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emapalumab-lzsg

Gamifant clinical trial in children with primary hemophagocytic lymphohistiocytosis

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.

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Study overview[1]

Background

Primary hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome characterized by immune dysregulation, hyperinflammation, and high mortality. The objective of treatment is to suppress inflammation in preparation for allogeneic hematopoietic stem cell transplantation (HSCT), the only curative therapy. Conventional treatments investigated by the Histiocyte Society have become the standard of care, but no protocol exists for patients with relapsed or refractory disease. Mounting evidence supports the pivotal pathogenic role of interferon gamma (IFNγ) in primary HLH.

Objective

The objective of this study was to test the safety and efficacy of intravenous emapalumab administered on a background of dexamethasone in patients with refractory, recurrent, or progressive disease or intolerance to conventional therapy.

- Emapalumab is a monoclonal antibody that binds to free and receptor-bound IFNγ to neutralize its activity

Patients

Previously treated and untreated patients 18 years of age or younger who had primary HLH were evaluated for safety (N=34) and efficacy (N=27).[1,2]

- Diagnosis was based on molecular assessment, family history, or the presence of ≥5 of the 8 HLH-2004 criteria
  - 82% of patients were confirmed and 18% were suspected to have primary HLH[2]
- Previously treated patients had worsened or reactivated disease, an unsatisfactory response to conventional therapy, or were unable to continue to receive conventional therapy due to adverse effects
- Prior regimens included combinations of dexamethasone, etoposide, cyclosporine A, anti-thymocyte globulin, methylprednisolone, alemtuzumab, anakinra, glucocorticoids, and/or methotrexate[1]

Primary endpoint

Overall response in previously treated patients

Secondary endpoints*

- Time to response
- Duration of response
- Progression to HSCT
- Number of patients in whom dexamethasone was decreased by at least 50%

*Please consult reprint for additional secondary endpoints evaluated.

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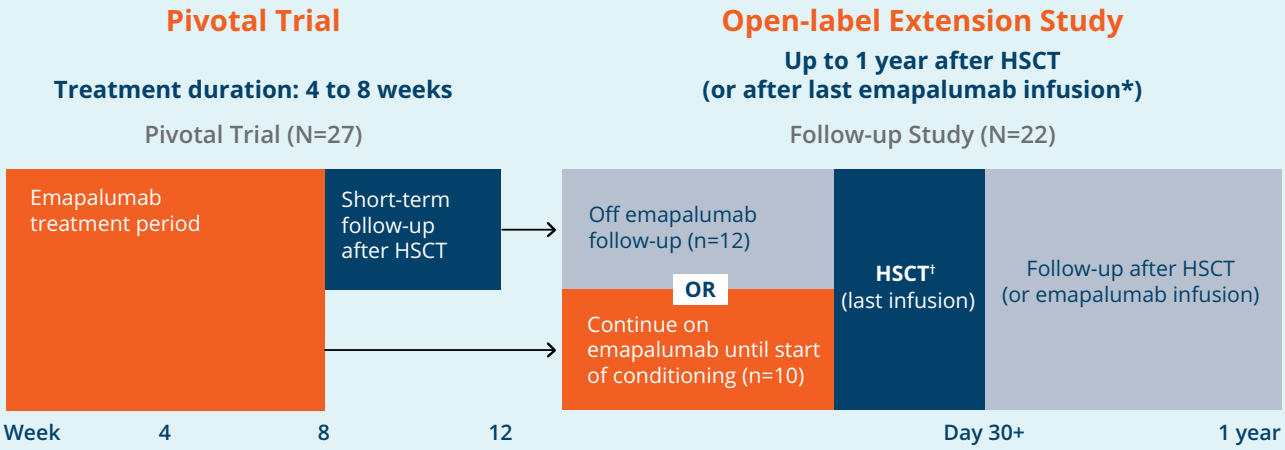
Pivotal trial design

- The efficacy of emapalumab was evaluated in a phase 2-3 multicenter, open-label, single-arm trial in 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[2]
- Twenty-seven patients enrolled and received treatment for 4 to 8 weeks in the study, and 20 patients (74%) completed the study. Seven patients (26%) were prematurely withdrawn[1,2]
- Twenty-two patients (81%) enrolled in the open-label extension study, which monitored patients for up to 1 year after HSCT or after the last emapalumab infusion[2]

Study design overview[1-3]



*Last infusion for patients who did not undergo HSCT.

†HSCT may occur either in the pivotal trial or follow-up study.

- All patients received dexamethasone as background HLH treatment with doses of between 5 mg/m^2 and 10 mg/m^2 per day[2]
- Emapalumab was administered at a starting dose of 1 mg/kg every 3 days, with subsequent dose increases up to 10 mg/kg based on clinical and laboratory parameters interpreted as an unsatisfactory response[2]
  - Forty-four percent of patients remained at a dose of 1 mg/kg, 30% of patients increased to 3 mg/kg to 4 mg/kg, and 26% of patients increased to 6 mg/kg to 10 mg/kg
  - The median time to dose increase was 27 days (range: 3-31 days)
  - Twenty-two percent of patients required a dose increase in the first week of treatment

Important Safety Information

Infections (continued)

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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Efficacy[1,2]

63% (17/27) overall response rate with emapalumab

(95% CI: 0.42, 0.81; *P* = .013)

70% of patients (19/27) proceeded to HSCT

- Overall response rate was defined as achievement of either a complete or partial response or improvement in measures of HLH[2,*]
- Median time to response was 8 days in previously treated patients and patients who received emapalumab
  - First response was maintained for 18 days in 75% of the previously treated patients and 26 days in 75% of patients who received emapalumab
- Median duration of first response, defined as time from achievement of first response to loss of first response, was not reached[2]

*Complete response: normalization of all HLH abnormalities (ie, no fever, no splenomegaly, neutrophils >1 x 10^9/L, platelets >100 x 10^9/L, ferritin <2000 µg/L, fibrinogen >1.50 g/L, D-dimer <500 µg/L, normal central nervous system symptoms, 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.

Important Safety Information

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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Safety

Serious adverse reactions were reported in 53% of patients. The most common serious adverse reactions (≥3%) included infections, gastrointestinal hemorrhage, and multiple organ dysfunction.[2]

Fatal adverse reactions occurred in two (6%) of patients and included septic shock and gastrointestinal hemorrhage.[2]

Infusion-related reactions were reported with emapalumab treatment in 27% of patients. In one-third of these patients, the infusion-related reaction occurred during the first infusion.[2]

The most commonly reported adverse reactions (≥10%) included[2]:

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

[a]Includes viral, bacterial, fungal, and infections in which no pathogen was identified.

[b]Includes secondary hypertension.

[c]Includes events of drug eruption, pyrexia, rash, erythema, and hyperhidrosis.

- Thirty-five percent of patients entered the study with ongoing infections or positive microbiological results[1]
- Disseminated histoplasmosis led to drug discontinuation in 1 patient[2]
- Serious infections such as sepsis, pneumonia, bacteremia, disseminated histoplasmosis, necrotizing fasciitis, viral infections, and perforated appendicitis were seen in 32% of patients taking emapalumab in clinical trials[2]
- Additional selected adverse reactions (all grades) reported in <10% of patients treated with emapalumab included vomiting, acute kidney injury, asthenia, bradycardia, dyspnea, gastrointestinal hemorrhage, epistaxis, and peripheral edema[2]

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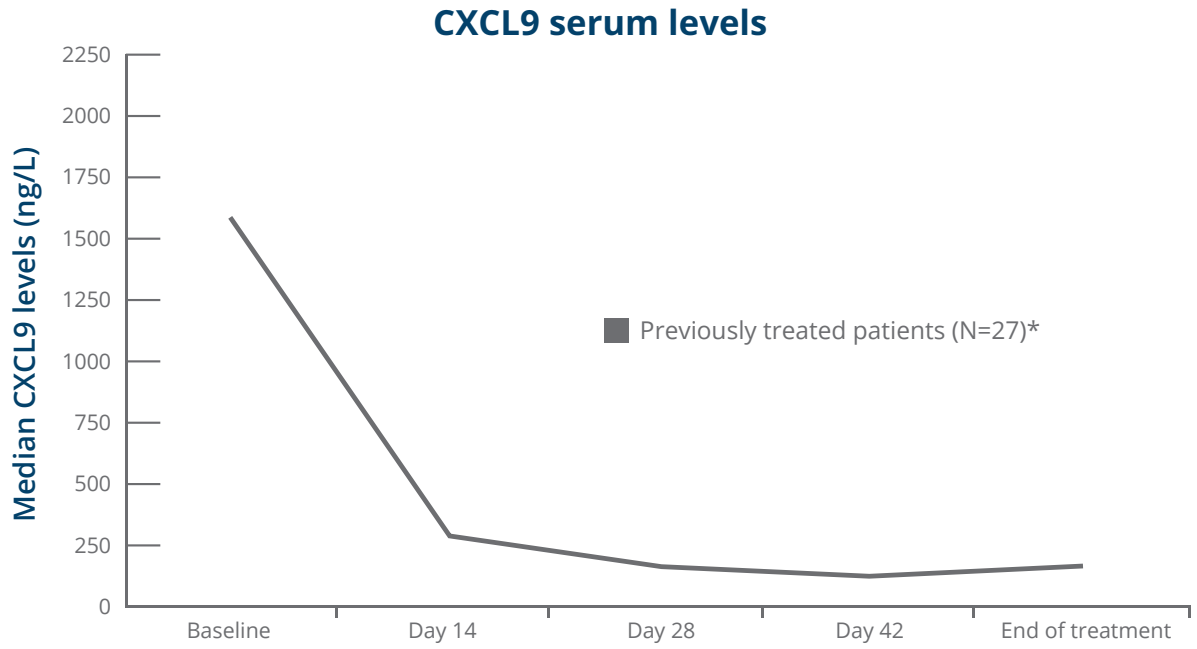
Additional analysis: CXCL9

Serum levels of CXCL9, an IFNγ-induced chemokine, were measured to assess IFNγ neutralization[1]

- During treatment with emapalumab, CXCL9 levels rapidly and markedly decreased (median, 30% of the baseline level on day 5)
- Logistic-regression analysis indicated that low CXCL9 levels were associated with a response at the end of treatment



*27 of the 34 patients treated with emapalumab had received other therapies prior to enrolling in the study.

Low levels of CXCL9 support neutralization of IFNγ as a therapeutic objective in patients with primary HLH

Important Safety Information

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.

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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

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Adverse Reactions

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References: 1. 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 **2.** Gamifant (emapalumab-lzsg) prescribing information. Stockholm, Sweden: Sobi, Inc. 2022. **3.** Data on file. Stockholm, Sweden: Swedish Orphan Biovitrum AB.

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Emapalumab was efficacious in neutralizing IFNγ and controlling hyperinflammation in patients in whom conventional therapies had failed[1]

"Most patients (N=19/27) who received emapalumab in our study proceeded to allogeneic hematopoietic stem-cell transplantation."[1]

Important Safety Information

Adverse Reactions

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sobi rare strength

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