

A large white circle with a small notch at the bottom right, containing the text for the drug administration.

**Administration of
Emapalumab-lzsg**
GAMIFANT®

A small white circle positioned to the left of the meeting information text.

**ICD-10 Coordination & Maintenance
Committee Meeting
September 2024**

Macrophage activation syndrome (MAS), a subtype of secondary hemophagocytic lymphohistiocytosis (sHLH), can occur in the context of rheumatic diseases

- HLH is a rare but potentially fatal disorder characterized by hyperinflammation caused by a dysfunctional, uncontrolled hypersecretion of proinflammatory cytokines¹⁻³
- sHLH/MAS occurs most frequently as a life-threatening complication of Still’s disease (i.e., systemic juvenile idiopathic arthritis [sJIA] and adult-onset Still’s disease [AOSD]); both rare, autoinflammatory disorders^{4,5}
- Life-threatening symptoms of MAS include fever, splenomegaly, cytopenias, and multiple organ failure⁴
- Diagnosis of MAS is often delayed due to the lack of awareness of the characteristic signs and because the complex pattern of presenting features overlaps with other hyperinflammatory conditions^{6,7}
- There is no consensus on a single set of validated criteria for diagnosis of sHLH/MAS⁸

sJIA	AOSD
Prevalence of sJIA ⁹ : ≤8.6/100,000	Prevalence of AOSD ⁵ : 0.73-6.77/100,000
<u>Incidence of MAS in sJIA⁶:</u> MAS is reported to be ~10%	<u>Incidence of MAS in AOSD⁷:</u> MAS occurs in up to 15% of adults with AOSD

References: 1. La Rosée P, et al. *Blood*. 2019;133(23):2465-2477. 2. Henderson LA, Cron RQ. *Paediatr Drugs*. 2020;22(1):29-44. 3. Griffin G, et al. *Best Pract Res Clin Rheumatol*. 2020;34(4):1015-15. 4. Bracaglia C, et al. *Pediatr Rheumatol Online J*. 2017;15(1):5. 5. Efthimiou P, et al. *Semin Arthritis Rheum*. 2021;51(4):858-874. 6. Ravelli A, et al. *Arthritis Rheumatol*. 2016;68(3):566-576. 7. Lerkvaleekul B, Vilaiyuk S. *Open Access Rheumatol*. 2018;10:117-128. 8. Schulert GS, et al. *Arthritis Care Res (Hoboken)* 2018;70(3):409-419. 9. Albaker AR. *Open Journal of Pediatrics*. 2020;10:769-801. 10. Giacomelli R, et al. *J Autoimmun*. 2018;93:24-36.

Current treatments are nonspecific and do not address the hyperinflammation caused by the overexpression of interferon gamma (IFN γ)

- Although the American College of Rheumatology created treatment guidelines for sJIA-MAS in 2021, **there are no FDA-approved treatment options indicated for MAS, and none address the hyperinflammatory overexpression of IFN γ** ¹⁻⁴
 - Biologics that inhibit Interleukin-1 (IL-1) or Interleukin-6 (IL-6) and systemic glucocorticoids are currently the cornerstone of initial therapy for MAS¹
 - IL-1 and IL-6 inhibitors (e.g., anakinra, tocilizumab, and canakinumab) are conditionally recommended to achieve inactive disease and resolve MAS^{1,*}



Long-term use of glucocorticoids is not recommended for patients with sJIA-MAS, AOSD-MAS, or SLE-MAS due to side effects such as⁵

- Decreases in bone density
- High blood pressure
- Weight gain
- Risk of infection
- Hyperglycemia
- Growth inhibition

>50% of patients with MAS secondary to sJIA do not respond to systemic glucocorticoids alone⁶

- If treatment escalation is required, immunosuppressants (e.g., cyclosporine) or chemotherapy agents (e.g., etoposide) may be considered as additions to the treatment regimen⁷

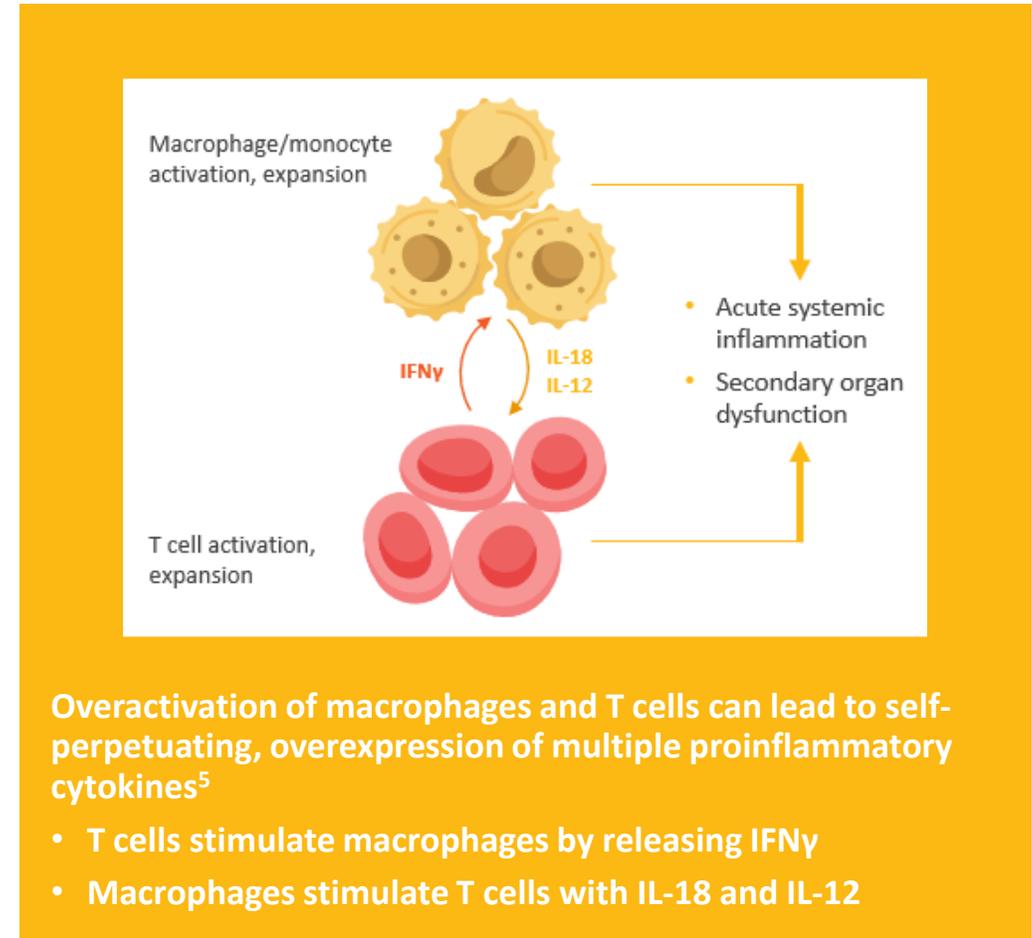
*Anakinra is not FDA-approved for the treatment of MAS. It is currently indicated to reduce the signs and symptoms and slow progression of moderate to severe active RA in adults, to treat NOMID, and to treat DIRA.⁹ DIRA=deficiency of interleukin-1 receptor antagonist; FDA=US Food and Drug Administration; NOMID=neonatal-onset multisystem inflammatory disease; RA=rheumatoid arthritis.

References: 1. Onel KB, et al. *Arthritis Rheumatol.* 2022;74(4):553-569. 2. Di Cola I, et al. *J Clin Med.* 2021;10(6):1164. 3. Wampler Muskardin TL. *ACR Open Rheumatol.* 2020;2(5):283-285. 4. FDA approves Gamifant® (emapalumab-lzsg), the first and only treatment indicated for primary hemophagocytic lymphohistiocytosis (HLH). [news release]. Waltham, Massachusetts: Business Wire; November 20, 2018. Accessed July 20, 2023. <https://www.businesswire.com/news/home/20181120005454/en/FDA-Approves-Gamifant%C2%AE-emapalumab-lzsg-the-First-and-Only-Treatment-Indicated-for-Primary-Hemophagocytic-Lymphohistiocytosis-HLH> 5. Oray M, et al. *Expert Opin Drug Saf.* 2016;15(4):457-465. 6. Minoia F, et al. *Arthritis Rheumatol.* 2014;66(11):3160-3169. 8. Hines MR, et al. *Crit Care Med.* 2022;50(5):860-872. 9. Kineret (anakinra) [prescribing information]. Stockholm, Sweden: Sobi, Inc; 2020.

Emapalumab is a fully human IgG1 anti-IFN γ monoclonal antibody that binds free and receptor-bound IFN γ , neutralizing its biological activity¹

The role of IFN γ in hyperinflammation

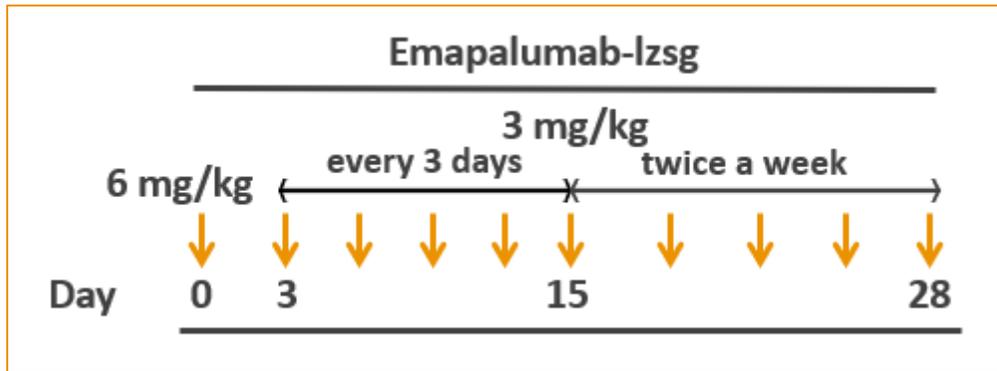
- Patients with MAS have an increased proportion of circulating, IFN γ -producing, activated T cells²
- Diagnosed patients have increased serum levels of IFN γ and IFN γ -induced products that correlate with disease activity²⁻⁴
- The excess cytokines lead to the signs and symptoms of MAS and adversely affects multiple organ systems^{4,5}



IFN γ =interferon gamma; IL=interleukin.

References: 1. Hot A, et al. *Medicine (Baltimore)* 2010;89(1):37-46. 2. De Matteis A, et al. *Blood*. 2022;140(3):262-273. 3. Bracaglia C, et al. *Pediatr Rheumatol Online J*. 2017;15(1):5. 4. Grom AA, et al. *Nat Rev Rheumatol*. 2016;12(5):259-268. 5. Griffin G, et al. *Best Pract Res Clin Rheumatol*. 2020;34(4):101515.

Dosing and administration of emapalumab in sHLH/MAS in Still's disease



- **GAMIFANT®** (emapalumab-lzsg)* is supplied as a solution in single-dose vials of 10 mg/2 mL, 50 mg/2 mL and 100 mg/2 mL for intravenous infusion; it must be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light
- For patient dosing, the diluted solution is administered intravenously over 1 hour through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2-micron inline filter
- The infusion procedure will be documented in the medical record in the same manner as other therapies that are administered via intravenous infusion
 - Alternate naming convention located in the medical record: **GAMIFANT®** or **emapalumab-lzsg**

*On November 20, 2018, the FDA approved GAMIFANT (emapalumab-lzsg) for the treatment of HLH in adult and pediatric (newborn and older) patients with primary HLH with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy.

Completed Phase 2 study¹

- Recommended dosing regimen: Initial 6 mg/kg dose on Day 0, followed by 3 mg/kg every 3 days to Day 15, then 3 mg/kg twice weekly until day 28, for a total of 10 doses over 4 weeks or until a complete response is received

A patient's dose may be increased or dosing frequency may be shortened based on clinical conditions and physician judgement

- The median treatment duration was 27 days (range, 7-39), with the number of infusions ranging from 3 to 17 per patient

1. De Benedetti F, et al. *Ann Rheum Dis* 2023;0:1-9.

Phase 2 study, completed

- The open-label, **single-arm**, international, multicenter **phase 2** study evaluating the use of emapalumab in patients who had MAS secondary to **sJIA or AOSD** and had previously failed high-dose glucocorticoids¹ (N=14: 13 diagnosed with underlying sJIA; 1 diagnosed with AOSD at age 16 years and 9 months)

Study objectives



To describe the **pharmacokinetic** profile of emapalumab



To preliminary assess the **efficacy** of emapalumab



To confirm the proposed **dosing regimen** of emapalumab



To assess the levels of relevant pharmacodynamic **biomarkers**, such as IFN γ , CXCL9 and CXCL10



To evaluate the **safety** and **tolerability** of the IV administrations of emapalumab

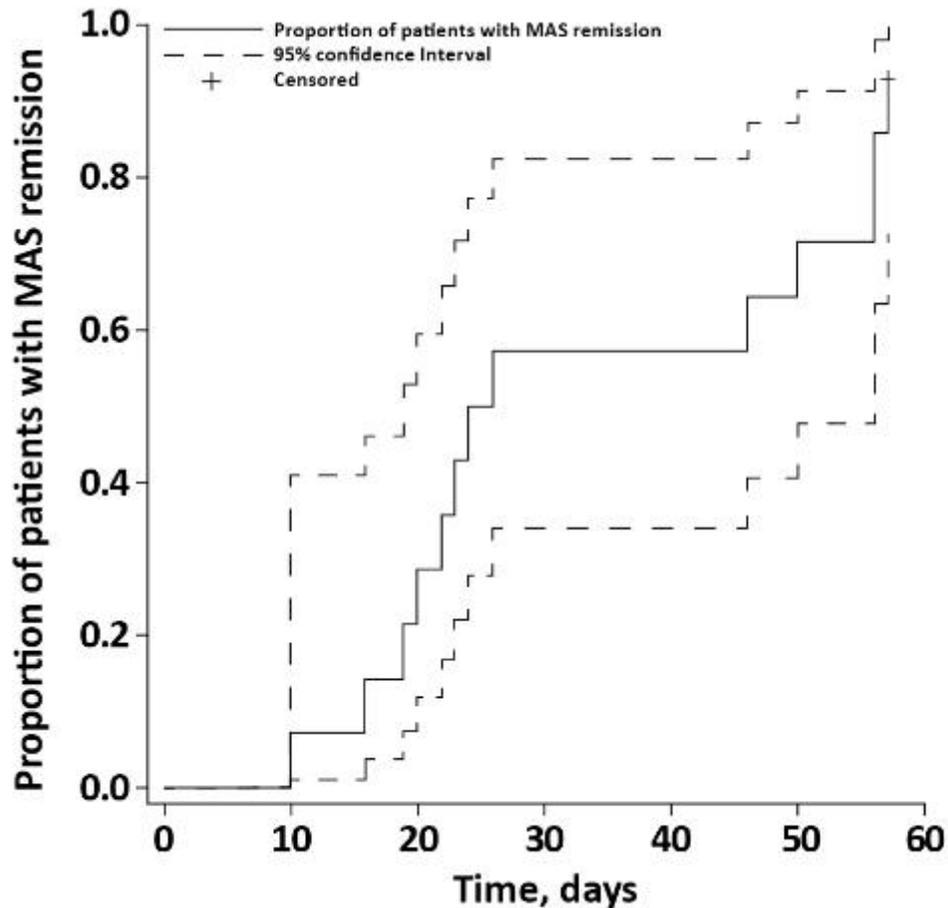


To assess the **immunogenicity** of emapalumab

AOSD, adult-onset Still's disease; CXCL, chemokine (C-X-C motif) ligand; IFN γ , interferon- γ ; IV, intravenous; MAS, macrophage activation syndrome; sJIA, systemic juvenile idiopathic arthritis.

1. De Benedetti F, et al. *Ann Rheum Dis* 2023.

Emapalumab treatment led to MAS remission in patients who failed high-dose glucocorticoids¹

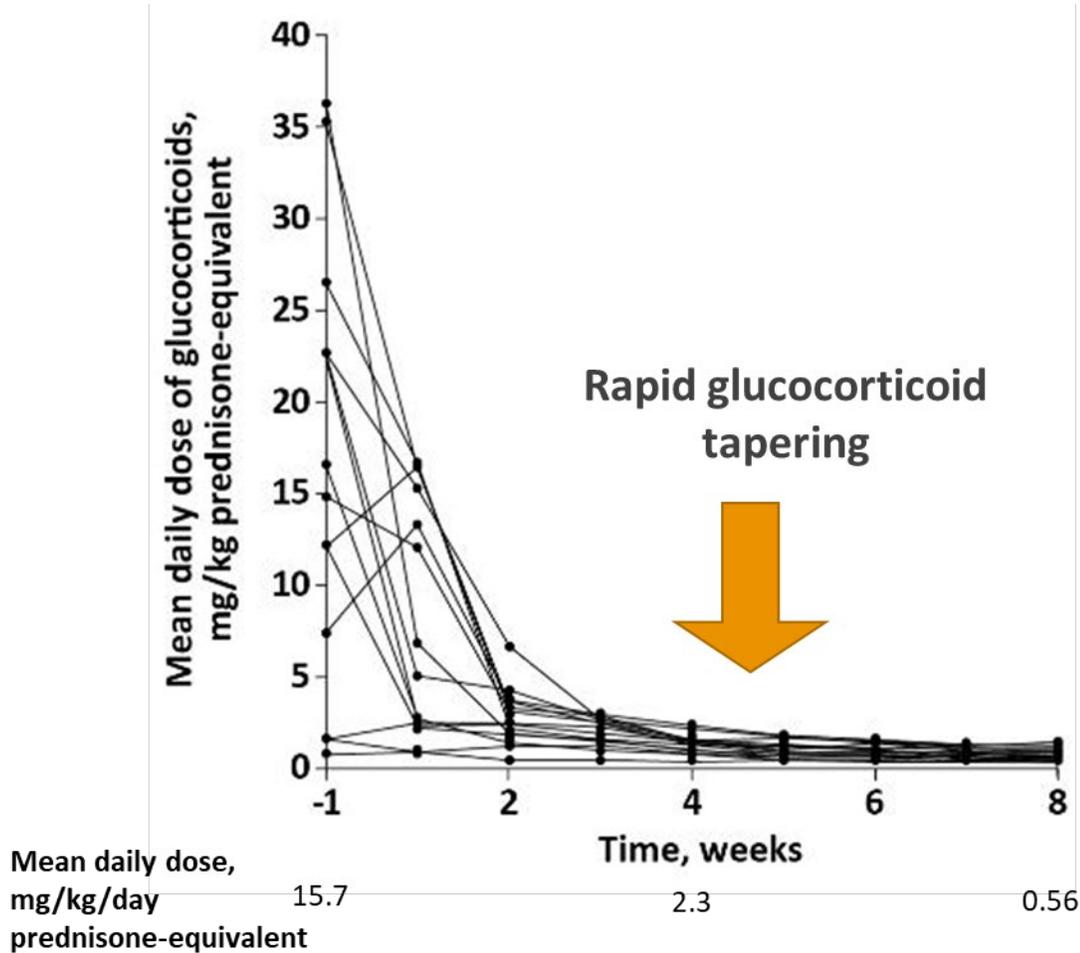


- 13/14 (93%) patients met MAS remission^a criteria by Week 8
 - Median time to remission: 25 days
 - Earliest remission: 9 days
- 2/13 patients who achieved MAS remission did not meet MAS remission criteria at Week 8 because of a single laboratory abnormality^b
- One patient with investigator-assessed remission stopped emapalumab after 3 doses without meeting MAS remission criteria^c
- Of the 11 patients who achieved MAS remission at Week 8, 10 continued to meet the MAS remission criteria 12 months post-treatment

^aMAS remission is defined as resolution of clinical signs and symptoms according to the physician global assessment (visual analogue scale $\leq 1/10$) and white blood cell and platelet count above lower limit of normal, LDH, alanine aminotransferase and aspartate aminotransferase below 1.5 times ULN, fibrinogen >100 mg/dL and ferritin levels decreased by at least 80% or below 2000 ng/mL, whichever was lower. ^bLDH 1.7-fold above the ULN (n=1); white blood cells at $4.8 \times 10^9/L$ (LLN, $5.5 \times 10^9/L$); ^cThe investigator assessed the patient as being in remission, but LDH levels remained 1.5-fold above the ULN. LDH, lactate dehydrogenase; LLN, lower limit of normal; MAS, macrophage activation syndrome; ULN, upper limit of normal.

1. De Benedetti F, et al. *Ann Rheum Dis* 2023.

Emapalumab treatment enabled glucocorticoid tapering in all patients¹



Glucocorticoids were rapidly tapered:

- Median average daily dose was 15.7 mg/kg/day prednisone equivalent
- 2.3 mg/kg during week 2 and 0.56 mg/kg during week 8

At 12 months post-emapalumab^a:

- 5 (38%) patients were no longer being treated with glucocorticoids
- 6 (46%) patients were receiving <0.3 mg/kg/day glucocorticoids
- 2 (15%) patients were receiving 1–2 mg/kg/day^b

^aData not available for one patient; ^bPatient with a MAS episode (n=1) and patient with lung disease associated with sJIA (n=1). MAS, macrophage activation syndrome; sJIA, systemic juvenile idiopathic arthritis.
1. De Benedetti F, et al. Ann Rheum Dis 2023.

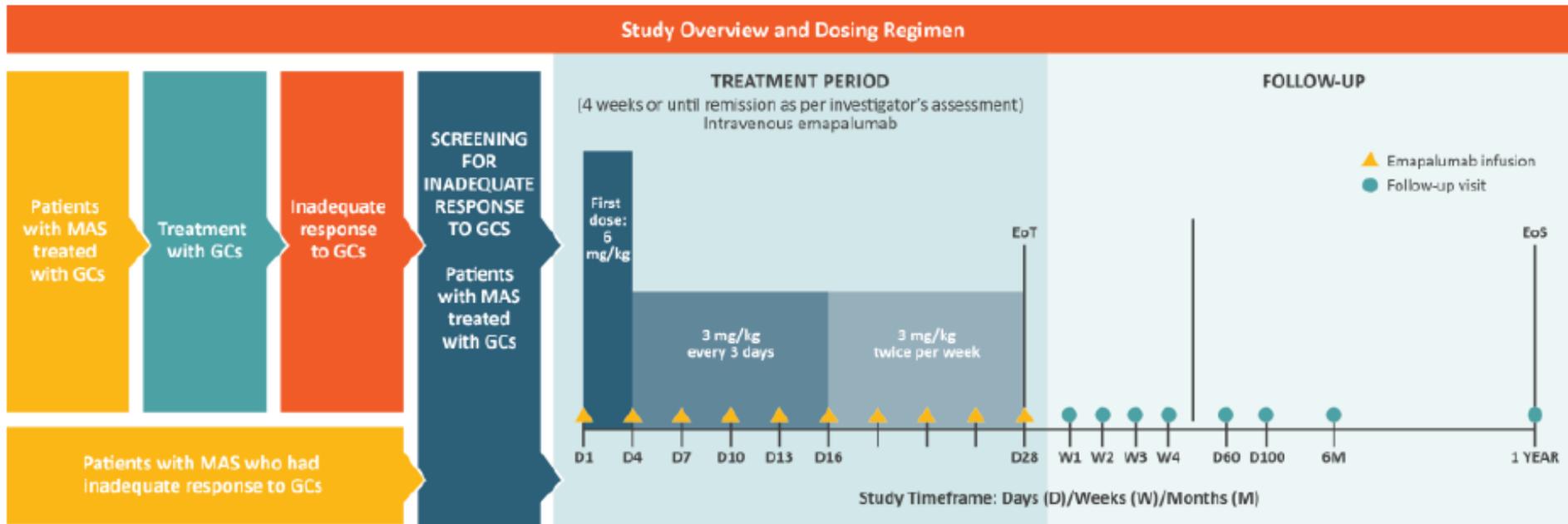
Emapalumab was well tolerated¹

- 88 adverse events (AEs) were reported in 13 patients
 - 86/88 events were mild or moderate in intensity
 - The two severe events were cardiopulmonary failure (n=1) and neutropenia (n=1); not related to emapalumab
- The most frequently reported AEs were infections and asymptomatic positive viral tests
 - All infectious events were of viral origin. No bacterial or opportunistic infections were reported.
 - All viral events resolved spontaneously or with standard treatment.
- Two infusion-related reactions (pruritic rash; not severe) occurred during a total of 128 infusions
- The rate of AEs and of infectious events was not increased during concomitant treatment with anakinra and emapalumab compared with treatment with emapalumab alone
- No deaths were reported during the trial and the long-term follow-up

1. De Benedetti F, et al. Ann Rheum Dis 2023.

Phase 2/3 EMERALD study is underway¹; results are expected in 2H 2024

- EMERALD is a Phase 2/3, open label, two-cohort, single-arm, multicenter study designed to evaluate the efficacy, safety and tolerability, PK, and PD of intravenous administration of emapalumab, an IFN γ - neutralizing monoclonal antibody, in patients with sJIA, AOSD, or SLE who developed MAS and who had an inadequate response to high-dose glucocorticoids^{1,2,3}



EoT= end of trial; EoS= end of study; GC=glucocorticoids.

References: 1. NCT05001737. Clinicaltrials.gov website. Accessed August 7, 2023. <https://classic.clinicaltrials.gov/ct2/show/NCT05001737> 2. Gamifant [prescribing information]. Waltham, MA: Sobi, Inc; 2022. 3. Data on file. NI-0501-14 Clinical Study Protocol/Sobi, Inc. February 2022.

AOSD=adult-onset Still's disease; IFN γ - interferon gamma; MAS=macrophage activation syndrome; PD=pharmacodynamics; PK=pharmacokinetics; sJIA=systemic juvenile idiopathic arthritis; SLE=systemic lupus erythematosus

Summary

- sHLH/MAS is a potentially life-threatening complication of sJIA/AOSD; there are no FDA-approved therapies
- IFN γ neutralization and resolution of hyperinflammation is a key therapeutic objective in sHLH/MAS
- Emapalumab is a fully human IgG1 anti-IFN γ monoclonal antibody that binds free and receptor-bound IFN γ , neutralizing its biological activity
- Neutralizing IFN γ with emapalumab leads to MAS remission and facilitates glucocorticoid tapering; it is well tolerated and has a positive benefit/risk profile with no new safety signals