gamifant®
emapalumab-lzsg

Gamifant® (emapalumab-lzsg) Clinical Overview

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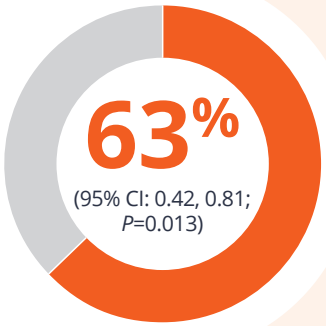
The Only FDA-Approved Drug for Primary HLH

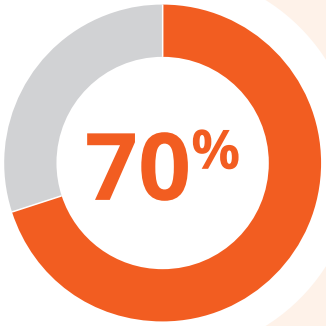
- Gamifant® (emapalumab-lzsg) is the only drug approved by the US Food and Drug Administration (FDA) for treating primary hemophagocytic lymphohistiocytosis (HLH) in adult and pediatric patients.[1,2]
- The efficacy of Gamifant was evaluated in a multicenter, open-label, single-arm trial in pediatric patients with primary HLH who were either treatment-naive (n=7) or treatment-experienced (n=27) with refractory, recurrent, or progressive disease or were intolerant of conventional HLH therapy.[1,3]
  — Efficacy was evaluated in 27 patients and safety was evaluated in 34 patients.



Primary endpoint: overall response rate (ORR)[1]

17 of 27 treatment-experienced patients achieved overall response*

- ORR was defined as achievement of either a complete or partial response or HLH improvement.[1]
- Median time to response was 8 days and responses were generally maintained.[3]
- Median duration of first response, defined as time from achievement of first response to loss of first response, was not reached.[1]



Key secondary endpoint: hematopoietic stem cell transplant (HSCT)[3]

19 of 27 treatment-experienced patients proceeded to HSCT[1,]*

- Median time to transplant was 83 days for patients who had an inadequate response to initial therapy.[4]

*All patients received dexamethasone as background HLH treatment, with doses of between 5 mg/m^2 and 10 mg/m^2 per day.[1]

Indication

Gamifant® (emapalumab-lzsg) is an interferon gamma (IFNγ)-blocking antibody 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.

Important Safety Information

Infections

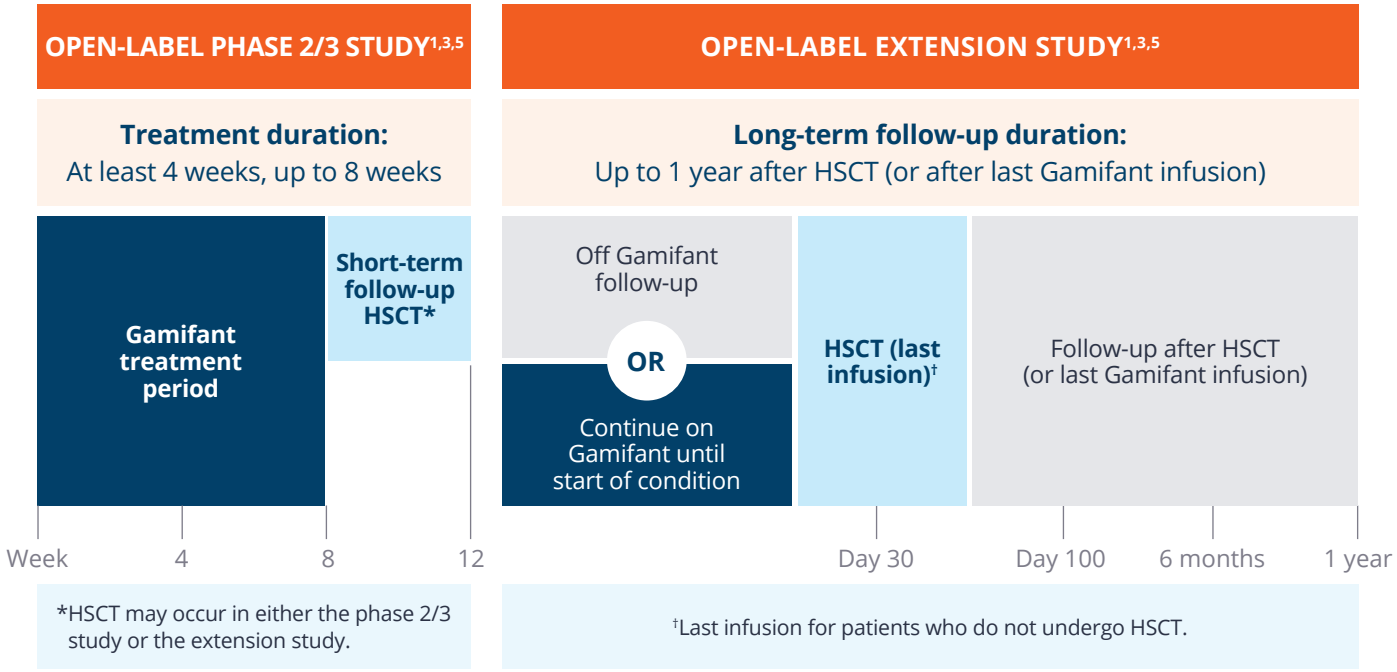
Before initiating Gamifant, patients should be evaluated for infection, including latent tuberculosis (TB). Prophylaxis for TB should be administered to patients who are at risk for TB or known to have a positive purified protein derivative (PPD) test result or positive IFNγ release assay.

Please see Important Safety Information on page 7. Click here for full Prescribing Information for Gamifant.

Pivotal Clinical Trial of Gamifant® (emapalumab-lzsg)

Study design

- A multicenter, open-label, single-arm trial in 27 pediatric patients with primary HLH.[1]
- Patients had a confirmed diagnosis of primary HLH through either fulfillment of 5 of the 8 HLH-2004 criteria, a positive genetic test for mutations associated with primary HLH, or a family history consistent with HLH.[1]
- Patients had refractory, recurrent, or progressive disease or intolerance to conventional therapy.[1]
- Patients received a median of 3 prior therapies before enrollment in the trial.[1]
- Treatment was planned for 8 weeks, but could be shortened to no less than 4 weeks or extended, if needed, for HSCT timing.[3]



- Twenty-seven patients enrolled and 20 patients (74%) completed the study.[1]
- Twenty-two patients enrolled in the open-label extension study for up to 1 year after HSCT or after the last Gamifant infusion.[1]

Important Safety Information *(cont'd)*

Infections *(cont'd)*

During Gamifant treatment, patients should be monitored for TB, adenovirus, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) every 2 weeks and as clinically indicated.

Patients should be administered prophylaxis for herpes zoster, *Pneumocystis jirovecii*, and fungal infections prior to Gamifant administration.

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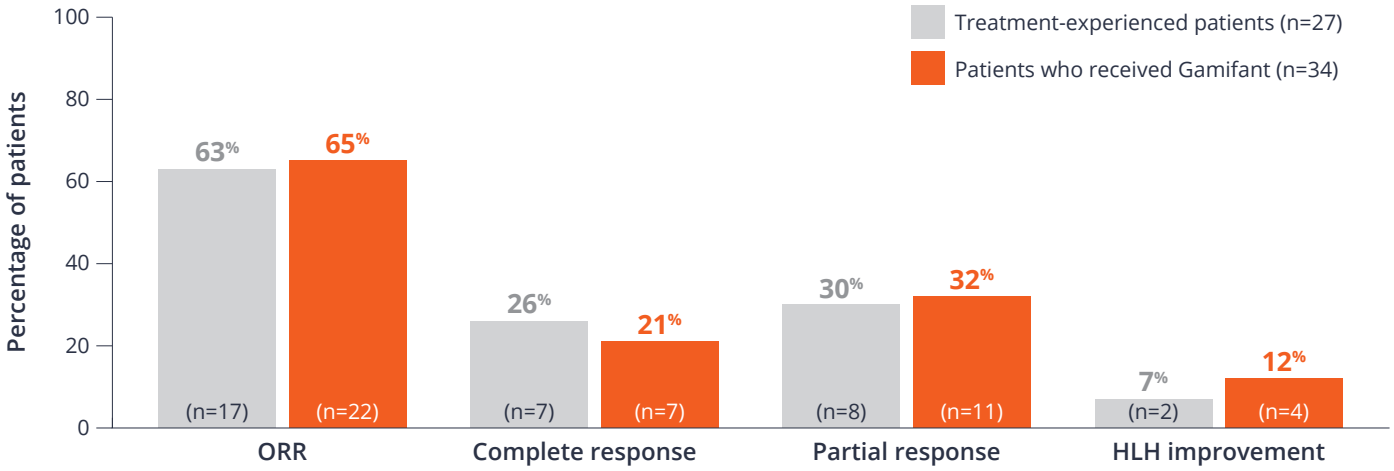
Pivotal Clinical Trial of Gamifant® (emapalumab-lzsg) *(cont'd)*

Clinical efficacy

Primary Endpoint: ORR

- Gamifant provided a statistically and clinically significant reduction in primary HLH disease activity.[1,3]
- **63%** of treatment-experienced patients (17/27) achieved overall response (95% CI: 0.42, 0.81; *P*=0.013*).[1,3,†]
- ORR was assessed at the end of treatment (4 to 8 weeks).[1,3]

ORR at end of treatment[3,5]



What Is ORR?[1]

ORR is defined as achievement of either a **complete response** or **partial response** or **HLH improvement** evaluated using an algorithm of objective clinical and laboratory parameters.

Complete response: Normalization of all HLH abnormalities (ie, no fever, no splenomegaly, neutrophils >1x10^9/L, platelets >100x10^9/L, ferritin <2000 µg/L, fibrinogen >1.50 g/L, D-dimer <500 µg/L, normal central nervous system symptoms, and no worsening of soluble CD25 >2-fold baseline‡)

Partial response: Normalization of ≥3 HLH abnormalities

HLH improvement: ≥3 HLH abnormalities improved by at least 50% from baseline

**P* value based on Exact Binomial Test at a one-sided significance level of 2.5% comparing proportion of patients with overall response with the null hypothesis of 40%.[1]
†All patients received dexamethasone as background HLH treatment, with doses of between 5 mg/m^2 and 10 mg/m^2 per day.[1]
‡Soluble CD25 is also referred to as soluble IL-2 receptor.[1]

Important Safety Information *(cont'd)*

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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Pivotal Clinical Trial of Gamifant® (emapalumab-lzsg) *(cont'd)*

Clinical efficacy *(cont'd)*

Key Secondary Endpoint: HSCT[3]

- **70%** of treatment-experienced patients (19/27) proceeded to HSCT.[1,*]
  - — HSCT is the only cure for primary HLH, but it requires that hyperinflammation be controlled prior to transplant.[6,7]

Open-label Extension (OLE) Study

- **81%** of pivotal study patients were enrolled in the OLE.[1]
- Patients were monitored for up to 1 year after HSCT or after the last Gamifant infusion.[1]
- The safety and efficacy observed in the OLE was consistent with what was observed in the pivotal trial.

Dosage and administration of Gamifant

Recommended Dosing[1]

Starting Dose	Titration	Frequency
• 1 mg/kg intravenously infused over 1 hour	Dose may be titrated up if disease response is unsatisfactory as assessed by a healthcare professional • Day 3: increase to 3 mg/kg • From Day 6 onward: increase to 6 mg/kg • From Day 9 onward: increase to 10 mg/kg (max dose)	• Twice a week (every 3 to 4 days) until HSCT

- After the patient's clinical condition is stabilized, the dose may be decreased to the previous level to maintain clinical response until HSCT.[1]

*All patients received dexamethasone as background HLH treatment, with doses of between 5 mg/m^2 and 10 mg/m^2 per day.[1]

Important Safety Information *(cont'd)*

Infusion-Related Reactions

Infusion-related reactions, 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.

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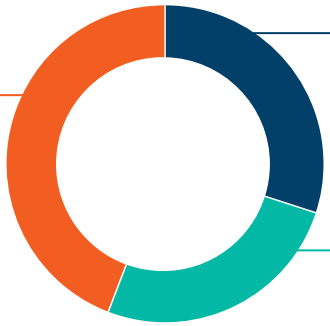
Pivotal Clinical Trial of Gamifant® (emapalumab-lzsg) *(cont'd)*

In the pivotal clinical trial, Gamifant was administered for 4 to 8 weeks and most patients remained on the lowest dosages[1,3]



44% of patients remained on the starting dose of 1 mg/kg

30% of patients required a modest dose escalation to 3 mg/kg to 4 mg/kg

26% of patients required a dose escalation to 6 mg/kg to 10 mg/kg

- The median time to dose increase was 27 days, with 22% of patients requiring a dose increase in the first week of treatment.[1]
- All patients received concomitant dexamethasone, which was tapered according to the treating physician's judgment.[1]

Safety information

- Infusion-related reactions were reported with Gamifant treatment in 27% of patients. In one-third of these patients, the infusion-related reaction occurred during the first infusion.[1]

The most commonly reported adverse reactions (≥10%) included[1]

- Infection (56%)
- Hypertension (41%)
- Infusion-related reactions (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%)

Disseminated histoplasmosis led to drug discontinuation in 1 patient.[1]

- Serious adverse reactions were reported in 53% of patients. The most common serious adverse reactions (≥3%) included infections, gastrointestinal hemorrhage, and multiple organ dysfunction.[1]
- Fatal adverse reactions occurred in 2 (6%) patients and included septic shock and gastrointestinal hemorrhage.[1]
- Additional selected adverse reactions (all grades) reported in <10% of patients treated with Gamifant included vomiting, acute kidney injury, asthenia, bradycardia, dyspnea, gastrointestinal hemorrhage, epistaxis, and peripheral edema.[1]
- 13 of 34 patients (38%) entered the study with ongoing infections or positive microbiological results.[4]

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Indication and Important Safety Information

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Infusion-Related Reactions

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Adverse Reactions

In the pivotal trial, the most commonly reported adverse reactions (≥10%) for Gamifant included infection (56%), hypertension (41%), infusion-related reactions (27%), pyrexia (24%), hypokalemia (15%), constipation (15%), rash (12%), abdominal pain (12%), CMV infection (12%), diarrhea (12%), lymphocytosis (12%), cough (12%), irritability (12%), tachycardia (12%), and tachypnea (12%).

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, gastrointestinal hemorrhage, epistaxis, and peripheral edema.

Click here for full Prescribing Information for Gamifant.

References: 1. Gamifant [prescribing information]. Waltham, MA: Sobi, Inc; 2022. **2.** FDA approves Gamifant® (emapalumab), the first and only treatment for primary haemophagocytic lymphohistiocytosis (HLH) [news release]. Stockholm, Sweden: Sobi; November 20, 2018. Accessed December 5, 2022. https://www.sobi.com/en/press-releases/fda-approves-gamifantr-emapalumab-first-and-only-treatment-primary-haemophagocytic **3.** Locatelli F, Jordan MB, Allen C, et al. Emapalumab in children with primary hemophagocytic lymphohistiocytosis. *N Engl J Med*. 2020;382(19):1811-1822. doi:10.1056/NEJMoa1911326 **4.** Data on File. Sobi, Inc. 2018. **5.** Locatelli F, Jordan MB, Allen C, et al. Emapalumab in children with primary hemophagocytic lymphohistiocytosis. Supplementary Appendix. Accessed December 5, 2022. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1911326/suppl_file/nejmoa1911326_appendix.pdf **6.** Henter JI, Horne A, Aricó M, et al; for the Histiocyte Society. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48(2):124-131. doi:10.1002/pbc.21039 **7.** Morimoto A, Nakazawa Y, Ishii E. Hemophagocytic lymphohistiocytosis: pathogenesis, diagnosis, and management. *Pediatr Int*. 2016;58(9):817-825 doi:10.1111/ped.13064

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