two clinical trials (NCT03311854 and NCT05001737)[5,6]
- Emapalumab has been approved by the US Food and Drug Administration for adult and pediatric (newborn and older) patients with MAS in known or suspected Still's disease with an inadequate response or intolerance to glucocorticoids (GCs), or with chronic relapsing MAS[7]
- Chemokine C-X-C motif ligand 9 (CXCL9; a specific biomarker primarily induced by IFNγ activity), soluble CD25 (sCD25; a marker of T-cell activation) and ferritin may have utility as PD markers in patients with MAS treated with emapalumab[8]

OBJECTIVE

- To evaluate changes in key PD markers by response status at Week 8 after treatment initiation and time to response

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])[5,9]
- Patients with Still's disease could continue to receive anakinra ≤4 mg/kg/day during the study

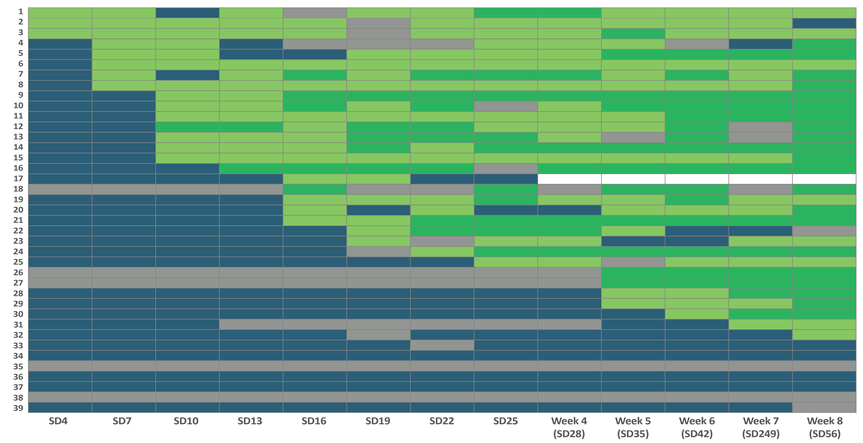
Endpoints

- 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 (visual analog scale [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, aspartate aminotransferase 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

RESULTS

- 39 patients were enrolled (31 [79.5%] females), with a median age of 12 years (range, 9 months–64 years)
  - 26 patients (66.7%) received concomitant anakinra (4 [10.3%] patients received at least one dose >4 mg/day)
- At Week 8, 53.8% (95% confidence interval [CI]: 37.2–69.9) of patients had achieved the 8-point composite primary endpoint of complete response
  - Overall (complete + partial) response rate at Week 8 was 76.3% (95% CI: 59.8–88.6)
- Patients with MAS in Still's disease administered emapalumab showed rapid and durable responses (**Figure 1**)

Figure 1: Response over time in individual patients with MAS in Still's disease administered emapalumab



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

- At Week 8, 82.1% of patients achieved MAS clinical activity score VAS ≤1/10 cm per clinicians' assessment after being administered emapalumab (**Figure 2**)

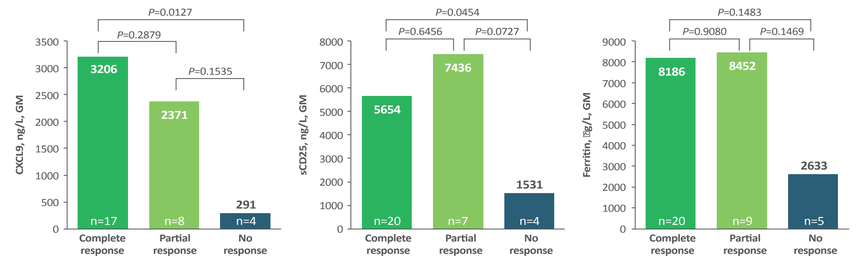
Figure 2: MAS clinical activity score over time in individual patients administered emapalumab

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

Pharmacodynamic markers

- Patients with a complete or partial response at Week 8 tended to present with higher CXCL9, sCD25, and ferritin levels at baseline compared with non-responders (**Figure 3**)

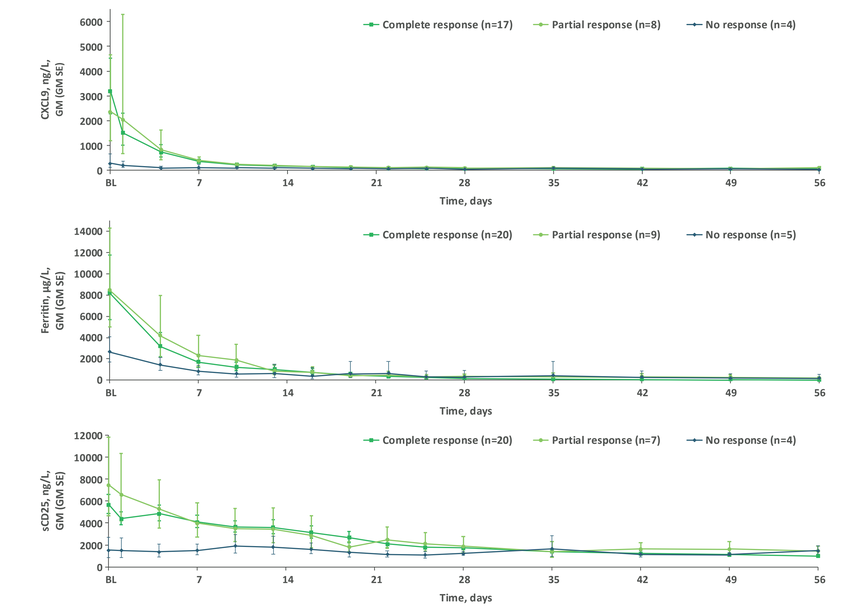
Figure 3: Baseline levels of pharmacodynamic markers in patients with MAS in Still's disease prior to emapalumab administration



[a]Evaluable analysis set – patients with a response status of no complete/partial response not applicable, not evaluable, or missing were excluded from this analysis.
CXCL9, chemokine C-X-C ligand 9; GM, geometric mean; MAS, macrophage activation syndrome; sCD25, soluble CD25.

- Patients with a complete or partial response had a median reduction in CXCL9 and ferritin levels of 98% and 99%, respectively, from baseline at Week 8 compared with 86% and 89% in non-responders (**Figure 4**)
- sCD25 levels decreased by 80% from baseline at Week 8 in patients with a complete response or partial response versus a 21% increase in non-responders (**Figure 4**)

Figure 4: Changes in pharmacodynamic markers in patients with MAS in Still's disease administered emapalumab



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

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behrens@chop.org