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emapalumab-lzsg

IFNγ and CXCL9 in MAS

Explore the relationship between IFNγ, a key mediator of hyperinflammation, and CXCL9, a recognized biomarker for IFNγ activity that is associated with macrophage activation syndrome (MAS).[1,2]

CXCL9=chemokine (C-X-C motif) ligand 9; IFNγ=interferon gamma.

INDICATION

Gamifant (emapalumab-lzsg) is an interferon gamma (IFNγ)-neutralizing antibody indicated for adult and pediatric (newborn and older) patients with HLH/macrophage activation syndrome (MAS) in known or suspected Still's disease, including systemic Juvenile Idiopathic Arthritis (sJIA), with an inadequate response or intolerance to glucocorticoids, or with recurrent MAS.

IMPORTANT SAFETY INFORMATION

Infections
Gamifant may increase the risk of fatal and serious infections with pathogens including mycobacteria, herpes zoster virus, and histoplasma capsulatum. Do not administer Gamifant in patients with these infections until appropriate treatment has been initiated.

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MAS—a hyperinflammatory syndrome with devastating effects in rheumatic diseases[3,4]

MAS is a subtype of hemophagocytic lymphohistiocytosis (HLH). HLH can be associated with a variety of underlying conditions, including infection, malignancy, and rheumatic disease. MAS is the term used for HLH that is associated with underlying rheumatic diseases.[3]

MAS is characterized by[5,6]:

IFNγ-activated macrophages that release an uncontrolled surge of proinflammatory cytokines

Systemic hyperinflammation that can quickly become life-threatening

The critical role of IFNγ

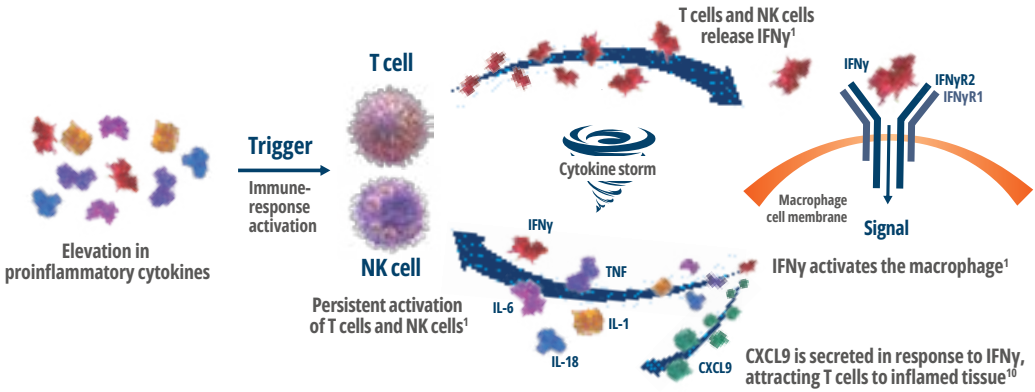
Significant upregulation of IFNγ, including high activation of the IFNγ pathway and elevated levels of IFNγ-induced chemokines, have been observed in MAS. Evidence from both human and murine studies suggests that IFNγ plays an essential pathogenic role in MAS development.[7-9]

In murine models, inhibition of this cytokine led to an improvement of clinical and laboratory features of MAS, including[9]:

- Body weight recovery
- Reduction of ferritin, fibrinogen, and ALT levels
- Decrease in downstream proinflammatory cytokines

ALT=alanine aminotransferase.

IFNγ is a central driver of hyperinflammation[1]



1. Active sJIA and AOSD are associated with elevated IL-18 and other proinflammatory cytokines. IL-18 induces IFNγ production from T cells and NK cells, which may overlap with other factors to initiate an uncontrolled inflammatory state.[11,12]

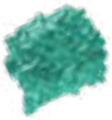
2. **High IFNγ levels overactivate macrophages** and increase monocyte sensitivity to IFNγ stimulation.[8]

3. **Activated macrophages release proinflammatory cytokines** including IL-1β, IL-6, IL-18, and TNF, which can contribute to the cytokine storm in MAS.[5]

4. **A continuous dysregulated feedback loop of cytokine production and macrophage activation** can result in systemic hyperinflammation and life-threatening organ damage.[7]

IFNγ is a key "macrophage-activating factor," triggering the cytokine storm—a surge of downstream hyperinflammation.[1]

AOSD=adult-onset Still's disease; IFNγR=interferon gamma receptor; IL=interleukin; NK=natural killer; sJIA=systemic juvenile idiopathic arthritis; TNF=tumor necrosis factor.



CXCL9: a recognized biomarker for IFNγ activity[1,2]

Diagnostic challenges

Because the symptoms of MAS are difficult to distinguish from other conditions and there is no single set of diagnostic criteria validated for all patient populations and background conditions, MAS can be challenging to diagnose.[3,6] Monitoring levels of CXCL9 may help identify these hyperinflammatory episodes.[1,4]

CXCL9 is[1,2]:

- Stable and easily measurable in serum
- Reflective of IFNγ production and activation of IFNγ-induced signaling pathways
- Useful as both an ancillary diagnostic tool and an emerging marker of treatment response

EVALUATING
CXCL9 levels

Monitoring CXCL9 levels may also be helpful in distinguishing MAS from a flare of the background rheumatic condition[2]

In a cross-sectional analysis of blood samples from patients with sJIA, including those with active MAS, active sJIA without MAS, and healthy controls, researchers measured levels of IFNγ and IFNγ-induced CXCL9. **Their findings suggest that IFNγ is a key driver of the hyperinflammation seen in MAS, but not the persistent autoinflammation of underlying sJIA.[2]**

Serum levels of IFNγ and CXCL9 are elevated in MAS in sJIA[2]

	MAS (n=20)	Active sJIA (n=28)
IFNγ pg/mL (range)	15.4 (5.1-52.6)	4.9 (3.2-8.6)
CXCL9 pg/mL (range)	13,392 (2,163-35,452)	837 (471-2,505)

CXCL9 levels have been shown to correlate with several laboratory features of MAS and decrease with reductions in disease activity.[2]

CXCL9 testing sites

CXCL9 testing may not be available at all institutions, and given that it may require a longer turnaround time, it is advisable to order this testing early in the diagnostic process. The following organizations offer CXCL9 testing to help with identifying MAS in your patients:

Machaon Diagnostics

Website	www.machaondiagnostics.com/test/cxcl9-level
Turnaround time	STAT: <24 hours Routine: <1 week
Lab hours	24/7
Phone	1-800-566-3462 510-839-5600
Fax	510-839-6153

Cincinnati Children's Hospital

Website	www.testmenu.com/cincinnatichildrens/Tests/723501
Turnaround time	4 days
Lab hours	Mon-Fri, 8:00 am to 5:00 pm (EST)
Phone	513-636-4685
Fax	513-636-3861

Disclaimer: This is not an exhaustive list of labs offering CXCL9 testing, as additional labs continue to build new capabilities. Please check for the availability of this test within your own institution prior to contacting these sites.

Managing MAS in Still's disease

Treatment for MAS with Still's disease has 2 urgent goals[5,13]:

Stabilize the patient
Control hyperinflammation to prevent irreversible organ damage

Minimize treatment toxicities
Reduce negative effects of broad-spectrum medications

Challenges with glucocorticoid use in MAS

While high-dose glucocorticoids are typically the first-line therapy for patients with MAS, there are various risks that can be associated with prolonged steroid use—especially in pediatric patients. Patients receiving steroids may experience dose-dependent side effects such as hyperglycemia, hypertension, myopathy, psychosis, growth suppression, reductions of bone density, and an increased rate of fractures.[14,15]

High-dose glucocorticoid pulse therapy produces an inadequate response in up to[4,16-18]:

33% of **pediatric** patients

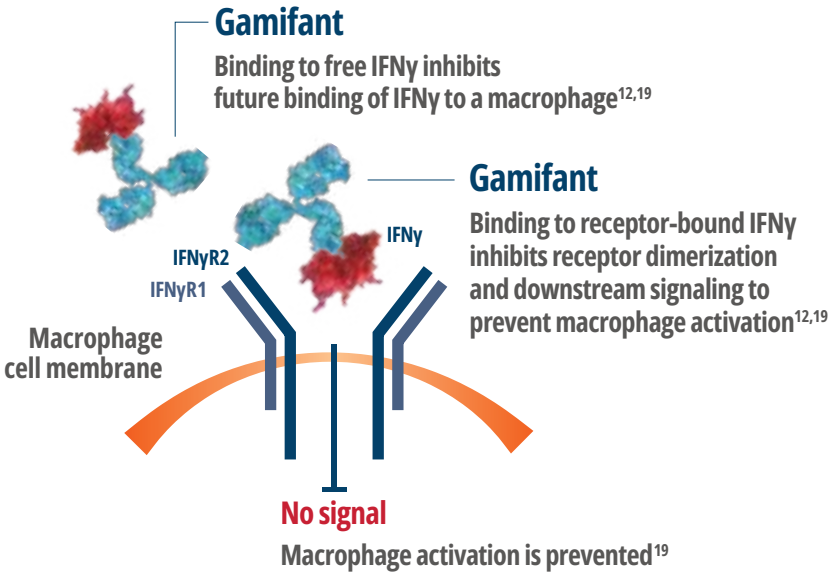
AND

80% of **adult** patients*

*According to data from individual centers.

Gamifant targets IFNγ, an upstream mediator of hyperinflammation[2,19]

Gamifant is a monoclonal antibody that binds to free and receptor-bound IFNγ. Binding to IFNγ neutralizes its activity, blocking its intracellular signaling to inhibit macrophage activation and the downstream release of proinflammatory cytokines.[19,20]



A targeted treatment option

There has been a critical need for a targeted therapy that can halt the cytokine storm and control hyperinflammation.[14] Gamifant provides a targeted treatment approach to controlling the hyperinflammation of MAS, reducing the risks of off-target effects.[2,19]

IMPORTANT SAFETY INFORMATION

Infections (continued)
In patients with HLH/MAS in Still's disease receiving Gamifant in clinical trials, serious infections such as pneumonia, cytomegalovirus infection, cytomegalovirus infection reactivation, and sepsis were observed in 13% of patients.

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Gamifant clinical trials in MAS

The efficacy and safety of Gamifant were studied in 2 open-label, single-arm, multicenter, interventional, phase 2/3, 8-week studies in 39 patients with HLH/MAS in Still's disease, including sJIA, with an inadequate response or intolerance to glucocorticoids, or with recurrent MAS. The efficacy of Gamifant was evaluated based on complete response at week 8.[12,19]

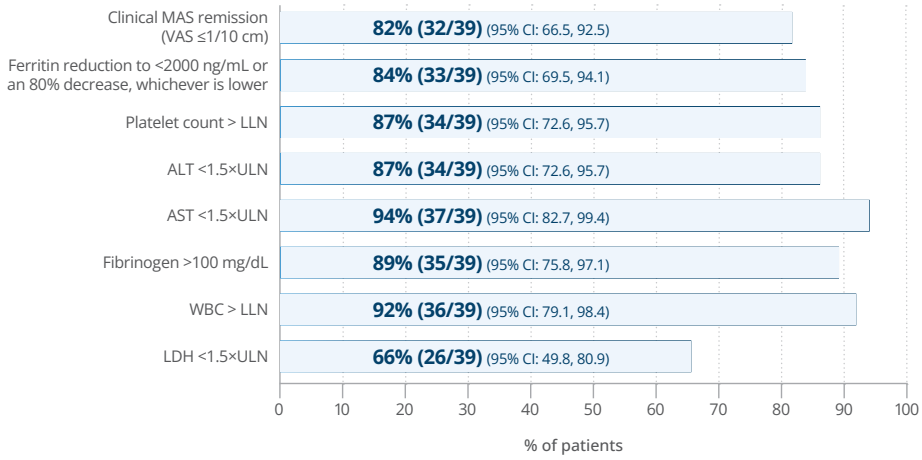
Complete response (CR)
An 8-component composite endpoint that included normalization of 7 laboratory parameters and resolution of clinical MAS activity measured by the clinician's assessment (visual analog scale [VAS] ≤1/10 cm).[19]

Key efficacy measure: CR at week 8

53% (21/39) of patients achieved CR (95% CI: 37.2, 69.9)[19]

- CR was observed as early as day 10 in 1 patient[12,*]

Individual components of the composite endpoint at week 8[19]



*The results and observations were not specifically designed or statistically powered to evaluate efficacy outcomes related to this secondary endpoint.[1]

AST=aspartate aminotransferase; LDH=lactate dehydrogenase; LLN=lower limit of normal; ULN=upper limit of normal; WBC=white blood count.

IMPORTANT SAFETY INFORMATION

Infections (continued)
Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating Gamifant. Administer tuberculosis prophylaxis to patients at risk for tuberculosis or known to have a positive purified protein derivative (PPD) test result.

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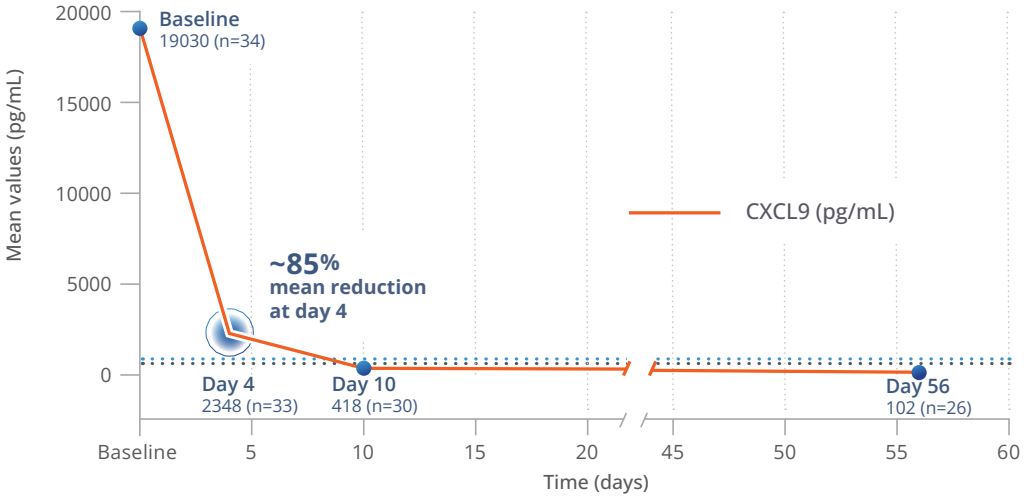
CXCL9 levels observed in the clinical trials

In the pivotal trials, a decrease in serum CXCL9 levels was observed. Reductions in CXCL9 were consistent with early onset of clinical action and time to response seen with Gamifant in the clinical trials.[12,19]



Reference values*:
Average CXCL9 levels in patients with AOSD and sJIA as measured in separate external studies

595 Average value in patients with AOSD: (595.6±790.8)[21]

837 Average value in patients with sJIA: 837 (471-2505)[2]

*The average CXCL9 levels above should be used for reference only and were not collected as part of Gamifant trials.

~85% mean reduction of CXCL9 levels was observed at day 4. Levels of CXCL9 were studied as a secondary endpoint for pharmacodynamic assessments.[12]

IMPORTANT SAFETY INFORMATION

Infections (continued)
Consider prophylaxis for herpes zoster, *Pneumocystis jirovecii*, and fungal infection while receiving Gamifant. Employ surveillance testing during treatment with Gamifant.

Closely monitor patients receiving Gamifant for signs or symptoms of infection, promptly initiate a complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

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Demonstrated safety profile

In patients with MAS in Still's disease, Gamifant demonstrated a safety profile consistent with the safety profile that has been previously established.[12]

Serious adverse reactions were reported in 31% (12/39) of patients. Fatal adverse events occurred in 5% (2/39) of adult patients and included circulatory shock and multiple organ dysfunction. 3% (1/39) of patients discontinued treatment due to an event of pneumonia.[12,19]

Adverse reactions[19]	Gamifant % (N=39)
Viral infection Cytomegalovirus infection or reactivation	44 36
Rash	21
Anemia	18
Leukopenia	15
Thrombosis	15
Bacterial infection	13
Headache	13
Hyperglycemia	13
Infusion-related reactions	13
Abdominal pain	10
Hypertension	10
Pyrexia	10
Thrombocytopenia	10

- The most common adverse reactions (≥20%) were viral infections, including CMV infection or reactivation, and rash[19]

CMV=cytomegalovirus.

IMPORTANT SAFETY INFORMATION

Increased Risk of Infection With Use of Live Vaccines
Do not administer live or live attenuated vaccines to patients receiving Gamifant and for at least 4 weeks after the last dose of Gamifant. The safety of immunization with live vaccines during or following Gamifant therapy has not been studied.

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Infections

Gamifant may increase the risk of fatal and serious infections with pathogens including mycobacteria, herpes zoster virus, and histoplasma capsulatum. Do not administer Gamifant in patients with these infections until appropriate treatment has been initiated.

In patients with HLH/MAS in Still's disease receiving Gamifant in clinical trials, serious infections such as pneumonia, cytomegalovirus infection, cytomegalovirus infection reactivation, and sepsis were observed in 13% of patients.

Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating Gamifant. Administer tuberculosis prophylaxis to patients at risk for tuberculosis or known to have a positive purified protein derivative (PPD) test result.

Consider prophylaxis for herpes zoster, *Pneumocystis jirovecii*, and fungal infection while receiving Gamifant. Employ surveillance testing during treatment with Gamifant.

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Increased Risk of Infection With Use of Live Vaccines

Do not administer live or live attenuated vaccines to patients receiving Gamifant and for at least 4 weeks after the last dose of Gamifant. The safety of immunization with live vaccines during or following Gamifant therapy has not been studied.

Infusion-Related Reactions

Infusion-related reactions in patients with HLH/MAS in Still's disease, including pyrexia, headache, paresthesia, bone pain, pruritic rash, and peripheral coldness, were reported with Gamifant treatment in 13% of patients. Infusion-related reactions were reported as mild in 8% of patients and as moderate in 5% of patients.

Monitor patients for infusion-related reactions, which can be severe. Interrupt the infusion for infusion reactions and institute appropriate medical management prior to continuing infusion at a slower rate.

Adverse Reactions

Serious adverse reactions were reported in 12 patients (31%), with the most common serious adverse reaction being pneumonia (5%). Fatal adverse reactions occurred in 2 patients (5%) and included multiple organ dysfunction and circulatory shock.

The most common adverse reactions (≥10%) for Gamifant included viral infection (44%), rash (21%), anemia (18%), leukopenia (15%), thrombosis (15%), bacterial infections (13%), headache (13%), hyperglycemia (13%), infusion-related reactions (13%), abdominal pain (10%), hypertension (10%), pyrexia (10%), and thrombocytopenia (10%).

Click here for full Prescribing Information for Gamifant.

For statutory pricing disclosures, click here.

References: 1. De Benedetti F, Prencipe G, Bracaglia C, Marasco E, Grom AA. Targeting interferon-γ in hyperinflammation: opportunities and challenges. *Nat Rev Rheumatol*. 2021;17(11):678-691. doi:10.1038/s41584-021-00694-z **2.** Bracaglia C, de Graaf K, Pires Marafon D, et al. Elevated circulating levels of interferon-γ and interferon γ-induced chemokines characterise patients with macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. *Ann Rheum Dis*. 2017;76(1):166-172. doi:10.1136/annrheumdis-2015-209020 **3.** Sen ES, Clarke SLN, Ramanan AV. Macrophage activation syndrome. *Indian J Pediatr*. 2016;83(3):248-253. doi:10.1007/s12098-015-1877-1 **4.** De Benedetti F, Grom AA, Brogan PA, et al. Efficacy and safety of emapalumab in macrophage activation syndrome. *Ann Rheum Dis*. 2023;82(6):857-865. doi:10.1136/ard-2022-223739 **5.** Schulert GS, Grom AA. Macrophage activation syndrome and cytokine directed therapies. *Best Pract Res Clin Rheumatol*. 2014;28(2):277-292. doi:10.1016/j.berh.2014.03.002 **6.** Ravelli A, Minoia F, Davì S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. *Arthritis Rheumatol*. 2016;68(3):566-576. doi:10.1002/art.39332 **7.** Crayne C, Cron RQ. Pediatric macrophage activation syndrome, recognizing the tip of the iceberg. *Eur J Rheumatol*. 2020;7(Suppl1):S13-S20. doi:10.5152/eurjrheum.2019.19150 **8.** Pascarella A, Bracaglia C, Caiello I, et al. Monocytes from patients with macrophage activation syndrome and secondary hemophagocytic lymphohistiocytosis are hyperresponsive to interferon gamma. *Front Immunol*. 2021;12:663329. doi:10.3389/fimmu.2021.663329 **9.** Prencipe G, Caiello I, Pascarella A, et al. Neutralization of IFN-γ reverts clinical and laboratory features in a mouse model of macrophage activation syndrome. *J Allergy Clin Immunol*. 2018;141(4):1439-1449. doi:10.1016/j.jaci.2017.07.021 **10.** Sylvest S. From the Clinical Laboratories of the Cancer & Blood Diseases Institute. Cincinnati Children's Hospital. Winter 2019;(15):1-4. **11.** Krei JM, Møller HJ, Larsen JB. The role of interleukin-18 in the diagnosis and monitoring of hemophagocytic lymphohistiocytosis/macrophage activation syndrome - a systematic review. *Clin Exp Immunol*. 2021;203(2):174-182. doi:10.1111/cei.13543 **12.** Data on file. Stockholm, Sweden: Sobi, Inc. 2025. **13.** Canna SW, Behrens EM. Making sense of the cytokine storm: a conceptual framework for understanding, diagnosing and treating hemophagocytic syndromes. *Pediatr Clin North Am*. 2012;59(2):329-344. doi:10.1016/j.pcl.2012.03.002 **14.** Shakoory B, Geerlinks A, Wilejto M, et al. The 2022 EULAR/ACR points to consider at the early stages of diagnosis and management of suspected haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). *Ann Rheum Dis*. 2023;82(10):1271-1285. doi:10.1136/ard-2023-224123 **15.** Hsu CH, Hsu CL, Langley A, Wojcik C, Iraganje E, Grygiel-Górniak B. Glucocorticoid-induced osteoporosis—from molecular mechanism to clinical practice. *Drugs Ther Perspect*. 2024;40:315-329. doi:10.1007/s40267-024-01079-4 **16.** Gavand P-E, Serio I, Arnaud L, et al. Clinical spectrum and therapeutic management of systemic lupus erythematosus-associated macrophage activation syndrome: a study of 103 episodes in 89 adult patients. *Autoimmun Rev*. 2017;16(7):743-749. doi:10.1016/j.autrev.2017.05.010 **17.** He L, Yao S, Zhang R, et al. Macrophage activation syndrome in adults: characteristics, outcomes, and therapeutic effectiveness of etoposide-based regimen. *Front Immunol*. 2022;13:955523. doi:10.3389/fimmu.2022.955523 **18.** Nam SH, Ahn SM, Oh JS, et al. Macrophage activation syndrome in rheumatic disease: clinical characteristics and prognosis of 20 adult patients. *PLoS One*. 2022;17(5):e0267715. doi:10.1371/journal.pone.0267715 **19.** Gamifant (emapalumab-lzsg) prescribing information. Stockholm, Sweden: Sobi, Inc. 2025. **20.** Young HA, Hodge DL. Interferon-γ. In: Henry HL, Norman AW, eds. *Encyclopedia of Hormones*. Academic Press; 2003:391-397. doi.org/10.1016/B0-12-341103-3/00151-0 **21.** Han JH, Suh C-H, Jung J-Y, et al. Elevated circulating levels of the interferon-γ–induced chemokines are associated with disease activity and cutaneous manifestations in adult-onset Still's disease. *Sci Rep*. 2017;7:46652. doi:10.1038/srep46652

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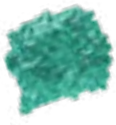
IFNγ and CXCL9: key considerations for identifying, monitoring, and managing MAS

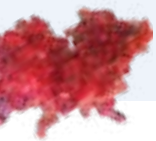
IFNγ is a key driver of the dangerous hyperinflammation in MAS in Still's disease, including sJIA[1]



CXCL9, a recognized biomarker for IFNγ activity, can be helpful as a diagnostic tool and an emerging marker of treatment response[1]

Gamifant targets and neutralizes IFNγ, an upstream mediator of the hyperinflammation in MAS in Still's disease[1,19]

For more information about the roles of IFNγ and CXCL9 in MAS, visit **Gamifant.com**.



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