

GAMIFANT

1. COMPOSITION AND PHARMACEUTICAL FORM

Each ml contains 5 mg of emapalumab. For the full list of excipients, see section 11.

Concentrate for solution for IV infusion

2. INDICATIONS AND USAGE

GAMIFANT is indicated for the treatment of:

- adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy.
- 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.

3. DOSAGE AND ADMINISTRATION

Recommended Dosage for Primary Hemophagocytic Lymphohistiocytosis

The recommended starting dose of GAMIFANT is 1 mg/kg given as a central or peripheral intravenous infusion over 1 hour twice per week (every three to four days). Doses subsequent to the initial dose may be increased based on clinical and laboratory criteria [*see Dosage and Administration(3); Dose Modification Based on Response for Primary Hemophagocytic Lymphohistiocytosis*].

Administer GAMIFANT until hematopoietic stem cell transplantation (HSCT) is performed or unacceptable toxicity. Discontinue GAMIFANT when a patient no longer requires therapy for the treatment of HLH.

Recommended Dosage for Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome

GAMIFANT is administered as a central or peripheral intravenous infusion over 1 hour according to the dosage schedule in Table 1. Doses may be increased based on clinical and laboratory criteria [*see Dosage and Administration (3); Dose Modification Based on Response for Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome*]. Discontinue GAMIFANT when a patient no longer requires therapy for the treatment of HLH/MAS.

Table 1. GAMIFANT Dosage in Patients with HLH/MAS

Treatment Day	GAMIFANT Dosage
Day 1	6 mg/kg
Days 4 to 16	3 mg/kg every 3 days for 5 doses
From Day 19 onward	3 mg/kg twice per week (i.e., every 3 to 4 days)

Monitoring to Assess Safety

Before Initiating GAMIFANT Treatment

Conduct testing for latent tuberculosis infections using the purified protein derivative (PPD) or IFN γ release assay and evaluate patients for tuberculosis risk factors prior to initiating GAMIFANT. Administer tuberculosis prophylaxis to patients at risk for tuberculosis, or known to have a positive PPD test result, or positive IFN γ release assay.

During GAMIFANT Treatment

Monitor for herpes zoster infection, adenovirus, EBV and CMV as clinically indicated.

Prophylaxis and Concomitant Medication Information

Prophylaxis

Consider prophylaxis for herpes zoster, *Pneumocystis jirovecii*, and for fungal infections prior to GAMIFANT administration.

Concomitant Medications

For primary HLH patients who are not receiving baseline dexamethasone treatment, begin dexamethasone at a daily dose of at least 5 mg/m² to 10 mg/m² the day before GAMIFANT treatment begins. For patients who were receiving baseline dexamethasone, they may continue their regular dose provided the dose is at least 5 mg/m². Dexamethasone can be tapered according to the judgment of the treating physician [see *Clinical Studies (14)*].

Dose Modification Based on Response for Primary Hemophagocytic Lymphohistiocytosis

The GAMIFANT dose may be titrated up if disease response is unsatisfactory (see Table 2) [see *Clinical Pharmacology (12)*; *Pharmacokinetics*]. After the patient's clinical condition is stabilized, decrease the dose to the previous level to maintain clinical response.

Table 2: Dose Titration Criteria

Treatment Day	GAMIFANT Dose	Criteria for Dose Increase
Day 1	Starting Dose of 1 mg/kg	N/A
On Day 3	Increase to 3 mg/kg	Unsatisfactory improvement in clinical condition, as assessed by a healthcare provider AND at least one of the following: ▪ Fever – persistence or recurrence ▪ Platelet count ▪ If baseline < 50,000/mm³ and no improvement to > 50,000/mm³ ▪ If baseline > 50,000/mm³ and less than 30% improvement ▪ If baseline > 100,000/mm³ and decrease to < 100,000/mm³ ▪ Neutrophil count ▪ If baseline < 500/mm³ and no improvement to > 500/mm³ ▪ If baseline > 500/mm³ to 1,000/mm³ and decrease to < 500/mm³ ▪ If baseline 1,000/mm³ to 1,500/mm³ and decrease to < 1,000/mm³ ▪ Ferritin (ng/mL) ▪ If baseline ≥ 3,000 ng/mL and < 20% decrease ▪ If baseline < 3,000 ng/mL and any increase to > 3,000 ng/mL ▪ Splenomegaly – any worsening ▪ Coagulopathy (both D-Dimer and Fibrinogen must apply) ▪ D-Dimer ▪ If abnormal at baseline and no improvement ▪ Fibrinogen (mg/dL)
From Day 6 onwards	Increase to 6 mg/kg	

Treatment Day	GAMIFANT Dose	Criteria for Dose Increase
		▪ If baseline levels $\leq$ 100 mg/dL and no improvement ▪ If baseline levels $>$ 100 mg/dL and any decrease to $<$ 100 mg/dL
From Day 9 onwards	Increase to 10 mg/kg	Assessment by a healthcare provider that based on initial signs of response, a further increase in GAMIFANT dose can be of benefit

Dose Modification Based on Response for Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome

Table 3: Dosage Adjustment Criteria

<u>Treatment Day</u>	<u>GAMIFANT Dose</u>	<u>Dose Adjustments</u>
Day 1	Initial dose of 6 mg/kg	If unsatisfactory improvement in clinical condition, as assessed by a healthcare provider, the dose of GAMIFANT may be increased to: • a maximum cumulative dose of 10 mg/kg over 3 days AND the frequency may be increased to: • every 2 days or once daily
Days 4 to 16	3 mg/kg every 3 days for 5 doses	
From Day 19 onwards	3 mg/kg twice per week (i.e., every 3 to 4 days)	After the patient's clinical condition has improved, consider decreasing the dose to the previous level and assess whether clinical response is maintained. If the clinical condition is not stabilized while receiving the maximum dosage, consider discontinuing GAMIFANT.

Instructions for Preparation and Administration

Preparation

GAMIFANT vials are for single dose only.

Prepare the solution for infusion as follows:

- Calculate the dose (mg/kg), total volume (mL) of GAMIFANT required and the number of GAMIFANT vials needed based on patient actual body weight [*see Dosage and Administration (3); Recommended Dosing*].

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. GAMIFANT is a clear to slightly opalescent, colorless to slightly yellow liquid. Do not administer if discolored or foreign particulate matter is present.
- Withdraw the necessary amount of GAMIFANT solution and dilute with 0.9% Sodium Chloride Injection, to a maximum concentration of 2.5 mg/mL. Do not dilute product to less than 0.25 mg/mL.
- Discard any unused portion left in the vial(s).
- The diluted solution can be placed in either a syringe or an infusion bag, depending on the volume needed.
- Use a gamma irradiated latex-free, polyvinyl chloride (PVC)-free syringe. Do not use with ethylene oxide-sterilized syringes.
- Use a non-PVC polyolefin infusion bag.

Administration

- Administer GAMIFANT diluted solution intravenously over 1 hour through a central or peripheral intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron in-line filter.
- Do not infuse GAMIFANT concomitantly with other agents and do not add any other product to the infusion bag or syringe.
- Do not store any unused portion of the infusion solution for reuse. Any unused product or waste material should be disposed of in accordance with local requirements.

Storage of Diluted Solution

This product does not contain a preservative.

If not administered immediately:

- Store the diluted solution of GAMIFANT under refrigeration at 2°C to 8°C for no more than 4 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature, typically 20°C to 25°C, prior to administration.
- Do not freeze. Do not shake.

4. DOSAGE FORMS AND STRENGTHS

GAMIFANT is a clear to slightly opalescent, colorless to slightly yellow preservative-free solution available as:

Concentrate for solution for IV infusion

- 10 mg/2 mL (5 mg/mL) in a single-dose vial
- 50 mg/10 mL (5 mg/mL) in a single-dose vial
- 100 mg/20 mL (5 mg/mL) in a single-dose vial

5. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (listed in section 11).

6. WARNINGS AND PRECAUTIONS

Infections

GAMIFANT may increase the risk of fatal and serious infections to include specific pathogens favored by IFN γ neutralization, including mycobacteria, herpes zoster virus, and *Histoplasma capsulatum*.

Do not administer GAMIFANT in patients with infections caused by these pathogens until appropriate treatment has been initiated.

In of patients with primary HLH receiving GAMIFANT in clinical trials, serious infections such as sepsis, pneumonia, bacteremia, disseminated histoplasmosis, necrotizing fasciitis, viral infections, and perforated appendicitis were observed in 32% of patients. The reported infections were viral (41%), bacterial (35%), fungal (9%), and the pathogen was not identified in 15% of cases.

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. The reported infections were viral (44%), bacterial (13%), fungal (3%) and the pathogen was not identified in (13%) of patients.

In the GAMIFANT clinical trials, additional infections were reported in patients treated with GAMIFANT including herpes zoster (2.4%) and mycobacterial infections (2.4%).

Evaluate patients for tuberculosis risk factors and test for latent infection (PPD testing, PCR, or IFN γ release assay) 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 [*see Dosage and Administration (3); Monitoring to assess safety*].

Consider prophylaxis for herpes zoster, *Pneumocystis jirovecii*, and fungal infection to mitigate the risk to patients while receiving GAMIFANT [*See Dosage & Administration (3) Monitoring to Assess Safety*]. 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.

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 primary HLH, including drug eruption, pyrexia, rash, erythema, and hyperhidrosis were reported with GAMIFANT treatment in 27% of patients. In one-third of these patients, the infusion-related reaction occurred during the first infusion.

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.

Infusion-related reactions were defined as any event reported to have occurred within 24 hours after the start of infusion and assessed as related to GAMIFANT.

In the GAMIFANT clinical trials, additional infusion-related reactions that were reported in less than 3% of patients treated with GAMIFANT included: malaise, sinus tachycardia, feeling hot, and acute respiratory failure.

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.

7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There is no information. However, emapalumab is not expected to influence or have negligible influence on the ability to drive or use machines.

8. ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Infections [*see Warnings and Precautions (6); Infections*]
- Infusion-Related Reactions [*see Warnings and Precautions (6); Infusion-Related Reactions*]
- Increased Risk of Infection with Use of Live Vaccines [*see Warnings and Precautions; Infections (6); Increased Risk of Infection with Use of Live Vaccines*]

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Primary HLH

The safety data described in this section reflect exposure to GAMIFANT in which 34 patients with untreated primary HLH and previously treated patients with primary HLH received GAMIFANT at a starting dose of 1 mg/kg every 3 days with dose increases up to 10 mg/kg [*see Dosage and Administration (3); Recommended Dosing and Clinical Studies (14)*]. The median

duration of treatment with GAMIFANT was 59 days (range: 4 to 245 days) and the median cumulative dose was 25 mg/kg (range: 4 to 254 mg/kg).

The median age of study population was 1 year (range: 0.1 to 13 years), 53% were female, and 65% were Caucasian.

Serious adverse reactions were reported in 53% of patients. The most common serious adverse reactions ($\geq 3\%$) included infections, gastrointestinal hemorrhage, and multiple organ dysfunction. Fatal adverse reactions occurred in two (6%) of patients and included septic shock and gastrointestinal hemorrhage.

Disseminated histoplasmosis led to drug discontinuation in one patient. The most commonly reported adverse reactions ($\geq 20\%$) were infections, hypertension, infusion-related reactions, and pyrexia. Adverse reactions reported in $\geq 10\%$ of patients during treatment with GAMIFANT are presented in Table 4.

Table 4: Adverse Reactions Reported in $\geq 10\%$ of Patients with Primary HLH

Adverse Reactions	GAMIFANT (%) (N = 34)
Infections ^a	56
Hypertension ^b	41
Infusion-related reactions ^c	27
Pyrexia	24
Hypokalemia	15
Constipation	15
Rash	12
Abdominal pain	12
Cytomegalovirus infection	12
Diarrhea	12
Lymphocytosis	12
Cough	12
Irritability	12
Tachycardia	12
Tachypnea	12

^aIncludes viral, bacterial, fungal, and infections in which no pathogen was identified

^bIncludes secondary hypertension

^cIncludes events of drug eruption, pyrexia, rash, erythema, and hyperhidrosis

Additional selected adverse reactions (all grades) that were reported in less than 10% of patients treated with GAMIFANT included: vomiting, acute kidney injury, asthenia, bradycardia, dyspnea, gastro-intestinal hemorrhage, epistaxis, and peripheral edema.

HLH/MAS

The safety of Gamifant was evaluated in two open-label clinical studies in patients with HLH/MAS in Still's disease, including sJIA [see Clinical Studies (14); Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome in Still's disease].

The pooled safety data from these two studies included 39 patients who received an initial dose of 6 mg/kg followed by 3 mg/kg every 3 days until Day 16, and then twice weekly thereafter. The median duration of treatment with GAMIFANT was 29 days (range: 7 to 220 days) and the median cumulative dose was 33 mg/kg (range: 12 to 175 mg/kg).

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

Pneumonia led to drug discontinuation in one patient (3%). The most common adverse reactions ($\geq 20\%$) were viral infections, including cytomegalovirus infection or reactivation, and rash. Adverse reactions reported in $\geq 10\%$ of patients in the pooled safety analysis up to Week 8 during treatment with GAMIFANT are presented in Table 5.

Table 5: Adverse Reactions Reported in $\geq 10\%$ of Patients with HLH/MAS in Still's disease

Adverse Reactions	GAMIFANT (%) (N = 39)
Viral infection ^a	44
Cytomegalovirus infection or reactivation	36
Rash ^b	21
Anemia ^c	18
Leukopenia ^d	15
Thrombosis	15
Bacterial infection	13
Headache	13
Hyperglycemia	13

Adverse Reactions	GAMIFANT (%) (N = 39)
Infusion-related reactions ^e	13
Abdominal pain	10
Hypertension	10
Pyrexia	10
Thrombocytopenia	10

^aIncludes: Cytomegalovirus infection reactivation, Cytomegalovirus infection, Adenovirus test positive, Cytomegalovirus test positive, BK polyomavirus test positive, Respirovirus test positive, Parainfluenzae virus infection, COVID-19, Rhinovirus infection, gastroenteritis Rotavirus, Adenovirus infection, Human herpesvirus 6 infection reactivation, Adenovirus reactivation

^bIncludes: rash maculo-papular, rash erythematous, rash pruritic, urticaria

^cIncludes: anemia macrocytic, and hypochromic anemia

^dIncludes: granulocytopenia, neutropenia

^eInfusion-related reactions were defined as any event reported to have occurred within 24 hours after the start of infusion and assessed as related to study treatment

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: <https://sideeffects.health.gov.il>

9. DRUG INTERACTIONS

Effect of GAMIFANT on Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (such as IFN γ) during chronic inflammation. By neutralizing IFN γ , use of GAMIFANT may normalize CYP450 activities which may reduce the efficacy of drugs that are CYP450 substrates due to increased metabolism.

Upon initiation or discontinuation of concomitant GAMIFANT, monitor for reduced efficacy and adjust dosage of CYP450 substrate drugs as appropriate.

10. USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on GAMIFANT use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. In an animal reproduction study, a murine surrogate

anti-mouse IFN γ antibody administered to pregnant mice throughout gestation crossed the placental barrier, and no fetal harm was observed (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

Data

Animal Data

In a mouse embryo-fetal development study, a murine surrogate anti-mouse IFN γ antibody was administered every 3-4 days throughout organogenesis and late gestation at doses of 0, 30, 75 or 150 mg/kg/occasion. The surrogate antibody was detected in the plasma of all treated pregnant mice and their corresponding fetuses. No maternal toxicity occurred and there was no evidence of teratogenicity or effects on embryo-fetal survival or growth.

Lactation

Risk Summary

There is no information regarding the presence of emapalumab in human milk, the effects on the breastfed child, or the effects on milk production. Published data suggest that only limited amounts of therapeutic antibodies are found in breast milk and they do not enter the neonatal and infant circulations in substantial amounts.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GAMIFANT and any potential adverse effects on the breastfed child from GAMIFANT or from the underlying maternal condition.

Pediatric Use

Safety and effectiveness of GAMIFANT have been established in pediatric patients, newborn and older, with primary HLH that is reactivated or refractory to conventional therapies and with HLH/MAS in Still's Disease (including sJIA) with an inadequate response to glucocorticoids [*see Clinical Studies (14)*]. Use of GAMIFANT is supported by 3 single-arm trials which included 57 pediatric patients: 27 with primary HLH and 30 with HLH/MAS in Still's disease. These studies included pediatric patients in the following age groups: 5 patients newborn to 6 months, 13 patients 6 months to 2 years, 27 patients from 2 years to <12 years and 12 patients from 12 years to <17 years.

Geriatric Use

Clinical studies of GAMIFANT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

11. DESCRIPTION

Emapalumab is an interferon gamma (IFN γ) neutralizing antibody. Emapalumab is produced in Chinese Hamster Ovary cells by recombinant DNA technology. Emapalumab is an IgG1 immunoglobulin with a molecular weight of approximately 148 kDa.

GAMIFANT (emapalumab) concentrate for solution for IV infusion for intravenous use is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution provided in single-dose vials that require dilution prior to intravenous infusion.

Each vial contains 10 mg/2 mL, 50 mg/10 mL, or 100 mg/20 mL emapalumab at a concentration of 5 mg/mL. Each mL also contains the following inactive ingredients: sodium chloride, L-histidine monohydrochloride, monohydrate, L-histidine, Super refined Polysorbate 80 (0.005%) and Water for Injection.

12. CLINICAL PHARMACOLOGY

Mechanism of Action

Emapalumab is a monoclonal antibody that binds to and neutralizes interferon gamma (IFN γ). Nonclinical data suggest that IFN γ plays a pivotal role in the pathogenesis of HLH by being hypersecreted.

Pharmacodynamics

IFN γ Inhibition

Emapalumab reduces the plasma concentrations of CXCL9, a chemokine induced by IFN γ .

Cardiac Electrophysiology

At a dose of 3 mg/kg GAMIFANT does not prolong the QT interval to any clinically relevant extent.

Pharmacokinetics

The pharmacokinetics of emapalumab were evaluated in healthy adult subjects and in patients with HLH.

Following a 1 mg/kg emapalumab dose, median steady state peak concentration was 44 mcg/mL, which was 2.9 times higher than after the first dose. The median steady state trough concentration was 25 mcg/mL, which was 4.3 times higher than after the first dose. Emapalumab AUC increases slightly more than proportionally between 1 and 3 mg/kg doses, and less than proportionally at 3, 6, and 10 mg/kg doses.

Emapalumab exhibits target-mediated-like clearance dependent on IFN γ production, which can vary between and within patients as a function of time and can affect the recommended dosage [see *Dosage and Administration (3); Monitoring to Assess Safety*]. Emapalumab steady state is achieved by the 7th infusion when the IFN γ production is moderate. At high IFN γ production, steady-state is reached earlier due to a shorter half-life.

Distribution

The central and peripheral volumes of distribution in a subject with body weight of 70 kg are 2.8 and 4.4 L, respectively.

Elimination

Emapalumab elimination half-life is approximately 22 days in healthy subjects, and ranged from 2.5 to 18.9 days in HLH patients.

In patients with HLH, the elimination half-life of emapalumab was significantly influenced by the amount of IFN γ within the patient, demonstrating a target mediated clearance-like mechanism. The elimination half-life of emapalumab is reduced as the concentration of IFN γ increases.

Emapalumab clearance is approximately 0.007 L/h in healthy subjects.

Metabolism

The metabolic pathway of emapalumab has not been characterized. Like other protein therapeutics, GAMIFANT is expected to be degraded into small peptides and amino acids via catabolic pathways.

Specific Populations

Body weight (3 to 80 kg) was a significant covariate of emapalumab pharmacokinetics, supporting body weight-based dosing.

No clinically significant differences in the pharmacokinetics of emapalumab were observed based on age (0.02 to 64 year), sex (53% Females), race (71.4% Caucasian, 12.2% Asian and 8.2% Black), renal impairment including dialysis, or hepatic impairment (mild, moderate, and severe).

Drug Interaction Studies

No drug-drug interaction studies have been conducted with GAMIFANT.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other emapalumab products may be misleading.

The immunogenicity of emapalumab has been evaluated using an electrochemiluminescence-based immunoassay (ECLIA). Treatment-emergent anti-drug antibodies (ADAs) were detected in 1/33 (3%) of patients in the primary HLH clinical trial. The ADAs in this patient were found to have neutralizing ability. Treatment-emergent ADAs were detected in 5/35 patients (14%) in the two HLH/MAS clinical trials. None of the ADAs in these 5 patients were found to have neutralizing ability. No evidence of an altered pharmacokinetic, safety or efficacy profile was identified in primary HLH or HLH/MAS patients who developed antibodies to emapalumab.

13. NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with emapalumab.

No studies have been conducted to evaluate the effects of emapalumab on fertility; however, no adverse effects on male or female reproductive organs were observed in the 8- or 13-week repeat-dose toxicity studies in cynomolgus monkeys.

14. CLINICAL STUDIES

Primary Hemophagocytic Lymphohistiocytosis (primary HLH)

The efficacy of GAMIFANT was evaluated in a multicenter, open-label, single-arm trial NI-0501-04 in 27 pediatric patients with suspected or confirmed primary HLH with either refractory, recurrent, or progressive disease during conventional HLH therapy or who were intolerant of conventional HLH therapy.

Patients were required to fulfill the following criteria for enrollment: primary HLH based on a molecular diagnosis or family history consistent with primary HLH or five out of the 8 criteria fulfilled: fever, splenomegaly, cytopenias affecting 2 of 3 lineages in the peripheral blood (hemoglobin < 9 , platelets $< 100 \times 10^9/L$, neutrophils $< 1 \times 10^9/L$), hypertriglyceridemia (fasting triglycerides > 3 mmol/L or ≥ 265 mg/dL) and/or hypofibrinogenemia (≤ 1.5 g/L), hemophagocytosis in bone marrow, spleen, or lymph nodes with no evidence of malignancy, low or absent NK-cell activity, ferritin ≥ 500 mcg/L, soluble CD25 ≥ 2400 U/mL. Patients had to have evidence of active disease as assessed by the treating physician. Patients had to fulfill one of the following criteria as assessed by the treating physician: having not responded or not achieved a satisfactory response or not maintained a satisfactory response to conventional HLH therapy, or intolerance to conventional HLH treatments. Patients with active infections caused by specific pathogens favored by IFN γ neutralization were excluded from the trial (e.g., mycobacteria and *Histoplasma Capsulatum*). Patients received prophylaxis for herpes zoster, *Pneumocystis jirovecii*, and fungal infections.

Twenty-seven patients enrolled and received treatment in the study and twenty patients (74%) completed the study. Seven patients (26%) were prematurely withdrawn. Twenty-two patients (81%) enrolled onto the open-label extension study which monitored patients for up to 1 year after HSCT or after the last GAMIFANT infusion (NI-0501-05).

The study treatment duration was up to 8 weeks after which patients could continue treatment on the extension study. All patients received an initial starting dose of GAMIFANT of 1 mg/kg every 3 days. Subsequent doses could be increased to a maximum of 10 mg/kg based on clinical and laboratory parameters interpreted as unsatisfactory response. Forty-four percent of patients remained at a dose of 1 mg/kg, 30% of patients increased to 3-4 mg/kg and 26% of patients increased to 6-10 mg/kg. The median time to dose increase was 27 days (range: 3-31 days) with 22% of patients requiring a dose increase in the first week of treatment.

All patients received dexamethasone as background HLH treatment with doses between 5 to 10 mg/m²/day. Cyclosporine A was continued if administered prior to screening. Patients receiving methotrexate and glucocorticoids administered intrathecally at baseline could continue these treatments.

In Study NI-0501-04, the median patient age was 1 year (0.2 to 13). Fifty-nine percent of the patients were female, 63% were Caucasian, 11% were Asian, and 11% were Black.

A genetic mutation known to cause HLH was present in 82% of patients. The most frequent causative mutations were FHL3-UNC13D (MUNC 13-4) (26%), FHL2-PRF1 (19%), and Griscelli Syndrome type 2 (19%).

The HLH mutations in the population enrolled are described in Table 6.

Table 6: HLH Mutations in Patients with Primary HLH with Prior Therapy

	GAMIFANT (N=27)
HLH Genetic Confirmation	22 (82)
FHL3 – UNC13D	7 (26)
FHL2 – PRF1	5 (19)
Griscelli Syndrome type 2 (RAB27A)	5 (19)
FHL5 – STXBP2 (UNC18B)	2 (7.4)
FHL4 – STX11	1 (3.7)
X-linked Lymphoproliferative Disorder 1	1 (3.7)
X-linked Lymphoproliferative Disorder 2	1 (3.7)

All patients received previous HLH treatments. Patients received a median of 3 prior agents before enrollment into the trial. Prior regimens included combinations of the following agents: dexamethasone, etoposide, cyclosporine A, and anti-thymocyte globulin.

At baseline entry into the study, 78% of patients had elevated ferritin levels, thrombocytopenia (70% with platelet count of < 100 x 10⁹ cells/L), hypertriglyceridemia (67%) with triglyceride level > 3 mmol/L. Central nervous system findings were present in 37% of patients. Forty-one percent of patients had active infections not due to specific pathogens favored by IFN γ neutralization at the time of GAMIFANT initiation.

The efficacy of GAMIFANT was based upon overall response rate (ORR) at the end of treatment, defined as achievement of either a complete or partial response or HLH improvement. ORR was evaluated using an algorithm that included the following objective clinical and laboratory parameters: fever, splenomegaly, central nervous system symptoms, complete blood count, fibrinogen and/or D-dimer, ferritin, and soluble CD25 (also referred to as soluble interleukin-2 receptor) levels. Complete response was defined as normalization of all HLH abnormalities (i.e., no fever, no splenomegaly, neutrophils > 1x10⁹/L, platelets > 100x10⁹/L, ferritin < 2,000 μ g/L, fibrinogen > 1.50 g/L, D-dimer < 500 μ g/L, normal CNS symptoms, no worsening of sCD25 > 2-fold baseline). Partial response was defined as normalization of $\geq$ 3 HLH abnormalities. HLH improvement was defined as $\geq$ 3 HLH abnormalities improved by at least 50% from baseline.

Table 7: Overall Response Rate at End of Treatment

GAMIFANT (N=27)	
Overall Response Rate	
N (%)	17 (63)
(95% CI)	(0.42, 0.81)
p-value†	0.013
Overall Response by Category	
Complete response, n (%)	7 (26)
Partial response	8 (30)
HLH improvement	2 (7.4)

†p-value based on Exact Binomial Test at a one-sided significance level of 2.5% comparing proportion of patients with overall response to hypothesized null hypothesis of 40%.

CI = confidence interval

The median duration of first response, defined as time from achievement of first response to loss of first response, is not reached (range: 4-56+ days). Seventy percent (19/27) of patients proceeded to HSCT.

Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome in Still's disease

The efficacy of GAMIFANT was evaluated in two open-label, single arm, multicenter studies which enrolled a total of 39 patients with hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS) in Still's disease, including systemic Juvenile Idiopathic Arthritis (sJIA), with an inadequate response to high-dose glucocorticoid treatment.

In each study, patients were required to fulfill the following criteria for enrollment: confirmed or suspected diagnosis of sJIA or AOSD; a diagnosis of active MAS with ferritin >684 ng/mL and any 2 of these 4 laboratory criteria: platelet count $\leq 181 \times 10^9/L$, AST >48 U/L, triglycerides >156 mg/dL, or fibrinogen levels ≤ 360 mg/dL; an inadequate response to high-dose IV glucocorticoids. Patients with active infections caused by specific pathogens favored by IFN γ neutralization were excluded from the trial (e.g., mycobacteria and Histoplasma Capsulatum).

In each study, GAMIFANT was administered at an initial dose of 6 mg/kg, followed by at least 3 mg/kg every 3 days until Day 16, and then twice weekly thereafter. Glucocorticoids and anakinra (<4 mg/kg/d) could be co-administered for the treatment of Still's disease.

Pooled Data

The pooled analysis includes all patients from Study NI-0501-06 and Study NI-0501-14. These two studies enrolled 39 patients who received GAMIFANT, and 37 patients completed the studies (95%). The majority of patients were female (80%) and the median age was 12.0 years (range: 0.9 to 64 years). The racial distribution was White (74%), Asian (10%), Black or African American (5%), and Other (3%), with 3 patients not reporting race (8%). Ethnicity was only collected in Study NI-0501-14 in which 88% reported Not Hispanic or Latino with 3 patients not reporting ethnicity (12%). At baseline, patients had elevated ferritin levels (median 6833 $\mu\text{g/L}$), elevated ALT (median 259 U/L), and elevated LDH (median 954 U/L).

The efficacy of GAMIFANT was based on complete response (CR), a composite endpoint consisting of clinical resolution of MAS signs and symptoms (a visual analogue scale (VAS), of ≤ 1 cm [range 0 to 10 cm]) and the following 7 laboratory parameter endpoints: WBC count and platelet count above the lower limit of normal (LLN), LDH, AST and ALT below 1.5×the upper limit of normal (ULN), fibrinogen >100 mg/dL, and ferritin levels decreased $\geq 80\%$ from values at screening or baseline (whichever was higher) or <2000 ng/mL, whichever was lower (see Table 8).

Table 8 – Pooled Efficacy Results

Composite endpoint and individual components at Week 8	n/N	% of patients	95% CI^a
Complete response (CR)	21/39	53.8	37.2, 69.9
Clinical MAS remission (VAS ≤ 1 cm) ^b	32/39	82.1	66.5, 92.5
Ferritin reduction to < 2000 ng/mL or an 80% decrease ^c	33/39	84.6	69.5, 94.1
Platelet count above the LLN	34/39	87.2	72.6, 95.7
ALT below 1.5× ULN	34/39	87.2	72.6, 95.7
AST below 1.5×ULN	37/39	94.9	82.7, 99.4
Fibrinogen > 100 mg/dL	35/39	89.7	75.8, 97.1
WBC above the LLN	36/39	92.3	79.1, 98.4
LDH below 1.5×ULN	26/39	66.7	49.8, 80.9

^aClopper-Pearson confidence interval is presented: two-sided 95% confidence interval

^bClinical MAS remission was assessed using a visual analogue scale (VAS) where 0 cm referred to no clinical signs or symptoms of MAS and 10 cm referred to the worst possible clinical signs and symptoms of MAS

^c80% decrease calculated from values at screening or baseline (whichever was highest) or < 2000 ng/mL, whichever was lowest

15. HOW SUPPLIED/STORAGE AND HANDLING

GAMIFANT (emapalumab) concentrate for solution for I.V infusion is a sterile, clear to slightly opalescent, colorless to slightly yellow solution supplied in the following packaging configuration:

containing one 10 mg/2 mL (5 mg/mL) single-dose vial

containing one 50 mg/10 mL (5 mg/mL) single-dose vial

containing one 100 mg/20 mL (5 mg/mL) single-dose vial

Store GAMIFANT in a refrigerator at 2°C to 8°C in original carton to protect from light. Do not freeze or shake. This product contains no preservatives.

The expiry date of the product is indicated on the packaging materials.

Not all pack sizes may be marketed.

16. REGISTRATION HOLDER

Truemed Ltd.,

10 Beni Gaon St., Poleg Industrial Park, P.O.B 8105, Netanya 4250499

17. MANUFACTURER

Swedish Orphan Biovitrum AB (publ), Stockholm, Sweden

18. REGISTRATION NUMBER

174-81-37435

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