SOCIETÀ ITALIANA DI FARMACOLOGIA

Riconosciuta con D.M. del MURST del 02/01/1996
Iscritta Registro Persone Giuridiche Prefettura di Milano n. 467 pag 722 vol. 2°
C.F.: 97053420150 – P.I.: 11453180157

UNI EN ISO 9001:2015 CERTIQUALITY SISTEMA DI GESTIONE QUALITÀ CERTIFICATO

EMAPALUMAB

Edited by: Annalisa Capuano, SIF Crisis Unit on SARS-CoV-2, Carmen Ferrajolo and Mario Gaio, University of Campania "Luigi Vanvitelli"

8 April 2020

Description of the drug

Emapalumab (Gamifant) is a fully human immunoglobulin G1 monoclonal antibody directed against interferon-γ (IFN-γ), which received in November 2018 the approval for the treatment of pediatric and adult patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent, or progressive disease or intolerance to HLH therapy [1, 2]. In Europe, emapalumab was accepted for review by the European Medicines Agency (EMA) in August 2018 and has been granted orphan designation and PRIority MEdicine (PRIME) status by the EMA.

Pharmacokinetic characteristics

The pharmacokinetics of emapalumab was evaluated in healthy adult subjects and in patients with primary HLH. Following a 1 mg/kg emapalumab-lzsg dose, median steady state peak concentration was 44 mcg/mL. AUC of emapalumab 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 clearance dependent on IFNγ production, and its steady state is achieved by the 7th infusion when the IFNγ production is moderate. At high IFNγ production, steady-state is reached earlier due to a shorter half-life. Like other therapeutic proteins, emapalumab is degraded into small peptides and amino acids via catabolic pathways.

Mechanism of action and pharmacodynamic characteristics

Emapalumab acts by binding and neutralizing interferon-gamma (IFNγ) [3].

Rationale for the use of emapalumab in the treatment of SARS-CoV-2 infection

The hyper-inflammation, caused by a cytokine storm resulting from an exaggerated response of the immune system to the presence of the virus, is considered to represent one of the most important negative prognostic factor in patients infected with SARS-CoV-2. It was assumed that the specific mechanism of action of emapalumab might inhibit pro-infiammatory cytokine expression [4]. Given the possible role of emapalumab in counteracting the excessive inflammatory response triggered at the lung level by the new coronavirus, the Italian Medicine Agency (AIFA) authorized an open label,

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

controlled, parallel group, 3-arm, multicenter study (Sobi.IMMUNO-101) to assess the efficacy and safety of emapalumab or anakinra (a human interleukin-1 receptor antagonist), versus standard of care [5]. Moreover, the study aims to evaluate, as far as possible, the effects of emapalumab and anakinra on CXCL9, IL-1, IL-6, IL-2R and other relevant biomarkers for hyperinflammation.

Treatment scheme in COVID-19 patients

The protocol of the ongoing clinical trial approved by AIFA [5] reported the following dosage regimes: intravenous infusion every 3rd day for a total 5 infusions. Day 1: 6mg/kg. Days 4, 7, 10 and 13: 3 mg/kg.

All patients participating in the study will receive background therapy with methylprednisolone (mPDN), even if the patient is not being treated with mPDN or is being treated with other glucocorticoids, according to the following scheme:

- Days 1-5: 20 mg/3 die;
- Days 6-10: 10 mg/3 die;
- Days 11-14: 5 mg/3 die.

In patients showing worsening of clinical condition, independently of the treatment arm, the Investigator is completely free to decide to introduce any drug considered necessary for a given patient as rescue treatment, but concomitant use of IL-6 inhibitors (e.g., tocilizumab), non-anakinra IL-1 inhibitors (i.e., canakinumab), TNF inhibitors, JAK inhibitors and hydroxychloroquine is not allowed.

Full version of the protocol is available on the AIFA website at the following link: https://www.aifa.gov.it/documents/20142/1131319/Sobi.IMMUNO-101_documenti.zip

Inclusion Criteria:

- Documented presence of SARS-CoV-2 infection as per hospital routine;
- Age > 30 to < 80 years at the time of screening;

a) Presence of respiratory distress, defined as: PaO2/FiO2 < 300 mm Hg and >200 mm Hg or Respiratory Rate (RR) ≥30 breaths/min or SpO2 < 93 percent in air at rest;

- Lymphocyte counts < 1000 cells/µL and two of the following three criteria:

i. Ferritin > 500ng/mL ii. LDH > 300 U/L iii. D-Dimers > 1000 ng/mL

Exclusion Criteria:

- Patients in mechanical ventilation or with modified early warning score (MEWS) >4 with evidence of moderate or above ARDS or severe respiratory insufficiency or evidence of rapid worsening;

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

Sito Web: https://www.sifweb.org/

- Impairment of cardiac function;
- Severe renal dysfunction or receive continuous renal replacement therapy, hemodialysis, or peritoneal dialysis;
- Uncontrolled hypertension;
- Administration of plasma from convalescent patients who recovered from SARS-CoV-2 infection;
- Clinical suspicion of latent tuberculosis;
- History of hypersensitivity or allergy to any component of the study drug;
- Pregnant women;
- Enrollment in another concurrent clinical interventional study, or intake of an investigational drug within three months or 5 half-lives prior to the inclusion in the study.
-

Toxicity monitoring

The safety data described in this section reflect exposure to emapalumab in which 34 patients with untreated primary HLH and previously treated patients with primary HLH [6] received emapalumab at a starting dose of 1 mg/kg every 3 days with dose increases up to 10 mg/kg. The median duration of treatment with emapalumab was 59 days and the median cumulative dose was 25 mg/kg. Serious adverse reactions were reported in 53% of patients. The most common serious adverse reactions (≥ 3%) included infections, gastrointestinal hemorrhage, and multiple organ dysfunctions.
The adverse reactions are summarized in the following table:

System Organ Class	**Adverse reactions (frequency %)**	**Precautions**
Infections and infestations	Infections[a] (36%), cytomegalovirus infection (12%)	Administer prophylaxis for Herpes Zoster, Pneumocystis jirovecii, and fungal infection to mitigate the risk to patients while receiving emapalumab.
Blood and lymphatic system disorders	Lymphocytosis (12%)	
Immune system disorders	Infusion-related reactions[c] (27%)	
Metabolism and nutrition disorders	Hypokalemia (15%)	
Psychiatric disorders	Irritability (12%)	

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

Sito Web: https://www.sifweb.org/

Cardiac disorders	Tachycardia (12%)	
Vascular disorders	Hypertension[b] (41%)	
Respiratory, thoracic and mediastinal disorders	Cough (12%), Tachypnea (12%)	
Gastrointestinal disorders	Constipation (15%), abdominal pain (12%), diarrhea (12%)	
Skin and subcutaneous tissue disorders	Rash (12%)	
General disorders and administration site conditions	Pyrexia (24%)	

[a]Includes viral (41%), bacterial (35%), fungal (9%) and infections in which no pathogen was identified (15%)
[b]Includes events of drug eruption, pyrexia, rash, erythema, and hyperhidrosis
[c]Includes secondary hypertension

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.

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of emapalumab has been evaluated using an electrochemiluminescence-based immunoassay (ECLIA). A total of 64 subjects were evaluated for anti-therapeutic antibodies (ATAs) to emapalumab after treatment with emapalumab. ATAs were detected in 3/64 subjects (5%). No evidence of an altered safety or efficacy profile was identified in the primary HLH patients who developed antibodies to emapalumab.

Safety endpoints of Sobi.IMMUNO-101:

- Treatment-emergent severe fatal and life-threatening serious adverse events (SAEs);
- Adverse events leading to premature discontinuation of study treatment;
- Anaphylactic/anaphylactoid reactions;
- Infections caused by pathogens potentially favored by IFN-γ neutralizations such as mycobacteria, salmonella, shigella, herpes zoster and histoplasma capsulatum;
- Severe infusion-related reactions;
- Treatment-emergent laboratory abnormalities.

Potential interactions

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

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

Sito Web: https://www.sifweb.org/

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

Bibliografia

1. FDA – Drug Approvals and Databases (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761107Orig1s000TOC.cfm)
2. Vallurupalli M, Berliner N. Emapalumab for the treatment of relapsed/refractory hemophagocytic lymphohistiocytosis. Blood 2019, 134:1783-86.
3. Kaplon H, Reichert JM: Antibodies to watch in 2018. MAbs. 2018 Feb/Mar;10(2):183-203. doi: 10.1080/19420862.2018.1415671. Epub 2018 Jan 16.
4. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020 Mar 28;395(10229):1033-1034.
4. ClinicalTrials.gov – Identifier: NCT04324021 (https://clinicaltrials.gov/ct2/show/NCT04324021?term=Emapalumab&draw=2&rank=3)
5. ClinicalTrials.gov – Identifier: NCT01818492 (https://clinicaltrials.gov/ct2/show/NCT01818492?term=NCT01818492&draw=2&rank=1)

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

Sito Web: https://www.sifweb.org/