CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761107Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

This NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761107
Priority or Standard	Priority
Submit Date(s)	March 20, 2018
Received Date(s)	March 20, 2018
PDUFA Goal Date	November 20, 2018
Division/Office	DHP/OHOP
Review Completion Date	November 19, 2018
Established Name	Emapalumab-lzsg
(Proposed) Trade Name	GAMIFANT
Pharmacologic Class	Interferon gamma (IFNγ) blocking antibody
Code name	NI-0501
Applicant	Novimmune S.A.
Formulation(s)	Injection (10 mg/2 ml, 50 mg/10 ml)
Dosing Regimen	1 mg/kg IV over one hour twice weekly (every 3 (b) (4) days)
Applicant Proposed Indication(s)/Population(s)	For the treatment of primary hemophagocytic lymphohistiocytosis
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	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

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BLA 761107
GAMIFANT(emapalumab)

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OPQ=Office of Pharmaceutical Quality, OPDP=Office of Prescription Drug Promotion, OSI=Office of Scientific Investigations OSE=Office of Surveillance and Epidemiology, DEPI=Division of Epidemiology, DMEPA=Division of Medication Error Prevention and Analysis, DRISK=Division of Risk Management

Glossary

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATG	anti-thymocyte antiglobulin
BLA	biologics license application
CFR	Code of Federal Regulations
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CSR	clinical study report
DHOT	Division of Hematology Oncology Toxicology
ECG	electrocardiogram
EOT	end of treatment
FDA	Food and Drug Administration
GVHD	graft versus host disease
HIT	hybrid immunotherapy trial
HSCT	hematopoietic stem cell transplant
HLH	hemophagocytic lymphohistiocytosis
IFNγ	interferon gamma
IV	intravenous
KLH	Keyhole Limpet Hemocyanin
mAb	monoclonal antibody
MHC	major histocompatibility complex
NDA	new drug application
ORR	overall response rate
pHLH	primary hemophagocytic lymphohistiocytosis
PK	pharmacokinetics
PMC	postmarketing commitment
PR	partial response
PRO	patient reported outcome
RAW	murine macrophage-like cell line
SAE	serious adverse event
SD	study day
TEAE	treatment emergent adverse event
USPI	United States prescribing information
VOD	veno-occlusive disease
WHO	World Health Organization

1 Executive Summary

1.1. Product Introduction

Trade Name:	GAMIFANT
Proper Name:	Emapalumab
Dosage Forms:	10 mg/2 ml solution, 50 mg/10 ml solution for intravenous injection
Therapeutic Class:	Immunosuppressant
Chemical Class:	Recombinant monoclonal antibody
Pharmacologic Class:	Anti-interferon gamma monoclonal antibody
Mechanism of Action:	Binds to soluble and receptor-bound forms of IFNγ

Novimmune (Applicant) submitted biologics license application (BLA) 761107 for emapalumab (GAMIFANT ™), also known as NI-0501, a new monoclonal antibody for the treatment of primary hemophagocytic lymphohistiocytosis (HLH). Emapalumab is an IgG1 immunoglobulin that binds and neutralizes free and receptor-bound interferon gamma (IFNγ).

The Applicant's proposed indication is, "treatment of primary hemophagocytic lymphohistiocytosis (HLH)". The recommended dose is 1mg/kg intravenously over one hour twice per week (every 3 or 4 days). Doses subsequent to the initial dose may be increased based on clinical and laboratory criteria. Emapalumab should be administered until stem cell transplant or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review teams recommend regular approval of emapalumab under 21 Code of Federal Regulations (CFR) 601 for the indication "treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent or progressive disease or intolerance to conventional HLH therapy". The information submitted by the applicant provides for substantial evidence for effectiveness. The approval recommendation is supported by the results of a single-arm, open-label, non-randomized trial in 27 pediatrics patients aged 1 month to 13 years old with primary HLH who had reactivated or refractory disease after standard therapy.

Patients in study NI-0501 received emapalumab until hematopoietic stem cell transplant (HSCT), disease progression, unacceptable toxicity, or HLH control. The endpoint of overall response rate (ORR,) which included complete response, partial response, and hemophagocytic lymphohistiocytosis improvement (HLH I), was used to assess efficacy and inform the regulatory decision making. Response was assessed at week 8, or sooner if patients had proceeded to HSCT prior to week 8. The overall response rate was 63% (95% CI: 0.42, 0.81) with complete

responses achieved by 7 of 27 (26%) patients, partial responses achieved in 8 of 27 (30%), and HLH improvement achieved in two patients (7%). 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) patients proceeded to subsequent hematopoietic stem cell transplant.

The study supporting this application was conducted in children however the review division recommends including adults based on the rare adult patient who may experience a delayed presentation of the disease. Additionally, the single-arm trial allowed enrollment of newly diagnosed patients with HLH and the applicant submitted data for seven patients with previously untreated HLH. The review division (b) (4) sufficient to support the Applicant's proposed broad indication of primary HLH. Therefore, indication is restricted to patients who have failed or are intolerant to standard first line therapy for primary HLH.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Emapalumab is an IgG1 monoclonal antibody against interferon gamma (IFNγ). The benefit-risk assessment supports regular approval of emapalumab for the treatment of primary HLH in patients who have refractory, recurrent, or progressive disease or intolerance to conventional HLH therapy.

Hemophagocytic lymphohistiocytosis is a life-threatening disorder characterized by lymphocyte dysfunction and hypercytokinemia resulting in coagulopathy, end organ damage and severe cytopenias. Hemophagocytic lymphohistiocytosis can be divided into primary and secondary HLH. Secondary HLH occurs in the setting of underlying immune dysfunction or infections and treatment is aimed and supportive care and treatment of the underlying disease. Primary HLH results from an underlying genetic defect in lymphocyte function. Primary HLH is rare, typically presents early in life and is fatal without immunosuppressive therapy. Allogeneic stem cell transplant is the only potential curative intervention for this disease. The hypercytokinemia characteristic of primary HLH contributes to disease symptoms, morbidity and pre-transplant mortality.

The efficacy of emapalumab was evaluated in single arm, open-label, non-randomized trial that enrolled27 patients, age 1 month to 13 years, with primary HLH who had disease that was refractory, reactivated, or who were intolerant to standard conventional therapies. In the analysis of the primary endpoint, the overall response rate was 63% (95% CI: 0.42, 0.82). Of the 19 of 27 patients who responded, complete response (CR) was achieved in 7 (25.9%), partial response (PR) in 8 (29.6%) and HLH improvement in 2 (7.4%).

The regulatory basis for the recommendation of approval is based on the response rates observed in patients with life-threatening, recurrent or refractory disease with no approved therapies and limited available therapy options. Of the patients who responded, 63% maintained the response until week 8 of therapy or hematopoietic stem cell transplant (HSCT), if performed earlier than week 8. Nineteen out of the 27 patients proceeded to subsequent HSCT.

Additional support for the conclusion of effectiveness is based two additional patients who experienced disease control after receiving extended emapalumab treatment and did not proceed to HSCT. These patients were reported to have disease control 6 and 12 months after the last dose of emapalumab

The safety database for emapalumab consists of 34 patients (27 second line patients and 7 first line patients) who received emapalumab on study NI-0501-05, and an additional 17 patients who received emapalumab in the Applicant's compassionate use program. In general, the safety profile for emapalumab was manageable in this population of patients with severe systemic illness. Common adverse events (≥20%) were infections, hypertension, infusion-related reactions and pyrexia. Serious adverse events occurred in 62% of the patients and the SAEs

occurring in more than one patient were infections (32%), gastrointestinal hemorrhage (9%), and multiple organ dysfunction (6%). Infusion related reactions occurred in 27%% of patients, and no infusion related reactions resulted in infusion discontinuation.

Emapalumab may increase the risk of fatal and serious infections to include specific pathogens favored by IFNgamma neutralization. In 32% of patients receiving emapalumab in clinical trials, serious infections such as sepsis, pneumonia, bacteremia, disseminated histoplasmosis, necrotizing fasciitis, viral infections, and perforated appendicitis were observed. The reported infections were viral (41%), bacterial (35%), fungal (9%), and the pathogen was not identified in 15% of the cases.

In summary, primary HLH is a serious and life-threatening condition for which there is no Food and Drug Administration (FDA) approved therapy. Patients with refractory or recurrent disease require disease control and have limited available options. Emapalumab demonstrated an overall response rate of 63% and this response rate can be considered a clinical benefit for a primary pediatric population with primary HLH who have failed or are intolerant to standard first line therapy.

Emapalumab may increase the risk of serious and fatal infections due to pathogens favored by IFNgamma neutralization and patients with these types of infections should not receive emapalumab until adequate treatment of the infection. In addition, patients should be evaluated for tuberculosis risk factors prior to starting emapalumab and prophylaxis for Herpes Zoster, *Pneumocystis jirovecii* and fungal infections should be administered to mitigate potential infectious risks while receiving emapalumab. The overall safety profile of emapalumab is acceptable. The risks of therapy are acceptable for patients with primary HLH who have not responded or whose disease has recurred after standard therapy. In conclusion, the overall response rate combined with the acceptable toxicity profile of emapalumab is the basis for the recommendation for regular approval. The rarity of disease, severity of clinical symptoms, and confounders to response assessment make an adequately powered, randomized trial impracticable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Patients with primary HLH that is reactivated or refractory to standard therapy suffer from severe organ compromise, cytopenias, and complications from steroids and other immunosuppressive therapies • Patients require immediate and aggressive treatment with intensive supportive care. • Survival for patients with primary HLH with refractory or reactivated disease is less than 50% with hematopoietic stem cell transplant and generally considered incurable without transplant. • 20-40% of patients require salvage therapy or die due to complications of the disease or treatment prior to transplant	Primary HLH is a rare, serious and life-threatening condition Without treatment primary HLH is fatal Current treatments for HLH are associated with serious and life-threatening complications
Current Treatment Options	• Current therapies for pHLH are immunosuppressive regimens including corticosteroids, etoposide, and cyclosporine followed by stem cell transplantation • Current treatment options result in long term survival in only 60% of patients • Salvage therapies include re-treatment with prior therapy or additional immunosuppressive agents such as anti-thymocyte globulin and alemtuzumab	There are no available therapies for treatment of primary HLH after failure of standard therapy. There is a need for effective agents for the treatment of primary HLH after failure of standard initial treatment.
Benefit	• In a single-arm, open-label, non-randomized trial (NCT 01818492), 27 patients with reactivated or refractory pHLH received emapalumab given every three days and then weekly until week 8 or HSCT. • The overall response rate (CR, PR, or HLH improvement) was 63% (95% CI: 0.42, 0.81). Complete response was reported in 26%	Emapalumab improves overall response rate and complete response rate in patients with primary HLH who have failed or are intolerant to standard first line therapy. Responses appear durable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Seventy percent of % patients proceeded to HSCT	
Risk and Risk Management	• The most common TEAEs (> 20%) were infections, hypertension, infusion-related reactions, and pyrexia. • Serious adverse reactions were reported in 53% of patients. The most common serious adverse reactions included infections, gastrointestinal hemorrhage and multiple organ dysfunction. • Infections were the most commonly reported SAE and were experienced by 32% of patients and reported infections were viral (41%), bacterial (35%), fungal (9%)and pathogen not identified in 15% of cases. • Disseminated histoplasmosis led to drug discontinuation in one patient. • Emapalumab infusions were generally well tolerated with no infusion-related reactions resulting in discontinuation of the emapalumab infusion	Overall safety profile of emapalumab is acceptable for patients with primary HLH who have failed initial therapy Risks of emapalumab can be sufficiently addressed through warnings and precautions in the United States Prescribing Information. To minimize infectious risks, labeling should include warning and precautions for infections and in the management and risk mitigation of serious infections and infections favored by pathogens by IFN gamma neutralization.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		Refer to section 8.2.6
X	Patient experience data was not submitted as part of this application.			

X

Tanya Wroblewski MD

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Hemophagocytic lymphohistiocytosis refers to a category of diseases characterized by immune system disturbances, hyperinflammation and defective lymphocyte and macrophage function. Within the HLH disorders, pHLH is a disease caused by an underlying and often inherited defect in the immune function, while secondary HLH refers to immune dysfunction occurring in response to infection, neoplasia or other primary immune system disorder. Primary HLH is generally divided familial lymphohistiocytosis (FHL), typically associated with autosomal inheritance of mutations in one of the genes involved in the perforin pathway of lymphocyte function, and HLH occurring in patients with other diseases associated with immune dysfunction, including X-linked lymphoproliferative disease, Griscelli syndrome type 2, Chediak-Higashi syndrome, and Hemansky-Pudlack syndrome.

The exact incidence of primary HLH is unknown, and it is generally accepted that the condition is underreported, given the clinical overlap with infectious disorders and challenges to diagnosis. There are reports of incidences between 1 and 342 per 100,000 children per year, depending on the geographic location (Gholam et al. 2011). Clinically, patients classically experience fever, hepatic and splenomegaly, cytopenias, hypotension, and coagulopathy. If untreated, patients with primary HLH progress to a sepsis-like clinical picture characterized by multiorgan failure and death. Primary HLH typically presents within the first year of life, often after an infectious trigger. In many cases, mutations affecting genes critical for normal T cell and NK cell function are identified.

Hypercytokinemia is a result of defective T cell and NK function contribute to the signs and symptoms of HLH. High levels of IFNγ, in addition to other cytokines associated with inflammation, is one of the hallmarks of HLH and therefore targeting and neutralization of IFNγ is a proposed treatment modality for HLH. Formal diagnosis of HLH can be made when patients meet five or more of the eight diagnostic criteria described by the Histiocytic Society (Henter et al. 2007) and listed in the table below.

Table 1: HLH Diagnostic Criteria

HLH Diagnostic Criteria (≥5 of 8 required for diagnosis)
Fever
Splenomegaly
Cytopenias (at least 2)
- Hemoglobin <9 g/dL
- Platelets <100 x 10^9/L
- Neutrophils <1 x 10^9/L

HLH Diagnostic Criteria (≥5 of 8 required for diagnosis)
Hypertriglyceridemia (fasting, >265 mg/dL) or hypofibrinogenemia (<150 mg/dL)
Hemophagocytosis in spleen, bone marrow, lymph nodes or liver
Low or absent NK cell activity
Ferritin >500 µg/L
Elevated soluble CD25 (interleukin 2 receptor alpha)

There are no FDA-approved drugs for treatment of untreated or previously treated primary HLH. Standard therapies include corticosteroids and etoposide as per the HLH-1994 and 2004 protocols (Henter et al. 2007). Patients then typically proceed to allogeneic stem cell transplant, the only curative option for primary HLH. For patients who experience reactivated disease after an initial response, or who are refractory to conventional treatment, there are no accepted therapies. Treatment strategies for recurrent and refractory primary HLH have targeted cytokines or defective lymphocytes and include anakinra, anti-thymocyte globulin, and alemtuzumab (Marsh et al. 2017). Therapies focus on continued immunosuppression in attempt to control disease prior to HSCT. Due to different response assessments and low patient numbers, determining response rates to standard therapies is challenging. The response rates for alemtuzumab were reported at 64% (all partial responses) in a series of 22 patients with previously treated pHLH (Marsh et al. 2013).

Standard therapies are often cytotoxic and lead to cytopenias and infections, or further worsen coagulopathies and bleeding complications. In addition, steroids, which are a mainstay of standard therapies, are associated with hypertension, gastrointestinal toxicity, and bleeding.

Patients diagnosed with pHLH in the United States are typically referred to specialized centers for treatment. The Histiocytic Society has sponsored several large multicenter studies of standard therapies (HLH-94, and more recently HLH-2004) detailed in the table below.

Table 2: Standard Therapies for HLH

Regimen	Population	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
HLH-2004 N=369 N=168 with family history or genetically verified HLH	Previously untreated pediatric patients with pHLH	Etoposide 150 mg/m^2 twice per week for 2 weeks then weekly for 6 weeks Dexamethasone 10 mg/m^2/daily tapered every 2 weeks until week 8 Cyclosporine with initial therapy IT methotrexate	Response rates: not reported Survival to transplant: 81% OS (5-year): 61% (95% CI: 0.56-0.67)	Survival to transplant non-significantly improved from HLH 1994 Addition of cyclosporine A upfront did not improve outcomes
HLH 1994 N=113	Previously untreated pediatric patients with pHLH	Etoposide 150 mg/m^2 twice per week for 2 weeks then weekly for 6 weeks Dexamethasone 10 mg/m^2/daily tapered every 2 weeks until week 8 Cyclosporine starting week 9 IT methotrexate	Response: not reported Survival to transplant: 73% OS (5-year): 54% (95% CI: 0.48-0.60)	
Anti-thymocyte based therapy N=38 10 second line	Previously untreated (N=28) and relapsed/ refractory HLH (N=10)	ATG Corticosteroids Cyclosporine ATG Corticosteroids Cyclosporine Etoposide (2 pts)	First Line CR: 73% PR: 24% OS: 61% Second Line CR: 50% PR – 40% OS: 40%	Infectious complications in 22% 10% infection-related mortality
Alemtuzumab N=22	Refractory HLH after standard therapy	Alemtuzumab IV or SQ daily (median 1 mg/kg over 4 days)	ORR: 63% CR: none Survival to transplant: 75%	40% of patients experienced candidemia or bacteremia
Hybrid immunotherapy trial (HIT) N=31	Primary HLH	ATG Etoposide Dexamethasone	(b) (4)	Trial ended prematurely Results not published

Abbreviations: ATG, anti-thymocyte antiglobulin; CI, confidence interval; CR, complete response; HLH, hemophagocytic lymphohistiocytosis; IT, intrathecal; IV, intravenous; ORR, overall response rate; OS, overall survival; PR, prevalence ratio; SQ, subcutaneous.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Emapalumab is a monoclonal antibody and is not marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

The table below summarizes regulatory interactions the occurred between the Agency and the Applicant regarding the proposed indication. A pre-BLA meeting was held with the Agency on January 3, 2018.

Table 3: Regulatory Interactions for Emapalumab

Date	Regulatory Interaction
March 10, 2011	Pre-investigational new drug meeting to discuss shelf-life requirements, toxicology package, and overall clinical development program
November 16, 2015	Discussion of a registrational path for the treatment of patients with primary HLH
August 3, 2016	Discussion of 04/05 trial design, dosing and initial results
December 20, 2016	End of Phase 2 meeting
February 3, 2017	(b) (4)
June 7, 2017	Discussion of follow on trial, NI-0501-09, and comparison to historical controls
June 21, 2017	BLA content meeting
January 3, 2018	Pre-BLA meeting

Orphan designation was granted on March 26, 2018, for the treatment of HLH.

Breakthrough designation was granted on March 11, 2016, for patients with pHLH with refractory disease or with recurrent or progressive disease during conventional HLH therapy.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

The Office of Scientific Investigations conducted inspections for Study NI-0501-04 at two clinical sites: Site No. 16 (Cincinnati Children's Hospital, Dr. Michael Jordan) and Site No. 07 (Ospedale Pediatrico Bambino Gesu, Rome, Italy, Dr. Franco Locatelli). These sites were selected based on highest patient accrual and high rate of treatment response.

The final regulatory classification of Dr. Jordan is No Action Indicated. The preliminary regulatory classification of Dr. Locatelli is No Action Indicated pending review of the Establishment Inspection Report.

The Office of Scientific Investigations concluded *that the study data derived from the inspected clinical sites and the Applicant are considered reliable in support of the requested indication.* Please refer to the Clinical Inspection Summaries by Dr. Anthony Orencia, M.D. (July 24, 2018,) for additional details.

4.2. Product Quality

Novel excipients: No

Any impurity of concern: None

See CMC review by Jennifer Swisher, PhD and Riley Myers PhD for details related to product quality.

4.3. Clinical Microbiology

Refer to the review by Office of Product Quality by Scott Nichols, PhD and Candace Gomez-Broughton, PhD.

4.4. Devices and Companion Diagnostic Issues

There are no companion diagnostic devices required for the proposed use of emapalumab.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Emapalumab is a high-affinity human IgG1 anti-human IFNγ monoclonal antibody, developed by Novimmune SA (Geneva, Switzerland) as a treatment for HLH. The proposed established pharmacological class of emapalumab is IFNγ blocking antibody. IFNγ is a cytokine produced mainly by T-cells and natural killer cells activated by antigens, mitogens, or alloantigens. Most immune cells express IFNγ receptors and respond to IFNγ-induced signaling by activating macrophages and up-regulating major histocompatibility complex (MHC) class I expression. IFNγ interacts with a heterodimeric receptor, IFNγ-R1 and IFNγ-R2, activating the JAK-STAT signaling pathway. HLH is caused by excessive amounts of IFNγ and too many activated lymphocytes (T cells, natural killer cells, and B cells) and macrophages (histiocytes) produced by the immune system. Thus, neutralization of IFNγ was proposed as a treatment strategy for HLH based on the observation that IFNγ is pathogenic in mouse models of HLH and the high production of IFNγ in HLH patients.

In in vitro studies, emapalumab (NI-0501) bound to human (hIFNγ) and cynomolgus monkey IFNγ with similar affinity, but did not bind to rodent IFNγ, supporting the use of cynomolgus monkeys as the single pharmacologically relevant species for toxicity assessment. Emapalumab was shown to act as a non-competitive inhibitor of IFNγ, as emapalumab binds both free IFNγ (with high affinity) and IFNγR1-bound IFNγ (with significantly lower affinity). Emapalumab inhibited STAT1 signaling when pre-bound to IFNγ, with equimolar concentrations of emapalumab and IFNγ producing complete inhibition of STAT1 activity. Mechanistic studies indicated that emapalumab remained associated with the receptor-bound IFNγ during intracellular trafficking and does not prevent the endocytosis of the IFNγ/IFNγR1/IFNγR2 complexes. Emapalumab did not induce in vitro antibody-dependent cell cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity and it did not cross-react with a variety of human tissues tested.

The Applicant characterized a commercially available rat IgG1 anti-mouse IFNγ monoclonal antibody (mAb), XMG1.2, and used it as a surrogate of emapalumab to conduct studies in murine HLH models, as well as in their assessments of potential effects on embryofetal development. For the disease model, perforin-deficient (pfp-/-) mice were infected with lymphocytic choriomeningitis virus and received single injections of XMG1.2 at 3, 10, 30 or 100 mg/kg on day 6 post-infection. Doses ≥30 mg/kg reduced the lymphocytic choriomeningitis virus induced weight loss and hypothermia, and dose dependently reduced ferritin and triglycerides levels and prevented cytopenia (monocytes and neutrophils decrease). Pharmacokinetic (PK) analysis indicated that XMG1.2 administered at 30 mg/kg saturated IFNγ in the model.

The Applicant evaluated the safety of emapalumab in GLP-compliant repeat-dose toxicology studies in cynomolgus monkeys. In a 13-week study, monkeys received weekly intravenous (IV) doses up to 200 mg/kg. However, significant gastrointestinal bacterial infections were identified prior to commencement of the study and during the study at frequent intervals demanding treatment with an antibiotic to control the infection. An increase in susceptibility to infection as consequence of an exaggerated immunomodulating (pharmacological) effect of emapalumab can't be ruled out, since IFNγ neutralization favors infections. Associated clinical signs included liquid feces, dehydration, and moribund sacrifices of seven emapalumab-treated monkeys; manifestation of the intestinal infections included changes in hematology (increases in white blood cells, neutrophils, lymphocytes, eosinophils, basophils, and large unstained cells), clinical chemistry (increases in total protein, albumin, globulin, and calculated ratios), and histopathology findings in early decedents that included atrophy of the thymus, spleen, bone marrow, depletion of lymphoid tissues, and microscopic findings of inflammation in the gastrointestinal organs. Additional microscopic findings in surviving monkeys included cholecystitis and pancreatitis. One male monkeys assigned to the recovery phase at the high dose presented moderate amounts of fat in the liver and kidney. All other findings in surviving monkeys were resolved by the end of the 8-week recovery phase.

A follow-up 8-week toxicology study was conducted that included immunotoxicology endpoints assessing humoral immune function. Monkeys received weekly IV doses up to 30 mg/kg, which resulted in systemic exposures consistent with its long half-life of between 6-8 days. Emapalumab transiently impaired monkey's capacity to mount a primary anti-Keyhole Limpet Hemocyanin (KLH) IgG response 14 days after the first KLH challenge; however, a robust IgG response was observed in all monkeys 21 days after the second KLH challenge.

Standalone fertility assessments were not conducted as they are not needed to support the marketing of this product for the intended treatment indication. No adverse effects on male or female reproductive organs were observed in the repeat-dose toxicity studies in cynomolgus monkeys. Embryo-fetal developmental toxicology studies were conducted in mice, with XMG1.2 used as surrogate for emapalumab. Pregnant Swiss OF1 mice received XMG1.2 IV doses at 30, 75 or 150 mg/kg/dose on gestation days (GD) 6, 9, 13, and 17 and C-sections were conducted on GD18. While XMG1.2-related increases in post-implantation loss reached statistical significance at the 150 mg/kg/dose level, the toxicological significance is unknown, given the relevance of a surrogate in the model, and that the value was two-fold higher than concurrent controls, but only 0.4% above the historical control range. Detectable levels of XMG1.2 were present in fetal plasma in all dose groups on GD18, corroborating that the antibody can cross the murine placenta. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for emapalumab and any potential adverse effects on the breastfed child from emapalumab or from the underlying maternal condition. The pharmacology/toxicology team recommends including in the label of emapalumab a statement regarding the experimental design of the study with the surrogate antibody and the presence of the antibody in maternal and fetal plasma.

Neither genetic toxicology or carcinogenicity studies were conducted or are required to support the use of emapalumab in the proposed indication. The nonclinical pharmacology and toxicology data submitted to this BLA are adequate to support the approval of emapalumab for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

A. In Vitro Studies

The current understanding of hIFNγ indicates it interacts with a heterodimeric receptor, consisting of IFNγ-R1 and IFNγ-R2, activating the JAK-STAT signaling pathway. The Applicant determined the binding affinities of NI-0501 (emapalumab) for human and cynomolgus monkey IFNγ using surface plasmon resonance (SPR- (b) (4) Study No. NI-0501-MIF-01) and compared them to an in-house generated mAb 1119. Emapalumab exhibited strong affinity for human and monkey IFNγ (See Table 4). The Applicant noted affinity and avidity issues pose a challenge to accurately determining binding affinities.

Table 4: In Vitro Binding of Emapalumab

	K_D
Binding of NI-0501 to human IFNγ	1.4 pM
Binding of NI-0501 to cyno IFNγ	49.3 pM
Binding of mAb 1119 to human IFNγ	7.3 pM
Binding of mAb 1119 to cyno IFNγ	Not detectable
Binding of human IFNγ to human IFNγ-R1	0.59 nM
Binding of NI-0501/hIFNγ to human IFNγ-R1	10.7 nM

Kinetic experiments data were fitted according to 1:1 Langmuir model local on $R_{max,}$ and the K_{on}, K_{off}, and K_D values were determined. Emapalumab binding to hIFNγ and recombinant rhesus IFNγ (rhIFNγ) were characterized as having relatively fast association phases and very slow dissociation phases that reflect high affinity (See Table 5).

Table 5: Kinetic Characterization of Emapalumab Binding to **hIFNγ** and **rhIFNγ**

Ligand	Analyte	K_{on} (1/Ms)	K_{off} (1/s)	KD (M)
NI-0501	Human IFNγ	$4.35x10^{6}$	$6.03x10^{-6}$	$1.39x10^{-12}$
	Cyno IFNγ	$9.61x10^{5}$	$4.74x10^{-5}$	$4.93x10^{-11}$
mAb 1119	Human IFNγ	$8.67x10^{6}$	$6.35x10^{-5}$	$7.32x10^{-12}$

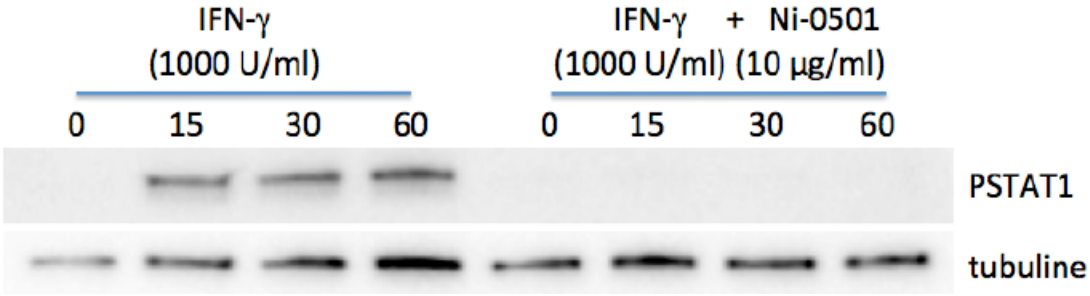
Source: excerpted from BLA 761107

Competition studies with the human receptor (hIFNγ-R1) showed that hIFNγ can bind the receptor when bound to emapalumab. In contrast, hIFNγ cannot bind the receptor when bound to mAb 1119 (Study No. NI-0501-MIF-03). While emapalumab binds both free and IFNγR1-bound IFNγ, the affinity of hIFNγ for hIFNγ-R1 when bound to emapalumab was significantly lower than that of free hIFNγ (See Table 4). Accordingly, emapalumab can be classified as a non-competitive inhibitor of IFNγ.

An additional study on the emapalumab mechanism of action (Study No. NI-0501- (b) (4) used hTERT-RPE1 cells, which are human epithelial cells that endogenously express high numbers of IFNγ-receptors. The study provided evidence that emapalumab can still bind to IFNγ that is already engaged in the IFNγ-R1-IFNγ-R2 complex at the cell surface, and that emapalumab does not prevent endocytosis of the IFNγ-IFNγ-R1-IFNγ-R2 complex. After cellular internalization of the complex, emapalumab was visualized within the same endosomes as IFNγ-R1 suggesting that emapalumab remains associated with IFNγ-R1 during its cellular trafficking. Based on the very slow dissociation phase noted above, it is likely that emapalumab may be recycled back to the surface complexed to IFNγ-R1, giving rise to potentially longer-term inhibitory activity.

(b) (4) also showed that emapalumab inhibits STAT1 and STAT3 activation and nuclear translocation, unless IFNγ has already bound to the cellular receptors. Data suggest emapalumab interferes with the ability of IFNγ to promote the proper association of the four IFNγ-R1-IFNγ-R2 subunits within lipid rafts where STAT signaling activation is initiated (See Figure 1).

Figure 1: Emapalumab Inhibits STAT1 Phosphorylation



Kinetics of STAT1 tyrosine phosphorylation (0 to 60 min) with IFNγ (left). No STAT1 phosphorylation was detected when hTERT-RPE1 cells were stimulated with IFNγ-preincubated with emapalumab.
Source: excerpted from BLA 761107

Amino acid sequence alignments of IFNγ from different species showed that cynomolgus and rhesus monkey IFNγ retained significant sequence identity to human IFNγ (See).

Table 6).

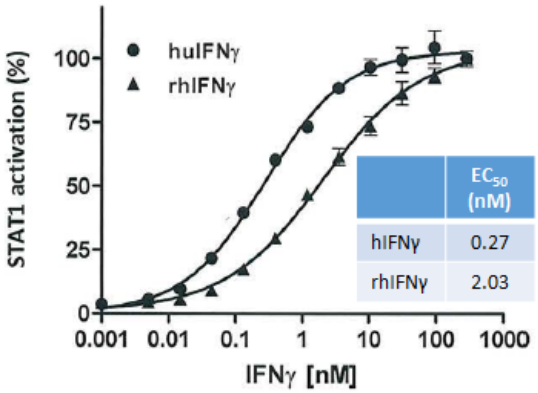
Table 6: **IFNγ** Amino Acid Sequence Identity Between Human and Non-Human Species

Human IFNγ sequence versus:	Identity (%)
Cynomolgus monkey	95
Rhesus monkey	95
Pig	60
Dog	60
Rabbit	60
Rat	38
Mouse	41

The Applicant used commercially available IFNγ from different non-human species to test cross-reactivity using SPR-(b) (4) (Study No. NI-0501-MIF-02). Emapalumab was cross-reactive to both cynomolgus and rhesus monkey, but no binding was detected in the dog, rat, or mouse. A slight but not pharmacologically relevant binding signal was detected for pig IFNγ. To further test the ability of emapalumab to neutralize rat and mouse IFNγ, the Applicant used in vitro models of encephalomyelocarditis virus infection of murine fibroblasts (Study No. P17262). The assays were based on protection of human or murine cell monolayers from encephalomyelocarditis virus, an IFNγ-sensitive picornavirus infection. Emapalumab neutralized human IFNγ in a dose dependent manner, with an IC_{50} of 0.9 μg/mL (equivalent to 6 nM), but was not active in mice or rats. Results from these studies support the use of cynomolgus monkeys as a pharmacologically relevant species for toxicity assessment with emapalumab.

The Applicant used the HeLa-STAT1-luc (referred to as HeLa) cell line expressing IFNyR1, IFNyR2, and the STAT-1 promoter and luciferase reporter gene to monitor the activity of the STAT1 transcription factor in the presence and absence of emapalumab (STAT1 activity was measured by the Firefly luciferase gene induced luminescent signal) (Study No. NI-0501-(b) (4)-01). Concentration response curves for human and rhesus monkey IFNγ are presented in Figure 2.

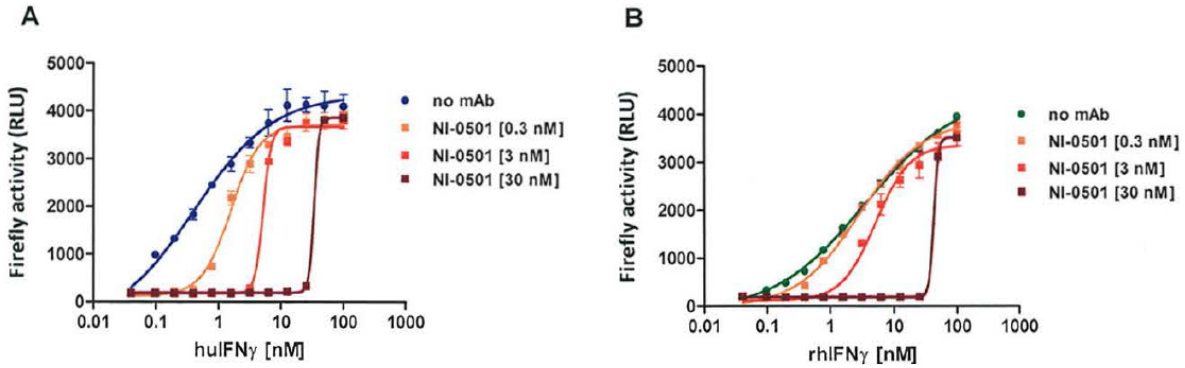
Figure 2: STAT-1 Activity in Human HeLa Cells



Source: excerpted from BLA 761107

HeLa cells were cultured with increasing concentrations of hIFNγ or rhIFNγ (Figure 3, panel A and B, respectively) in the absence or presence of emapalumab at three concentrations (0.3, 3 and 30 nM). Cells were collected after exposure for 18 hours to measure luciferase activity. The EC_{50} for hIFNγ in the absence of emapalumab was 0.4 nM, which increased 4-, 15- or 100-fold with the increase of emapalumab concentration (See Table 7). Similarly, the EC_{50} for rhIFNγ in the absence of emapalumab was 3.6 nM, which increased 0-, 1.5- or 12-fold with the increase of emapalumab concentration. Results indicate that STAT1 activity is completely inhibited with equimolar concentrations of emapalumab and hIFNγ. The IC_{50} of emapalumab for the STAT1 activity inhibition was similar in potency in the presence of 3 nM of hIFNγ or rhIFNγ (See Figure 4).

Figure 3: Dose Response of **IFNγ** at Various Concentrations of Emapalumab

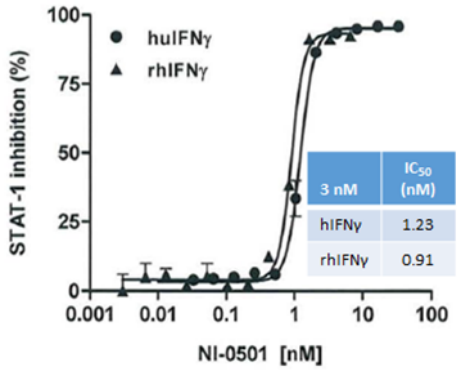


Source: excerpted from BLA 761107

Table 7: Emapalumab Dose-Response Inhibition of STAT1 Activity Induced by **hIFNγ** or **rhIFNγ**

EC50	Emapalumab concentration (nM)			
	0	0.3	3	30
hIFNγ	0.4	1.5	5.1	33.8
rhIFNγ	3.6	2.9	5.1	42.3

Figure 4: Emapalumab Inhibits STAT1 Activity Induced by Human and Rhesus **IFNγ**



Source: excerpted from BLA 761107

The Applicant evaluated the ability of emapalumab to induce in vitro ADCC and CDC activity. The human myeloma cell line, KMS-12-BM, susceptible to ADCC and CDC induced by the mAb directed against human CD52, MabCampath, was used as target cell line. The presence of IFN-γR1 and IFN-γR2 was confirmed by flow cytometry prior to the start of the study. An isotype-matched mAb (huIgG1) was used as negative control. To evaluate ADCC, natural killer cell-enriched human PBMCs obtained from three healthy donors were used as effector cells (Study No. AG/110301_ADCC). To evaluate CDC, human and rabbit serum complement proteins were commercially sourced (Study No. AG/110307 _CDC). Emapalumab with and without 150 nM of hIFNγ and control samples were incubated with the fluorescent-labeled target cells at several concentrations from 22.5 to 1850 µg/mL (150 to 14640 nM; emapalumab to target ratios of 1:1 to 98:1). In the ADCC assays, MabCampath positive control induced ADCC activity. No ADCC was observed in the presence of emapalumab after the addition of emapalumab/IFN-γ complexes to the cultures, with results comparable to the human isotype negative control. In the CDC assays, MabCampath demonstrated a dose-dependent CDC activity in the presence of human or rabbit complement. The percentage of the antibody independent cell lysis observed with emapalumab in combination with hIFNγ was comparable to that observed with the negative control and the human isotype negative control.

The Applicant conducted a GLP-compliant immunohistochemical study using biotin-labeled emapalumab, and found no cross-reactivity across a panel of 35 different human tissues (Study No. 26906).

B. In Vitro Characterization of XMG1.2 as Surrogate for Emapalumab

The Applicant investigated the binding affinity of XMG1.2 to its target, mouse IFNγ (mIFNγ), using SPS (b) (4) and experiments similar to those done for emapalumab (Study No. NI-0501-XMG1.2-MIF-01) (See Table 8). Competition studies with the mouse receptor (mIFNγ-R1) showed that mIFNγ cannot bind the receptor when bound to XMG1.2.

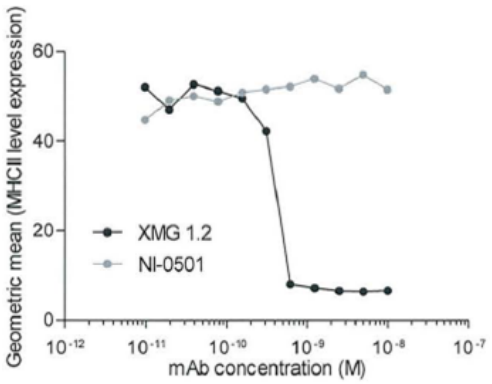
Table 8: Kinetic Characterization of XMG1.2 Binding to **mIFNγ**

1st Replicate					2nd Replicate					Average	
Date	KD (M)	k_{on} (1/Ms)	k_{off} (1/s)	Chi^2	Date	KD (M)	k_{on} (1/Ms)	k_{off} (1/s)	Chi^2	KD (M)	SD (M)
22.10.2009	**2.14E-11**	1.97E+06	4.20E-05	0.08	04.12.2009	**9.52E-12**	2.05E+06	1.96E-05	0.19	**1.55E-11**	**8.40E-12**

Source: excerpted from BLA 761107

The induction of the MHC class II (MHC-II) on antigen-presenting cells, including macrophages, dendritic cells, and B cells by IFNγ is a key function of this cytokine. RAW cells exposed to mIFNγ upregulate the MHC-II as measured by flow cytometric analysis for cell surface expression (Study No. NI-0501-XMG1.2- (b) (4) -01). XMG1.2 neutralized IFNγ-induced MHC II upregulation on RAW cells in a concentration-dependent manner, with an IC_{50} of 0.4 nM (See Figure 5). Emapalumab did not inhibit mIFNγ activity.

Figure 5: XMG1.2 Inhibits MHC Class II Upregulation on RAW Cells



Source: excerpted from BLA 761107

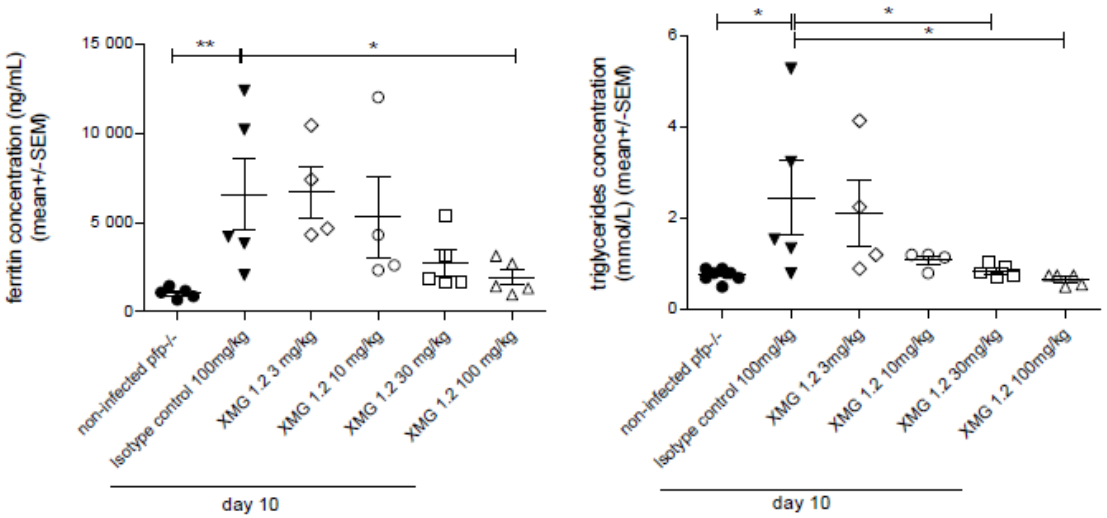
C. In Vivo Studies with XMG1.2

The Applicant used perforin-deficient (pfp-/-) mice infected with lymphocytic choriomeningitis virus as a model of human HLH to investigate XMG1.2 activity in vivo. The model develops characteristic clinical (fever, splenomegaly, pancytopenia, hypertriglyceridemia, hypofibrinogenemia, and hemophagocytosis) and histological features (activated lymphohistiocytic infiltrates, splenic/lymph node follicular depletion, periportal infiltrates, bone marrow hyperplasia, and meningeal infiltrates) of human HLH (Jordan et al. 2004). The HLH-like pathology in this murine model is dependent on IFNγ and $CD8^+$ T cells.

Increases in serum ferritin and triglyceride levels are used to diagnose HLH in patients. In the mouse HLH model, anti-IFNγ treatment reduced ferritin and triglycerides levels in a dose

dependent and statistically significant manner (See Figure 6). XMG1.2 treatment also prevented cytopenia (monocytes and neutrophils decrease), in a dose-dependent manner, with a statistically significant effect seen at 30 and 100 mg/kg for leukocytes and neutrophils.

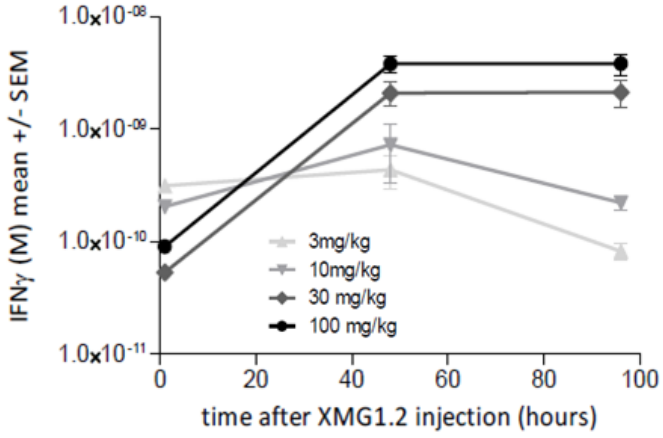
Figure 6: **Anti-IFNγ** Treatment Reduced Ferritin and Triglycerides Levels in HLH Mouse Model



Source: excerpted from BLA 761107

Patients with HLH also present hypercytokinemia or cytokine storm with increased levels of IFNγ, tumor necrosis factor α, interleukin6 and interleukin 10. Anti-IFNγ treatment produced a reduction, although not statistically significant, in hypercytokinemia in a dose dependent manner in the HLH mouse model. At all XMG1.2 doses, an increase of total serum mIFNγ was detected. XMG1.2 doses of 30 or 100 mg/kg resulted in the saturation by 48 hours and maintenance of mIFNγ circulating concentrations. Results suggest that ≥30 mg/kg XMG1.2 saturates IFNγ in the serum in this disease model (See Figure 7).

Figure 7: **Anti-mIFNγ** Binding



Source: excerpted from BLA 761107

Characterization of XMG1.2 indicates that it is a suitable surrogate mAb for emapalumab investigative studies.

Table 9: Comparison of Emapalumab and Surrogate Mouse mAb XMG1.2

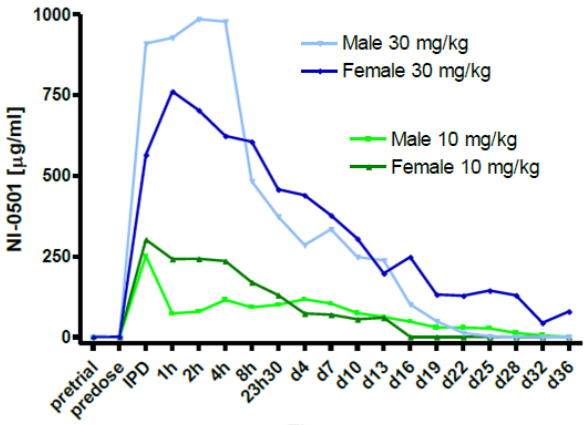
	XMG1.2	NI-0501
Affinity to IFNγ (K_D) [1)]	15 pM (to mouse IFNγ)	1.4 pM (to human IFNγ)
***In vitro* activity**	IC_{50}: 0.4 nM	IC_{50}: 1.23 nM
***In vivo* activity**	In a mouse model of HLH, treatment with XMG1.2 results in a decrease of the IFNγ-inducible chemokines, CXCL9 and CXCL10	In HLH patients, treatment with NI-0501 results in a decrease of the IFNγ-inducible chemokines CXCL9 and CXCL10

IC_{50}=half maximal inhibitory concentration; IFNγ=interferon gamma; HLH=hemophagocytic lymphohistiocytosis; K_D=dissociation constant.
1) The very slow dissociation phase of both mAbs precludes the establishment of an accurate affinity value. Thus, in both cases the affinity should be considered to be in the low picomolar range.

Source: excerpted from BLA 761107

5.4. Absorption,Distribution, Metabolism, Excretion/PK

Type of Study	Major Findings
Absorption	
NI-0501 single dose pharmacokinetic intravenous study in cynomolgus monkeys / 26811	<u>C_{max} at 1-2 h post-infusion</u> 10 mg/kg: M: 260 µg/mL; F: 300 µg/mL 30 mg/kg: M: 990 µg/mL; F: 760 µg/mL



Sex	Dose (mg/kg)	T½* Days
Male	10	14.7
Female	10	11.4
Male	30	6.9
Female	30	10.6

*T½ = ln2/k (k=slope of curve)

Source: excerpted from BLA 761107

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: NI-0501 13 Week Intravenous Infusion Toxicity Study in Cynomolgus Monkeys with an 8 Week Recovery Period / 26965

Reviewer's note: Significant gastrointestinal bacterial infections caused by *Shigella flexneri, Shigella boydii, and Campylobacter sp.* were identified prior to commencement of the study and during the study at frequent intervals. Treatment of monkeys with Enrofloxacin (2.5% Baytril, 5 mg/kg) occurred during Weeks 1 and 8 in a 5-consecutive day intramuscular dosing regimen.

Key Study Findings:

- An increase in susceptibility to infection as consequence of an exaggerated immunomodulating (pharmacological) effect of NI-0501 can't be ruled out.
- Associated clinical signs included liquid feces, dehydration, and moribund sacrifices of seven NI-0501-treated monkeys; manifestation of the intestinal infections included changes in clinical pathology and histopathology.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 10, 100, or 200 mg/kg weekly

Dose Group	Dose Level (mg/kg)	Duration of Infusion	Animal Designation	Animal Numbers	
				Males	Females
1 – Control	0	2 h	Main Study	1-3	17-19
			Recovery	4, 5	20, 21
2 – Low	10	6 min	Main Study	6-8	22-24
3 – Intermediate	100	1 h	Main Study	9-11	25-27
4 – High	200	2 h	Main Study	12-14	28-30
			Recovery	15, 16	31, 32

Source: excerpted from BLA 761107

Doses selected based on results from the DRF Study No. 26704

Route of administration: Infusion (via the tail vein or other appropriate vein) for 13 consecutive weeks (a total of 13 doses)

Formulation/Vehicle: 25 mM histidine pH 6 with 125 mM NaCl in Water for Injection

Species/Strain: Cynomolgus monkeys (*Macaca fascicularis*)

Number/Sex/Group: 3/sex/group plus 2/sex in control and HD for 8-week recovery

Age: 14 to 16 months (juvenile)

Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	Antibiotic treatment for 5 days during Week 8 was performed to treat gastrointestinal bacterial infections. Cytometric analysis and assessment of immune function was non-GLP. Conclusions should be considered exploratory in nature.

Observations and Results: Changes From Control

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>Total of 7 early sacrifices because of severe clinical signs
<table>
<tr><th>Animal No./Sex</th><th>Dose Group/Dose Level, mg/kg</th><th>Time on Study</th></tr>
<tr><td>24F</td><td>Group 2, 10 mg/kg</td><td>Day 44 (Week 7)</td></tr>
<tr><td>26F</td><td>Group 3, 100 mg/kg</td><td>Day 56 (Week 8)</td></tr>
<tr><td>10M</td><td>Group 3, 100 mg/kg</td><td>Day 57 (Week 9)</td></tr>
<tr><td>12M</td><td>Group 4, 200 mg/kg</td><td>Day 84 (Week 12)</td></tr>
<tr><td>6M</td><td>Group 2, 10 mg/kg</td><td>Day 85 (Week 13)</td></tr>
<tr><td>31F</td><td>Group 4, 200 mg/kg</td><td>Day 108
(Week 3 of Recovery Period)</td></tr>
<tr><td>16M</td><td>Group 4, 200 mg/kg</td><td>Day 137
(Week 7 of Recovery Period)</td></tr>
</table>
Source: excerpted from BLA 761107</td></tr>
<tr><td>Clinical Signs</td><td>Control: infrequent mild liquid feces with no dehydration

NI-0501-treated: prolonged episodes of liquid feces (7-13 consecutive days), dehydration, reduction in body weight, low body temperature, subdued behavior (between 2 and 6 days) during dosing and recovery phase.</td></tr>
<tr><td>Body Weights</td><td>No attempt to assess NI-0501-related effects was made due to large number of monkeys found with gastrointestinal bacterial infections.</td></tr>
<tr><td>Ophthalmoscopy]</td><td>No NI-0501-related findings occurred.</td></tr>
<tr><td>ECG</td><td>No NI-0501-related electrocardiography findings or changes in blood pressure were noted.</td></tr>
<tr><td>Hematology</td><td>Dosing phase: MD females and all HD monkeys exhibited increases in neutrophils, lymphocytes, eosinophils, basophils and large unstained cells as a response to inflammation in the intestine.

Recovery phase: parameter values were similar between control and HD monkeys assigned for recovery.

Fold-Increase of Hematological Parameters Compared to Controls - End of Dosing</td></tr>
</table>

	<table><tr><th>Dose (mg/kg)</th><th>Sex</th><th>Reti</th><th>WBC</th><th>Neut</th><th>Lymp</th><th>Eos</th><th>Baso</th><th>LUC</th><th>Plat</th></tr><tr><td rowspan="2">10</td><td>Male</td><td>--</td><td>1.4</td><td>2.7*</td><td>--</td><td>--</td><td>--</td><td>--</td><td>1.4</td></tr><tr><td>Females</td><td>--</td><td>1.3</td><td>1.4</td><td>1.3</td><td>--</td><td>1.8</td><td>1.7</td><td>1.3</td></tr><tr><td rowspan="2">100</td><td>Male</td><td>1.2</td><td>1.6</td><td>2.6</td><td>1.3</td><td>--</td><td>2.0</td><td>1.6</td><td>1.1</td></tr><tr><td>Females</td><td>1.3</td><td>2.2**</td><td>2.7</td><td>1.7**</td><td>3.0**</td><td>6.5**</td><td>4.1***</td><td>1.4</td></tr><tr><td rowspan="2">200</td><td>Male</td><td>1.3</td><td>1.7**</td><td>3.1**</td><td>1.2</td><td>--</td><td>2.4</td><td>1.9</td><td>1.5</td></tr><tr><td>Females</td><td>1.3</td><td>1.8**</td><td>2.0</td><td>1.7**</td><td>1.8</td><td>3.3</td><td>2.4*</td><td>1.4</td></tr></table> Reti= reticulocytes; WBC= white blood cells; Neut= neutrophils; Lymp= lymphocytes Eos= eosinophils; Baso= basophils; LUC= large unstained cells; Plat= platelets Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001; -- no change Source: excerpted from BLA 761107
Clinical Chemistry	Dosing phase: Changes in total protein, albumin, globulin and calculated ratios as well as calcium and bilirubin were related to dehydration, malnutrition and/or malabsorption caused by the gastrointestinal infection. Recovery phase: parameter values were similar between control and HD monkeys assigned for recovery. Fold-Increase of Clinical Chemistry Parameters Compared to Controls - End of Dosing <table><tr><th>Dose (mg/kg)</th><th>Sex</th><th>Urea</th><th>ALT</th><th>TP</th><th>Alb</th><th>Glob</th><th>AG-R</th><th>Chol</th><th>Ca</th><th>T-Bil</th></tr><tr><td rowspan="2">10</td><td>Male</td><td>0.7*</td><td>0.4**</td><td>--</td><td>--</td><td>--</td><td>--</td><td>--</td><td>--</td><td>--</td></tr><tr><td>Females</td><td>0.6**</td><td>0.4**</td><td>--</td><td>0.8*</td><td>--</td><td>--</td><td>--</td><td>--</td><td>--</td></tr><tr><td rowspan="2">100</td><td>Male</td><td>0.9</td><td>0.9</td><td>1.2*</td><td>--</td><td>--</td><td>--</td><td>0.8</td><td>--</td><td>--</td></tr><tr><td>Females</td><td>0.6**</td><td>0.6</td><td>--</td><td>0.8**</td><td>1.3*</td><td>0.6*</td><td>0.8*</td><td>--</td><td>0.7*</td></tr><tr><td rowspan="2">200</td><td>Male</td><td>0.8*</td><td>0.5**</td><td>1.2**</td><td>0.8*</td><td>1.6***</td><td>0.5***</td><td>0.7**</td><td>0.9**</td><td>--</td></tr><tr><td>Females</td><td>0.8*</td><td>0.7*</td><td>--</td><td>0.9**</td><td>1.3**</td><td>0.6**</td><td>0.8*</td><td>--</td><td>0.7*</td></tr></table> ALT= alanine aminotransferase; TP= total protein; Glob= globulin proteins; AG-R= albumin-globulin ratio; Chol= cholesterol; Ca= calcium; T-Bil= total bilirubin. Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001; -- no change Source: excerpted from BLA 761107
Urinalysis	No NI-0501-related findings occurred.
Gross Pathology	Early decedents Colon: red foci, raised foci, and thickened mucosa. Intestines: distension and abnormal contents. Gall bladder: thickening and abnormal contents. Abdominal lymph nodes enlarged in one MD and HD male; the HD male also presented a pale liver, enlarged spleen, ureter, and a mass in the pancreas. Surviving monkeys Enlarged lymph nodes, distended colon, abnormal intestinal contents, abnormal abdominal contents, enlarged gall bladder, and pancreatic mass. Recovery monkeys No NI-0501-related findings noted

<table>
<tr><td>Organ Weights</td><td>No attempt to assess NI-0501-related effects was made due to large number of monkeys found with gastrointestinal bacterial infections.</td></tr>
<tr><td>Histopathology

Adequate battery: Yes</td><td><u>Early decedents</u>

NI-0501-related moderate to marked thymic atrophy present in all early decedents, some of which also showed moderate to marked lymphoid atrophy or depletion in spleen and mandibular and mesenteric lymph nodes. Minimal sternal marrow atrophy in one LD and one MD female.

NI-0501-related Histological Findings in Lymphatic Organs of

Early Decedents

<table>
<tr><th rowspan="2">HISTOLOGICAL FINDINGS</th><th colspan="3">Males</th><th colspan="3">Females</th></tr>
<tr><th>Grp 2
10 mg/kg</th><th>Grp 3
100 mg/kg</th><th>Grp 4
200 mg/kg</th><th>Grp 2
10 mg/kg</th><th>Grp 3
100 mg/kg</th><th>Grp 4
200 mg/kg</th></tr>
<tr><td>THYMUS</td><td>(1)</td><td>(1)</td><td>(1)</td><td>(1)</td><td>(1)</td><td>(1)</td></tr>
<tr><td>Atrophy</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>SPLEEN</td><td>(1)</td><td>(1)</td><td>(2)</td><td>(1)</td><td>(1)</td><td>(1)</td></tr>
<tr><td>Lymphoid atrophy</td><td>0</td><td>1</td><td>1</td><td>1</td><td>1</td><td>0</td></tr>
<tr><td>LYMPH NODE (MANDIBULAR)</td><td>(1)</td><td>(1)</td><td>(2)</td><td>(1)</td><td>(1)</td><td>(1)</td></tr>
<tr><td>Lymphoid depletion</td><td>0</td><td>1</td><td>1</td><td>0</td><td>1</td><td>0</td></tr>
<tr><td>LYMPH NODE (MESENTERIC)</td><td>(1)</td><td>(1)</td><td>(2)</td><td>(1)</td><td>(1)</td><td>(1)</td></tr>
<tr><td>Lymphoid depletion</td><td>0</td><td>1</td><td>2</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>STERNUM</td><td>(1)</td><td>(1)</td><td>(2)</td><td>(1)</td><td>(1)</td><td>(1)</td></tr>
<tr><td>Atrophy, marrow</td><td>0</td><td>0</td><td>0</td><td>1</td><td>1</td><td>0</td></tr>
</table>

Source: excerpted from BLA 761107

NI-0501-related but not dose-related increase in the incidence and severity of inflammation or inflammatory cell infiltration in organs such as large intestine, mesenteric and other abdominal lymph nodes, heart, liver, gall bladder, pancreatic duct, lung (males) and trachea, and mild to moderate colitis.</td></tr>
</table>

Additional NI-0501-related Histological Findings in Early Decedents

HISTOLOGICAL FINDINGS	Males			Females		
	Grp 2 10 mg/kg	Grp 3 100 mg/kg	Grp 4 200 mg/kg	Grp 2 10 mg/kg	Grp 3 100 mg/kg	Grp 4 200 mg/kg
CAECUM	(1)	(1)	(2)	(1)	(1)	(1)
Caecitis	0	0	0	1	1	0
Inflammatory cell infiltration, lamina propria	0	1	1	0	0	1
COLON	(1)	(1)	(2)	(1)	(1)	(1)
Colitis	0	1	1	1	1	0
Inflammatory cell infiltration, lamina propria	1	0	1	0	0	1
RECTUM	(1)	(1)	(2)	(1)	(1)	(1)
Proctitis	1	1	0	1	1	0
Inflammatory cell infiltration, lamina propria	0	0	2	0	0	1
LYMPH NODE (MESENTERIC)	(1)	(1)	(2)	(1)	(1)	(1)
Lymphadenitis	1	1	1	0	0	0
LYMPH NODE (PANCREATIC)		(1)	(1)			
Lymphadenitis		1	1			
LIVER	(1)	(1)	(2)	(1)	(1)	(1)
Hepatitis, widespread, chronic	0	0	1	0	0	0
GALL BLADDER	(1)	(1)	(2)	(1)	(1)	(1)
Cholecystitis	0	1	0	0	0	0
Inflammatory cell infiltration, lamina propria	0	0	0	0	0	1
PANCREAS (EXOCRINE)	(1)	(1)	(2)	(1)	(1)	(1)
Inflammation, duct	0	0	0	0	1	0
TRACHEA	(1)	(1)	(2)	(1)	(1)	(1)
Tracheitis	0	0	1	0	0	0

Source: excerpted from BLA 761107

Surviving monkeys

NI-0501-related minimal to mild thymic atrophy present in one MD and one HD female. NI-0501-related but not dose-related increase in the incidence of inflammation in organs such as heart, trachea, lung, liver, kidney, mesenteric and other lymph nodes, colitis (one HD female), gall bladder, and pancreas. Meningeal inflammatory cell infiltration was noted in one LD and one MD male and one MD female. Minimal to mild amount of fat in the liver and kidney of one HD male and one LD and HD female.

Recovery monkeys

NI-0501-related moderate amount of fat in the liver and kidney of one HD male. No other findings present in HD recovery monkeys.

<table>
<tr><td></td><td>NI-0501-related Histological Findings in Main Study Surviving Monkeys
<table>
<tr><th rowspan="2">HISTOLOGICAL FINDINGS</th><th colspan="4">Males</th><th colspan="4">Females</th></tr>
<tr><th>Grp 1
0 mg/kg</th><th>Grp 2
10 mg/kg</th><th>Grp 3
100 mg/kg</th><th>Grp 4
200 mg/kg</th><th>Grp 1
0 mg/kg</th><th>Grp 2
10 mg/kg</th><th>Grp 3
100 mg/kg</th><th>Grp 4
200 mg/kg</th></tr>
<tr><td>LYMPH NODE (MESENTERIC)</td><td>(3)</td><td>(2)</td><td>(2)</td><td>(2)</td><td>(3)</td><td>(2)</td><td>(2)</td><td>(3)</td></tr>
<tr><td>Lymphadenitis</td><td>0</td><td>1</td><td>0</td><td>1</td><td>0</td><td>0</td><td>2</td><td>0</td></tr>
<tr><td>LYMPH NODE (RENAL)</td><td></td><td>(1)</td><td></td><td></td><td></td><td></td><td></td><td>(1)</td></tr>
<tr><td>Lymphadenitis, chronic</td><td></td><td>1</td><td></td><td></td><td></td><td></td><td></td><td>0</td></tr>
<tr><td>LYMPH NODE (INGUINAL)</td><td></td><td></td><td></td><td>(1)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Lymphadenitis</td><td></td><td></td><td></td><td>1</td><td></td><td></td><td></td><td></td></tr>
<tr><td>GALL BLADDER</td><td>(3)</td><td>(2)</td><td>(2)</td><td>(2)</td><td>(3)</td><td>(2)</td><td>(2)</td><td>(3)</td></tr>
<tr><td>Cholecystitis</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td><td>0</td></tr>
<tr><td>Inflammatory cell infiltration, lamina propria</td><td>1</td><td>1</td><td>2</td><td>1</td><td>0</td><td>0</td><td>1</td><td>3</td></tr>
<tr><td>PANCREAS (EXOCRINE)</td><td>(3)</td><td>(2)</td><td>(2)</td><td>(2)</td><td>(3)</td><td>(2)</td><td>(2)</td><td>(3)</td></tr>
<tr><td>Inflammation, chronic active</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td><td>0</td></tr>
<tr><td>Inflammatory cell infiltration, focal</td><td>0</td><td>0</td><td>1</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td></tr>
</table>
Source: BLA 761107</td></tr>
<tr><td>Anti-NI-0501 Antibody</td><td>Anti-drug antibodies were not detected; however, the results are inconclusive due possible interference of the drug itself. Conducted non-GLP.</td></tr>
<tr><td>Cytometric Analysis and Assessment of Immune Function</td><td>No NI-0501-related alterations to immune cell levels in peripheral blood. Monkeys maintained an intact capacity to mount an antigen specific humoral response. Conducted non-GLP.</td></tr>
<tr><td>Microbiology analysis</td><td>Pre-study: confirmed the presence of Shigella flexneri, Shigella boydii (a Shigella dysenteriae-like organism) and Campylobacter sp.

Necropsy: Campylobacter sp. identified in a number of monkeys from all dose groups including controls.</td></tr>
</table>

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control.

On day 1, systemic exposure to NI-0501, based on AUC_{0-t}, increased in a greater than dose-proportional manner between the 10 and 100 mg/kg doses in males and females. The increase in exposure between the 100 and 200 mg/kg doses was dose-proportional in males and less than proportional in females. After repeated dosing, systemic exposure to NI-0501, based on AUC_{0-t}, was greater than on day 1 at all dose levels indicating accumulation. Preliminary estimates of elimination half-life suggest it may extend to several hundred hours. Serum concentration data did not support the accurate estimation of slope dependent parameters $AUC_{0-\infty}$, $t_{1/2}$, Cl, and Vd and these parameters values were not reported.

Table 10: Toxicokinetics – 13-Week Monkey Study

Dose (mg/kg)	Time	Sex	$AUC_{(0-t)}$[1] (µg*h/mL)	C_{max} (µg/mL)	T_{max} range (h)
10	Day 1	Male	19679	282	0.1-0.1
		Female	18513	232	0.1-0.1
	Week 6	Male	62639	952	0.1-0.1
		Female	56033	1118	0.1-0.1
	Week 12	Male	94027	757	24.1-120
		Female[2]	91656	699	6.1-72.0
100	Day 1	Male	464620	5752	120-168
		Female	439079	4298	120-168
	Week 6	Male	634241	6793	1.0-168
		Female	630791	6014	1.0-7.0
	Week 12	Male[2]	692219	6731	1.0-1.0
		Female[2]	738749	7187	1.0-25.0
200	Day 1	Male	901273	6704	2.0-168
		Female	604724	6407	2.0-8.0
	Week 6	Male	1032585	9831	2.-26.0
		Female	1114013	11186	8.0-72.0
	Week 12	Male	1044519	8863	2.0-8.0
		Female	1358615	12029	2.0-72.0

[1] Geometric mean.

[2] LD and MD n=3 except n=2 on week 12. HD n=5.

Source: excerpted from BLA 761107

General toxicology; additional studies

Follow-up monkey toxicology study with immunotoxicology endpoints

Study title/ number: NI-0501: An 8-Week Intravenous Infusion Toxicity Study in Cynomolgus Monkeys Followed by a 4-Week Recovery Period / SNBL.173.01

Key Study Findings

- NI-0501 in monkeys transiently impaired their capacity to mount a primary anti-KLH IgG response 14 days after the first KLH challenge; a robust IgG response was observed in all monkeys 21 days after the second KLH challenge.
- Systemic exposure after IV dosing over 8-weeks was consistent with a long half-life ($t_{½}$: 159 to 201 hours) and exposure estimates (C_{max} and AUC) that were approximately dose proportionate.
- NI-0501 was tolerated in monkeys up to 30 mg/kg/week, the highest dose tested.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 3, 10, or 30 mg/kg weekly

Treatment Group	Dose Route	Dose Level (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	Number of Animals Females	Males
1	IV	0	0	4.69	3a + 2b	3 a + 2 b
2	IV	3	6.4	0.47	3 a	3 a
3	IV	10	6.4	1.56	3 a	3 a
4	IV	30	6.4	4.69	3 a + 2 b	3 a + 2 b

Note: Total dose volumes (mL) were calculated based on the most recent body weight.
[a] Terminal Necropsy: D57
[b] Recovery Necropsy: D85

(Table excerpted from BLA 761107)

Doses selected based on results from the 13-week repeat dose Study No. 26965

Route of administration: IV over an approximate 10-minute interval

Formulation/Vehicle: 25 mM histidine pH 6 with 125 mM NaCl in Water for Injection

Species/Strain: Cynomolgus monkeys (*Macaca fascicularis*)

Number/Sex/Group: 3/sex/group, 2/sex for 8-week recovery in control and HD

Age: M; 3-5 years; F: 3-6 years

Satellite groups/ unique design: None

Deviation from study protocol affecting interpretation of results: The bioanalytical and PK analysis and the ELISA method for anti-KLH antibody analysis were conducted non-GLP compliant. Conclusions should be considered exploratory in nature. Initial fecal examinations during animal screening were performed prior to the signing of the protocol.

Observations and Results: Changes From Control

Parameters	Major findings
Mortality	None.
Clinical Signs	No NI-0501-related clinical signs of toxicity occurred.

Parameters	Major findings
Body Weights	No NI-0501-related changes in body weight occurred.
Ophthalmoscopy	No NI-0501-related findings occurred.
ECG	All electrocardiograms were qualitatively and quantitatively within normal limits; no NI-0501-related effects on the RR, PR, QRS, or QTc intervals were found comparing pre-dose and post-dose group average values. No arrhythmias were noted.
Hematology	No NI-0501-related findings occurred.
Clinical Chemistry	No NI-0501-related findings occurred.
Urinalysis	No NI-0501-related findings occurred.
Gross Pathology	No NI-0501-related findings occurred at the end of the dosing phase or the recovery phase.
Organ Weights	No NI-0501-related changes in organ weight were noted at the end of the dosing phase or the recovery phase.
Histopathology Adequate battery: Yes	No NI-0501-related microscopic findings were noted at the end of the dosing phase or the recovery phase.
[Other evaluations]	
Fecal Swabs Microbiology and Fecal Occult Blood	No NI-0501-related findings. Non-GLP compliant.
Anti-NI-0501 Antibody	No samples were analyzed for anti-NI-0501 antibody from the HD based on high NI-0501 concentration (72.4 µg/mL) in blood. Antibodies to NI-0501 were found on days 22 and 50 serum samples in one 3 mg/kg/week male.
Anti-Keyhole Limpet Hemocyanin (KLH) Antibody (IgM and IgG) Analysis	The ELISA method for anti-KLH antibody analysis was conducted non-GLP compliant. First challenge day 29: 3/6 at MD and 6/10 at HD generated anti-KLH IgG antibodies. Second challenge day 50: All monkeys generated anti-KLH IgG antibodies.

-: indicates reduction in parameters compared to control.
*: [if the answer is “no” explain why the histopath battery is not adequate]
Abbreviations: LD: low dose; MD: mid dose; HD: high dose.

Table 11: Toxicokinetics – 8-Week Monkey Study

Dose (mg/kg)	Sampling Day	C_{max} (µg/mL)	AUC_{0-t} (µg.h/mL)	$AUC_{0-\infty}$ (µg.h/mL)	$t_{1/2}$ (h)	CL (mL/h)/kg
0 – 46 hour data						
3	1	105.5	2802	6081	52.3	0.50
	22	169.6	6085	17236	79.3	0.18
	50	250.0	7292	22051	78.2	0.15
10	1	309.5	8910	22455	71.4	0.48
	22	554.0	19802	71766	116.9	0.14
	50	619.2	22375	74878	90.3	0.15
30	1	1064.6	30481	72189	56.8	0.46
	22	1759.0	61321	155370	72.8	0.21
	50	1932.0	65447	184011	82.0	0.17

Dose (mg/kg)	Sampling Day	C_{max} (µg/mL)	AUC_{0-t} (µg.h/mL)	$AUC_{0-\infty}$ (µg.h/mL)	$t_{1/2}$ (h)	CL (mL/h)/kg
0 – 168 hour data						
3	1	105.5	7283	14258	164.7	0.22
	22	169.6	17815	36086	163.4	0.10
10	1	309.5	25096	50764	200.6	0.21
	22	554.0	56850	136075	241.2	0.08
30	1	1064.6	80916	153118	159.3	0.21
	22	1759.0	177184	396851	188.7	0.09

Source: Excerpted from BLA 761107

Table 12: Toxicokinetics – 8-Week Monkey Study Sex Differences

Mean AUC_{0-168} values (µg*h/mL)			
Dose (mg/kg)	Sex	Day 1	Day 22
3	Male	6948	18293
	Female	7617	17497
10	Male	30419	68932
	Female	19772	44767
30	Male	82893	184003
	Female	78938	170365

5.5.2. Genetic Toxicology No genotoxicity studies were conducted with emapalumab as per International Conference on Harmonisation S6.

5.5.3. Carcinogenicity

No carcinogenicity studies were conducted with emapalumab as per International Conference on Harmonisation S6.Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

No standalone fertility studies were conducted with emapalumab. No adverse effects on male or female reproductive organs were observed in the 8- or 13-week repeat-dose toxicity studies in cynomolgus monkeys.

Embryo-Fetal Development

Study title/ number: XMG1.2 – GLP Embryo-fetal development (EFD) toxicity study by the intravenous route (bolus injection) in the mouse (Segment II) / AB21426

Key Study Findings

- Potential XMG1.2-related increase in post-implantation loss, 0.4% above the highest historical background control value, and approximately two-fold higher than in the concurrent control.

Conducting laboratory and location:	 (b) (4)
GLP compliance:	Yes, except the bioanalytical work

Methods

Dose and frequency of dosing:	30, 75 or 150 mg/kg/dose on GD 6, 9, 13, and 17. Based on DRF study AB21417.
Route of administration:	Intravenous (bolus)
Formulation/Vehicle:	Phosphate Buffered Saline, 0.01 % Tween 80, pH8.0
Species/Strain:	Swiss OF1 mouse: Crl: OF1
Number/Sex/Group:	25 mated females/group
Satellite groups:	None. Maternal and fetal blood samples collected from five pregnant females (F0) and respective litters per group for evidence of exposure determinations on GD18.

Methods

Study design:	Control, LD, MD and HD. XMG1.2 is an anti-mouse IFNγ mAb functional surrogate for NI-0501.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	No XMG1.2-related.
Clinical Signs	No XMG1.2-related.
Body Weights	No XMG1.2-related.
Necropsy findings Cesarean Section Data	Pregnancy incidence: Control: 21; LD: 24; MD: 18; HD: 21 Post-implantation loss (%): Control: 6.3; LD: ↑7.0; MD: ↑10.4; HD: ↑13.0* Historical control: 2.6 – 12.6 *one HD female had 100% post-implantation loss skewing the mean of the HD group.
Necropsy findings Offspring	External Observations: LD: malrotated hindlimb 3 fetuses/2 litters (fetal incidence 1.0%) Historical control: 0.53% MD: meningoencephalocele (comparable to exencephaly) 1 fetus/1 litter, fetal incidence 0.4%. Historical control: 0 – 0.5%. Visceral observations: HD: malformed eye (ectopic lens and major retinal fold) 1 fetus/1 litter, fetal incidence 0.8% Historical control: 0 – 2.3%. Skeletal observations:

Parameters	Major findings
	MD: the fetus with external observation of meningoencephalocele had gross disruption of the cranium with a hole affecting the interparietal and supraoccipital. HD: split palatine, 2 fetuses/2 litters, fetal incidence 1.5% Historical control: 0-2.7%.

Abbreviations: LD: low dose; MD: mid dose; HD: high dose

Detectable levels of XMG1.2 were present in fetal plasma in all dose groups on GD18, corroborating that the antibody can cross the murine placenta.

Table 13: Toxicokinetics – Mouse EFD Study

Dose (mg/kg)	XMG1.2 Concentrations on			
		Maternal	Fetal	Fetal/ Maternal Ratio G18
		Concentration (µg/mL)		
30	Mean	86.8	119.4	1.4
	SD	45.1	37.4	
75	Mean	201.7	224.2	1.1
	SD	54.8	44.0	
150	Mean	463.3	249.8	0.5
	SD	164.3	53.5	

Source: Excerpted from BLA 76110

Prenatal and Postnatal Development

No prenatal and postnatal development studies were conducted with emapalumab.

5.5.5. Other Toxicology Studies

Study Title/ number: Subcutaneous and Paravenous Local Tolerance Study of NI-0501 in the Rabbit / RTL0003

The local tolerance of NI-0501 was evaluated in three male New Zealand White rabbits. Clinical signs of skin reactions at injection sites was assessed daily up to and including the day of necropsy on day 4. The results were not remarkable except for some erythema after paravenous administration in one rabbit 24-hour post dose, which was resolved at 48 hours.

Study Title/ number: NI-0501-biotin: An Immunohistochemical Investigation of Cross-Reactivity in a Range of Human Tissues / 26906

NI-0501 conjugated to biotin and a negative control IgG1, lambda isotype antibody, conjugated to biotin were used to determine their cellular localization in a range of normal human tissues from three unrelated donors to identify sites, other than target sites, with which the antibody cross-reacts. All positive staining recorded was observed in controls as well as the tissues treated with the test antibody.

X	X
Primary Reviewer Pedro L. Del Valle, PhD	Team Leader Christopher M. Sheth, PhD

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant is seeking approval of emapalumab (Gamifant) 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.

The clinical pharmacology section of the BLA is supported by 3 studies (NI-0501-03, NI-0501-04 and NI-0501-05). The applicant also conducted population pharmacokinetic (PPK) analyses, PK/ pharmacodynamic (PD) analyses relating emapalumab exposures (PK) to potential PD measures such as serum total IFNγ, chemokine receptor 9 (CXCL9), 10 (CXCL10), serum interleukin 2 receptor (sIL2R) as well as exposure-response for efficacy (clinical response) and safety.

The exposure-response analysis for efficacy showed that the clinical response at the end of the treatment was highly correlated with pharmacodynamics measures such as concentrations of CXCL9, IFNγ, CXCL10 (in decreasing order). The relationship between emapalumab exposure and response is inconclusive because it is confounded by the dose-escalation scheme, and the high correlation between PK and PD measures. The exposure-response evaluation for safety did not reveal any significant relationships between exposure and observed incidence rates of adverse events, serious adverse events, infections, or infusion-related reactions, or laboratory measures such as elevation in total bilirubin, alanine transferase, and creatinine clearance.

The distribution of doses over time revealed that approximately 30% patients in the pivotal phase 2/3 trial received higher dose as early as the third day (within first week). However, based on exploratory analyses, it is unlikely for patients to achieve substantial additional benefit by starting at higher dose of 3 mg/kg. The overall efficacy and safety profiles support the proposed dosing regimen.

The recommended starting dose of 1 mg/kg emapalumab dose administered as intravenous infusion over 1 hour twice per week (every three to four days), and the subsequent dose increases to 3, 6, 10 mg/kg based on clinical and laboratory criteria, is acceptable.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in BLA 761107. This BLA is approvable from a clinical pharmacology perspective.

The key review issues with specific recommendations and comments are summarized below in **Table 1.**

Table 14 Clinical Pharmacology Related Review Issues and Recommendations

Review Issues	Recommendations and Comments
Evidence of effectiveness	An open-label, single arm, multicenter study in patients with primary HLH <18 years old (0.1 -13.8 yo, N=34) provides primary evidence of effectiveness.
General dosing instructions	The recommended dose regimen of 1.0 mg/kg on Day 1 and 4, subsequently increased to 3 mg/kg, 6 mg/kg, and 10 mg/kg.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustment is needed for age, race, gender, renal impairment including dialysis, or hepatic impairment (mild, moderate, and severe).
Immunogenicity	Anti-therapeutic antibodies (ATAs) to emapalumab after treatment with GAMIFANT were detected in 3/64 subjects (5%). The ADAs in one patient in Study NI-0501-04 were found to have neutralizing ability.
Labeling	Generally acceptable. **Table 1 Dose Titration Criteria** in **Section 1.1.2. Dose Modification Based on Response** to inform prescribers on when and how to increase the dose has been added. The review team made recommendations for specific content and formatting changes.

Post-marketing Requirements and Commitments

There are no post-marketing requirements or post-marketing commitments from clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Emapalumab is a 148 kDa fully human IgG1 anti-human IFNγ monoclonal antibody (mAb), for the treatment for hemophagocytic lymphohistiocytosis (HLH). Emapalumab binds to soluble (Kd 1.4 pM) and receptor-bound forms of IFNγ and neutralizes IFNγ activity.

Following the infusion (over 2 hours) of single dose of emapalumab in healthy subjects (18-50 years), emapalumab AUC increased proportionally within the dose range of 0.01 to 1 mg/kg. However, the increase in AUC was less than dose proportional at 3 mg/kg dose. At 1 mg/kg, the average volume of distribution was 63.2 mL/kg. At emapalumab doses of 0.1 and 1 mg/kg, the average elimination half-life $t_{1/2}$ was 19 and 23 days, respectively. In patients with HLH, emapalumab AUC increased slightly more than proportionally from 1 and 3 mg/kg doses, and less than proportionally at 3, 6, and 10 mg/kg doses.

In patients, emapalumab PK is highly influenced by the production rate of IFNγ due to target mediated drug disposition (TMDD). With a twice weekly dosing regimen, emapalumab steady state is achieved by the 7th infusion. At high IFNγ production, steady-state is reached earlier due to a shorter half-life. At the 1 mg/kg dose, median steady state peak and trough concentrations of emapalumab corresponded to 44 and 25 mcg/mL and were 2.9 and 4.3 higher than the peak and trough concentrations after the first dose.

The immunogenicity of emapalumab was evaluated using an electrochemiluminescence-based immunoassay (ECLIA). Anti-therapeutic antibodies (ATAs) to emapalumab after treatment with GAMIFANT were detected in 3/64 subjects (5%). Treatment-emergent ADAs were detected in 1/33 (3%) of patients in the primary HLH clinical trial in 04 study. The ADAs in this patient were found to have neutralizing ability. No evidence of an altered safety or efficacy profile in patient with NAb.

6.2.2. **General Dosing and Therapeutic Individualization**

General Dosing

The proposed dose regimen of emapalumab is a starting dose of 1.0 mg/kg, administered as an IV infusion over 1 hour twice per week, subsequently titrated to 3, 6, 10 mg/kg based on clinical and laboratory criteria as described below in **Table 2.** Emapalumab should be continued until HSCT is performed or unacceptable toxicity. Emapalumab must be concomitantly administered with dexamethasone. After the patient's clinical condition is stabilized, the dose of emapalumab may be decreased to previous level to maintain clinical response.

Table 15 Dose Titration Criteria

Treatment Day	**GAMIFANT Dose**	**Criteria for Dose Increase**
Day 1	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/mm^3 and no improvement to >50,000/mm^3 ▪ If baseline > 50,000/mm^3 and < 30% improvement ▪ If baseline > 100,000/mm^3 any decrease to < 100,000/mm^3 ▪ Neutrophil count ▪ If baseline < 500 and no improvement to > 500/mm^3 ▪ If baseline > 500 -1000 and decrease to < 500/mm^3 ▪ If baseline 1000-1500 and decrease to < 1000/ mm^3 ▪ Ferritin ▪ If baseline ≥ 3000 and < 20% decrease ▪ If baseline < 3000 and any increase to > 3000 ▪ Splenomegaly – any worsening ▪ Coagulopathy (both D-Dimer and Fibrinogen must apply) ▪ D-Dimer ▪ If abnormal at baseline and no improvement ▪ Fibrinogen ▪ If baseline levels ≤ 100mg/dL and no improvement ▪ If baseline levels > 100 and any decrease to < 100 mg/dL
From Day 6 onwards	Increase to 6 mg/kg	
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

Therapeutic Individualization

No therapeutic individualization for intrinsic or extrinsic factors is recommended.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The clinical pharmacology, pharmacokinetics and ADME information of emapalumab is summarized below in **Table 3.**

Table 3. Summary of Clinical Pharmacology Findings

Pharmacology	
Mechanism of Action	Emapalumab is a fully human monoclonal antibody that binds to and neutralizes interferon gamma (IFNγ) (Kd = 1.4 pM).
Active Moieties	Emapalumab is the active moiety.
QT Prolongation	GAMIFANT, as a large protein (MW = 148 kDa), has a low likelihood of direct ion channel interactions. Clinical study showed that at a dose of 3 mg/kg, GAMIFANT does not prolong the QT interval to any clinically relevant extent.
General Information	
Bioanalysis	Emapalumab concentrations in treated patients were determined by analysis of serum samples using a sandwich immunoassay format on the Gyrolab platform. The assay is based on a bridging immunoassay in a sequential format. The capture antibody is a mouse anti-NI-0501 Biotinylated antibody that becomes bound to the streptavidin on the column. Biotinylated BSA is used in combination with the coating antibody to ensure “spacing” of the coating antibody. Following addition of the samples detection is achieved using mouse anti-NI-0501 conjugated to Alexa 647. Detection is performed by the measurement of laser induced fluorescence using a built in fluorometer. See **Section 19** for the details of bioanalytical methods for ADA, nAB, IFNy and CXCL9.

Drug total exposure at steady state following the therapeutic dosing regimen	The median peak emapalumab concentration 21 days (steady state) after first administration were about 44,000, 154,000, 250,000 and 260,000 ng/mL for 1, 3, 6 and 10 mg/kg dose.
Minimal effective dose or exposure	1 mg/kg administered by infusion over 1 hour.
Dose Proportionality	In healthy subjects, emapalumab concentrations increased proportionally with dose over the dose range of 0.01 to 1 mg/kg but less than dose proportional at 3 mg/kg dose.
Accumulation	No accumulation is observed at the doses evaluated.
Immunogenicity	A total of 64 subjects were evaluated for anti-therapeutic antibodies (ATAs) to emapalumab after treatment with GAMIFANT. ATAs were detected in 3/64 subjects (5%) who received GAMIFANT. Treatment-emergent ATAs were detected in 1/33 (3%) of patients in the primary HLH clinical trial (Study 04). The ATAs in this patient were found to have neutralizing ability. One patient receiving GAMIFANT through compassionate use (Study 05) developed transient non-neutralizing treatment-emergent ATAs. In both patients, ATAs occurred within the first 9 weeks following the initiation of GAMIFANT treatment. In addition, one healthy subject tested positive for ATAs following a single dose of GAMIFANT. No evidence of an altered safety or efficacy profile was identified in the primary HLH patients who developed antibodies to emapalumab.
Distribution	
Volume of Distribution	Based on population pharmacokinetic analysis, the mean central and peripheral volumes of distribution in a subject with body weight of 70 kg are 4.2 and 5.6 L, respectively.
Plasma Protein Binding	Not evaluated. Emapalumab is not expected to bind to plasma proteins.
Blood to Plasma Ratio	Not evaluated.
Substrate transporter	Not evaluated. As a large recombinant protein, emapalumab is not expected to be a substrate of metabolic transporters.
Elimination	

Mean terminal elimination half-life	The terminal phase half-life was 23 days in healthy subjects, however in HLH patients the terminal half-life varied between 2.5 -19 days, depending upon the IFNγ concentrations, implying target mediated clearance.
Metabolism	
Primary metabolic pathway(s)	Not evaluated. As a recombinant protein, emapalumab is expected to be degraded into small peptides and amino acids via catabolic pathways.
Inhibitor/Inducer	Not evaluated. 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. Upon initiation or discontinuation of concomitant GAMIFANT, monitor for reduced efficacy and adjust dosage of CYP450 substrate drugs as appropriate.
Excretion	
Primary excretion pathways (% dose) ± SD	Not evaluated. As a recombinant protein, emapalumab is expected to be degraded into low-molecular-weight peptides and amino acids via catabolic pathways

6.3.2. **Clinical Pharmacology Questions**

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The primary evidence of effectiveness is based on the Overall Response Rate (ORR) at the End of Treatment in Study NI-0501-04 (EOT 04) compared to pre-specified null hypothesis of 40% ORR.

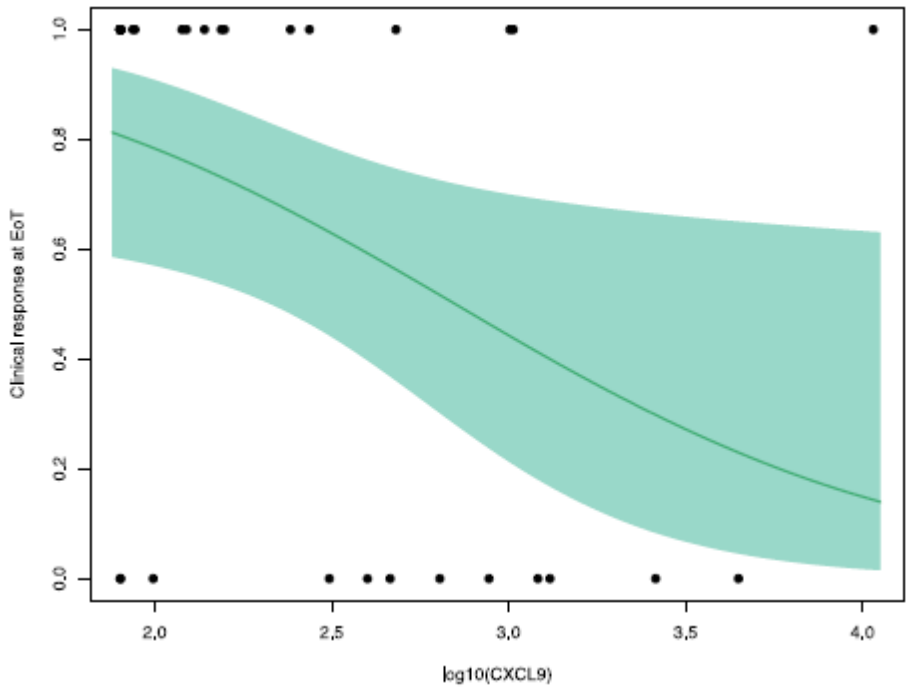
Study NI-0501-04 is an open label, single-arm, multicenter study in patients with primary HLH patients whose age ranged between 0.1 – 13.8 years. The starting dose of emapalumab was 1 mg/kg given as intravenous infusion over 1 hour twice per week (three to four days) and subsequently increased to 3, 6, 10 mg/kg based on clinical and laboratory criteria (See **Table 2** for more details). The primary efficacy endpoint (ORR) at EOT 04 (End of Treatment in Study 04) was defined as the achievement of either a complete or partial response or HLH improvement based on a pre-specified algorithm. EOT was defined as 3 days after last emapalumab infusion with allowed time-

windows. The primary efficacy endpoint results suggest that the treatment was effective in all the treated population (both treatment experienced and treatment naïve subjects) as well as treatment experienced, but not statistically different for the treatment naïve subjects. See section 1.3 for details for the efficacy results.

The exposure-response analysis for efficacy show that the clinical response at the end of the treatment was highly correlated with pharmacodynamics measures such as concentrations of CXCL9, IFNγ, CXCL10 (in decreasing order). **Figure 1** shows the relationship between the predicted likelihood of clinical response at the EOT 04 as a function of the log-transformed CXCL9 plasma concentrations at the EOT 04, suggesting that the likelihood of clinical response increases with decreasing CXCL9 plasma concentrations at EOT 04 due to emapalumab concentrations. The model predicts that achieving a (median) CXCL9 concentration threshold of 465 pg/ml at week 2 and 296 pg/ml at the EOT was predictive of ORR at the EOT.

In summary, clinical pharmacology analyses provide supportive evidence of the effectiveness of emapalumab for the treatment of patients with HLH.

Figure 1. **Predicted likelihood of clinical response at the end of treatment as a function of the log-transformed CXCL9 levels at the end of treatment. The green area represents the 95% confidence intervals and the black dots represent the actual observed clinical responses (0 = no response and 1 = response) with their corresponding CXCL9 levels.**



Source: Applicant's Exposure-response safety (M 5.3.3.5) Study Report 180307, Figure 15 on Page 47

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen in the general population for which the indication is being sought is acceptable. The applicant's rationale for the proposed starting dose was based on PK simulations, which showed that 1 mg/kg resulted in 99% inhibition of IFNγ concentrations in patients with baseline IFNγ ≤ 3400 pg/ml. Given the large inter- and intra-subject variability in plasma IFNγ concentrations in HLH patients (100 -10^6 pg/ml) depending on the severity of disease, the sponsor's proposed subsequent (frequent) dose adjustment (every three to four days) in order to quickly neutralize IFNγ concentration in each patient.

Given that approximately 30% patients in the pivotal trial received dose increase to 3 mg/kg as early as the third day (within first week), the applicant conducted simulations based on the developed population PK, PK/PD model, along with the PD/efficacy analysis, to explore a higher starting dose of 3 mg/kg. The time profiles of PK (emapalumab plasma concentrations), PD (CXCL9 plasma concentrations) and clinical response (probability of ORR at EOT 04) were simulated for (a) a 40 kg individual [solid line] and a 5 kg individual [dashed line] with (b) baseline values of IFNγ of 10,000, 50,000 and 250,000 pg/ml following the two dosing regimens below:

A. "*1 + 3 + 6 + 10 biw*" (similar to the proposed regimen): 1 mg/kg on day 0, 3 mg/kg on day 3, 6 mg/kg twice a week from days 7 to 23, 10 mg/kg twice a week starting from day 24;
B. "*3 + 6 + 10 mg/kg biw*" (regimen with higher starting dose): 3 mg/kg on days 0, 3 and 7, 6 mg/kg twice a week from days 10 to 23, and 10 mg/kg twice a week starting from day 24.

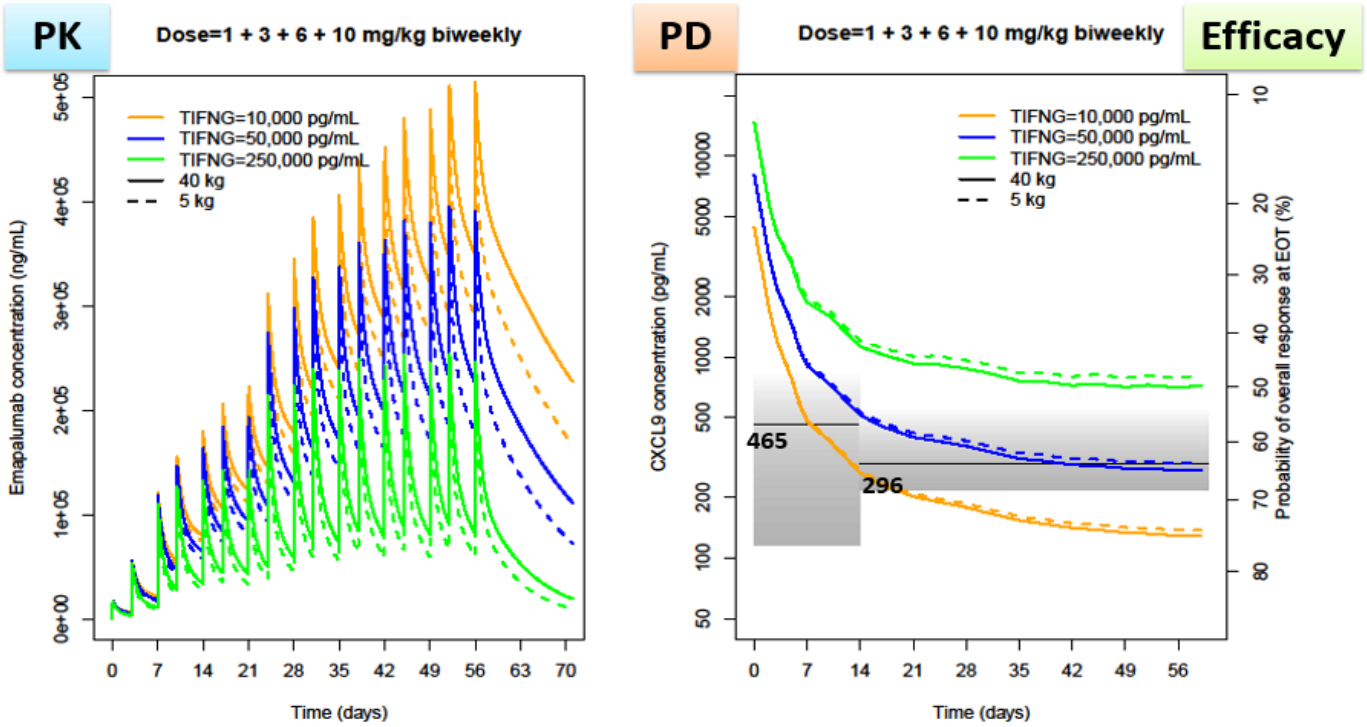
The results for dosing regimen A are shown in **Figure 2.** It can be noted that as the emapalumab plasma concentrations increases, the CXCL9 concentrations decreases and the probability of ORR at EOT increases. Furthermore, these trends are consistent across each of the INFγ cut-off values and there is no apparent difference between 40 and 5 kg individuals. The horizontal lines at 465 pg/ml and 296 pg/ml represents the CXCL9 plasma concentration threshold at week 2 and at the EOT that was predictive of ORR at EOT.

The comparison of simulated CXCL9 plasma concentrations over time between regimens A and B are shown in **Figure 3**, with each panel representing the each of (arbitrarily chosen) baseline values of IFNγ of 10,000, 50,000 and 250,000 pg/ml for an individual weighing 10 kg (median body weight in Study 0501-04). The results from these simulations suggested that the regimen with the higher starting dose was in general, comparable to the proposed dosing regimen (and evaluated in the pivotal trial). Furthermore, the cumulative distribution of subjects reaching the

CXCL9 concentration threshold of week 2 (465 pg/ml) shown in **Figure 4** suggest that there may not be substantial additional benefit by starting at a higher dose (3 mg/kg).

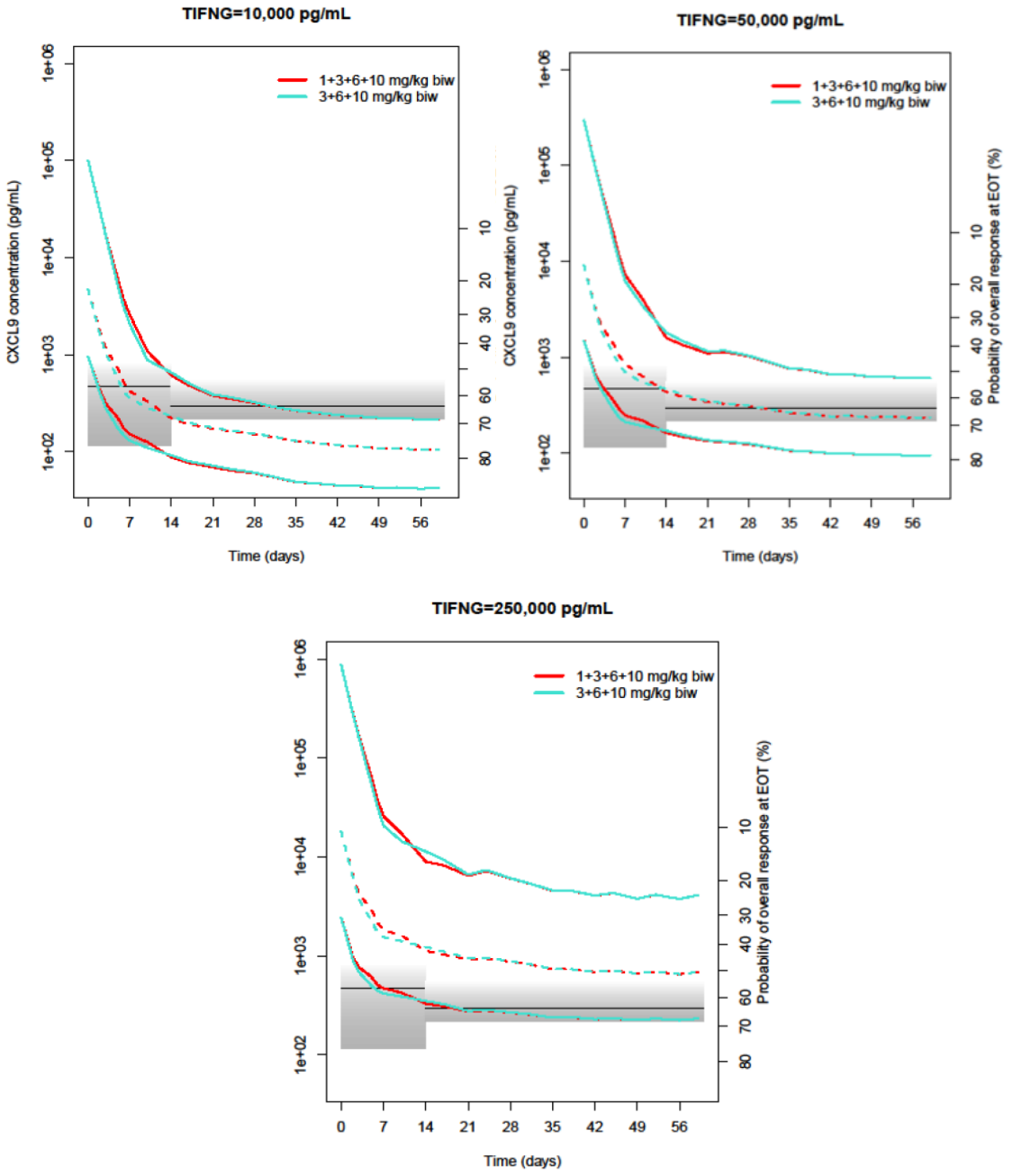
Of note, there is caveat with these simulations that they were performed under fixed dose titration regimen, that is, the dose increases are arbitrary according to planned schedule described above. While for the proposed dosing regimen, the dose titration is based on clinical and laboratory parameters, and clinical response.

Figure 2. Applicant's population PK-PD-Clinical Response simulations to support the proposed dosing regimen



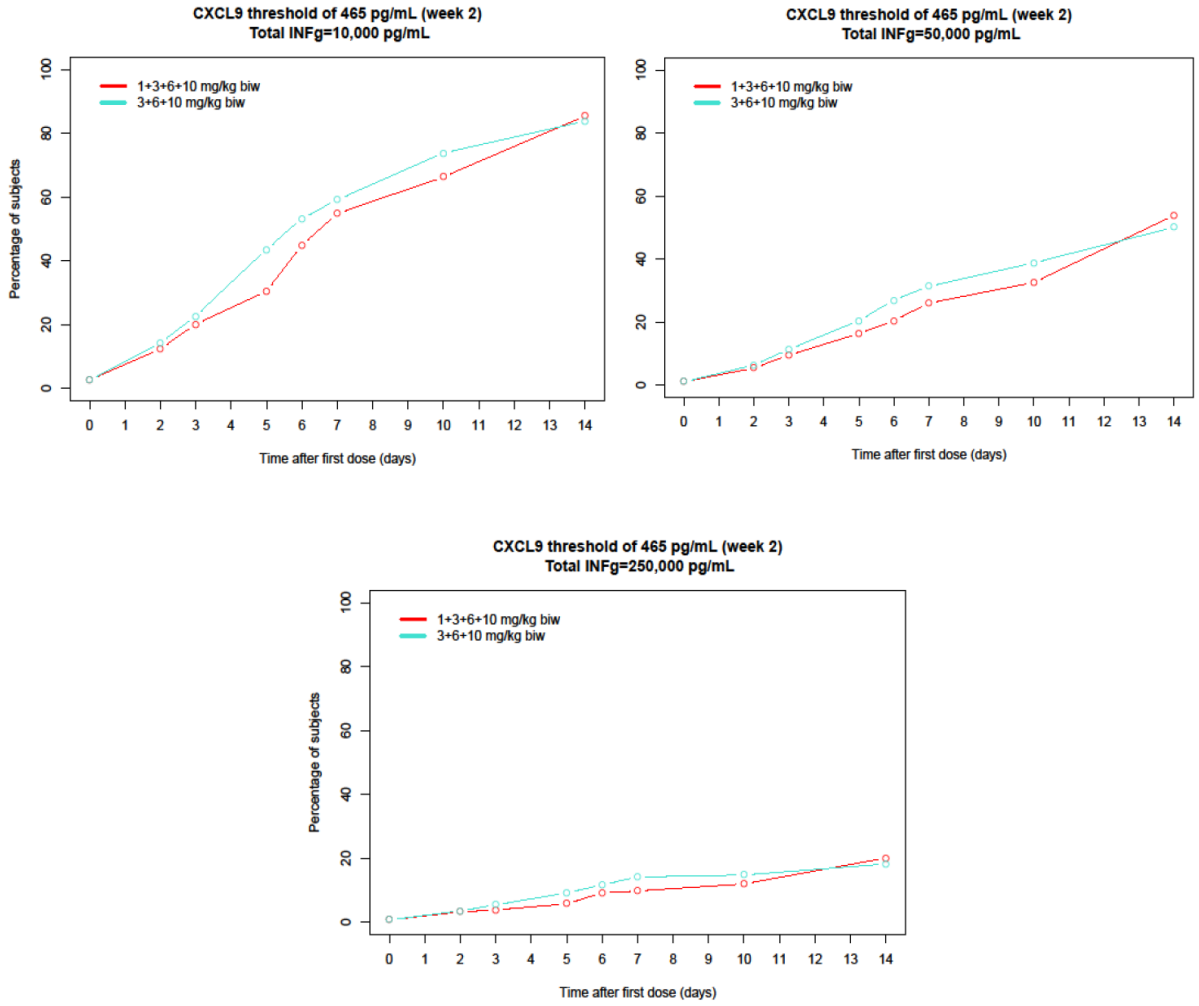
Source: Summary of Clinical Pharmacology – Scenario 7, Figure on Page 55

Figure 3. Population PD (CXCL9 plasma concentrations) – Clinical Response (probability of ORR at EOT) simulations comparing the dosing regimens with initial starting dose of 1 mg/kg (red) vs. 3 mg/kg (teal)



Source: Sponsor's response (Dated:08-09) to FDA's Information Request (sent on 08-03) – Figures on Page 6 and 7

Figure 4. Cumulative distribution of subjects reaching the CXCL9 concentration threshold of week 2 as a function of time: comparing the dosing regimens with initial starting dose of 1 mg/kg (red) vs. 3 mg/kg (teal)



Source: Sponsor's response (Dated:08-09) to FDA's Information Request (sent on 08-03) – Figures on Page 13 and 14

Overall, given the efficacy and safety profiles (and lack of obvious exposure-response for safety relationship for incidence of AEs, SAEs, IRRs) as noted in the sections above, the sponsor's proposed dosing regimen appears to be acceptable.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No, there is no need for alternative dosing regimen(s) for subpopulations based on intrinsic factors. The following covariates were tested in the population PK model: total body weight (BW), total IFNγ concentrations (IFNG), age (AGE), gender (SEX), creatinine clearance (CRCL), alanine aminotransferase (ALT), total bilirubin (TBIL) and anti-drug antibody (ADA). Based on the population PK analysis, only total body weight (BW) and baseline IFNγ concentrations (IFNγ) had a statistically significant impact on CL. This supports the body weight-based dosing of emapalumab, as studied in the clinical trials.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Emapalumab is a biologic product administered by IV infusion; food-drug interaction is not anticipated. The metabolism of emapalumab is presumed to occur via catabolic degradation into small peptide as such drug-drug interactions due to the inhibition or induction of CYPs, other metabolizing enzymes, or transporters are not expected to affect the PK of emapalumab. Therefore, no management strategy for emapalumab is needed for food-drug or drug-drug interactions. Given that CYP450 enzymes may be suppressed by increased levels of cytokines (such as IFNγ) during chronic inflammation and by neutralizing IFNγ, emapalumab may normalize CYP450 activities which may reduce the efficacy of drugs that are CYP450 substrates due to increased metabolism. As such, upon initiation or discontinuation of concomitant GAMIFANT, drugs that are substrates of CYP450 should be monitored for reduced efficacy and their dosage adjusted as appropriate

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant submitted data from three clinical studies of emapalumab alone or in combination with corticosteroids.

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
NI-0501-04	NCT01818492	Phase 2/3, single arm, open label, multicenter (United States and Europe)	1mg/kg IV every 3 days, dose increased up to 10mg/kg based on clinical condition	Primary: Overall response rate; achievement of complete, partial response or HLH improvement at end of treatment Secondary: Duration of response, percentage of patients proceeding to HSCT, percentage of patients with steroid reduction, overall survival pre-and post-transplant	Treatment for 8 weeks or sooner if HSCT occurred prior to 8 weeks Follow-up for 1 year after transplant or last emapalumab dose	34 27 second line 7 de novo	Patients <18 Y with pHLH recurrent or refractory to standard therapy or de novo	Four countries: United States Italy Spain Germany 12 centers
NI-0501-05	NCT02069899	International, multicenter (United States and Europe), long-term, follow-up study	1-10mg/kg IV	Efficacy: Duration of response after completion of emapalumab treatment Survival time up to 1-year post-HSCT or 1 year after last emapalumab treatment Post HSCT outcome indices (engraftment rate, donor chimerism, incidence of acute and chronic graft versus host disease). Safety: Incidence and seriousness of AEs	Treatment until HSCT or until HLH disease control Follow up: 12 months from HSCT or last dose of emapalumab	37 22 second line patients from NI-0501-04	HLH patients who received emapalumab treatment in either study NI-0501-04 or compassion-ate use	Three countries: United States Italy Spain 11 centers

Studies to Support Safety								
NI-0501-03	NCT01045962	Phase 1, randomized, placebo controlled	0.01mg/kg – 3 mg/kg IV X one dose	Safety, PK, immunogenicity	Single dose	20 14 received emapalumab	Healthy volunteers	One country Two centers

7.2. Review Strategy

The FDA clinical and statistical review consisted of one primary clinical reviewer and one primary statistical reviewer.

The key materials used for the review of efficacy and safety include the following:

- BLA 761107
- Relevant published literature
- Relevant information in the public domain

The review of efficacy was based on analysis of study NI-0501-04.

The primary review of safety was based on safety data from study NI-0501-04. Supportive data from the follow-on study NI-0501-05 was included in the safety review. Study NI-0501-05 included 28 patients from study NI-0501-04 and seven patients with pHLH who received emapalumab in the compassionate use program.

Summaries of the data and analysis by the reviewer were performed using JMP 13.

- Data Sources

Analysis datasets, SDTM tabulations, and software codes are located on network with network path:

\\CDSESUB1\evsprod\BLA761107\0001\m5\datasets

- Data and Analysis Quality

The applicant submitted this BLA to the FDA Center for Drug Evaluation and Research Electronic Document Room. The data included in this submission are in electronic Common Technical Documents format, in accordance with FDA guidance on electronic submission. The data sets were well documented and included definition files.

The efficacy endpoints such as overall response rate were derived and saved in analysis datasets “ADDR” and “ADEFF”, demographic and disease characteristics were derived and saved in analysis datasets “ADDR”. The statistical reviewer is able to reproduce the derived ORR datasets from the BLA tabulation datasets.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

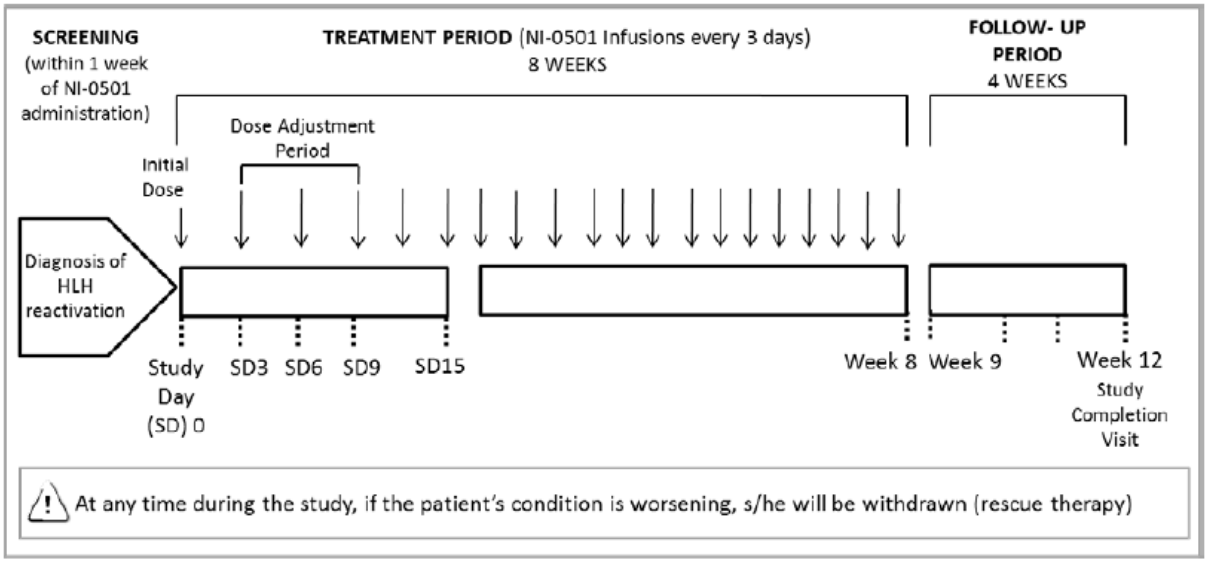
8.1.1. NI-0501-04: A phase 2/3, open-label, single-arm, multicenter study to assess safety, tolerability, pharmacokinetics and efficacy of intravenous multiple administrations of NI-0501 (emapalumab), an anti- IFNγ monoclonal antibody, in pediatric patients with primary hemophagocytic lymphohistiocytosis

Trial Design

NI-0501-04 was an open-label, single-arm, international multicenter phase 2/3 study of emapalumab for the treatment of pediatric patients (≤18 years of age at the time of HLH diagnosis) with suspected or confirmed pHLH. The study was initially designed and conducted as a pilot phase 2 study enrolling only those patients with reactivating pHLH. The study was later amended to allow enrollment of patients with inadequate response to or intolerance of conventional HLH therapy (second-line patients) as well as treatment-naïve patients (first-line patients), and to allow the study to continue as a phase 2/3 study based on the positive benefit-risk profile observed in enrolled patients at the time of the amendment.

The study design is illustrated in Figure 8.

Figure 8: NI-0501-04 Study Design



Source: NI-0501-04 Protocol page 23

Screening was carried out within 1 week prior to first administration of NI-0501 (study day [SD] 0).

Emapalumab was administered for 8 weeks (20 consecutive administrations) as re-induction treatment for HLH. Patients received a starting dose of 1mg/kg IV over one hour in combination with dexamethasone at a dose of at least 5mg/m2/day. In later versions of the study, the dose of emapalumab was sequentially increased to 3 mg/kg, 6 mg/kg, or 10 mg/kg if it was determined that the patient had inadequate response to treatment as determined by clinical and laboratory criteria detailed in the table below:

Table 16: Clinical and Laboratory Criteria to Guide Dose Increase

Study Day	Emapalumab dose	Criteria to be met
0	Starting dose of 1mg/kg	
3	Increase to 3 mg/kg	- If fever persists or reoccurs (if present at baseline) Or - If significant worsening of clinical condition
From day 6 onward	Increase to 3 mg/kg (if dose as already been increased at least two infusions have to be administered prior to reassessment)	If no satisfactory improvement in clinical conditions as assessed by investigator And At least one of the following ● *Platelet count (x10³/mcl)* If Baseline <50 → no improvement to >50 Baseline 50-100 → less than 30% improvement Baseline >100 → any decrease to <100 ● *ANC (**count**/mcl)* If Baseline <500 → no improvement to >500 Baseline 500-1000 → any decreased to less than 500 Baseline >1000 → any decrease to <1000 ● Ferritin (ng/ml) If Baseline ≥3000 → no improvement (<20% decrease) Baseline <3000 → any increase to >3000 ● Splenomegaly → worsening (at clinical or US examination) ● Coagulopathy (both D dimer and fibrinogen apply) D-Dimer If abnormal at baseline → no improvement Fibrinogen (mg/dL) If Baseline ≤100 → no improvement Baseline >100 → any decrease to <100
From study day 9 or 12 onward	Increase to 6mg/kg	If, after a minimum of two infusions at 3 mg/kg the criteria above have been reassessed and are found to be still met

Upon a successful induction treatment, HSCT was performed if an adequate donor was available and if it was determined to be clinically indicated. Emapalumab treatment was shortened to 4 to 7 weeks when a patient's condition and the availability of a donor allowed for earlier HSCT. If an appropriate donor was not identified by week 8, or in cases where HSCT was delayed for reasons unrelated to emapalumab administration, then emapalumab treatment was continued beyond 8 weeks at the request of the Investigator for patients with favorable benefit-risk profiles.

Patients were monitored for 4 weeks after the last administration of emapalumab. In the event that emapalumab concentrations were still measurable after the 4-week follow-up period (i.e., short-term follow-up), concentration monitoring continued in the context of the long-term follow-on study NI-0501-05.

The study objectives included:

- To determine the safety and tolerability profile of multiple IV administrations of emapalumab
- To determine efficacy and benefit-risk profile of emapalumab in primary HLH patients
- To describe the PK profile of emapalumab in primary HLH patients
- To define an appropriate emapalumab therapeutic dose regimen for primary HLH
- To determine the pharmacodynamics effects (levels of circulating total IFNγ and biomarkers of its neutralization, namely chemokine C-X-C motif ligand [CXCL] 9 and CXCL10)
- To determine other biomarkers, e.g., soluble chronotropic dose 25 (sCD25)
- To assess the immunogenicity of emapalumab

The trial as originally designed enrolled 10 evaluable patients. Following initial results, the protocol was amended and expanded to enroll treatment-naïve patients. The sample size calculation assumed an overall response rate of 70%, with a power of 90% to show a statistically significant difference from a background response rate of 40% using exact binomial test at a one-sided significance level of 2.5%. A total of 34 patients were enrolled in the trial and treated: seven (20.6%) first-line patients and 27 (79.4%) second-line patients.

Statistical reviewer's comment:

Without therapy, survival of patients with active familial HLH is ~2 months. The current standard of care consists of a decrescendo course of etoposide and dexamethasone, with or without intrathecal therapy. The treatment in the current trial of NI-0501-04 was given together with dexamethasone. There was little literature reporting the response rates to dexamethasone alone. The Applicant conducted consultation with community experts, and the historical rate was set to be 40% based on the consultation for dexamethasone alone.

Clinical reviewer's comment:

All patients on this study received dexamethasone in combination with emapalumab therapy. Per protocol, patients were to receive dexamethasone between 5-10mg/m2 day with a planned

taper based on clinical condition. Two patients received a starting dose higher than 10mg/m2 based on investigator's decision due to disease severity. Of the 17 second-line patients who responded to treatment, 11 had no increase in dexamethasone during the treatment period supporting that anti-HLH effect was due to emapalumab. Of the six responders who did have an increase in dexamethasone dose during therapy, the increase was typically due to a flare of HLH symptoms and occurred early in treatment (prior to day 24) in five of six patients. Since the efficacy assessment was at day 56, increases in dexamethasone dose early in the treatment would not be expected to contribute to response at day 56. The timing of the increase in the dexamethasone dose as well as the lack of previous response to prior dexamethasone therapy supports that efficacy results can be attributed to emapalumab therapy.

Concomitant dexamethasone therapy is consistent with the standard approach to pHLH, which involves multi-agent immunosuppression. Patients on this study had all received dexamethasone therapy and had reactivated or refractory disease or were intolerant to dexamethasone therapy. In general, the baseline dexamethasone dose is not usually altered even if there is no further response. Therefore, it is reasonable to attribute efficacy to emapalumab in the setting of background dexamethasone.

Because only seven patients received first-line treatment, the efficacy is evaluated only in patients receiving second-line treatment. Given the 27 patients who received second-line treatment, the power would be 85.5% instead of 90%. The power would be enough to detect a statistically significant difference in ORR from a background response rate of 40%. Due to the small number of patients with first line HLH enrolled in the trial, only the 27 patients who failed initial therapy were considered for the efficacy evaluation.

An unplanned, informal descriptive interim analysis was conducted to prepare for a requested regulatory data submission prior to the database lock, in the context of application to the FDA for Breakthrough Therapy designation and to the European Medicines Agency for PRIME designation. This interim analysis was done on a partially cleaned database when 11 patients had received at least one infusion of the study drug.

Trial Endpoints

The primary efficacy endpoint was the overall response rate at the end of treatment in study NI-0501-04 (EOT 04), defined as achievement of either a complete or partial response or HLH improvement based on a pre-specified algorithm. End of treatment (EOT) was defined as 3 days after last emapalumab infusion with allowed time windows (between -3 and +5 days of the EOT). The definitions of response are summarized in Table 17.

Table 17: Definitions of Response in NI-0501-04

Overall Response Rate	
Complete Response	Complete Response (CR) was assigned if: No fever = body temperature < 37.5°C Normal spleen size as measured by 3D abdominal ultrasound No cytopenia = Absolute Neutrophil Counts ≥ $1.0x10^9$/L and platelet count ≥ $100x10^9$/L [absence of G-CSF and transfusion support must be documented for at least 4 days to report no cytopenia] No hyperferritinemia = serum level is < 2000 µg/L No evidence of coagulopathy, ie, normal D-Dimer and/or normal (> 150 mg/dL) fibrinogen levels No neurological and CSF abnormalities attributed to HLH No sustained worsening of sCD25 (as indicated by at least 2 consecutive measurements that were > 2-fold higher than baseline)
Partial Response	Partial Response (PR) was assigned if: At least 3 of the HLH clinical and laboratory abnormalities (including CNS abnormalities) met the aforementioned criteria for "Complete Response". In the case of "reactivated patients" who entered the study with 3 abnormal HLH features, at least 2 criteria were to meet the definition given There was no progression of other aspects of HLH disease pathology (eg, jaundice, liver size, edema, CNS clinical alterations)
HLH Improvement	HLH improvement (HI) was assigned if: Improvement (>50% change from baseline) of at least 3 HLH clinical and laboratory abnormalities (including CNS involvement). In the case of "reactivated patients" who entered the study with 2 abnormal HLH features, a change from baseline greater than 50% for both defined HLH as improved.

Source: Definitions of response, NI-0501-04 Study Report Page 44

Key secondary efficacy endpoints included:

- Time to response, defined as elapsed time from the date of the first dose of emapalumab to first achievement of at least HLH improvement
- Duration of response, including
  - Duration of first response, defined as the total elapsed time from first achievement of response to first loss of response
  - Cumulative duration of response, defined as the total time in response from the achievement of a first response up to HSCT conditioning, calculated by adding together the separate time periods in which patients have remained "in response"
- Survival, including
  - Overall survival, i.e., from the date of first dose to the date of death or to the date of last assessment (either in study NI-0501-04 or NI-0501-05)
  - Survival to HSCT, i.e., from the date of first dose to the date of death or to the date of HSCT or Day 180 (whichever occurred first)
  - Survival after HSCT, i.e., from the date of HSCT to the date of death or to the date of last assessment (either in study NI-0501-04 or NI-0501-05)

- Percentage of patients with a ≥50% reduction in glucocorticoids from baseline

Statistical Reviewer's Comment:

The time-to-event endpoints specified as key secondary endpoints would not be interpretable because of single-arm trial.

Other secondary efficacy endpoints included:

- Percentage of patients who underwent HSCT
- HSCT outcomes, including engraftment, acute or chronic GVHD and a relapse of HLH following HSCT
- Overall response at week 2
- Response assessed by the investigator
- Post-HSCT event-free survival

Clinical Reviewer's Comment:

The trial endpoints of overall response rate defined as CR, PR, or HLH improvement are reasonable and in this reviewer's opinion, represent clinical benefit. Patients with pHLH with reactivated or refractory disease experience organ damage, coagulopathy, and infections related to cytopenias that contribute to morbidity and mortality. Therefore, therapy that results in symptom improvement in this disease can be considered of clinical benefit to patients.

In addition, the signs and symptoms of HLH as defined by the response criteria can prevent patients from proceeding to transplant, the only cure for this disease. Since the goal of therapy for pHLH is HSCT, therapy can result in disease control until transplant is clinically meaningful in this disease.

Statistical Analysis Plan

Analysis Populations

All-treated analysis set: patients who received any part of an emapalumab infusion; this was the primary analysis set for safety.

Second-line all-treated analysis set: patients who had received conventional HLH therapy before enrollment in the NI-0501-04 study; this was the primary analysis set for efficacy.

Evaluable analysis sets: patients, within the all-treated analysis set who were evaluable for efficacy.

Selected efficacy and safety endpoints were also analyzed in the subgroup of first-line patients.

Statistical Method

Overall response at EOT 04 was analyzed for the all-treated and second-line all-treated analysis sets using an exact binomial test and exact methods for confidence intervals (CI) to evaluate the null hypothesis that the ORR was at most 40%. This test was undertaken at the one-sided 0.025 significance level.

The secondary efficacy endpoints were viewed as supportive, so no formal statistical testing was conducted.

Time to response was analyzed until EOT 04 or EOT 04/05.

Duration of first response was analyzed until EOT 04 and, as an exploratory analysis, until the start of HSCT conditioning, including data from study NI-0501-05. Cumulative duration of response was calculated by adding the separate time periods in which patients remained in response prior to HSCT conditioning. Patients who did not respond had a value of 0 days in this analysis.

Duration of response was assessed as:

- Duration of first response: the total elapsed time from first achievement of response to first loss of response. Response should last for at least 4 days to be considered as first achievement of response, and loss of response should persist for at least 4 days to be considered as first loss of response. Duration of response was assessed until EOT 04 and, as an exploratory analysis, until HSCT conditioning (i.e., including data from study NI-0501-05).
- Cumulative duration of response: the total time the patient remained in response from the first achievement of a response until HSCT conditioning. For patients who achieved a response, lost that response, but then subsequently achieved again a response, the total time in response was calculated by adding together these separate periods.

The number and percentage of patients with a ≥50% reduction in glucocorticoids from baseline was calculated together with two-sided 95% CIs at EOT 04.

The number and percentage of patients who underwent HSCT and who had each of HSCT outcomes was calculated together with two-sided 95% CIs using data from the NI-0501-04 and NI-0501-05 studies.

Survival was analyzed overall and pre- and post-HSCT using data from studies NI-0501-04 and NI-0501-05.

All time-to-event endpoints were assessed with Kaplan-Meier analysis. Kaplan-Meier survival probability estimates and associated two-sided 95% CIs were calculated. Median survival times were calculated with the PROC LIFETEST procedure. Kaplan-Meier survival curves were plotted with the number of patients at risk through time indicated.

Statistical Reviewer's Comment:

The time-to-event endpoints specified as key secondary endpoints would not be interpretable because of single-arm trial.

No imputations of missing data were performed. However, the following rules were applied in the final analysis:

- Patients who withdrew from the study prior to week 8 because of safety concerns or poor efficacy were classified as non-responders from the time of their withdrawal in all

analyses of response status, and their data was censored at time of withdrawal in all time-to-event analyses. For such patients, analysis of continuous endpoints beyond the point of withdrawal excluded missing data.

- Patients who did not reach week 8 because of early transplant were classified as responders beyond their time of withdrawal in all analyses of response status, and their data was censored at time of withdrawal.

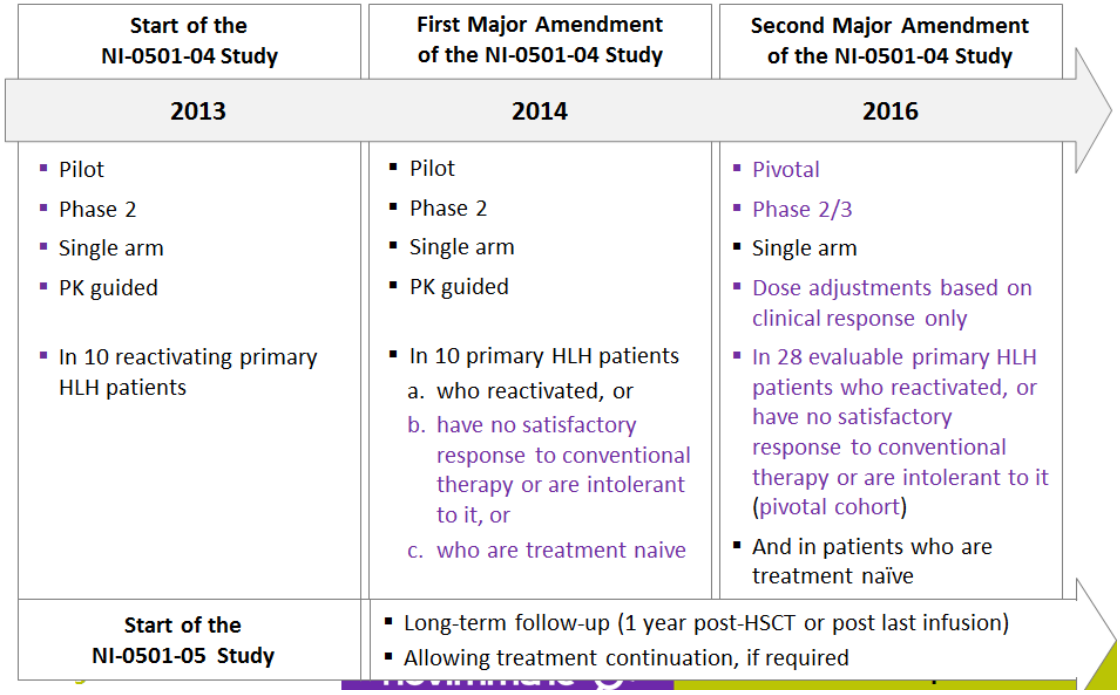
Two sensitivity analyses for overall response were performed using the all-treated and second-line all-treated analysis sets:

- A more stringent time window at EOT (i.e., -3/+3 days rather than -3/+5 days)
- A conservative approach for determining the rates of overall response at EOT 04 in which patients who received additional HLH treatments (i.e., etoposide and alemtuzumab) within study NI-0501-04 were categorized as non-responders or were excluded from the analysis
- Overall response at EOT 04/05, i.e., assessed either in study NI-0501-04 or in study NI-0501-05 (for patients who continued emapalumab treatment). Both -3/+3 day and -3/+5 day windows were applied.

Protocol Amendments

The study's two major protocol amendments are summarized in Figure 9 and Table 18.

Figure 9: Summary of Major Protocol Amendments to NI-0501-04



Source: The Applicant's application orientation meeting slides page 9

Table 18: Main Changes in Protocol Amendments

Protocol Amendment Date	Key Changes
EU version 2.1 11 January 2013	• Addition of advice on contraception, and exclusion of pregnancy and lactation • Clarification on the dose escalation process • Revision of the IMP preparation form • Clarification of the 4-week follow-up period after treatment discontinuation
US version 2.1 05 December 2013	• Clarification of a few protocol sections (eg, treatment periods and follow-up period, dosing regimen, prophylactic and concomitant therapies, monitoring of NI-0501 concentration, DMC role) • Additional measurements requested by the Study Scientific Committee to assess any drug action on lymphocytes (ie, CBC with differential count at certain time points) • Differentiation between infusion visits and safety/efficacy assessment visits during treatment period 2
EU version 3.0 13 December 2013	• Amendment of the protocol number to reflect the introduction of the US twin protocol • Implementation of a combined analysis of the data generated by the EU and US protocol • Clarifications of a few protocol sections (eg, Inclusion/Exclusion Criteria, study design, study outline and stopping rules) and introducing few additional clinical assessments (non-invasive), as well as PK and laboratory measurements, aimed at facilitating the analysis of the data
US version 3.0 16 April 2014 EU version 4.0 07 May 2014	• Broadening of the patient population eligible to receive NI-0501 in the study: In addition to primary HLH patients reactivating after having achieved Partial Response following conventional therapy, the protocol allowed the inclusion of primary HLH patients who received conventional therapy and: 1. Worsened or showed no further improvement for at least 4 weeks from initiation of treatment after achieving at least Partial or Incomplete Response 2. Showed no response after at least 2 weeks from initiation of conventional therapy or worsening of the disease 3. Showed intolerance to conventional treatment of HLH
US version 4.0 17 November 2014 EU version 5.0 15 December 2014	• Broadening of the target patient population to include patients naïve to HLH treatment • Revision of the title of the study to reflect the changes made to the Study Population and the Inclusion Criteria • Revision of the dose regimen, the dose determination criteria, and the background therapy requirements
EU version 6.0 26 February 2016 US Version 5.1 24 March 2016	• Prolongation of the study to continue as Phase 2/3, with determination of sample size for the pivotal cohort (defined as patients who receive NI-0501 in second line) • Definition of primary and secondary efficacy endpoints, consistently with the amended phase of the study consistently with the amended phase of the study • Revision of the dosing regimen and implementation of a standardized approach to dose increase. Clinical criteria were indicated to guide the dose increase by the Investigator. Dose increase was allowed at any time during the course of the study • Possibility to add other HLH treatments, primarily etoposide, if pre-defined criteria were met • Update to the stopping rules to reflect the experience gathered with the drug and the amended phase of the study

Source: NI-0501-04 Study report Page 56

8.1.1. Study Results Compliance with Good Clinical Practices

The Applicant provided attestation that the protocols, protocol amendments, and patient informed consent forms for studies NI-0501-03, NI-0501-04 and NI-0501-05 were reviewed and approved by the institutional review boards or independent ethics committees of the

participating study centers. The Applicant also provided a list of institutional review boards and independent ethics committees for the participating study center.

The Applicant provided a statement that studies NI-0501-04 and NI-0501-05 were conducted in accordance with the International Council for Harmonisation guideline for Good Clinical Practice, the principles of the Declaration of Helsinki, and the U.S. Code of Regulations, Title 21, Parts 50, 56, and 312 providing the protection of the rights and welfare of human patients participating in biomedical research. All patients or their legal representatives voluntarily consented prior to trial enrollment.

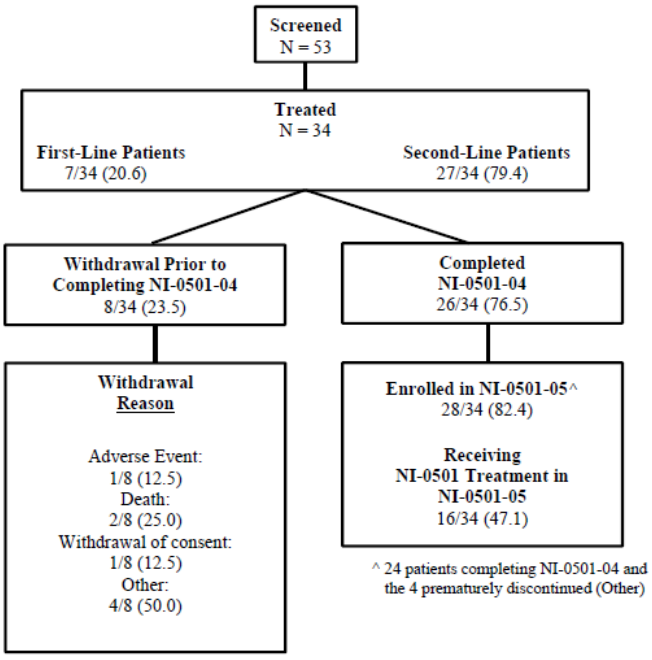
Financial Disclosure

The Applicant submitted financial disclosure information from three investigators and 12 sub investigators from study NI-0501-03, 34 investigators and 111 sub investigators from the NI-0501-04 study and 12 investigators and 43 sub investigators from study NI-0501-05 indicating that none of the investigators had disclosable financial interests or arrangements. For details, refer to the Clinical Investigator Financial Disclosure Review Template in Section 19.2. None of the disclosures submitted revealed a potential conflict of interest.

Patient Disposition

The patient disposition is summarized in Figure 10 and Table 19Error! Reference source not found.

Figure 10: Patient Disposition



Source: NI-0501-04 Study Report Page 61; verified by Statistical Reviewer's analysis

Table 19: Patient Disposition

Disposition Category	Statistic	NI-0501-04 (N=34)
Patients Completed NI-0501-04 Study [1]	N (%)	26 (76.5)
Patients Withdrawal Prior to Completing NI-0501-04 Study	N (%)	8 (23.5)
Reason for Not Completing NI-0501-04 Study [2]		
Adverse Event	N (%)	1 (12.5)
Death [3]	N (%)	2 (25.0)
Withdrawal of consent	N (%)	1 (12.5)
Other [4]	N (%)	4 (50.0)
Patients Enrolled in NI-0501-05 Study [5]	N (%)	28 (82.4)
Patients Receiving NI-0501 Treatment in NI-0501-05 Study	N (%)	16 (47.1)
Patient who died in Study NI-0501-05 [6]	N (%)	6 (17.6%)

Note: Percentages are based on number of patients treated unless otherwise specified.
[1] Received a minimum of 4 weeks of treatment (from study day 0 to EOT) unless discontinued subsequently due to lack of efficacy or safety reasons and completed the 4-week short-term follow-up or continued treatment in the NI-0501-05 study.
[2] Percentage based on total number of patients withdrew prior to completing Study NI-0501-04.
[3] Three patients died soon after completion/withdrawal from Study NI-0501-04.
[4] Patients discontinued due to the Investigator's decision to administer additional HLH treatments (withdrawal criterion under the protocol version current at that time). In 2 of these patients emapalumab treatment was resumed in CU upon the Investigator's request.
[5] All patients completing Study NI-0501-04 entered Study NI-0501-05, except for 2 patients (1 patient denied consent and 1 died after study completion). Additionally, the 4 patients prematurely withdrawn consented to the long-term study, including 1 patient who entered Study NI-0501-05 after the period of CU treatment.
[6] Three patients died after HSCT due to transplant complications (1 patient died after the database cut-off of (b) (6) (b) (6) and 3 patients died before HSCT (1 patient after start of conditioning)
Source: Table 14.1.1.1b and Listing 16.2.1.1.

Source: NI-0501-04 Study report Page 62

Study NI-0501-05

Of the 27 second line patients who were enrolled in study NI-0501-04, 22 patients were enrolled on follow-on study NI-0501-05. Of the 22 patients in study NI-0501-05, 10 continued to receive emapalumab therapy until transplant or until no longer needed. The remaining 12 patients had only follow up assessments. Including longer follow-up on study NI-0501-05, seven patients died (two after HSCT) and 20 patients were alive at the last follow up.

Reviewer's comment:

The additional data from patients who received either follow-up or continued emapalumab on study NI-0501-05 can be used to inform further studies and is supportive of efficacy since some patients were able to receive HSCT after study NI-0501-04 with additional emapalumab treatment. (b) (4)

Protocol Violations/Deviations

Seventy-one protocol deviations were reported in 25 patients on study NI-0501-04. The breakdown of the categories of protocol violations are detailed in the table below.

Table 20: Protocol Violations Occurring in Patients on Study NI-0501-04

	Total	Assessment	Study Drug	Co-medications	Eligibility Criteria	Other *	Informed Consent
N (%)	17	40 56%	13 18%	11 15%	4 5%	2 3%	1 1%

Source: Clinical Reviewer generated from Applicant ADPD dataset

Protocol violations related to the study drug were mainly due to an increase in the protocol-directed emapalumab dose due to investigator request based on the patient's clinical conditions. These violations occurred prior to the protocol amendment that allowed for dose escalation based on clinical condition. Four protocol violations were related to patient eligibility. Two of these were related to patients not receiving appropriate screening for infectious etiology prior to study entry. One was related to the post-mortem diagnosis of NK-T cell lymphoma, which was considered pre-existing. A final protocol eligibility violation was related to a centralized review that determined the patient ((b) (6)) did not have sufficient active HLH to meet study inclusion criteria. A brief summary of this patient's course is provided below:

Pt (b) (6) who was diagnosed with pHLH 1 week after birth. He was initially treated per HLH-94 therapy plus alemtuzumab with an incomplete response. He was assessed to be intolerant to dexamethasone and etoposide due to hypertension and profound pancytopenia. The patient had genetic confirmation of FHL2. The patient had been treated with intrathecal therapy for presumed neurologic involvement based on abnormal eye movements and the presence of macrophages in the CSF. The patient had an MRI, which was significant for periventricular leukomalacia prior hemorrhage. Expert review did not confirm that the patient had evidence of central nervous system (CNS) involvement due to HLH. At the time of study entry, the only abnormal finding was an elevated ferritin. At the EOT, this patient was assessed as a complete responder based on resolution of the elevated ferritin. The patient then proceeded to HSCT on day 43 and was reported to have normal labs and full HLH control 12 months after HSCT.

Clinical reviewer's comment:

It is questionable from the narrative and clinical study report (CSR) if patient (b) (6) met criteria for "presence of active disease" since the only abnormal finding reported for this patient was an elevated ferritin. The patient was reported to have skin lesions, however, while skin findings are characteristic of the disease, this is not considered one of diagnostic criteria or a sign of active disease. This patient was assessed as a complete responder based on resolution of the elevated ferritin. Exclusion of this patient from the analysis results in an ORR of 62% (95% CI: 0.405, 0.80),

which still meets the threshold for the primary efficacy assessment. From a clinical perspective, the clinical scenario described for this patient of an elevation of a lab parameter (ferritin) warrants attempts at disease stabilization prior to HSCT and emapalumab therapy would be applicable to this situation. An additional sensitivity analysis that excludes this patient as well as two additional patients, one who was not evaluable for response due to death due to infection on day 3 and one who had underlying NK T cell lymphoma resulted in an ORR of 66.7% (16/24 (95% CI: 0.45, 0.84).

Two additional patients in the second line group had protocol violations regarding eligibility. Both patients received limited treatment prior to study enrollment, therefore, it is questionable if the study criteria "not responded, not achieved a satisfactory response, worsened after, or were intolerant to conventional therapy" was fulfilled. Conventional therapy is not specifically defined in the protocol but would typically be considered HLH-1994 or HLH-2004 therapy, which would include etoposide. Neither of these patients received etoposide therapy. Patient (b) (6) received only intrathecal hydrocortisone and dexamethasone prior to receiving emapalumab, and patient (b) (4) received cyclosporine and dexamethasone prior to receiving emapalumab. Patient (b) (6) continued to worsen and eventually received etoposide therapy. At that time, emapalumab was discontinued, and she was considered a non-responder. Patient (b) (6) received cyclosporine and dexamethasone as initial therapy with worsening HLH symptoms prior to enrollment on study and emapalumab administration. This patient did not receive etoposide therapy as her initial therapy. She experienced improvement of laboratory findings and neurologic symptoms during therapy and was considered a partial responder at the EOT.

Clinical Reviewer's comment:

The inclusion of two patients in the efficacy analysis who were considered as second-line patients but did not receive etoposide as part of their initial therapy could be considered problematic as these patients more closely represent a first-line or treatment-naïve population. There are clinical scenarios, however, when patients with pHLH would not be considered candidates for etoposide therapy, therefore it is reasonable to include these patients in the population of second-line patients. An efficacy analysis that excludes these two patients results in an ORR of 16 of 25 or 64% (95% CI: 0.42, 0.82). Therefore, these protocol deviations in eligibility are not considered to change the overall analysis of efficacy.

Demographic and Other Baseline Characteristics

Demographic characteristics of patients enrolled are summarized in Table 21. All were pediatric patients and the majority were <2 years of age. Other baseline characteristics (e.g., disease characteristics, important concomitant drugs) are included in Table 22.

Table 21: Demographic Characteristics in the Trial NI-0501-04

Parameter	Statistic	NI-0501-04 All Treated (N=34)	NI-0501-04 Second-Line All Treated (N=27)
Age at parental/family Informed Consent (years) [1]	N Mean (SD) Median Min, Max	34 2.24 (2.992) 1.00 0.1, 13.0	27 2.55 (3.231) 1.00 0.2, 13.0
Age Category			
< 2 years	N (%)	21 (61.8%)	15 (55.6%)
≥ 2 - < 12 years	N (%)	12 (35.3%)	11 (40.7%)
≥ 12 - < 18 years	N (%)	1 (2.9%)	1 (3.7%)
Sex			
Female	N (%)	18 (52.9)	16 (59.3)
Male	N (%)	16 (47.1)	11 (40.7)
Race			
White	N (%)	22 (64.7)	17 (63.0)
Asian	N (%)	5 (14.7)	3 (11.1)
African Descent	N (%)	3 (8.8)	3 (11.1)
Mixed/multi-racial	N (%)	0	0
Other	N (%)	4 (11.8)	4 (14.8)
Country of Origin			
US	N (%)	8 (23.5)	7 (25.9)
Italy	N (%)	4 (11.8)	3 (11.1)
Others	N (%)	16 (47.1)	12 (44.5)
Missing	N (%)	6 (17.6)	5 (18.5)

[1] Age (in years) is calculated from date of informed consent and date of birth. For patients greater than 1 year of age, age is rounded down to the nearest integer; for patients less than 1 year of age, age is rounded to the nearest hundredth.
Source: Table 14.1.2.1 and Table 14.1.2.2.

Source: NI-0501-04 Study Body Page 65; verified by statistical reviewer's analysis

Table 22: Other Baseline Characteristics in NI-0501-04

Parameter	Statistic	NI-0501-04 All Treated (N=34)	NI-0501-04 Second-Line All Treated (N=27)
Age at HLH Diagnosis (years) [1]	N Mean (SD) Median Min, Max	34 2.089 (3.1591) 0.850 0.03, 13.81	27 2.324 (3.4324) 0.910 0.03, 13.81
HLH Genetic Confirmation	N (%)	27 (79.4)	22 (81.5)
FHL1	N (%)	2 (5.9)	0
FHL2	N (%)	7 (20.6)	5 (18.5)
FHL3	N (%)	8 (23.5)	7 (25.9)
FHL4	N (%)	1 (2.9)	1 (3.7)
FHL5	N (%)	2 (5.9)	2 (7.4)
Griscelli Syndrome type 2	N (%)	5 (14.7)	5 (18.5)
X linked Lymphoproliferative Disorder 1	N (%)	1 (2.9)	1 (3.7)
X linked Lymphoproliferative Disorder 2	N (%)	1 (2.9)	1 (3.7)
Number of Patients Meeting Each HLH Criteria [2]			
Fever	N (%)	30 (88.2)	23 (85.2)
Splenomegaly	N (%)	30 (88.2)	24 (88.9)
Cytopenias affecting 2 of 3 lineages in the peripheral blood	N (%)	33 (97.1)	26 (96.3)
Hypertriglyceridemia or hypofibrinogenemia	N (%)	25 (73.5)	19 (70.4)
Hemophagocytosis in bone marrow, spleen or lymph nodes, with no evidence of malignancy	N (%)	13 (38.2)	11 (40.7)
Low or absent natural killer (NK)-cell activity	N (%)	14 (41.2)	11 (40.7)
Ferritin ≥ 500 µg/L	N (%)	29 (85.3)	23 (85.2)
Soluble CD25 (sCD25; ie, soluble IL-2 receptor) ≥ 2400 U/mL	N (%)	20 (58.8)	17 (63.0)

[1] Age at initial HLH diagnosis is defined as (Date of Diagnosis – Date of Birth + 1) / 365.25.
[2] HLH-2004 diagnostic criteria at initial diagnosis of primary HLH.
Source: Table 14.1.4.1.2 and Table 14.1.4.1.1.

Source: NI-0501-04 Study Body Page 67; verified by statistical reviewer's analysis

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All patients received concomitant dexamethasone therapy during the study. The median dexamethasone dose at the initiation of therapy was 10mg/m2 (range 2,131). Per protocol patients were to receive dexamethasone at a dose of 5-10mg/kg day starting at least one day prior to the start of therapy. Dexamethasone could be tapered per clinical symptoms. At the EOT, the median dexamethasone dose was 5.3 mg/m2 (range 1,21).

All patients received concomitant anti-herpes simplex virus prophylaxis. Seventy five percent of patients received PCP prophylaxis, and 91% received antifungal prophylaxis.

Of the 27 second-line patients, five (19%), received additional anti-HLH treatment prior to the EOT due to worsening HLH. Anti-HLH therapy included alemtuzumab (two patients), etoposide (two patients) and alemtuzumab + etoposide (one patient). Depending on the version of the protocol, this resulted in study withdrawal or emapalumab therapy was continued. One of the five patients was reported to have a PR at the EOT, the remaining four were non-responders.

Efficacy Results – Primary Endpoint

The primary endpoint of the trial is objective response rate, which is defined based on patient response in any of three categories: complete response, partial response, HLH improvement. The results for both all-treated and second-line patients are summarized in Table 23.

Table 23: Primary Endpoint for NI-0501-04

	Statistic	EOT 04 All Treated (N=34)	EOT 04 Second-Line All Treated (pivotal cohort) (N=27)
Overall Response [1]			
Complete response	N (%)	7 (20.6)	7 (25.9)
Partial response	N (%)	11 (32.4)	8 (29.6)
HLH Improvement	N (%)	4 (11.8)	2 (7.4)
None	N (%)	12 (35.3)	10 (37.0)
Overall Response Rate	N (%) 95% CI	22 (64.7) (0.46, 0.80)	17 (63.0) (0.42, 0.81)
p-value [2]		0.0031	0.0134

Abbreviations: CI = confidence interval; HLH = hemophagocytic lymphohistiocytosis; EOT 04 = End of Treatment Study NI-0501-04.
[1] Overall Response Rate comprises of Complete Response, Partial Response or HLH improvement as defined in the SAP.
[2] p-value based on Exact Binomial Test at a one-sided significance level of 2.5% comparing proportion of patients with Overall Response to null hypothesis of 40%.
Source: Table 14.2.2.1 and Table 14.2.2.2

Source: NI-0501-04 Study report Page 75; verified by statistical reviewer's analysis

Statistical Reviewer's comment:

Treatment-naïve patients (N=7) were enrolled as an amendment to the original protocol. The number of treatment-naïve patients is too small to be used as confirmatory evidence in this population. The population to be considered the primary analysis population will remain the second-line treatment population. Because this is single-arm trial, the p-value reported excluding 40% background rate is not relevant for making statistical inference.

Primary Endpoint-Sensitivity Analysis

The sensitivity analysis on the primary endpoint of ORR was performed, and the results are included in Table 24 and Table 25. The sensitivity results show that the results are robust.

Table 24: Sensitivity Analysis on Primary Endpoint of ORR in NI-0501-04; Changing definition in HLH determination

		EOT 04 All Treated		EOT 04 Second-Line All Treated	
	Statistic	Analysis [1] (N=34)	Analysis [2] (N=29)	Analysis [1] (N=27)	Analysis [2] (N=22)
Overall Response					
Complete response	N (%)	7 (20.6)	7 (24.1)	7 (25.9)	7 (31.8)
Partial response	N (%)	10 (29.4)	10 (34.5)	7 (25.9)	7 (31.8)
HLH Improvement	N (%)	4 (11.8)	4 (13.8)	2 (7.4)	2 (9.1)
Overall Response Rate	N (%) 95% CI	21 (61.8) (0.44, 0.78)	21 (72.4) (0.53, 0.87)	16 (59.3) (0.39, 0.78)	16 (72.7) (0.50, 0.89)
p-value [3]		0.0085	0.0004	0.0337	0.0019

EOT 04 = End of Treatment study NI-0501-04.
[1] Patients who started receiving other HLH treatments within 04 study are considered as non-responders.
[2] Patients who started receiving other HLH treatments within 04 study are excluded from the analysis.
[3] 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%.
Source: Table 14.2.2.11 and Table 14.2.2.12; Table 14.2.2.15 and Table 14.2.2.16

Source: NI-0501-04 Study report Page 76; verified by statistical reviewer's analysis

Table 25: Sensitivity Analysis at Evaluation Timepoint of EOT04/05 in NI-0501-04

	Statistic	EOT 04/05 All Treated (N=34)	EOT 04/05 Second-Line All Treated (N=27)
Overall Response [1]			
Complete response	N (%)	7 (20.6)	5 (18.5)
Partial response	N (%)	9 (26.5)	9 (33.3)
HLH Improvement	N (%)	3 (8.8)	2 (7.4)
Overall Response Rate	N (%) 95% CI	19 (55.9) (0.38, 0.73)	16 (59.3) (0.39, 0.78)
p-value [2]		0.0444	0.0337

EOT 04/5 = End of Treatment overall.
[1] Overall Response Rate comprises of Complete Response, Partial Response or HLH improvement as defined in the SAP.
[2] p-value based on Exact Binomial Test at a one-sided significance level of 2.5% comparing proportion of patients with Overall Response to the hypothesized null hypothesis of 40%.
Source: Table 14.2.2.13 and Table 14.2.2.14

Source: NI-0501-04 Study report Page 77; verified by statistical reviewer's analysis

Efficacy Results – Secondary and other relevant endpoints

Durability of Response

Results for duration of response are included in Table 26 and Table 27. The duration of response is evaluated as time to first loss of response and cumulative response duration.

Table 26: Secondary Endpoint of Time to First Loss of Response

	Statistic	Until EOT 04 All Treated (N=34)	Until EOT 04 Second-Line All Treated (N=27)
At Least 1 Response	N (%)	30 (88.2)	24 (88.9)
Time to First Loss of Response (days)	75th Percentile (95% CI)	NE (58.0, NE)	NE (NE, NE)
	Median (95% CI)	58.0 (28.0, NE)	NE (22.0, NE)
	25th Percentile (95% CI)	26.0 (7.0, 38.0)	18.0 (4.0, NE)
Censored Observations	N (%)	18 (60.0)	15 (62.5)

Notes: Durability of response is defined as the total elapsed time from achievement of first response to first loss of response. Patients who were in response at last observation point were censored at that date. Patients who did not achieve at least HLH improvement once were excluded from the analysis.
Source: Table 14.2.4.1 and Table 14.2.4.2

Source: NI-0501-04 Study report Page 81

Table 27: Secondary Endpoint of Cumulative Response Duration

	Statistic	Until HSCT conditioning All Treated (N=34)	Until HSCT conditioning Second-Line All Treated (N=27)
Cumulative response duration (days)	N Mean (SD) Median Q1, Q3 Min, Max	34 58.1 (60.1) 33.5 12.0, 88.0 0.0, 247.0	27 45.1 (42.7) 31.0 11.0, 86.0 0.0, 148.0
Percent days in response (%) [1]	N Mean (SD) Median Q1, Q3 Min, Max	34 62.2 (32.2) 75.7 33.3, 91.2 0.0, 100.0	27 60.6 (32.7) 75.4 30.8, 91.2 0.0, 100.0

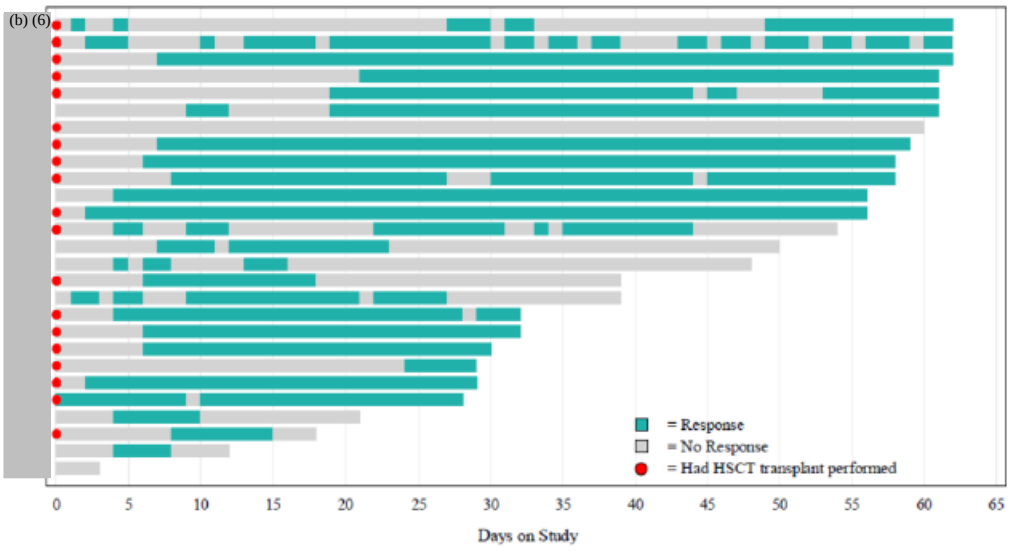
[1] Total time in response divided by number of days from first infusion until HSCT conditioning (or EOT04/05 if the patient did not have HSCT performed)
Source: Table 14.2.5.1 and Table 14.2.5.2

Source: NI-0501-04 Study report Page 83

Swimmer plots and other relevant secondary endpoints are included in Figure 11.

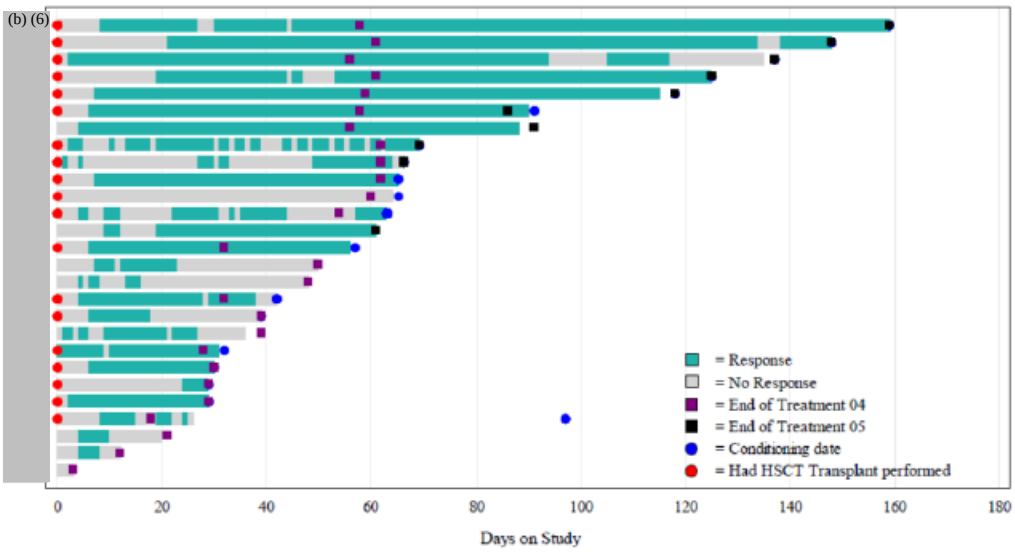
Figure 11: Time to Response for NI-0501-04

(a)



Source: Figure 14.2.4.1B

(b)



Source: Figure 14.2.5.1A

Abbreviations: EOT = end of treatment; HSCT = hematopoietic stem cell transplantation

Source: NI-0501-04 Study report Page 84

Dose/Dose Response

In the second-line treatment group, the majority of patients received no more than 1mg/kg per dose of emapalumab. A breakdown of responses and dose groups is provided in the table below.

Table 28: Responses Per Dose Group

	Max dose 1mg/kg	Max dose 3-4mg/kg	Max dose 4-6mg/kg	Max dose 8-10mg/kg
N (%)	12 (44%)	7 (26%)	5 (19%)	3 (11%)
ORR	9 (75%)	3 (42%)	3 (11%)	1 (4%)
Response Category (n)				
CR	6	0	1	0
PR	3	3	1	1
HLH I	1	0	1	0
Non-CR	2	4	2	2

Source: Reviewer table

Reviewer's comment:

The majority of responses were observed in patients who received no more than 1mg/kg per dose (44% of patients) and less frequent responses were observed in those who received higher per kilogram individual doses. Protocol therapy evolved throughout the conduct of the study to allow for increased per/kg dosing of emapalumab for those patients who had an unsatisfactory response to the 1mg/kg dose.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

There were no COA endpoints reported for this submission. The patient population ranged from 2 months to 13 years with a median age of 1 year. The young age as well as the clinical acuity of these patients poses challenges to patient-reported outcome (PRO) assessments and would require caregiver assessments.

Reviewer's comment:

The lack of COA endpoints or assessments in this trial did not significantly impact the regulatory decision. (b) (4)

Additional Analyses Conducted on the Individual Trial

Additional Clinical Analysis on the Primary Endpoint

HLH improvement was defined as an improvement (>50% changed from baseline) of at least three HLH clinical and laboratory abnormalities (including CNS improvement). In the case of reactivated patients, who entered the study with two abnormal HLH features, a change from baseline greater than 50% for both features defined HLH as improved. Two patients in the second-line analysis population experienced HLH improvement and were included as responders.

Patient (b) (6) was reported to have HLH improvement based on the resolution of fever and a >50% improvement of platelet count. This patient eventually died of ARDs and pulmonary histoplasmosis after additional HLH therapy.

Patient (b) (6) was reported to have HLH improvement based on CNS improvement, D-dimer normalization. This patient received a HSCT on SD 139 and was reported to be alive and well more than 1-year post transplant.

An analysis of ORR excluding those patients in the second line population who experienced HLH improvement as their best response resulted in an ORR of 56% (95%: CI .35, .74), which falls below the null hypothesis 40% response rate.

Reviewers comment:

HLH improvement is a less stringent definition of response compared to partial or complete response, however in this patient population a 50% improvement is still clinically meaningful.

Additional Analysis on the Primary Endpoint (Removal of Splenomegaly as a Response Criteria)

In the NI-0501-04 study, improvement in splenomegaly was included as one of the response criteria, and could be assessed by either imaging or clinical exam. Due to discrepancy in clinical exam versus ultrasound assessments of splenomegaly for several patients, and lack of radiologic assessment in some patients, the Applicant was asked to provide an assessment of response without the contribution of splenomegaly. The following table displays responses with and without improvement in splenomegaly as a contributing factor.

Table 29: Responses With and Without Improvement in Splenomegaly

	Including Spleen Assessment N=27 n (%)	Not Including Spleen Assessment N=27 n (%)
Overall Response Rate	17 (63) (95% CI: 0.42, 0.81)	17 (63) (95% CI: 0.42, 0.81)
Complete Response	7 (25.9)	10 (37.0)
Partial Response	8 (29.6)	5 (18.5)
HLH Improvement	2 (7.4)	2 (7.4)
None	10 (37)	10 (37)

Source: Applicant IR, SD #009

Reviewer's comment:

The impact of inconsistent and discrepant assessments of spleen size did not change the overall response rate for the second-line patients. Removal of spleen assessment increased the number of complete responders. This was primarily due to situations where there was noted splenomegaly on imaging but not detected on clinical exam.

8.1.2. Assessment of Efficacy Across Trials

Efficacy was assessed based on data from a single clinical trial.

Additional Efficacy Considerations

Assessment of First-Line Patients:

The application included data from seven patients with previously untreated HLH.

Table 30: Response in First-Line Patients with Previously Untreated HLH

Response	N=7 n (%)
Overall Response Rate	5 (71) (95% CI: 0.29, 0.96)
Complete Response	0 (0)
Partial Response	3 (42.8)
HLH Improvement	2 (28.5)
None	2 (28.5)

Source: Reviewer generated from efficacy datasets

Reviewer's comment:

Conclusion cannot be drawn regarding efficacy in the frontline population due to low numbers. In addition, there were no complete responders in the primary efficacy analysis set. This raises the possibility that emapalumab may be less effective in achieving full HLH control in patients who have not yet received standard therapy. It is unclear at this time if patients with pHLH who have not yet received standard therapy would benefit from foregoing standard therapy and receive only emapalumab and dexamethasone. Given the lower CR rates in this group, it is possible that previously untreated patients may fare worse than with standard therapies. For these reasons, it is this reviewer's opinion that the data provided supports approval in previously treated patients, and additional data is needed to determine the role for emapalumab in the frontline setting.

8.1.3. Integrated Assessment of Effectiveness

One study, NI-0501-04, was submitted to support the efficacy of emapalumab for patients with primary HLH. The efficacy of emapalumab was demonstrated by an overall response rate (CR, PR or HLH improvement) of 63% (95% CI: 0.42, 0.81) in 27 patients with primary HLH who were either refractory or had reactivated disease after standard therapy. Response to HLH signs and symptoms as defined by the protocol are considered by this reviewer to be of clinical benefit to

the patient for whom there are no available therapies and for whom symptoms such as cytopenias and organ dysfunction can directly and indirectly result in morbidity and mortality.

Patients with primary HLH who are unable to receive a HSCT typically succumb to multiorgan dysfunction, infections, or bleeding due the disease involvement. Patients often require care in intensive care settings with a high level of supportive care due to the disease manifestations and complications of therapy. Furthermore, standard therapies such as etoposide and dexamethasone can result in life threatening cytopenias and hypertension, requiring therapy discontinuation or reduction. Therefore, therapy that can reduce the signs and symptoms of HLH prior to HSCT are considered of direct clinical benefit.

Efficacy of emapalumab is further supported by the secondary endpoints of study, response by investigator and duration of response.

Response as assessed by investigator was assessed in 22 of 27 second line patients. A response was reported in 18 of 22 (82%) patients. Five patients were assessed by the investigator to have a CR. Given the complexity of the disease and severity of the clinical status of most patients with HLH, assessment by investigators, who are experienced in caring for these complex patients, is meaningful.

Duration of response, defined as the time from first achievement of response to first loss of response, also supports the efficacy of emapalumab. In the second-line population, 89% of patients experienced at least one response, and 62% maintained the response. The median time to first loss of response was not evaluable (22 days, NE). For an aggressive disease in which a lack of response can be life-threatening, durability of response is clinically meaningful. An unusual finding in this study was that two patients who received emapalumab survived without receiving HSCT and were reported to be without HLH symptoms at 6 and 12 months after the last dose of emapalumab. This finding supports the role of IFNγ in modulating disease symptoms that may be related to an inciting infection.

Allogeneic stem cell transplant is the only considered cure for pHLH. In this study, 70% (17 of 19) of patients proceeded to HSCT. Responses were maintained for 75% of the time prior to conditioning for HSCT. Transplant-related complications were typical for a pHLH population, and there were no transplant specific complications that could be related to emapalumab use.

The Applicant's proposed indication was for pHLH with no requirement for failure of, or relapse after initial therapy. It is this reviewer's opinion that the data included in this application does not support this broad indication and should be limited to patients who have failed or recurred after standard therapies. There in insufficient data to support emapalumab for patients with previously untreated disease, as standard therapies are reported to be 54% at 5 years (Bergsten et al. 2017). In this study, seven patients with previously untreated disease were studied. Three of the seven patients died, two prior to transplant and one following transplant. There were no complete responders at the end of the therapy in the previously untreated population, and one of the survivors required additional etoposide therapy for disease control.

8.2. Review of Safety

8.2.1. Safety Review Approach

The Applicant's safety database consists of 65 patients treated with emapalumab in either the NI-0501-04 study (34 patients), compassionate use (17 patients) or the phase 1 healthy volunteer study (14 patients). The primary safety database for this review was the 34 patients(27 second line and 7 untreated primary HLH patients) from study NI-0501-04, some of whom had additional follow-up on the NI-0501-05 study. Safety data from the compassionate use population provided supportive safety information. Patients received emapalumab starting at 1 mg/kg every 3 days until HSCT, disease response, or unacceptable toxicity. Doses of emapalumab were increased to 3 mg, 6 mg, or 10 mg incrementally starting at day 3 based on clinical response.

For patients who received a HSCT, safety results were analyzed prior to and after the start of conditioning for stem cell transplant. Noting, however, that the safety results after transplant are confounded by transplant regimen and transplant related toxicities.

Safety analysis was conducted on the complete dataset provided by the Applicant for study NI-0501-04/05 with a cut-off date of July 20, 2017. In addition, the Applicant submitted a safety update with a safety cut-off date of January 31, 2018. This 90-day safety update included five additional patients. Three of these patients were enrolled on study NI-0501-04 (two previously untreated and one previously treated) and two of the five received emapalumab in compassionate use.

Case report forms and narratives were provided and reviewed for all serious AEs and deaths that occurred in the primary safety population. Particular attention was placed on the treatment emergent adverse events (TEAE) of infections, infusion reactions, and transplant-related complications.

The clinical review of safety was based upon:

- CSR for study NI-0501-04/05 and the compassionate use program
- Protocol and statistical analysis plan for NI-0501-04/05
- Integrated data sets for the populations described above
- Summary of clinical safety
- 90-day safety update
- Integrated summary of safety
- Patient narratives

8.2.2. Review of the Safety Database

Overall Exposure

All patients received at least one dose of emapalumab at 1 mg/kg. Patients received additional dosing at 1 mg/kg or increased doses based on insufficient laboratory or clinical response every

3 to 4 days. Some patients with stabilized disease then received weekly infusions while awaiting transplant. The highest dose administered was 10 mg/kg. The table below summarizes emapalumab exposure for second-line and all-treated patients in the NI-0501-04 study, and for those who received additional treatment on the NI-0501-05 follow-on study.

Table 31: Emapalumab Exposure in the Safety Populations

	NI-0501-04 Second-Line N=27	NI-0501-04/05 Second-Line N=27	NI-0501-04 All Treated N=34	NI-0501-04/05 All Treated N=34
Duration of Dosing (days)				
Median	48	48	54	59
Min, Max	(4,60)	(4, 157)	(4, 60)	(4, 245)
Cumulative Dose (mg/kg)				
Median	16	19	19	25
Min, Max	(4, 123)	(4, 152)	(4, 210)	(4, 254)
Average Dosing Frequency (days)				
Median	3.2	3.3	3.2	3.3
Min, Max	(2, 6)	(2, 9)	(1.4, 6)	(1.4, 9)

Source: Applicant CSR Table 28

Fifteen patients (44%) received emapalumab doses >1 mg/kg at any point during NI-0501-04 or the follow-on study. Six patients (18%) received emapalumab infusions >6 mg/kg. The maximum emapalumab dose received in a single administration was 10 mg/kg.

Table 32: Populations Considered in the Safety Review

Clinical Trial Groups	Second-Line	All Treated	Compassionate Use	Healthy Volunteer
Primary safety population	27	34 Includes 27 second-line plus 7 first-line patients		
Additional supportive safety population			17	14

Source: Reviewer generated from Applicant SCS

An additional three patients (one second-line and two first-line) were enrolled after the initial submission cutoff date and included in the 90-day safety update.

Relevant characteristics of the safety population:

In the all-treated patient population, 27 patients had either refractory or recurrent disease and had received prior HLH therapy. Seven patients in the all-treated analysis set received either no prior therapy or only dexamethasone prior to starting emapalumab therapy.

Adequacy of the safety database:

The safety database represents a population of patients with characteristics that would be expected in a population of patients with pHLH who have undergone initial standard therapies. Prior therapies varied according to localities and institutions where patients were treated, but in general represent standard therapies used for HLH treatment. There are only seven patients with previously untreated HLH in the safety population, so limited conclusions can be drawn with regard to safety of emapalumab in the previously untreated population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The quality of the safety data submitted was adequate to allow substantial primary review. The Applicant provided analysis-ready datasets for the individual studies as well as an integrated dataset including patients who continued therapy on the NI-0501-05 study and who received emapalumab in compassionate use. The Applicant also provided narratives for all patients with AEs resulting in death, SAEs, and AEs leading to discontinuation of emapalumab.

Categorization of Adverse Events

Adverse events were reported using the verbatim term and coded using Medical Dictionary for Regulatory Activities version 20.0. Events were considered treatment emergent if they occurred any time after the first infusion of emapalumab. Intensity of adverse events was graded on a three-parameter scale of mild, moderate or severe corresponding to the World Health Organization (WHO) toxicity scale. Mild AEs were considered WHO grade 1 (noticeable discomfort but no interruption of normal activity), moderate AEs were WHO grade 2 (discomfort sufficient to reduce or affect normal daily activity), and severe AEs were considered WHO grade 3 or 4 (inability to work or perform normal daily activity). Given the high rates of co-morbidities and hospitalization due to underlying disease, events were reported as all events, serious adverse events (life-threatening or considered medically significant requiring intervention), adverse events leading to treatment discontinuation, or fatal adverse events.

An adverse event was considered serious if, in the view of either the investigator or Applicant, it:

- Resulted in death
- Was life threatening
- Required in patient hospitalization or prolonged existing hospitalization
- Resulted in persistent or significant disability or in capacity
- Resulted in a congenital anomaly/birth defect

Adverse events of clinical interest were infusion related reactions and infections. AEs were considered suspected infusion-related reactions if they occurred within 24 hours of receiving an infusion of emapalumab. Separate analyses for adverse events occurring prior to and after the start of conditioning were performed for patients who received HSCT.

Since HLH is commonly associated with hematology and chemistry abnormalities at presentation, laboratory findings were reported as mean and median changes from baseline, as well as worst post-baseline change.

Routine Clinical Tests

Hematology, chemistry and coagulation assessments were obtained prior to initiation of emapalumab, on SD 1, 2, and 3, prior to infusions one through six, and then at least once every 6 days until the EOT (week 8). For those patients who received HSCT, assessments were also obtained weekly thereafter until preconditioning. Screening for tuberculosis was performed prior to treatment and then as clinically indicated. Screening for Epstein-Barr virus, cytomegalovirus (CMV), and adenovirus (viral load) was performed prior to treatment, and then every 2 weeks or as clinically indicated.

8.2.4. Safety Results

Deaths

Seven of 27 (26%) patients in the primary efficacy analysis set died. Of these seven patients, five died prior to receiving stem cell transplant and two died post-transplant. Six of the seven deaths in the primary efficacy population occurred during study treatment, and the seventh patient died several days after withdrawing from study treatment (and was therefore considered with the deaths on study). Events leading to death are described below:

Pre-transplant deaths:

Patient (b) (6) who had an incomplete response to the HLH-2004 regimen prior to enrollment. The patient had a history of CMV infection and intolerance to prior therapy due to renal failure. The patient had a diagnosis of Griscelli syndrome type 2. On presentation, the patient was febrile, cachectic, and in respiratory distress with pneumonia and rapidly developed pseudomonas bacteremia. He received one dose of emapalumab at 1 mg/kg on SD 1 and a second dose of 3 mg/kg on SD 3 due to a worsening of HLH laboratory parameters and clinical status. He died on SD 3 due to septic shock. Blood cultures were positive for pseudomonas. Both infusions of emapalumab were reported to have been administered without incident.

Patient (b) (6) who had been non-responsive to HLH-2004 treatment. The patient began the study treatment with 1 mg/kg of emapalumab, which was increased to 2 mg/kg and then 4 mg/kg by SD 6. After an initial brief response, the patient's condition worsened. She was started on additional therapy (etoposide and rituximab) without response. On SD 18, the patient re-started emapalumab on the

compassionate use program at a dose of 6 mg/kg. There was a brief reported improvement in symptoms, but on SD 36 the patient died of multi-organ failure. Concomitant infections were influenza and Epstein-Barr virus. Blood cultures were positive for Enterococcus faecium. Post-mortem liver biopsy revealed NK T-cell lymphoma.

Patient (b) (6) diagnosed with HLH (FHL3) at 1 month of age. He initially received therapy under the HIT-HLH protocol (anti-thymocyte antiglobulin [ATG], dexamethasone and etoposide) and did not respond. The patient began emapalumab 1 mg/kg day for six infusions. He had some response to treatment with a decrease in ferritin and improvement in liver function test results. Based on this response, infusion frequency was decreased to weekly. The patient developed worsening of laboratory and clinical parameters on SD 44. Parainfluenza virus type 3 and hyperlymphocytosis were noted. The patient's planned HSCT was placed on hold, and he was treated with alemtuzumab. His condition continued to deteriorate, and he died on SD 76, 11 hours after ATG infusion administered as salvage therapy. The patient was reported to have developed cardiovascular decompensation associated with severe anemia and upper gastrointestinal (GI) bleeding, which was assessed as potentially related to ATG.

Patient (b) (6) whose HLH (FHL5) had been treated with HSCT and chemotherapy per the HLH-2004 regimen. The patient had documented chest X-ray findings of lung nodules. The patient received emapalumab 1 mg/kg with an improvement in laboratory parameters and clinical condition. A chest CT performed as a pre-HSCT workup demonstrated nodules consistent with potential infection. Further workup was positive for *Histoplasma capsulatum* (urine antigen was positive but bronchoalveolar lavage and serum antigen were negative). Bronchoalveolar lavage was positive for pseudomonas, *Klebsiella pneumoniae*, and CMV. Emapalumab was discontinued and the patient then developed symptoms consistent with HLH reactivation and received alemtuzumab. She developed acute respiratory distress syndrome and died of respiratory decompensation following a prolonged intensive care unit stay.

Patient (b) (6) with a history of FHL2 treated with ATG, etoposide, and dexamethasone. She was reported to have disease reactivation 2 days after completing 8 weeks of initial therapy and was not a candidate for continued etoposide due to profound pancytopenia. She entered the study with organomegaly, ongoing parvovirus and *Clostridium difficile* infections, and significantly elevated transaminases and bilirubin. She initially received emapalumab 1 mg/kg followed by a dose of 2 mg/kg and 3 mg/kg. After initial signs of improvement by SD 14, she developed worsening organomegaly and HLH laboratory parameters. Emapalumab dose was increased to 8 mg/kg on SD 18 and dexamethasone dose was increased at the same time. The patient experienced several episodes of GI bleeding during therapy (SD 3, SD 24, and SD 35). After an increase in emapalumab to 10 mg/kg, she was reported to have continued progression of HLH, and her parents requested withdrawal from study on SD 48. She died on SD 53 due to progression of HLH.

Reviewer's comment:

Deaths in the primary efficacy population generally occurred in patients who had minimal or no response to initial therapy or who developed worsening HLH after emapalumab discontinuation. Four of the five patients who died before transplant developed a new infection or had worsening of a pre-existing infection. These deaths highlight the risk of emapalumab administration in the setting of ongoing infection or new infection after the administration of emapalumab. Two of the patients had documented bacteremia. The risk of infections and the need to aggressively monitor for and treat infections in patients receiving emapalumab will be included in the warnings and precautions section of the label. Several patients had episodes of GI bleeding at the time of their deaths. The events of GI bleeding were assessed as not related to emapalumab due to concomitant steroids and coagulopathy. There is no clear causality between emapalumab and GI bleeding, however additional follow-up is warranted.

Deaths (deaths that occurred in patients who proceeded to subsequent transplant and that occurred after transplant):

Patient (b) (6) who had been treated with dexamethasone and etoposide with reactivated disease after an initial partial response and then reactivated disease. The patient was reported to have severe hypertension related to prior therapy as well as a positive CMV serology. She began treatment with emapalumab 1 mg/kg for three doses. She had some clinical improvement, and infusions were spaced to weekly. She inadvertently received a dose of 5 mg/kg on SD 28, which was reported to be uneventful. At the EOT, she was assessed as a complete responder and began conditioning for HSCT. She received HSCT from a matched unrelated donor on SD 71. Her transplant course was complicated by *Acinetobacter* bacteremia and CMV infection, from which she reportedly recovered. The patient continued systemic treatment for GVHD. She developed sepsis and shock on SD 115 (44 days after transplant), and died 3 days later. Emapalumab was not detectable in serum after SD 118. The Applicant and the date monitoring committee assessed this patient's death to be related to poorly controlled GVHD, and possibly CMV reactivation.

Patient (b) (6) with a history of FHL2 who had been treated according the HLH-2004 protocol and with ATG and prednisone. The patient had reactivated disease at the time of study entry and began treatment with emapalumab 1 mg/kg. After an initial improvement in laboratory parameters, he developed worsening organomegaly. He developed CMV and parvovirus reaction, resulting in reduction in dexamethasone therapy and initiation of antiviral treatment. His HLH disease parameters improved, and he was considered in partial response at the EOT. The patient then received conditioning with fludarabine, melphalan, thiotepa, and alemtuzumab, followed by a haploidentical HSCT from his father on SD 81. The patient experienced graft rejection 3 weeks after transplant (ANC 0, with 0% donor cells) with documented CMV reactivation and *Klebsiella* pneumoniae sepsis. The patient continued to have signs of HLH reactivation, and initiated dexamethasone and etoposide therapy. The patient received

additional emapalumab (one dose of 1 mg/kg followed by two doses of 3 mg/kg) in compassionate use in an attempt to control disease prior to a second attempt at stem cell transplant. The patient was reported to have HLH flare and *Klebsiella* pneumoniae pneumonia (bronchoalveolar lavage culture positive). The patient continued to have significant pulmonary disease, and required ventilator support as well as continuous renal replacement therapy dialysis. The patient had ongoing respiratory decompensation after technical difficulties with the continuous renal replacement therapy, which was eventually discontinued along with other aggressive supportive measures. The patient was moved to comfort care only and he died the following day.

Reviewer's comment:

Both post-transplant deaths occurred in patients with known post-transplant complications; acute GVHD in one patient and graft rejection and HLH reactivation in the second patient. These post-transplant deaths are consistent with reports of other patients who received HSCT for HLH. The rate of survival among second-line patients with at least 6 months of follow-up post-transplant (17 of 19) is consistent with recently reported survival rates (Messina et al. 2018), however the interpretation of survival in single-arm trial is not-interpretable Additionally, there are multiple confounders impacting the ability to interpret safety findings in patients who receive study and proceed to subsequent transplant.

An additional three of the seven patients with previously untreated pHLH died during this study. Three died prior to HSCT and one died 45 days after HSCT. Events leading to these deaths are summarized below.

Deaths in First-line Patients:

Patient (b) (6) with FLH1 who presented with fever, profound cytopenias, coagulopathy, and organomegaly. He was started on dexamethasone and emapalumab at 1 mg/kg. Emapalumab was rapidly escalated to 3 mg and then 6 mg/kg and given every 2 days due to worsening clinical status. He received 10 mg/kg of emapalumab on SD 5. On SD 6, an abdominal ultrasound demonstrated findings consistent with veno-occlusive disease, and defibrotide was initiated. The patient continued to receive high doses of emapalumab, with some improvement in liver function parameters, but experienced continued coagulopathy and cytopenias. He developed a GI bleed on SD 20 and subsequently had several other GI bleeding episodes, with a diagnosed ileal bleeding site noted on endoscopy. A fatal event of circulatory collapse occurred on SD 33. Autopsy showed lymphohistiocytosis of liver, spleen and lymph nodes, intestinal hemorrhages, and pulmonary edema. The patient had received emapalumab 10 mg/kg every other day until the day of death; the infusions of emapalumab were reported as uneventful and the GI hemorrhage was assessed as not related to emapalumab but related to the underlying disease and the concomitant dexamethasone and defibrotide.

Patient (b) (6) with FLH3. The patient presented with hepatosplenomegaly, marked elevations in transaminases and bilirubin, DIC and respiratory failure. He was initially treated with dexamethasone with a 10-day improvement in symptoms leading to a dexamethasone taper, but developed new fever and worsening laboratory findings consistent with HLH at the time of study enrollment. He began emapalumab at 1 mg/kg followed by escalating doses to 3 mg/kg (one dose) and 6 mg/kg (two doses) due to worsening laboratory parameters. Upon improvement in laboratory parameters, emapalumab dose was decreased to 3 mg/kg on SD 27. Ten days later, he developed viral gastroenteritis and signs of HLH reactivation resulting in emapalumab dose increase and increase in dexamethasone. He continued emapalumab therapy, and due to ongoing HLH reactivation received five doses of etoposide therapy. The patient began conditioning for HSCT (ATG, fludarabine, rituximab, and busulfan). However shortly after day 3 of busulfan, the patient developed decreased level of consciousness, oxygen desaturation and fever. Chest X-ray showed bilateral opacities, and he was empirically treated with antibiotics. Over the next several days, his clinical condition deteriorated. He was diagnosed with right heart failure, liver failure, and pulmonary hemorrhage. Supportive care was withdrawn at the family's request, and the patient died on SD 182 prior to stem cell infusion.

Patient (b) (6) diagnosed with FHL2. The patient began treatment with emapalumab and initiated intrathecal therapy after findings on brain MRI and analysis of cerebrospinal fluid suggested CNS involvement of HLH. The patient received 3 mg/kg of emapalumab starting with infusion 2, which he continued until the EOT period of NI-0501-04. He was also given intrathecal chemotherapy. He developed refractory seizures on SD 6 requiring medical management with thiopental coma. He was assessed to have HLH improvement at the EOT based on improvement in CNS symptoms. He continued in study NI-0501-05 and received 20 infusions of emapalumab at 3 mg/kg. He developed neurologic deterioration on SD 126 (seizures, hemiparesis, decreased level of consciousness with evidence of HLH reactivation), cytopenias, and hepatosplenomegaly. Following withdrawal from the study and transition to comfort care, he died on SD 132.

Death in a First-line Patient who proceeded to subsequent transplant:

Patient (b) (6) with clinical features of HLH (cytopenias, elevated inflammatory markers, high ferritin and sIL-2r) and CMV infection (viral load 12 million copies/mL at screening) prior to starting therapy. She began emapalumab at the dose of 1 mg/kg with dexamethasone 5 mg/kg and was reported to have improvement in laboratory and clinical parameters. Emapalumab dose was increased to 3 mg/kg on SD 15 due to ongoing cytopenias. Dexamethasone was tapered and discontinued on SD 24 but restarted in SD 28 when she had a mild HLH reactivation. Emapalumab dose was increased to 6 mg/kg, and she had a partial response at the end of therapy. She began conditioning on SD 74 and received alemtuzumab, fludarabine, and melphalan and a cord

blood transplant from a 6/10 unrelated donor. Her post-transplant course was complicated by CMV reactivation 1 week after transplant, engraftment syndrome, and ARDS. She died on SD 133, 68 days after transplant, due to graft failure and drug-resistant CMV pneumonitis.

Serious Adverse Events

Table 33 summarizes serious adverse events prior to conditioning for HSCT. Separate analysis was performed for AEs occurring in the post-conditioning period for the 19/27 second-line patients and 23 of 34 all-treated patients who received a HSCT (Table 34). Serious adverse events occurring in the post-conditioning period were defined as AEs occurring after the start of the first conditioning treatment.

Table 33: Serous Adverse Events

System Organ Class Preferred Term	Second Line Preconditioning N=27 n (%)	All Treated Preconditioning N=34 n (%)
At Least 1 SAE	17 (63.0)	21 (61.8)
Blood and lymphatic system	1 (3.7)	1 (2.9)
Lymphocytosis	1 (3.7)	1 (2.9)
Cardiac disorders	1 (3.7)	1 (2.9)
Cardiopulmonary failure	1 (3.7)	1 (2.9)
Eye disorders	1 (3.7)	1 (2.9)
Eye movement disorders	1 (3.7)	1 (2.9)
Gastrointestinal disorders	3 (11.1)	4 (11.8)
Gastrointestinal hemorrhage	2 (7.4)	3 (8.8)
Pneumatosis intestinalis	1 (3.7)	1 (2.9)
General disorders and administration site conditions	5 (18.5)	7 (20.6)
Condition aggravated	3 (11.1)	5 (14.7)
Multiple organ dysfunction syndrome	2 (7.4)	2 (5.9)
Immune system disorders	1 (3.7)	1 (2.9)
Anaphylactic reaction	1 (3.7)	1 (2.9)
Infections and infestations	8 (29.6)	11 (3.2)
Bacterial	2 (7.4)	2 (5.9)
Fungal	1 (3.7)	2 (5.9)
Viral	1 (3.7)	4 (11.8)
Unspecified	4 (14.8)	6 (17.6)

System Organ Class Preferred Term	Second Line Preconditioning N=27 n (%)	All Treated Preconditioning N=34 n (%)
Injury, poisoning and procedural complications	1 (3.7)	1 (2.9)
Spinal compression fracture	1 (3.7)	1 (2.9)
Investigations	1 (3.7)	1 (2.9)
Blood creatinine increased	1 (3.7)	1 (2.9)
Metabolic and nutrition disorders	1 (2.9)	1 (3.7)
Hypokalemia	1 (2.9)	1 (3.7)
Nervous system disorders	2 (7.4)	3 (8.8)
Cerebral disorders	1 (3.7)	1 (2.9)
Neurological decompensation	1 (3.7)	1 (2.9)
Seizure	1 (3.7)	1 (2.9)
Subdural hygroma	1 (3.7)	1 (2.9)
Renal and urinary disorders	1 (3.7)	1 (2.9)
Acute Kidney Injury	1 (3.7)	1 (2.9)
Respiratory, thoracic and mediastinal disorders	5 (14.7)	4 (14.8)
Acute respiratory distress syndrome	1 (3.7)	1 (2.9)
Aspiration	1 (3.7)	1 (2.9)
Pulmonary artery thrombosis	1 (3.7)	1 (2.9)
Respiratory distress	1 (3.7)	1 (2.9)
Respiratory failure	1 (3.7)	0 (0)
Vascular disorders	1 (3.7)	1 (2.9)
Circulatory collapse	1 (3.7)	1 (2.9)

Source: Applicant CSR, reviewer verified

Reviewer's comment:

Serious adverse events in the preconditioning period were most commonly infections, including bacterial, viral, and fungal. Infections are frequently reported in the setting of active HLH and as a consequence of study therapy. Respiratory events were also common and occurred in the setting of sepsis, fluid overload, and progressing HLH. Given the overlap between infections and the signs and symptoms of progressive HLH in a small number of patients in this trial, additional follow-up for infectious complications will be needed to more fully understand any potential increased risk of infections associated with emapalumab.

Table 34: Serious Adverse Events Post-Conditioning for those who proceeded to HSCT

System Organ Class Preferred Term	Second Line Post-Conditioning N=19 n (%)	All Treated Post-Conditioning N=23 n (%)
At Least 1 SAE	13 (68.4)	15 (65.2)
Blood and lymphatic system	2 (10.5)	2 (8.7)
Hemolytic anemia	1 (5.3)	1 (4.3)
Thrombotic microangiopathy	1 (5.3)	1 (4.3)
Cardiac disorders	2 (10.5)	2 (8.7)
Cardiac tamponade	1 (5.3)	1 (4.3)
Right ventricular dysfunction	1 (5.3)	1 (4.3)
Eye disorders	1 (5.3)	1 (4.3)
Eye movement disorders	1 (5.3)	1 (4.3)
Gastrointestinal disorders	2 (10.5)	2 (8.7)
Abdominal pain	1 (5.3)	1 (4.3)
Inguinal hernia	1 (5.3)	1 (4.3)
General disorders/administration site conditions	4 (21.1)	5 (21.7)
Condition aggravated	1 (5.3)	2 (8.7)
Multiple organ dysfunction syndrome	1 (5.3)	1 (4.3)
Pyrexia	2 (10.5)	2 (8.7)
Immune system disorders	2 (10.5)	3 (13)
Acute GVHD in intestine	2 (10.5)	2 (8.7)
Engraftment syndrome	1 (5.3)	2 (8.7)
Infections and infestations	8 (42.1)	8 (34.7)
Bacterial	5 (14.7)	5 (21.7)
Fungal	0 (0)	0 (0)
Viral	6 (31.5)	6 (26.0)
Injury, poisoning and procedural complications	2 (10.5)	3 (13.0)
Stem cell transplant failure (graft rejection)	1 (4.3)	1 (4.3)
Engraft failure	1 (4.3)	2 (8.7)
Respiratory, thoracic and mediastinal disorders	5 (14.7)	3 (13.0)
Acute respiratory distress syndrome	0 (0)	1 (4.3)
Acute respiratory failure	1 (5.3)	1 (4.3)
Pulmonary hypertension	1 (5.3)	1 (4.3)
Vascular disorders	1 (5.3)	1 (4.3)
Hypertension	1 (5.3)	1 (4.3)

Source: Applicant CSR Table 39, Reviewer verified

Reviewer's comment:

The analysis of serious adverse events in the post-transplant period among patients who received HSCT are confounded by concomitant conditioning therapy and known association of HSCT with a high rate of serious AEs. In the NI-0501-04 study, rates of deaths in patients with disease reactivation due to transplant-related infections, GVHD, and multiorgan failure are comparable to rates published in a study of 112 pediatric patients with HLH who underwent HSCT (Messina et al. 2018). Rates of graft failure were 13% in the NI-0501-04 study and 7% in the Messina report. Rates of moderate or severe GVHD were 20% and 25% in the NI-0501-04 study and Messina study, respectively. Given that the NI-0501-04 study population was made of primarily reactivated and refractory patients, and that all graft failure/rejection episodes occurred in the setting of haploidentical transplants, it does not appear that emapalumab treatment prior to transplant is associated with higher rates of graft failure or acute GVHD.

Dropouts and/or Discontinuations Due to Adverse Effects

Two patients in the all-treated analysis set (both second-line patients) had study treatment withdrawn due to an AE. No patient discontinued emapalumab due to infusion-related reaction.

Patient (b) (6) had a diagnosis of histoplasmosis with pulmonary symptoms resulting in discontinuation of emapalumab due to the possible relation of IFNγ neutralization and worsening of histoplasmosis. This patient discontinued emapalumab and eventually died due to ARDS on SD 95.

Patient (b) (6) developed HLH worsening during her initial treatment with emapalumab, and additional HLH therapy (etoposide) was administered resulting in discontinuation of study therapy due to the version of the protocol at the time. This patient subsequently received additional doses of emapalumab in the compassionate use program and was followed in the NI-0501-05 study. She eventually underwent a HSCT and was reported to have fully controlled HLH at the last study visit 1 year after transplant.

Reviewer's comment:

The low rates of treatment discontinuation due to AEs on this study support the tolerability of emapalumab in a pediatric patient population with considerable underlying morbidities.

Significant Adverse Events

Infections

Infections prior to conditioning for those who proceeded to transplantation were reported in 56% of patients in the all-treated analysis set. Patients were carefully monitored for infections that could be favored by interferon neutralization to include mycobacteria (atypical and typical), *Salmonella*, *Shigella*, *Campylobacter*, herpes zoster, and *Histoplasma capsulatum*. One healthy volunteer developed a moderately severe herpes zoster infection, but this AE was not

reported in the patient population. Patients received prophylaxis for herpes zoster, *Pneumocystis carinii*, and fungal infections.

In the pre-transplant period, CMV infection was the most frequent infectious event and was reported in five (15%) of patients. All events of CMV infection in the preconditioning period were mild or moderate and reported as resolved.

Serious infections occurred in 32% of patients in the pre-transplant period, including one fatal event of sepsis. Of the serious infections, 46% had no organism identified, 30% were viral, 15% were bacterial, and 15% were fungal. Specific organisms identified in patients with serious infectious AEs were histoplasmosis, *Enterococcus faecium, Pseudomonas aeruginosa,* respiratory syncytial virus, and norovirus. Serious infections included necrotizing fasciitis (one), sepsis or septic shock (three), pneumonia (two), respiratory infection (three), gastroenteritis (two), and perforated appendix (one).

Infections occurred in 70% of patients who received a HSCT. CMV infections were reported in four patients in the post-transplant period. One AE of CMV pneumonitis was fatal and occurred 45 days post-HSCT.

Reviewer's comment:

Infections are a known complication of HLH and anti HLH therapy. Of the 13 SAEs of infection, only 4 (31%) occurred in the setting of severe neutropenia, raising the possibility that emapalumab contributed to the AE. Analysis is confounded by concomitant steroids, which were received by all patients and may have contributed to infection. Most infections were reported as recovered. Infection complications are associated with emapalumab therapy and warrant close observation, and early and prompt intervention and therefore are included in the warnings and precautions in the USPI.

Rates of infections in the post-transplant period were consistent with those previously reported among patients with HLH who received HSCT (Ouachee-Chardin et al. 2006) In a study published by Chardin et. al, which reported on 48 patients with pHLH who received HSCT, 60% of patients had serious infections, 17% were reported to have acute GVHD, and 14% were reported to have veno-occlusive disease (VOD). In this study, rates of infection in the post conditioning period in the all treated analysis population were 34%, acute GVHD rates were 8.7%, and there were no reported incidences of transplant related VOD post conditioning. No pattern emerged with regard to infections in the post-transplant period.

Infusion Related Reactions (IRRs)

IRRs were defined as AEs reported within 24 hours of infusion excluding the following System Organ Classes: Infections and infestations, congenital and familial and genetic disorders, neoplasms benign, malignant and unspecified, product issues, social circumstances, and surgical and medical procedures. IRRs occurred in nine (26.5%) patients in the all-treated analysis set. The most common IRRs reported were pyrexia and drug eruption. Other IRRs reported were generally skin and subcutaneous disorders and included erythema,

hyperhidrosis, and rash. There were no IRRs graded as severe, and no reported anaphylaxis or anaphylactoid reactions.

Reviewer's comment:

Infusions of emapalumab were well-tolerated in the patients treated in the NI-0501-04 study. All patients in the study received concomitant dexamethasone, which may have mitigated more severe reactions. The USPI will provide recommendations for concomitant dexamethasone administration.

Treatment Emergent Adverse Events and Adverse Reactions

Adverse events prior to transplant in the primary efficacy and all-treated populations are summarized in the table below.

Table 35: Common AEs **(≥10%)** Reported

AE Preferred Term	Second Line N=27 n (%)	All Treated N=34 n (%)
Any AE	26 (96.3)	32 (94.1)
Condition aggravated	12 (44.4)	17 (50)
Hypertension	9 (33.3)	12 (35.3)
Pyrexia	7 (25.9)	8 (23.5)
Constipation	4 (14.8)	5 (14.7)
Hypokalemia	5 (18.5)	5 (14.7)
Lymphocytosis	4 (14.8)	4 (11.8)
Tachycardia	4 (14.8)	4 (11.8)
Abdominal pain	4 (14.8)	4 (11.8)
Diarrhea	3 (11.18)	4 (11.8)
CMV infection	4 (14.8)	4 (11.8)
Irritability	3 (11.1)	4 (11.8)
Cough	2 (7.4)	4 (11.8)
Tachypnea	4 (14.8)	4 (11.8)
Rash	2 (7.4)	4 (11.8)

Source: Applicant CSR Table 33, Reviewer verified

Reviewer's comment:

In study NI-0501-04, nearly all patients experienced a TEAE. The most commonly reported was "condition aggravated," which consisted of signs and symptoms of worsening HLH and is indicative of lack of efficacy rather than an AE related to emapalumab. Importantly, signs and symptoms related to HLH worsening often overlap with signs and symptoms of organ damage and infections, and cannot conclusively be ruled out with regard to the study drug. Symptoms

such as fever, coagulopathy, and aspartate aminotransferase/ alanine aminotransferase (AST/ALT) elevation can be seen in both infections and reactivated HLH. When these symptoms are also associated with elevations in ferritin, sIL2α, and organomegaly, they are more likely to be indicative of HLH activation. Upon review of the narratives for the AEs of condition aggravated, this reviewer agrees with the Applicant's assessment of the AE as being primarily driven by HLH worsening.

Table 36: Common AEs in the Post-Transplant Period

AE Preferred Term	Second Line N=19 n (%)	All Treated N=23 n (%)
Any AE	19 (100)	23 (100)
Condition aggravated	12 (44.4)	17 (50)
Hypertension	9 (33.3)	12 (35.3)
Pyrexia	7 (25.9)	8 (23.5)
Constipation	4 (14.8)	5 (14.7)
Hypokalemia	5 (18.5)	5 (14.7)
Lymphocytosis	4 (14.8)	4 (11.8)
Tachycardia	4 (14.8)	4 (11.8)
Abdominal pain	4 (14.8)	4 (11.8)
Diarrhea	3 (11.18)	4 (11.8)
CMV infection	4 (14.8)	4 (11.8)
Irritability	3 (11.1)	4 (11.8)
Cough	2 (7.4)	4 (11.8)
Tachypnea	4 (14.8)	4 (11.8)
Rash	2 (7.4)	4 (11.8)

Source: Applicant CSR, Table 33 reviewer verified

An analysis of AEs by dose group was performed by the Applicant and verified by this reviewer. There was no noted increase in AEs with increasing dose of emapalumab. In the all-treated analysis set, serious AEs occurred in 5.1%, 6.6%, 4.9% and 4.7% of the patients who received 1 mg/kg, 1 to ≤3 mg/kg, 3 to ≤6 mg/kg, and >6 mg/kg, respectively.

Laboratory Findings

Non-Hematologic Laboratory findings

Liver function assessments

Alanine aminotransferase , aspartate aminotransferase , and bilirubin assessments were obtained prior to and 2 days after infusions 1, 2, 3, and then at least every 6 days until the EOT. For those patients who received HSCT, assessments were obtained weekly until preconditioning. Clinical laboratory shifts were reported as the highest levels (worst high)

during treatment. In the primary analysis patients (second line, N=27), all patients had either AST (100%), ALT (81%), and bilirubin (40%) elevations prior to emapalumab treatment.

For the all-treated analysis set, of the 24 patients who had AST elevations ≤2.6 X ULN at baseline, five (21%) had a worst AST elevation between 2.5X and 5X ULN, seven (29%) had a worst AST elevation between 5X and 20X ULN and four (17%) had a worst AST elevation of >20X ULN.

For ALT, of the 25 patients who had ALT elevations ≤2.6X ULN at baseline, five (20%) had a worse ALT elevation between 2.5X and 5X ULN, three (12%) had a worse ALT elevation between 5X and 20X ULN, and one (4%) had a worst ALT elevation of >20X ULN.
At the EOT, no patients were reported to have AST or ALT >20X ULN, and four patients who had baseline AST or ALT elevations <2.5X ULN, were reported to have AST or AST elevations >2.5X ULN.

The Applicant concluded that no pattern of clinically significant changes in liver function parameters were identified. See safety assessment of hepatotoxicity for additional details.

Since the underlying disease and disease progression can result in AST, ALT, and bilirubin abnormalities, and analysis of liver chemistry abnormalities was performed for the patients who responded to treatment.

Reviewer's comment:

The confounding factors of underlying disease, infections, and concomitant medications in patients with HLH receiving emapalumab pose challenges to assessment of potential hepatotoxicity related to emapalumab. In the healthy volunteer study (NI-0501-03), six of the 14 volunteers who received a single dose of emapalumab had mildly elevated AST/ALT (n=2) or bilirubin (n=4) during the study. However, all laboratory abnormalities were mild (<1.5X ULN), and all volunteers had returned to baseline by the end of the assessment period.

Renal Function Assessments:

Changes in serum creatinine compared baseline to worst high on treatment. In the all-treated analysis set, 90.5 % of patients were reported to have normal creatinine at baseline. Two patients (9.5%) were reported to have a worst post baseline value as high. At the EOT, no patient with a normal baseline creatinine had a high creatinine value. Overall, there were no significant trends in creatinine during treatment that were attributed to emapalumab therapy.

Vital Signs

Vital sign results were reported over the first 24 hours after emapalumab infusion. As a group, there were no significant changes in mean body temperature, systolic blood pressure, or respiratory rate during or immediately after emapalumab infusion. Three patients were reported to experience pyrexia within 24 hours of receiving emapalumab, consistent with an IRR.

No significant changes in systolic blood pressure were reported during, immediately after, or at the EOT. For patients who continued on emapalumab, at SD 126, (N=5) mean and median systolic blood pressure was reported to be 5.4 mm Hg and 14 mm Hg higher than baseline, respectively.

Electrocardiograms

Electrocardiograms (ECGs) were performed at screening, after the first infusion and last infusions, and at the end of study. No pattern of ECG abnormalities was reported in patients receiving emapalumab. The most common ECG abnormalities reported were bradycardia (N=3) and tachycardia (N=4). All were assessed as mild, did not require intervention, and were attributed to intercurrent illness.

A separate ECH analysis was performed independently by a central ECG laboratory, Cardiabase. No significant changes in heart rate, QRS, PR or QTcF were reported.

QT in the second line patients, mean QTcF value was 361 ms. The maximum mean (90% CI) change from baseline in QTcF was 3.3 (-3.7, 10.4) ms. Similar results were reported in the all-treated analysis set.

Immunogenicity

The presence of an anti-drug antibody was detected in one (3%) of the 33 patients in the all-treated analysis group on which anti-drug antibody testing was performed. The one patient with a detectable anti-drug antibody was assessed as a partial responder at the EOT. The patient continued to receive emapalumab after the EOT period and did not receive HSCT. Disease assessment 12 months after the last emapalumab treatment was assessed as fully controlled.

8.2.5. Analysis of Submission-Specific Safety Issues

Post-Transplant Complications

The specific complications related to HSCT, including, GVHD, graft rejection, and graft failure, reported in this study were similar to those that have been reported in patients with HLH receiving transplant. All reports of graft rejection or failure occurred in patients receiving a haploidentical transplant, known to be associated with a higher rate of graft failure.
No episodes of VOD were reported in the post-transplant period (one reported in the pre-transplant period).

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

No clinical outcome assessment analysis was included in this submission. The median age of the patients on this study was 1 year. The young age of patients and the clinical severity of the condition present challenges to the use of COA analysis.

8.2.7. Safety Analyses by Demographic Subgroups

There were no significant differences in AEs between the second-line, all-treated, and compassionate use populations. Age and gender subgroups were too small to make meaningful safety comparisons.

8.2.8. Specific Safety Studies/Clinical Trials

Not Applicable

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

One patient in study NI-0501-04 (pt (b) (6) who died of respiratory failure and sepsis on SD 36 after discontinuing emapalumab and receiving etoposide. Autopsy revealed NK T-cell lymphoma with involvement of liver and spleen. NK T-cell lymphoma is extremely rare in pediatric patients but is thought to drive HLH and likely preceded administration of emapalumab in this patient, who did not have a genetic diagnosis of HLH. Additional follow-up is warranted in a larger population to evaluate any association of emapalumab with development of secondary malignancy.

Human Reproduction and Pregnancy

Not Applicable

Pediatrics and Assessment of Effects on Growth

There were no specific assessments of growth, and there is limited information on long-term effects of emapalumab on growth without the confounding effects of HSCT. Only three patients in the all-treated population were survivors without HSCT (one previously untreated and two second line). In these patients, the longest follow-up was 13 months after the last emapalumab infusion. Longer follow-up is needed to assess the effect of emapalumab on growth in pediatric patients.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not Applicable

Additional Submissions/Safety Issues

NI-0501-04 Safety Update:

The Applicant submitted a 90-day safety update that included data from three additional patients who were enrolled on the study after the initial safety cutoff on July 20, 2017. The safety update included additional updates with longer follow-up for six patients treated on NI-0501-04 included in the initial application. The updates on the six existing patients did not include any new SAEs that occurred in the preconditioning setting. One patient experienced

pneumonia and myositis approximately 1 year after transplant and recovered.
There were several serious AEs, including one that was fatal, reported in the three new patients. Of the three new patients, one had previously treated pHLH and the other two had emapalumab as first line therapy.
Second-line patient: Patient (b) (6), who had previously treated pHLH, experienced the SAE of GI bleed on SD 13 and thrombotic macroangiopathy on SD 34. The additional SAEs of respiratory failure, pulmonary hemorrhage, enterococcal sepsis, intracranial hemorrhage, and fatal multiorgan failure were reported after the discontinuation of emapalumab on SD 32 and initiation of additional anti-HLH therapy due to worsening disease. This patient was reported be acutely ill at baseline, and experienced overall disease progression despite escalating emapalumab infusions.
First-line patients: Two first-line patients were enrolled in the NI-0501-04 study after the original safety cutoff date. One patient (b) (6) received escalating doses up to 10mg/kg with disease control, and no SAEs were reported. The second patient (b) (6) received emapalumab dosing up to 6mg/kg and had the AE of *Enterobacter faecium* bacteremia reported SD 22. The patient continued receiving emapalumab on study NI-0501-05 until HSCT on SD 100. The patient was reported to have a fatal AE of hemorrhage alveolitis on SD 37 after HSCT, after the safety update cutoff date of (b) (6)

Reviewer comment:

SAEs reported in the 90-day safety update were consistent with what was observed during with the original study report. Bleeding, infections, and multiorgan failure in the setting of progressive disease continue to occur. The 90-day safety update information does not significantly change the safety assessment from the original safety assessment.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Post-Market Experience

Not Applicable

Expectations on Safety in the Postmarket Setting

Expectations for safety in the postmarket setting are similar to what was observed in the study. Given the low numbers of patients included in this application due to the rarity of the disease, it is possible that additional safety signals will be noted in the postmarket setting. Patients treated in this study were managed at specialty centers with experience in treating severely ill children requiring intensive supportive care to include intensive care unit care and blood banking. This is also expected to be the case in the postmarket setting.

8.2.11. Integrated Assessment of Safety

Sixty-five patients received emapalumab either on the NI-0501-04/05 studies (34 patients), in compassionate use (17 patients), or as one of the 14 healthy volunteers. Fifty-one patients with pHLH received emapalumab either on NI-050104/05 (34) or in compassionate use (17), and

comprise the integrated safety patient population, with a focus on the 34 patients with pHLH who received treatment on study NI-0501-04. Ten of the 34 patients from the NI-0501-04 study received additional emapalumab treatment on the NI-0501-05 study.

In study NI-0501-04/05, the median duration of dosing was 59 days, with a range of 4 to 245 days. The average dosing frequency was 3.2 days, and the average dose per day was 0.7mg/kg. The safety review focused on AEs occurring in the preconditioning period for those patients who proceeded to HSCT as safety assessment in the post-transplant setting is confounded by toxicity related to transplant.

The most common TEAEs by preferred term reported in patients on study NI-0501-04 in the were condition aggravated (50%), hypertension (35%), pyrexia (23%), constipation (15%), and hypokalemia (15%). Condition aggravated as a TEAE reflects lack of response and is therefore not considered an adverse reaction. Infections were reported in 56% of patients, with the most common reported infection of CMV. Mild or moderate infusion related reactions were reported in 26% of patients, and did not result in discontinuation of emapalumab. The majority of TEAEs reported in study NI-0501-04 have overlap with underlying disease or co-morbidities associated with underlying disease or treatment, and therefore the safety assessment is confounded.

As assessment of the seven complete responders who experienced TEAEs, in which the confounding aspects of underlying disease would be predicted to be less, the most common TEAEs were hypertension (100%), hypokalemia (100%), rash (85%), and vomiting (71%). These reactions were mild to moderate. Serious adverse events were reported in two of seven complete responders: perforated appendicitis and GI aspiration.

Serious TEAEs occurred in the 62% of patients in the NI-0501-04/05 study. The most frequent SAEs were infections (32%), condition aggravated (15%), respiratory and thoracic disorders, and gastrointestinal disorders (9%).

Infections are of particular concern for patients with pHLH, and contribute to morbidity and mortality. Of the 51 patients in the safety population (NI-0501-04/05 plus CU), 75% had TEAE of infection, 41% were severe, and four were fatal. Infections such as mycobacterial, herpes, histoplasmosis, and salmonella, which can be related to IFNγ neutralization, are a particular concern in patients receiving emapalumab therapy. Patients were screened for mycobacteria prior to and during study treatment. All patients received prophylaxis for herpes simplex virus per study protocol and *P. jirovecii* pneumonia and fungal prophylaxis were administered per institutional standards. Although numbers are small, the risk for favored by IFNγ neutralization appears small and mitigated by screening and prophylaxis. No patients on study developed herpes simplex virus, or mycobacterial infections. One patient discontinued therapy due to histoplasmosis, which is an infection that may be favored by IFNγ.

Fatal TEAEs occurred in 11 patients on study NI-0501-04/05, . The deaths in the NI-0501-04/05 population were due to septic shock (two), GI bleeding (two), multiorgan failure in the setting NK T cell lymphoma (one), ARDs (one), and neurologic deterioration (one). Deaths occurred in

one patient during conditioning and in the three others on days +45, 44, and 65 after HSCT. There were no reported TEAEs of VOD or unexpected AEs in the post conditioning period.

In summary, emapalumab was tolerated in a fragile patient population with significant co-morbidities and concomitant illness and medications. The safety evaluation of emapalumab in the setting of pHLH is confounded by the overlap of symptoms related to the underlying disease, the waxing and waning course of the disease. All patients in this study were able to receive scheduled emapalumab infusions without interruption, and no infusions were discontinued due to acute infusion-related reactions. The relatively high incidence of AEs, SAEs, and deaths on this study was not unexpected given the underlying disease. The primary SAE associated with emapalumab was infections, which in many cases can be mitigated and managed with screening, prophylaxis, and aggressive supportive care. Overall, the safety profile of emapalumab is acceptable in patients with reactivated and refractory primary HLH.

8.2.12. SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

None

8.4. Conclusions and Recommendations

Emapalumab is a novel, high-affinity human IgG1 anti-human IFNγ monoclonal antibody that binds and neutralizes both free and receptor bound IFNγ. IFNγ is a cytokine that has been shown to be elevated in inflammatory conditions including pHLH. Primary HLH is due to genetic defects in lymphocyte function resulting in hypercytokinemia, to include high levels of IFNγ. Hypercytokinemia and uncontrolled lymphocyte activity results in cytopenias, coagulopathy, and organ damage, resulting in high morbidity and mortality without eventual stem cell transplant.

Therapy for primary HLH requires immune suppression and supportive care until allogeneic HSCT can occur. Targeting the inflammatory cytokine, IFNγ, is a novel approach to the treatment of pHLH in combination with background immunosuppression with corticosteroids.

The efficacy of emapalumab is based on the results of study NI-0501-04, in which 27 patients with primary HLH who had reactivated or refractory disease after conventional HLH therapy or were intolerant to conventional therapy received emapalumab in combination with dexamethasone. The primary endpoint of the study was overall response rate at 8 weeks, or sooner if the patient received HSCT prior to week 8. Overall response was defined as either a CR, PR or HLH improvement of clinical and laboratory parameters.

In this study, an ORR of 63% (95% CI is 0.42 to 0.81) was demonstrated with seven patients (26%) obtaining CR, eight patients (30%) obtaining PR, and two patients (7.4%) having HLH improvement. In this population of patients with a severe and life-threatening disease who have failed or are intolerant to conventional therapy and for whom there are no approved therapies, an overall response rate of 63% is clinically meaningful.

The secondary endpoints of durability of response, was used to support the primary efficacy endpoint. Responses were durable in the majority of responders. The median duration of response, defined as time from achievement of first response to loss of first response, is not reached(range:4-56+days).

Since the disease manifestations of HLH can result in direct morbidity, mortality and preclude the definitive therapy, duration of response is clinically meaningful in this patient population and supports the efficacy of emapalumab. Interestingly, two patients on this study who received emapalumab responded and did not receive HSCT due to difficulties in identifying a suitable donor in combination with symptom resolution. These patients were reported to be alive with HLH disease control 6 months and 12 months after last emapalumab therapy.

Although this study was conducted in pediatric patients (ages <1 month to 13 years), the pathophysiology of pHLH is not expected to be different in the rare adult patient who may present with pHLH. Therefore, approval is recommended for both pediatric and adult patients with previously treated pHLH.

The safety review focused on the 34 patients with pHLH who received multiple doses of emapalumab in combination with dexamethasone. In general, the safety profile for emapalumab is manageable. The most frequent AEs reported (>10%) were hypertension and pyrexia. Serious AEs occurring in more than one patient included infections (32%), gastrointestinal hemorrhage (9%), and multiple organ dysfunction. With protocol defined screening, prophylaxis, and surveillance, there was no specific pattern of infections that was different than what would be expected in a pHLH population

In summary, there is no current standard of care for patients with reactivated, refractory pHLH or for patients who are intolerant to conventional agents. Effective new treatments are needed for this disease to include treatments that ameliorate the life-threatening manifestations of the hypercytokinemia that is characteristic of this disease. The overall response rate combined with the acceptable toxicity profile of emapalumab is the basis for the recommendation for regular approval. The rarity of disease, severity of clinical symptoms, and confounders to response assessment make an adequately powered, randomized trial impracticable. Therefore, the results of this based on overall response rate and complete response in this single-arm trial are acceptable to support regular approval.

The safety profile of emapalumab demonstrated in this study is acceptable given the expected toxicities and comorbidities in this population of patients. I recommend full approval of emapalumab for the treatment of adult and pediatric patients with pHLH with refractory, recurrent, or progressive disease or intolerance with conventional HLH therapy.

X	X
Jingjing Ye, PhD Primary Statistical Reviewer	Thomas Gwise, PhD Statistical Team Leader
X	X
Margret Merino MD Primary Clinical Reviewer	Tanya Wroblewski MD Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The application was not presented to the Oncology Drug Advisory Committee or any other external consultants.

10 Pediatrics

Emapalumab has Orphan Designation for “Treatment of hemophagocytic lymphohistiocytosis” and therefore, this submission is exempt from the pediatric assessment required under the Pediatric Research Equity Act.

The patients in the NI-0501-4/05 study supporting efficacy and safety of emapalumab were exclusively pediatric patients whose age ranged from <1 month to 13 years. Therefore, safety and efficacy of emapalumab has been demonstrated in pediatric patients aged newborn and higher.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Substantial changes were made to the proposed USPI. Changes recommended by the Agency are summarized in the table below.

Summary of Significant Labeling Changes (High Level Changes and Not Direct Quotations)		
Section	Proposed Labeling	Approved Labeling
Indications and Usage	(b) (4)	Indicated for the treated of primary hemophagocytic lymphohistiocytosis "in patients with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy
Dosage and Administration	(b) (4)	Added table with guidelines for dose increases based on specific criteria Removed (b) (4) Added recommendations for prophylaxis and monitoring for infections Added dexamethasone as concomitant medication
Warnings and Precautions		Added breakdown and incidence of infections, clarified that some were fatal Included mitigation strategies to include prophylaxis
Adverse Reactions	Included (b) (4) (b) (4) Did not include rare AEs	Removed (b) (4) (b) (4) Added text to describe rare select AEs

	(b) (4)	
Pediatric Use	(b) (4)	The pediatric population of the study was clarified
Clinical Studies	(b) (4) (b) (4)	Revised data to reflect the second line (primary efficacy population) (b) (4)

12 Risk Evaluation and Mitigation Strategies

There are no additional risk management strategies needed beyond recommended labeling.

13 Postmarketing Requirements and Commitment

The following clinical postmarketing commitments are recommended:

PMC 1: Submit the complete final clinical study report from study NI-0501-09: An Open-label, Single-Arm, Multicenter Study to Broaden Access to Emapalumab, an Anti-Interferon Gamma (anti-IFNγ) Monoclonal Antibody, and to Assess its Efficacy, Safety, Impact on Quality of Life, and Long-Term Outcome in Pediatric Patients with Primary Hemophagocytic Lymphohistiocytosis. Include summary analysis of overall response and updated information on safety.

PMC 2: Submit the complete final study report from study NI-0501-06: A Pilot, Open-Label, Single-Arm, Multicenter Study to Evaluate Safety, Tolerability, Pharmacokinetics and Efficacy of Intravenous Administration of NI-0501, an Anti-Interferon Gamma (anti-IFNγ) Monoclonal Antibody in Patients With Systemic Juvenile Idiopathic Arthritis (sJIA) Developing Macrophage Activating Syndrome/Secondary HLH(MAS/sHLH). Include summary analysis of overall response and updated information on safety.

The following CMC postmarketing commitments are recommended:

1. To re-evaluate emapalumab drug substance lot release and stability specifications after 12 additional lots have been manufactured at the commercial scale. The corresponding data, the analysis and the statistical plans used to evaluate the specifications, and any proposed changes to the specifications should be provided in the final report.

2. To re-evaluate emapalumab drug product lot release and stability specifications after 12 additional lots have been manufactured at the commercial scale. The corresponding data, the analysis and the statistical plans used to evaluate the specifications, and any proposed changes to the specifications should be provided in the final report.

3. To complete the development of an assay to detect host-cell proteins with improved sensitivity, and to re-evaluate host cell protein release acceptance criteria following analysis of all clinical, PPQ, and commercial drug substance lots with the improved host cell protein assay. The corresponding validation report, data, analysis and the statistical plans used to evaluate the specifications, and the proposed change to the specification should be provided in the final report.

4. To complete investigations into the root-cause, prevalence and size distribution of the visible particles in your clinical, PPQ, and commercial drug substance lots, and based on

these investigations, to propose a control strategy for visible particles in your final drug substance to ensure the drug product will be “free from visible particles”.

5. To perform a leachable study to evaluate the filled drug product container closure systems through the end of shelf-life when stored under the recommended conditions. Testing will be performed at regular intervals and will include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC- MS) species and metals (e.g., ICP-MS). The complete data and risk evaluation for potential impact of leachables on product safety and quality will be submitted to the BLA.

14 Division Director (Division of Hematology Oncology Toxicology)

X

Ann T. Farrell, MD

15 Division Director (OCP)

X

Nam Atiqur Rahman, PhD

16 Division Director (OB)

X

Rajeshwari Sridhara, PhD

17 Division Director (Clinical)

I concur with the recommendations for regular approval of GAMIFANT, emapalumab, for treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent or progressive disease or intolerance to conventional HLH therapy based on durable response with acceptable safety. Emapalumab is an IgG1 monoclonal antibody against interferon gamma (IFNγ). IFNγ is the primary contributor to the HLH symptoms, morbidity and pre-transplant mortality.

HLH is an extremely rare disease life-threatening disorder characterized by lymphocyte dysfunction and hypercytokinemia resulting in coagulopathy, end organ damage and severe cytopenias. Patients with the primary form of this disorder are initially treated with immunosuppression typically steroids and chemotherapy. Allogeneic stem cell transplant is the only potential curative intervention for this disease.

Additional support for the conclusion of effectiveness is based additional patients who experienced disease control after receiving extended emapalumab treatment and did not proceed to HSCT. These patients were reported to have disease control 6 and 12 months after the last dose of emapalumab. A significant adverse reaction associated with emapalumab is the increased risk of fatal and serious infections which include specific pathogens favored by IFNgamma neutralization. Therefore the label recommends patients should be evaluated for tuberculosis risk factors prior to starting emapalumab and given prophylaxis for Herpes Zoster, *Pneumocystis jirovecii* and fungal infections to mitigate potential infectious risks.

No data was presented to support use in other disorders where IFNγ has a key role in the disorder/disease.

X

Ann Farrell M.D.
Division Director
Division of Hematology Products

18 Office Director (or Designated Signatory Authority)

The risk-benefit of Gamifant (emapalumab) was assessed by Tanya Wrobleski and Margret Merino, and I concur with their recommendation to approve this drug. My signature below represents an approval recommendation for the clinical portion of this application under CDER.

X

Ann Farrell M.D.
Division Director
Division of Hematology Products

19 Appendices

19.3 OCP Appendices (Technical documents supporting OCP recommendations)

19.3.1. Bioanalytical Method Validation and Performance

The Office of Clinical Pharmacology review team has assessed the adequacy and acceptability of the following bioanalytical methods used in clinical studies.

Pharmacokinetic (PK) Immunoassay on Gyrolab Platform for the Determination of Emapalumab Concentrations

Emapalumab concentrations in treated patients were determined by analysis of serum samples using a sandwich immunoassay format on the Gyrolab platform. PK samples collected in the NI-0501-03 Clinical Protocol were analyzed at the contract research organization (CRO) facility (b) (4) using a validated method (NI-0501-PK-VAL-(b) (4)-01). PK samples collected in the NI-0501-04 and NI-0501-05 clinical studies, as well as from the patients treated under compassionate use from European hospitals were analyzed at Novimmune SA (Geneva, Switzerland). PK samples collected in these studies and under the CU treatment from US hospitals were analyzed at the CRO facility (b) (4) The bioanalytical method was validated at Novimmune (NI-0501- PK-GYR-VAL-01, NI-0501-PK-GYR-cVAL-01-v01) and a cross-validation was performed at the CRO (b) (4) after its qualification ((b) (4). The bioanalytical method was also validated at a third CRO, (b) (4) although no clinical samples were analyzed there. Long term stability of emapalumab was evaluated at (b) (4)_PK_LTS_Report (b) (4)).

The Gyrolab instrument uses a compact disk (CD) BioAffy 200, embedded with microstructures for reagent addition and separation; a spinning platform to apply centrifugal force to move reagents in the micro-channels and a laser detection system for the measurement of fluorescent label in micro-affinity columns. The BioAffy 200 CD micro-affinity columns are nanostructures packed with streptavidin coated beads. **Figure 19.1.** shows the schematic of the Gyrolab PK assay. A biotinylated mAb, specific to emapalumab (4A7-biot, capture antibody) was added to the column. Biotinylated bovine serum albumin was used as a diluent for this step to completely bind reactive sites on the beads and to act as a "spacer" to ensure that the drug specific antibody was bound evenly throughout the column. Following antibody addition, the columns were washed to remove excess reagent. Samples, standards and controls are then delivered to reservoirs in the CD and the spinning action caused these to flow through the columns, allowing the biotin to bind to the streptavidin beads. This step was followed by a wash and a second anti-emapalumab mAb coupled with a fluorescent label was subsequently added. The CD was spun to advance the liquids through the column where the antibody could bind to exposed epitopes and the unbound reagent was then washed out. The instrument measured the fluorescence in all of the columns simultaneously. The bioanalytical method review summary is give in **Table 19.1.**

Calibration standard solutions were prepared from an emapalumab stock by diluting in pooled human serum to concentrations of 16,000, 8,000, 4,000, 2,000, 1,000, 500, 250, 125, 62.5 and 31.25 ng/mL. Quality Control (QC) samples were included on every run and were comprised of the pooled human serum spiked with emapalumab at three concentration levels: low (LoQC) at 140, medium (MeQC) at 850 and high (HiQC) at 6,000 ng/mL. Two additional QC samples were included as dilution controls: Dilution level-B (DL-B)-1/60 and HiQC-1/60. DL-B was prepared by spiking reference standard NI-0501 into pooled human serum at 250,000 ng/mL. On the day of the assay, the DL-B and the HiQC were diluted 1/60 in pooled human serum prior to dilution to 1/3 of the Minimum Required Dilution (MRD) in parallel to study samples.

Clinical samples were thawed at room temperature and tested without further dilution (i.e. at MRD only), diluted 1/60 or, exceptionally, diluted 1/160 in pooled human serum prior to MRD based on the amount of emapalumab expected to be present in the sample. Calibration standards, QCs and samples were added to polymerase chain reaction (PCR) plate(s) according to the Loading List generated by the Gyrolab Control software. Each sample was run in duplicate. Capture antibody, Alexa Fluor-labeled detection antibody (4A7-AF) and wash reagents were added to a second Gyros microplate R-MP1, according to the Loading List. The plates and BioAffy 200 CD were loaded onto the Gyrolab XP workstation as prompted by the software and the assay was run. The raw data were analyzed using the Gyrolab Evaluator software (Gyros Protein Technologies, Uppsala, Sweden).

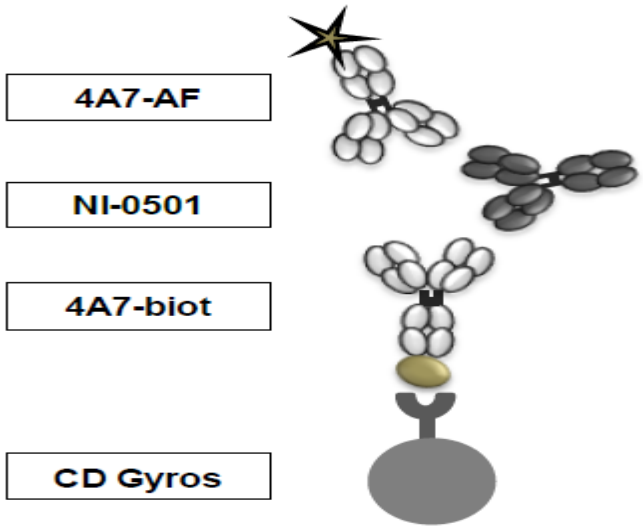


Figure 19.1. Schematic of the PK Immunoassay on Gyrolab Platform for the Determination of Emapalumab (NI-0501) Concentrations

Table 19.1 Bioanalytical method review summary

Bioanalytical method review summary			
Method description	The Gyros is a flow though immunoassay system which uses miniature streptavidin columns which are immobilized on a CD with microstructures which control the addition of reagents to the column. The assay is based on a bridging immunoassay in a sequential format. The capture antibody is a mouse anti-NI-0501 Biotinylated antibody that becomes bound to the streptavidin on the column. Biotinylated BSA is used in combination with the coating antibody to ensure "spacing" of the coating antibody. Following addition of the samples detection is achieved using mouse anti-NI-0501 conjugated to Alexa 647. Detection is performed by the measurement of laser induced fluorescence using a built in fluorometer. Increasing counts corresponds to higher NI-0501 levels.		
Materials used for calibration curve & concentration	Material used for Calibration: NI-0501; Supplied by: NovImmune Batch Number: NIMx008; Concentration: 5.0 mg/mL The nominal concentrations of the calibrators were: 16000, 8000, 4000, 2000, 1000, 500, 250, 125, 62.5 and 31.3 ng/mL. 16000 and 31.3 ng/mL are anchor points. For the validation the calibration standards were prepared fresh on the day of assay.		
Validated assay range	Dynamic range from 70 ng/mL to 8000 ng/mL		
Material used for QCs & concentration	Quality controls were prepared by spiking NI-0501 into human serum. The nominal concentrations of the QC's were as follows: 70 (LLOQ), 140 (LQC), 850 (MQC), 6000 (HQC) and 8000 (ULOQ) ng/mL.		
Source & lot of reagents (LBA)	NI-0501: Human IgG1 Lambda anti-hIFNϒ monoclonal Ab at 5.00 mg/mL- NovImmune batch NIMz004 (b) (4) batch #8 4A7-biot: Mouse IgG1 kappa NI-0501-anti-idiotype-4A7 biotynilated monoclonal Ab at 2.2 mg/mL- Conjugated: (b) (4) batch #4 BSA-biot: Biotinylated Bovine Serum Albumin at 5.0 mg/mL- (b) (4) #B-2007, lot #X0310; (b) (4) batch #1 4A7-AF: Mouse IgG1 kappa NI-0501-anti-idiotype-4A7 monoclonal Ab coupled with Alexa Fluor 647 at 1000 nM - Conjugated: (b) (4) batch #3		
Regression model & weighting	Model Equation: y = (A - B) / (1 + (x/C)D)E + B		
Validation parameters	**Method validation summary**		**Acceptability**
Calibration curve performance during accuracy & precision	No of standard calibrators from LLOQ to ULOQ: 16000, 8000, 4000, 2000, 1000, 500, 250, 125, 62.5 and 31.3 ng/mL. 16000 and 31.3 ng/mL are anchor points.		Yes

Per BMV, At least 75% and minimum of 6 non-zero calibrators without anchor points and LBA: ±20% bias (±25% at LLOQ), ≤ 20%CV	Cumulative accuracy (%bias) from LLOQ to ULOQ The cumulative precision ranged (for 8 concentrations, excluding anchor points) -7.3 to 4.3%		Yes
	Cumulative precision (%CV) from LLOQ to ULOQ The cumulative precision ranged (for 8 concentrations, excluding anchor points) -2.2 to 6.7%		Yes
QCs performance during accuracy & precision Per BMV, LBA QCs: ±20% bias (±25% at LLOQ), ≤ 20%CV and ≤ 30% total error (≤ 40% at LLOQ)	Cumulative accuracy (%bias) in 5 QCs 3.4 to 16.8%		Yes
	Inter-batch %CV 9.3 to 16.7%		Yes
	Percent total error (TE) 15.0-33.4		Yes
Selectivity & matrix effect	Pass, 17/18 (94.44%) Individual blank <LLOQ 16/18 (88.89%) LoQC spiked individuals & 18/18 (100.00%) HiQC spiked individuals with %RE <±20.00%		Yes
Interference & specificity	Not reported		
Hemolysis effect	Not reported		
Lipemic effect	Not reported		
Dilution linearity & hook effect	Pass: 1/20, 1/40, 1/80 and 1/160 dilutions had %RE <±20.00% and %CV <20.00% 2 of 3 replicates of 1/10 dilution had %RE of 21.13% & 21.88% Impact: Dilutional QCs included in sample analysis to determine acceptability of data after dilution No hook effect was observed up to a concentration of Emapalumab of 800.00 µg/mL		Yes

Bench-top/process stability	QC stability for 8 and 24 hours at room temperature	
Freeze-Thaw stability	5 cycles with 6 hours at room temperature for thawing and storage in deep freezer (below -65°C)	
Long-term storage	18 months at -65 F	
Parallelism	Not provided	
Carry over	Not provided	
Method performance in study NI-0501-04		
Assay passing rate	Pass: at least 88.89 % of individuals within ±20 %RE of nominal concentration at LoQC and at HiQC	
Standard curve performance	•	
QC performance	•	
Method reproducibility	•	
Study sample analysis/ stability		

Anti-Emapalumab Antibody ECLIA on Meso Scale Discovery Platform to Support Phase 2/3 Studies

The bioanalytical method was validated at (b) (4) NI-0501_ADA_Validation Report_(b) (4). A positive control Reference Material (rabbit polyclonal antibodies against emapalumab) was utilized for preparation of the positive control samples. The assay involved the assumption that anti-emapalumab antibodies present in samples act in a way comparable to that of the positive control material in the assay. Samples were depleted of target IFN□ □with 1-D1K-biot and streptavidin magnetic beads. The depleted samples (collected supernatants) were then subjected to 30 minutes of acidic dissociation, before pH neutralization through the addition of 1M Tris pH 8.0 and finally the addition of a solution of biotinylated NI-0501 and sulfoTAG-labelled NI-0501.

The mixtures (depleted samples + capture and detection antibodies) were then incubated to allow anti-emapalumab antibodies to form an antibody bridge complex. During this incubation, streptavidin MSD plates were blocked before being washed. Samples were then transferred in duplicate to the MSD plate and incubated, allowing the biotin associated with the antibody bridge complex to bind to the streptavidin. Negative control, positive control and unknown samples were added to designated sample wells on the MSD plate. The sulfoTAG associated with the antibody bridge complex allowed visualization of the assay by ECL detection.

Figure 19.2 Schematic of the Anti-Emapalumab Antibody Assay Procedure

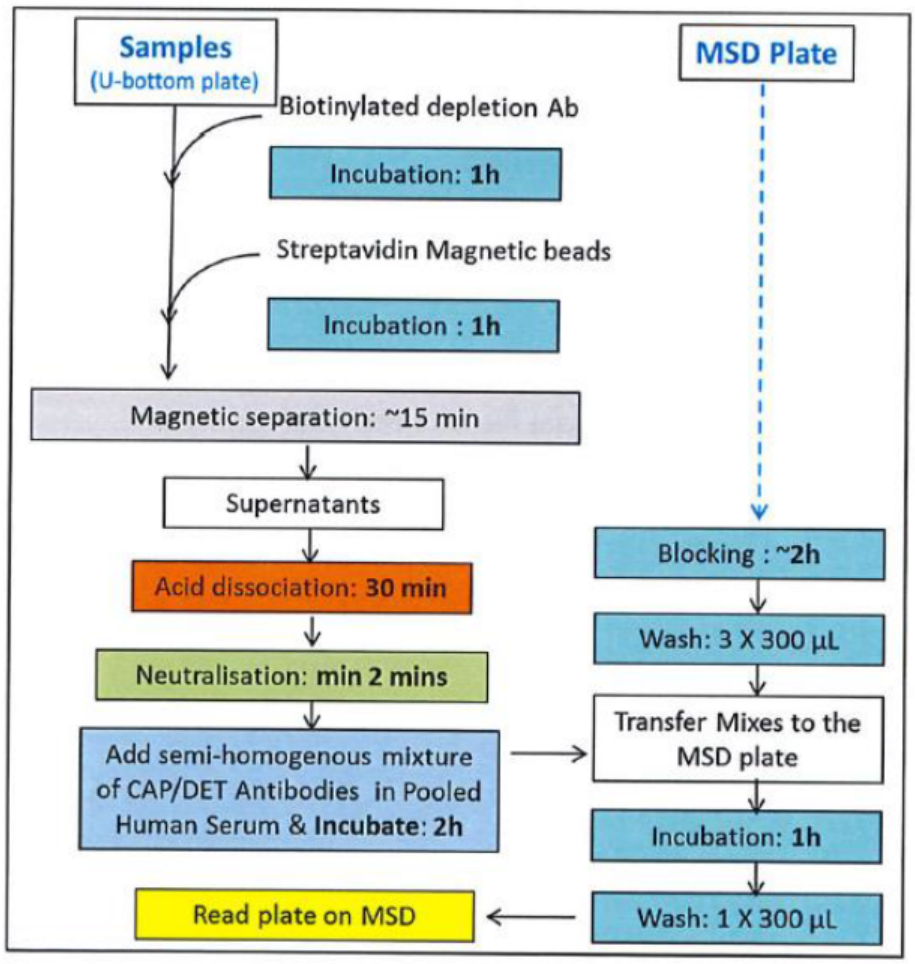


Table 19.2. Summary of Anti-Emapalumab Antibodies Bioanalytical Method Validation on Meso Scale Discovery Platform

Study References	Section 5.3.1.4 (b) (4) NI-0501_ADA_Validation Report_ (b) (4)
Sample Matrix	Human serum
Analyte	Anti-emapalumab (NI-0501) antibodies
Assay Format & Platform	Bridging ECLIA on Meso Scale Discovery (MSD)
Sample Dilution	Target immuno-depletion procedure: 1 in 3 Acid dissociation: 1 in 10 Dilution with CAP/DET: 2:1 Total dilution: 1 in 45 The sample dilution is not factored into titer results
Screening Cut Point (SCP)	95th Percentile: 1.145 x median negative control (NC) signal on plate
Confirmatory Cut Point (CCP)	99th Percentile: Signal inhibition ≥24.0 %
Titer Cut Point	Median NC signal multiplied by factor of 1.203
Positive Controls (PC): low positive control (LPC); medium positive control (MPC); high positive control (HPC)	Rabbit anti-NI-0501 polyclonal antibodies LPC: 10 ng/mL MPC: 100 ng/mL HPC: 10,000 ng/mL Depletion control NC with 250 ng/mL IFNγ
Hook Effect	Not evident to 20,480 ng/mL of positive control
Intra-Assay Precision (% CV)[1]	6.7, 3.5, 9.2 and 7.8 % CV for HPC, MPC, LPC and NC, respectively
Inter-Assay Precision (% CV)	4.2, 4.2, 6.3 and 8.9 % CV for HPC, MPC, LPC & NC respectively
End Point Titer	Demonstrated that 6/6 individual sera spiked to the concentration of the HPC met acceptance criteria of median titer value within ± 1 titer dilution
Drug Tolerance	HPC (10,000 ng/mL) showed tolerance to drug at 250 µg/mL MPC (100 ng/mL) showed tolerance to drug up to 50 µg/mL LPC (10 ng/mL) showed tolerance to drug at up to 20 µg/mL
Target Interference	NC showed no responses greater than SCP with IFNγ up to 1000 ng/mL LPC, MPC and HPC showed no change in response with IFNγ up to 1000 ng/mL

[1]Coefficient of variation (expressed in percentage)

Selectivity Screening	Analyst 1 (A1) and Analyst 2 (A2): A1: 11 of 13 (84.6%) unspiked individuals <plate cut point A2: 9 of 9 (100%) unspiked individuals<plate cut point 9 of 9 (100%) spiked individuals (10 & 100 ng/mL of positive control) gave a signal response > plate cut point meeting the criterion of greater than 80% of individuals
Selectivity Confirmation	A1 & A2: 100% unspiked individuals <plate cut point of 24.0% A1: 12 of 13 (92.3%) spiked individuals (10 & 100 ng/mL of positive control) > plate cut point of 24.0% A2: 9 out of 9 (100%) spiked individuals (10 & 100 ng/mL of positive control) > plate cut point of 24.0% Over two analysts, Selectivity Confirmation met the criterion of greater than 80% of individuals
Room Temperature Stability	24 hours for PCs
Freeze-Thaw Stability	6 cycles for PCs from nominally -80°C to +22°C
Frozen Storage Stability	101 days for PCs at nominally -80°C
Estimated Sensitivity	6.1 ng/mL

Cell-Based Assay for the Determination of the Neutralizing Capacity of Anti-Emapalumab Antibodies

Immunogenicity samples collected as per the NI-0501-04 and NI-0501-05 Clinical Protocols, as well as from the patients treated under compassionate use in Europe and the US, were analyzed to determine the presence of anti-emapalumab Antibodies. Samples which were confirmed positive for ADA were then assessed in a cell-based assay to determine the neutralizing capacity of the ADA detected.

Assessment of the neutralizing capacity of Anti-emapalumab Antibodies was performed at a CRO facility, [redacted] (b) (4). The bioanalytical method was validated at [redacted] (b) (4) NI- 0501_Nab_Validation Report Amendment 01 v.01).

Immuno-Depletion Method for Removal of Drug and Target

In order to test the neutralizing effect of anti-drug antibodies (ADA) present in serum samples, drug (emapalumab) and human interferon-gamma (hIFNγ) were removed from the samples. This was achieved by first acidifying the serum sample to dissociate the ADA from the emapalumab and to denature the hIFNγ. Then, an excess of biotinylated antiemapalumab antibody (clone 4A7, anti-idiotypic) was prepared in 1M Tris, pH 8.0 and incubated with those mixtures to neutralize the pH of the acidified serum samples. Finally, a magnetic separation was performed, where

magnetic beads with trapped emapalumab were discarded and the supernatants were collected. The supernatants were then subjected to a buffer exchange into PBS, after which depleted samples were tested in the neutralizing assay.

Total IFNγ Pharmacodynamic ECLIA on the MSD Platform

The bioanalytical method was validated at Novimmune SA (NI-0501-PDMSD VAL-01 v01). MSD streptavidin plates were coated with capture antibody, a biotinylated mouse anti-hIFNγ mAb (clone 1-D1K). Calibration standards were prepared with recombinant hIFNγ, ranging from 20 to 100,000 pg/mL, in pooled human serum. Samples were tested neat or diluted in pooled human serum. Three QCs were prepared with recombinant hIFNγ spiked in pooled human serum at 160 (LoQC), 2,000 (MeQC) and 40, 000 pg/mL (HiQC), respectively.
All samples, standards and QCs were diluted at the 1/3 MRD, in the presence of a final concentration of 50 μg/mL of NI-0501 and incubated to push the equilibrium towards the bound form in all samples. These were then added to the plates in duplicate.
After incubation, plates were washed to remove unbound material and detection antibody added: Sulfo-TAG labelled mouse anti-hIFNγ mAb (clone 1-D1K). After incubation, plates were washed and 2X MSD read buffer T was added and the ECL was measured on the MSD Meso Sector® S600 instrument. A summary of total IFNγ bioanalytical method validation on Meso Scale Discovery Platform is shown in **Table 19.3.**

Table 19.3. Summary of Total IFNγ bioanalytical method validation on Meso Scale Discovery platform

Study References	Section 5.3.1.4 NI-0501-PD-MSD VAL-01 v01
Sample Matrix	Human serum
Analyte	Total hIFNγ
Assay Format & Platform	Sandwich ECLIA on Meso Scale Discovery (MSD)
Quantification Range of the Method	50.00 – 50000.00 pg/mL
Minimum Required Dilution (MRD)	1 in 3
Intra-Assay and Inter-Assay Accuracy (%RE)[1] for Calibration Standard Points	Pass: <±20.00%, <±25.00% at LLOQ[2] and ULOQ[3]
Intra-Assay and Inter-Assay Precision (%CV)[4] for Calibration Standard Points	Pass: <20.00%, <25.00% at LLOQ and ULOQ
Intra-Assay and Inter-Assay Accuracy (%RE) for QC Samples	Pass: <±20.00%, <±25.00% at LLOQ and ULOQ
Intra-Assay and Inter-Assay Precision (%CV) for Quality Control (QC) Samples	Pass: <20.00%, <25.00% at LLOQ and ULOQ
Whole Plate and Sample Imprecision	Pass, no relevant positional effects
Dilutional Linearity	Dilutional linearity up to 1 in 1 250 (in addition to MRD). Preferential dilution is 1 in 50.
Parallelism	Pass, acceptable parallelism between dilutions of 1 in 10 and 1 in 200 (in addition to the MRD)
Hook Effect (Prozone)	No hook effect was observed with a concentration of hIFNγ of 2000.00 ng/mL
Matrix Effect (Selectivity/Individual Spike Recovery)	Low QC level: 65% of individuals sera within ±20 %RE of nominal concentration Medium QC level: 85% of individuals sera within ±20 %RE of nominal concentration
Hemolysis	Presence of hemolysis up to 2% had no impact on the result obtained
Drug Interference	No interference of NI-0501 up to 50µg/mL on the quantification of hIFNγ
Freeze/Thaw Stability	5 cycles with 3 hours on ice for thawing and storage in deep freezer (below -65°C)

[1] Relative error (expressed in percentage); [2] Lower limit of quantification; [3] Upper limit of quantification; [4] Coefficient of variation (expressed in percentage)

CXCL9 Biomarker Assay

Pharmacodynamic samples, collected as per the NI-0501-04 and NI-0501-05 Clinical Protocols as well as from the patients treated under compassionate use in Europe and the US, were analyzed to determine the level of CXCL9 using a MSD-based immunoassay at Novimmune SA where the bioanalytical method was validated (Section NI-0501-CXCL9-MSD-VAL-01 v02). MSD streptavidin plates were coated with capture antibody, a biotinylated mouse antihuman CXCL9 mAb. Calibration standards were prepared with recombinant human CXCL9, ranging from 30 to 100,000 pg/mL in FBS surrogate matrix. Samples were tested neat or diluted in FBS. Three MatrixQC samples were prepared from a human serum pool containing endogenous

CXCL9 only (LoMatrixQC) or containing endogenous plus spiked recombinant CXCL9 (MeMatrixQC and HiMatrixQC). Summary of total CXCL9 bioanalytical method validation on Meso Scale Discovery platform is shown in **Table 19.4.**

Table 19.4. Summary of Total CXCL9 Bioanalytical Method Validation on Meso Scale Discovery Platform

Study References	Section 5.3.1.4 NI-0501-CXCL9-MSD-VAL-01 v02 NI-0501-CXCL9-MSD-Stability-01 (LTS in progress)
Sample Matrix	Human Serum
Calibration Standard Matrix	Fetal Bovine Serum (FBS) surrogate matrix
Analyte	CXCL9
Assay Format & Platform	Sandwich ECLIA on Meso Scale Discovery (MSD)
Quantification Range of the Method	80.00 – 50000.00 pg/mL
Minimum Required Dilution (MRD)	1 in 10
Intra-Assay and Inter-Assay Accuracy (%RE)[1] for Calibration Standard Points	Pass: <±20.00%, <±25.00% at LLOQ[2] and ULOQ[3]
Intra-Assay and Inter-Assay Precision (%CV)[4] for Calibration Standard Points	Pass: <20.00%, <25.00% at LLOQ and ULOQ
Intra-Assay and Inter-Assay Accuracy (%RE) for MatrixQC Samples	Acceptance criteria established at <±24.74%
Intra-Assay and Inter-Assay Precision (%CV) for MatrixQC Samples	Acceptance criteria established at <24.74%
Whole Plate and Sample Imprecision	Pass, no relevant positional effects
Parallelism	Pass acceptable parallelism between dilutions of 1 in 10 (MRD) and 1 in 500 (1 in 50 in addition to the MRD)
Biomarker levels in Normal Human Subjects	31.48 – 186.28 pg/mL
Hook Effect (Prozone)	No hook effect was observed with a concentration of recombinant CXCL9 of 2000.00 ng/mL
Hemolysis Interference on Quantification	None detected on CXCL9 quantification at 2% hemolysis
Drug and Target Interference on Quantification	No interference of recombinant hIFNγ up to 100 ng/mL in the presence or absence of 50 µg/mL NI-0501
Room Temperature Stability	Endogenous CXCL9 stable up to 24 hours at room temperature
Refrigerated Stability	Endogenous CXCL9 stable up to 24 hours at 0.5-10°C
Freeze/Thaw Stability	5 cycles (thawing for 3 hours on ice and freezing below -65°C for at least 12 hours)
Long Term Stability	Assessment ongoing. Stability of endogenous CXCL9 shown up to 21 months as of December 2017

[1] Relative error (expressed in percentage); [2] Lower limit of quantification; [3] Upper limit of quantification; [4] Coefficient of variation (expressed in percentage)

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19.3.2. Pharmacometrics Assessment: Population PK and PK/PD Analyses

Population PK and PK/PD analyses were conducted by the sponsor using data from studies: NI-0501-04 and NI-0501-05 in primary HLH patients and from the Compassionate Use (CU) experience in both primary and secondary HLH patients receiving emapalumab. The main objectives of the sponsor's popPK and popPKPD analyses was to (1) characterize the quantitative, longitudinal relationship between emapalumab PK, total IFNγ (free + complex with emapalumab) and PD biomarkers, especially, CXCL9, as it integrates the stimulation of production of IFNγ and its neutralization by emapalumab PK, (2) to identify potential covariates that can explain the variability in PK and/or PD effect and (3) to derive exposure metrics to perform the exposure-response analyses for efficacy and safety.

The protocols allowed for titration of emapalumab doses with the aim to achieve clinical response. The starting dose was 1 mg/kg, titrated every three to four days based on clinical and laboratory parameters. Blood samples were collected at trough and peak of each administration at days 0, 1, 2, 5 and 8 after treatment initiation. Additional samples were collected on days 3, 6, 9 (and/or EOT), as deemed necessary by the sponsor's clinical team. The samples were assayed for PK – free emapalumab, and PD (mainly pre-dose samples except after the first administrations during which more samples were taken) for biomarkers including total IFNγ, CXCL9, CXCL10 and sIL2R.

Overall, the final popPK dataset included 2414 data records (PK) from a total of 49 patients and the final popPKPD dataset included 1110 data records (PK and PD) from a total of 47 patients. The demographics and descriptive statistics of the emapalumab exposures (stratified based on the dose, at day 21) in the dataset used for popPK analyses is shown in Table- 3 and 4 respectively. The popPK and popPK/PD data were modeled using non-linear mixed effects in NONMEM. The schematic representation of the PK-PD-disease interactions between emapalumab, biomarkers such as IFNγ, CXCL9, sIL2R and ferritin are shown in Figure-4 below.

The structural PK model consisted of a two compartment model that characterized the emapalumab PK. In addition, the total clearance of emapalumab was significantly influenced by the production of IFNγ, leading to target mediated drug disposition. The tested covariates for popPK analyses included total body weight, total IFNγ concentrations, age, sex, creatinine clearance, alanine aminotransferase (ALT), total bilirubin (TBIL) and anti-drug antibody (ADA). Only bodyweight and total IFNγ concentrations were found to significantly influence emapalumab PK and the final model parameter estimates are shown in Table – XX below. Although some graphical trends were noted for Black/African American patients (lower emapalumab clearance), and (high emapalumab clearance for high values of) ALT and TBIL, these are unlikely to be clinically meaningful.

The structural PK-PD model, i.e., the emapalumab – IFNγ – CXCL9 interaction was characterized by an indirect response model (target mediated drug disposition) with emapalumab inhibiting (neutralizing) the stimulation by IFNγ of the production rate of CXCL9. The neutralization of IFNγ by emapalumab was described by inhibitory EMAX model acting on the total IFNγ concentration and leading to an estimation of the virtual (model-predicted) free IFNγ concentrations, which is in equilibrium with CXCL9 production. The large variability in the IFNγ production (observed in

HLH patients depending on severity) has an impact on both emapalumab PK, and also PD (CXCL9 levels). Consequently, the corresponding emapalumab half-lives can vary between 2.5 – 19 days.

The tested covariates in the popPKPD analyses included age, sex, bodyweight and time-varying corticosteroid doses (data was available in 29 out of 47 patients). The effect of corticosteroid use (implemented as power parameter) was statistically significant, indicating that the stimulation of CXCL9 production by IFNγ was lower at higher corticosteroid doses (which was noted to be less pronounced at high emapalumab concentrations). The final parameters are shown in Table-6.

Table 37 Demographics for PopPK Analyses

Patient status	Age at baseline (year)					
	N	Mean	SD	Median	Minimum	Maximum
NI-0501-04 patients	33	2.6	3.2	1.1	0.088	14
CU patients	16	8.4	15	1.6	0.019	56
OVERALL	**49**	**4.5**	**9.3**	**1.2**	**0.019**	**56**

Patient status	ALT at baseline (IU/L)					
	N	Mean	SD	Median	Minimum	Maximum
NI-0501-04 patients	33	125	106	97	8.0	481
CU patients	16	142	139	83	16	522
OVERALL	**49**	**130**	**117**	**85**	**8.0**	**522**

Patient status	Weight at baseline (kg)					
	N	Mean	SD	Median	Minimum	Maximum
NI-0501-04 patients	33	14	10	10	3.3	53
CU patients	16	21	27	8.5	2.0	82
OVERALL	**49**	**16**	**18**	**9.9**	**2.0**	**82**

Patient status	Creatinine clearance at baseline ($mL/min/1.73m^2$)					
	N	Mean	SD	Median	Minimum	Maximum
NI-0501-04 patients	31	174	66	185	39	315
CU patients	3.0	91	91	48	29	195
OVERALL	**34**	**166**	**71**	**184**	**29**	**315**

Source: Population PK Study Report 180307: Tables 3-6 on Page 25

Table 38 Demographics for PopPK Analyses

Patient status	Total bilirubin at baseline (µmol/L)					
	N	Mean	SD	Median	Minimum	Maximum
NI-0501-04 patients	32	35	75	12	1.7	364
CU patients	15	139	228	19	2.7	770
OVERALL	**47**	**68**	**148**	**13**	**1.7**	**770**

	Race/Ethnicity									
Patient status	Asian		Black/Afr		Caucasian		Others		OVERALL	
	N	%	N	%	N	%	N	%	N	%
NI-0501-04 patients	4	12.1	3	9.1	22	66.7	4	12.1	33	67.3
CU patients	2	12.5	1	6.3	13	81.3	.	.	16	32.7
OVERALL	**6**	**12.2**	**4**	**8.2**	**35**	**71.4**	**4**	**8.2**	**49**	**100.0**

Patient status	Interferon gamma at Day 3 (pg/mL)					
	N	Mean	SD	Median	Minimum	Maximum
NI-0501-04 patients	33	12896	27891	730	50	113157
CU patients	16	36030	72100	5425	64	270842
OVERALL	**49**	**20450**	**47574**	**1963**	**50**	**270842**

	Sex					
Patient status	Female		Male		OVERALL	
	N	%	N	%	N	%
NI-0501-04 patients	18	54.5	15	45.5	33	67.3
CU patients	8	50.0	8	50.0	16	32.7
OVERALL	**26**	**53.1**	**23**	**46.9**	**49**	**100.0**

Source: Population PK Study Report 180307: Tables 7-10 on Page 26

Table 39 Distribution of Emapalumab concentrations as a function of dose (mg/kg) and PK samples from day 21 onwards after the first dose of emapalumanb

Dose (mg/kg) / PK Sample		Emapalumab concentration (ng/mL)			
		N	P5	Median	P95
1	Peak	184	19270	43695	70176
	Trough	186	5759	25450	48593
3	Peak	224	70871	154221	394328
	Trough	219	24692	97366	303153
6	Peak	186	101455	250356	478994
	Trough	177	31094	152415	376085
10	Peak	38	120981	259933	480000
	Trough	39	7057	161669	346047

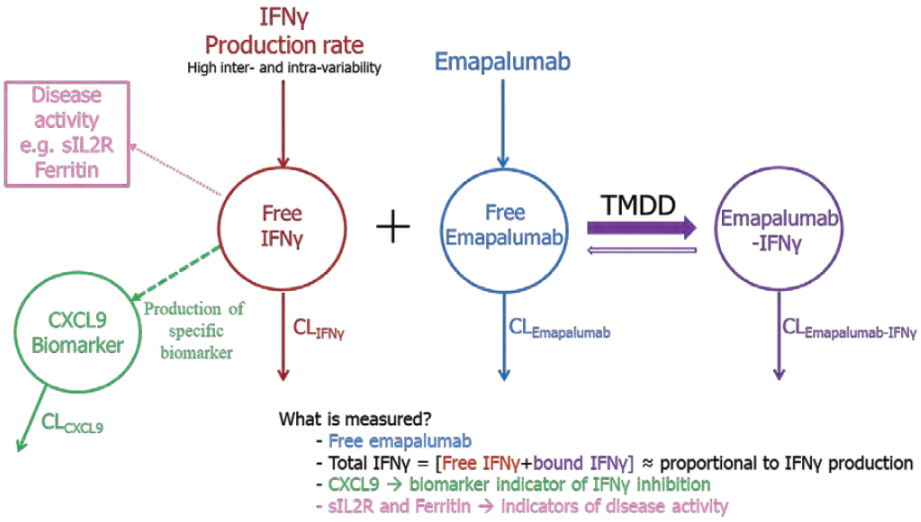
Source: Population PK Study Report 180307: Tables 11 on Page 42

Table 40 Final PopPK model parameters

	49 patients for 2414 concentrations	OFV= -2851.507		
Parameters	Description	Estimate	RSE (%)	95 % CI
CLL L/h/70 kg	Linear clearance	0.0116	29.7	0.00486 - 0.0183
CLNL L/h/70 kg	Non-linear clearance (IFNγ dependent)	0.133	33.5	0.0456 - 0.220
V1 L/70 kg	Central volume of distribution	4.16	4.4	3.80 - 4.52
Q L/h/70 kg	Intercompartmental clearance	0.102	26.3	0.0495 - 0.155
V2 L/70 kg	Peripheral volume of distribution	5.55	20.7	3.30 - 7.80
CLNL_IFNγ	Influence IFNγ on CLNL (power function)	+0.746	12.3	0.567 - 0.925
CL_BW	Allometric exponent on CLs	+0.886	11.9	0.680 - 1.09
V_BW	Allometric exponent on Vs	1 fixed	-	-
Inter-individual variability (IIV)		Estimate	IIV (%)	Shrinkage (%)
$OMEGA^2$_CLI	Variance of CL	0.240	49.0	4.1
$OMEGA^2$_V1	Variance of V1	0.0721	26.9	7.1
$OMEGA^2$_V2	Variance of V2	0.766	87.5	5.4
$OMEGA^2$_V1_V2	Correlation (V1/V2)	+0.728	-	-
residual variability (RSV)		Estimate	RSV (%)	Shrinkage (%)
SIGMA	Standard deviation of residual (Additive in log domain)	0.306	30.6	2.4

Source: Population PK Study Report 180307: Tables 17 on Page 50

Figure 12 Schematic representation of PK-PD-disease interactions between IFNγ, emapalumab, CXCL9 and HLH disease activity reflected by sIL2R and ferritin



Source: Population PK/PD Study Report 180307: Figure 2 on Page 14

Table 41. Model parameter estimates of structural (506b) and final popPKPD model (dexgam)

			RUN506b OBJV=46.036			RUNDEXGAM* OBJV=35.014		
THETHA	Parameters	Description	Mean	RSE(%)	95%CI	Mean	RSE(%)	95%CI
1	log(IC50)	IC50 of emapalumab determining the free fraction of IFNγ log (ng/mL)	3.21	10.3	2.56 - 3.86	3.78	25.6	1.88 - 5.68
	IC50	IC50 of emapalumab determining the free fraction of IFNγ (ng/mL)	24.8	-	12.9 - 47.5	43.8	-	6.55 - 293
2	FCX	Scaling factor between derived free IFNγ and CXCL9	83.5	6.51	72.8 - 94.2	64.8	38.3	16.2 - 113
3	KOUT	Elimination rate of CXCL9 (day^{-1})	0.574	4.91	0.519 - 0.629	0.562	5.18	0.505 - 0.619
4	GAM	Exponent of free IFNγ concentration	0.371	10.8	0.293 - 0.449	0.365	11.5	0.283 - 0.447
5	SIGMA	SD of residual error	0.492	6.24	0.432 - 0.552	0.487	6.34	0.426 - 0.548
6	DEX on GAM	Exponent of effect of corticosteroid dose on GAM	-	-	-	-0.154	39.2	-0.272 - -0.0358
OMEGA2	Parameters	Description	Mean	RSE(%)	95%CI	Mean	RSE(%)	95%CI
1	IC50	Variance of IC50	NA	NA	NA	NA	NA	NA
2	FCX	Variance of FCX	0.427	10.4	0.264 - 0.590	0.423	18.0	0.274 - 0.572
3	KOUT	Variance of KOUT	NA	NA	NA	NA	NA	NA
4	GAM	Variance of GAM	0.193	45.4	0.0442 - 0.342	0.207	46.3	0.0190 - 0.395
5	F1	Variance of CXCL9 baseline	0.0909	47.2	0.00603 - 0.176	0.0948	46.2	0.00895 - 0.181

*Mean parameters of RUNDEXGAM are obtained for a corsticosteroid dose of 5 mg/m2

Source: Population PK/PD Study Report 180307: Table 6 on Page 47

Reviewer's Comments:

The sponsor modeled the emapalumab PK and PD (biomarker) data, which included plasma IFNγ and CXCL9 concentrations from studies NI-0501-04/05 primary HLH patients and from the Compassionate Use (CU) experience in both primary and secondary HLH patients. The parameters for both the popPK and popPK/PD models seem to be precisely estimated. Body weight and total IFNγ concentrations were found to be significant covariates affecting the emapalumab PK, which supported the weight-based dosing of emapalumab. Additionally, as noted by the applicant, there is high variability in IFNγ production rate in HLH patients depending on the severity of the disease, which necessitates frequent dose adjustments based on the clinical and lab parameters. Like the sponsor pointed out in the popPKPD analyses, the model-estimated IC50 (24.8 ng/mL) of emapalumab is lower than the circulating emapalumab concentrations after multiple administrations of 1 mg/kg dose (median trough > 10,000 ng/ml), suggesting that a strong neutralization of IFNγ is likely to be achieved in HLH patients. Lastly, corticosteroid use was reported as a statistically significant covariate in popPKPD analyses, with higher corticosteroid doses associated with lower stimulation of CXCL9 production by IFNγ. However, this effect need to be interpreted with caution because the corticosteroid use data was available only in 29 out of 47 patients.

19.3.3 Pharmacometrics Assessment: Exposure-Response for Efficacy and Safety

The sponsor conducted exposure-response analyses to identify concentrations of emapalumab and/or biomarkers that are associated with favorable clinical response (for efficacy) and who might be predisposed to safety concerns (for safety).

For efficacy, the sponsor performed univariate and multivariate logistic regression analyses using overall clinical response yes – no (i.e., complete response, partial response and HLH improvement) at week 2 and at EOT were used and were correlated to the corresponding emapalumab, total IFNγ, CXCL9 and CXCL10 concentrations. Additionally, the sponsor also conducted a Receiver Operating Characteristic (ROC) analysis to identify if there are certain thresholds in terms of CXCL9 concentrations, that would ensure best chances of a favorable clinical response.

The exposure-response analyses for safety was conducted using the observed emapalumab exposure at the time of adverse event for patients experiencing an event and the highest observed exposure to emapalumab for those patients experiencing no adverse event indicated that the incidence of adverse events did not increase as a function of increasing emapalumab concentrations.

The logistic regression analyses for efficacy revealed that CXCL9, IFNγ and CXCL10 (in decreasing order) at the EOT were significant prognostic factors for the clinical response at EOT. The higher exposures of biomarkers (especially CXCL9) was associated with decrease in the predicted likelihood of the clinical response at EOT. ROC analyses showed that the levels of CXCL9 were able to significantly discriminate between responders and non-responders at the EOT. The median threshold level of CXCL9 at EOT for discrimination of clinical response at EOT was 292 pg/ml and at week 2 was 465 pg/ml.

The logistic regression analyses for safety did not show obvious/clear trends for the observed incidence rates of AEs, SAEs, IRRs and laboratory parameters such as TBIL, ALT (liver) and CrCL (kidney).

Reviewer's Comments:

Overall, the applicant's exposure-response analyses are acceptable and support proposed dosing regimen. The review team also explored and noted that a higher starting dose of 3 mg/kg is unlikely to provide substantial additional benefit for the overall population. The relationship between emapalumab exposure and efficacy endpoints is inconclusive because it is confounded by the dose titration (that is based on clinical and lab parameters) and high impact of IFNγ concentrations on PK due to target-mediated drug disposition.

19.1. References

Bergsten, E, A Horne, M Arico, I Astigarraga, RM Egeler, AH Filipovich, E Ishii, G Janka, S Lasisch, K Lehmberg, L McClain, M Minkov, S Montgomery, V Nanduri, D Rosso, J Henter, 2017. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: Long Term results of the cooperative HLH-2004 study. Blood, 130(25):2728-2738.

Gholam C, S Grigoriadou, KC Gilmour, HB Gaspar, 2011. Familial haemophagocytic lymphohistiocytosis: advances in the genetic basis, diagnosis and management. Clin Exp Immunology, 163(3):271-283.

Henter, JI, A Horne, M Arico, RM Egeler, AH Filipovich, S Imashuku, S Ladisch, K McClain, D Webb, J Winiarski, G Janka, 2007. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer, 48(2):124-131.

Jordan MB, et al., 2004. An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8+ T cells and interferon gamma are essential for the disorder. Blood, 104(3):735-743.

Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL, 2011. How I treat hemophagocytic lymphohistiocytosis. Blood, 118(15):4041-4052.

Mahlaoui N, M Ouachee-Chardin, G de Saint Basile, B Neven, C Picard, S Blanche, et al., 2007. Immunotherapy of familial hemophagocytic lymphohistiocytosis with antithymocyte globulins: a single-center retrospective report of 38 patients. Pediatrics, 120(3):e622-628.

Marsh RA, CE Allen KL McClain, JL Weinstein, J Kanter, J Skiles, et al., 2013. Salvage therapy of refractory hemophagocytic lymphohistiocytosis with alemtuzumab. Pediatr Blood Cancer, 60(1):101-109.

Marsh RA, MB Jordan, JA Talano, KE Nichols, A Kumar, A Naqvi, et al., 2017. Salvage therapy for refractory hemophagocytic lymphohistiocytosis: A review of the published experience. Pediatr Blood Cancer, 64(4).

Messina, C, M Zecca, F Fagioli, A Rovelli, S Giardino,P Merli, F Porta, M Arico, E Sieni, G Basso, M Ripaldi, C Favre, M Pillon, A Marzollo, M Rabusin, S Cesaro, M Algeri, M Caniglia, P Di Bartolomeo, O Ziino, F Saglio, A Prete, F Locatelli, 2018. Outcomes of Children with Hemophagocytic Lymphohistiocytosis Given Allogeneic Hematopoietic Stem Cell Transplantation in Italy. Biol Blood Marrow Transplant, 24(6);1223-1231.

Ouachee-Chardin M, C Elie, G de Saint Basile, F Le Deist, N Mahlaoui C Picard, et al., 2006. Hematopoietic stem cell transplantation in hemophagocytic lymphohistiocytosis: a single-center report of 48 patients. Pediatrics, 117(4):e743-50.

19.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): NI-0501-03

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 15, 3 investigators and 12 sub investigators		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): NI-0501-04

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 145, 111 investigators 34 investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): NI-0501-05

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 55, 12 investigators 43 investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.5. Additional Clinical Outcome Assessment Analyses

None

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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