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An observational, multicenter study to evaluate levels of Interferon gamma (IFNγ) and other inflammatory mediators in Adult Patients with Hemophagocytic Lymphohistiocytosis (A-HLH)

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Confidentiality Agreement

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Background and Rationale

HLH and rationale for targeting Interferon gamma (IFNγ)

HLH is a syndrome of severe immune activation and deregulation characterized by hyperactive macrophages and lymphocytes, pro-inflammatory cytokine hypersecretion, hemophagocytosis, and tissue and organs damage. HLH occurs as either a primary (pHLH, familial) or secondary (sHLH, sporadic) disorder (Henter et al., 1998; Janka, 1983).

Primary HLH is an autosomal recessive disease with an incidence of 1/50,000 live-born children (Henter et al. 1991; Arico et al. 1996). pHLH typically presents in the first years of life with or without a positive family history. It is caused by homozygous mutations in the genes coding for perforin, Munc13-4, Syntaxin 11, Munc18-2 and other proteins involved in cytotoxic granule activation, polarization, priming, fusion, or function (Jordan et al., 2011; Zhang et al., 2014). These mutations result in impaired cytotoxic function, and lead to an uncontrolled inflammatory response with activation of histiocytes, and pathognomic clinical manifestations of HLH.

Secondary HLH has been generally reported to occur as a result of pathological immune activation in response to a trigger, in the absence of homozygous mutations in known HLH causative genes. It can occur in children or adults, typically in a setting of malignancies, infections or autoimmune disorders (Dhote et al., 2003; Rouphael et al., 2007; Li et al., 2014; Rivière et al., 2014).

In recent years, an apparent inexplicable rise in the reported cases of HLH has been observed especially in the adult population, although the incidence of HLH in adults is still unknown (Schram and Berliner, 2015).

Case series from the United States (Parikh et al., 2014), France (Rivière et al., 2014), Japan (Takahashi N et al., 2001) and China (Li et al., 2014) all reported that the majority of adult patients had a malignancy (commonly non-Hodgkin lymphoma and acute leukemia), with infections (mostly EBV) being the second more frequent triggers. Rheumatologic diseases, namely adult-onset Still disease (AOSD) and systemic lupus erythematosus (SLE), were also reported and, of note, in a consistent proportion of patients (ranging from 6% up to 23%) no trigger could be identified and HLH was defined of unknown origin or idiopathic.

When HLH occurs in the setting of a rheumatologic disease, HLH is usually termed macrophage activation syndrome (MAS). Reports have recently described patients who developed MAS on the background of systemic juvenile idiopathic arthritis (sJIA), but were identified to be heterozygous for rare variants in the primary HLH-associated genes (Zhang et al., 2014) highlighting potential etiological, clinical, and pathological similarities between familial and acquired forms of HLH. A link between mutations in the perforin gene and predisposition to hematological malignancies has also been described (Clementi et al., 2005; Zhang et al., 2014). Although pHLH and sHLH have historically been considered separate entities, it is now thought

that overlaps between primary and secondary forms is more than previously recognized (Voskoboinik et al, 2013; Lehmberg 2015).

The presentation of sHLH is clinically the same as pHLH and the HLH-2004 diagnostic criteria developed for primary forms (Henter et al., 2007) generally apply. Acute clinical signs and symptoms of immune activation including fever, spleno/hepatomegaly, adenopathy, rash are accompanied by high serum levels of pro-inflammatory cytokines including interferon gamma (IFNγ), tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), IL-10, and macrophage–colony-stimulating factor (M-CSF) (Akashi et al., 1994; Ohga et al., 1993). Furthermore, biopsies of lymphoid tissues or histological examination of liver tissue from HLH patients reveal highly activated macrophages and lymphocytes, further supporting striking activation of the immune system. Therefore, categorizing patients into primary or secondary HLH based on clinical manifestations is often difficult and may be of limited value. Treatment should be initiated expeditiously if the diagnosis of HLH is suspected, regardless of the classification/trigger, in order to control the overactive immune system and to halt any underlying trigger.

Secondary forms of HLH in adults are reported to carry a significant mortality rate, with the worse prognosis for patients with malignancy-associated HLH. In a series of 103 adult patients (Li et al., 2014), among patients with malignancy-related HLH only 20.4% of patients survived, among patients with infection-related HLH survival was 33% (but none of patients with bacterial infections survived), in autoimmune-related HLH survival was 43%. In 24 patients HLH was of unknown origin and outcome was very poor with only 4 patients achieving clinical improvement and surviving.
Although statistics are limited by the small number of cases, case series of adults treated with different regimens report an overall mortality rate from 40% to 75% (Takahashi N et al., 2001; Shabbir et al., 2011; Park et al., 2012; Parikh et al., 2014; Ramos-Casals et al., 2014; Arca et al, 2015).

The therapeutic approach to adult HLH is matter of discussion, since no prospective multicenter studies have been conducted so far. Generally, treatment of adult HLH has been based on the HLH-94 study, the only published prospective study conducted in children with HLH. However, the complex etiology and the inducing triggers need to be considered in the selection of the treatment regimen. As an example, it is yet unclear if immunosuppressive regimens, such as etoposide, dexamethasone, alemtuzumab, are suitable depending of the different underlying causes of HLH in adults (e.g., history of immunosuppression, presence of infective triggers). Furthermore, although short-term immunosuppressive regimens may control the excessive inflammatory status, they may not be tolerated if the therapy needs to be prolonged while assessing the long-term strategy with regard to potential hematopoietic stem cell transplantation. The availability of new agents, ideally non-immunosuppressive, would be of great value to improve the therapeutic armamentarium to tackle this severe and increasingly diagnosed disease in adult patients.

NI-0501 is a fully human anti-interferon gamma (IFNγ) monoclonal antibody (mAb) that binds to and neutralizes IFNγ. NovImmune is developing NI-0501 as the first targeted therapy for HLH. Several lines of evidence support the relevance of IFNγ as a target in HLH:

1. Two animal models of pHLH and two animal models of sHLH have been investigated:
   - Perforin knockout mice and Rab27-deficient mice develop all the diagnostic and many of the clinical and laboratory characteristics of human primary HLH when infected with lymphocytic choriomeningitis virus (LCMV) as a trigger. Neutralization of the high circulating IFNγ levels in both animal models led to the reversal of HLH clinical and laboratory abnormalities, and dramatically improved survival in the animal model characterized by high mortality (pfp -/- mice) (Pachalopnik Schmid et al., 2009, Jordan et al., 2004).
   - Repeated administration of CpG, causing TLR9 stimulation, has been used to mimic a chronic severe hyperstimulation in healthy mice as a model of HLH secondary to infection. Although these mice do not necessarily die, they develop typical clinical and laboratory features of HLH (Behrens et al., 2011). Administration of an anti-IFNγ antibody led to reversal of clinical and laboratory features of HLH. Importantly, in this model it was demonstrated that administration of the anti-IFNγ antibody also led to full neutralization of IFNγ effects in relevant target tissues, such as liver and spleen (Buatois et al, submitted).
   - An animal model has been generated using IL-6 transgenic mice expressing high levels of IL-6, to mimic what occurs in patients with sJIA. When triggered with TLR ligands, these mice die with many of the features of the human HLH (Stippoli et al. 2012). In these mice, when IFNγ was neutralized by administration of an anti-IFNγ antibody, survival was markedly improved and HLH laboratory parameters reverted.

   In conclusion, in all presented animal experiments, IFNγ has been shown to be a key pathological effector in disease onset and progression.
2. Primary and secondary HLH patients have hypercytokinemia with elevated levels of several pro-inflammatory cytokines including IFNγ (Henter et al., 1991; Janka et al., 1998; Xu et al. 2012). More recently, high levels of IFNγ were demonstrated both in patients with HLH secondary to infections and in sJIA patient developing MAS (Buatois et al., manuscript submitted; Bracaglia et al. manuscript submitted). The levels of CXCL9, CXCL10 and CXCL11, three chemokines known to be induced by IFNγ, were also significantly elevated. Noteworthy, levels of IFNγ and IFNγ-inducible chemokines were found to significantly correlate with laboratory parameters of disease severity, such as ferritin, platelet count and transaminases.
3. An international multicenter study is presently ongoing to evaluate the efficacy and safety of treatment with NI-0501 in pHLH in children and young adults. Based on data gathered so far, NI-0501 treatment has been well tolerated and has shown a favorable impact on relevant

clinical and laboratory features of HLH such as fever, splenomegaly, cytopenia, hyperferritinemia, hypofibrinogenemia, and also CNS signs/symptoms (Jordan et al, 2015).

The numerous pathophysiological and clinical features shared by primary HLH and HLH secondary to inflammatory/autoimmune diseases or infections strongly suggests that IFNγ may play a key role in adult HLH (Brisse et al., 2015).

Objectives and brief outline of the study

The present observational study is designed to provide a better understanding of IFNγ and IFNγ-inducible chemokines as markers of HLH disease activity in adults, and of the potential of IFNγ to represent a therapeutic target in this patient population.

Adult patients (≥18 years old) are eligible, if having consented to the use of their clinical data for research purposes.

Clinical data and sample collection may be performed either retrospectively (provided that sufficient clinical information is available to allow for a meaningful interpretation of the biomarker results) and prospectively.

If retrospective cases are evaluated, the presence of a malignancy and the diagnosis of primary HLH (defined as homozygous mutation in a known HLH causative gene) represent exclusion criteria for the study. On the contrary, if prospective patients are considered, inclusion in the study may occur before the diagnostic work-up has been completed. In case the diagnosis of malignancy-related HLH or primary HLH (as above defined) is made, the data collected will be analyzed separately. In particular, malignancy-HLH cases will be considered in the parallel observational protocol NI-0501-07.

The present study will be conducted in the United States and in Europe, until the required number of patients has been recruited.

The detailed study outline is presented below.

Study Title	An observational, multicenter study to evaluate Interferon gamma (IFNγ) and other inflammatory mediators in Adult Patients with Hemophagocytic Lymphohistiocytosis (A-HLH)
Study Code	NI-0501-08
Study Objectives:	• To determine the levels of inflammatory markers including, but not limited to interferon gamma (IFNγ), interleukin 1 beta (IL-1β), interleukin 6 (IL-6), interleukin 10 (IL-10), interleukin 17 (IL-17), interleukin 18 (IL-18), soluble IL-2 Receptor α (sCD25), C-X-C chemokine ligand 9 (CXCL9), C-X-C chemokine ligand 10 (CXCL10), C-X-C chemokine ligand 11 (CXCL11), soluble CD163 (sCD163), neopterin and Tumor Necrosis Factor alpha (TNFα) in adult patients diagnosed with HLH and whenever possible, to monitor the evolution over time of these markers. • To assess the relationship between the above mentioned inflammatory cytokines and disease activity. • To explore the presence of genetic variants of the genes typically causing primary HLH in these patients and any association with the course of the HLH disease.
Sample Size:	A minimum of 14 (maximum of 40) adult patients with HLH will be studied, including a minimum of 7 patients with HLH of unknown origin (i.e. in whom a trigger for HLH cannot be identified). Retrospective patients may be considered with no limitation in their number, provided that sufficient medical history and clinical information is available.
Study Population:	Male and female adult (≥18 years old) patients who are diagnosed with HLH and meet the inclusion criteria listed below.
Inclusion Criteria:	1. Patients ≥18 years old diagnosed with active HLH as established by the treating physician. 2. HLH forms of unknown origin or secondary to infections or rheumatologic disorders. 3. Primary HLH (diagnosed by the presence of homozygous mutations in a known HLH causative gene) and secondary HLH due to malignancy are excluded; should the diagnosis of pHLH or malignancy become apparent after inclusion, the data

	collected will be analysed separately as additional cohorts. 4. The patient must have consented to the use of their clinical data for research purposes at the site.
Study Design and Procedures:	This is a non-interventional study designed to determine the levels of pro-inflammatory markers (as listed above) in adult patients diagnosed with HLH and to assess the relationship between the biomarkers and disease activity. Whenever possible, the evolution of inflammatory markers will be followed during HLH treatment and the relationship with the disease outcome explored. Data collection may be performed retrospectively if sufficient clinical information is available to allow for a meaningful interpretation of the biomarker results. For biomarker analysis, a maximum of 5 ml of whole blood will be required per time point. Details on sample processing and shipment will be described in a separate brief laboratory manual provided to the site. Whenever possible, serum (and not plasma) should be obtained for shipment, as this is the preferred matrix for the biomarker analysis. Relevant clinical information gathered by the treating physician will be collected in a data collection form. This will include information on the clinical presentation of HLH, the assessments performed to characterize the secondary form, in particular those for identification of the potential HLH trigger, the date of onset of the background disease (if any) in relation to HLH manifestations, treatment regimen prior to and/or ongoing at the time of HLH onset, clinical and laboratory parameters relevant to HLH, specific HLH therapy with best response to the therapy, other concomitant medications, patient follow-up and disposition, stem cell transplant status, duration of response, and survival. As appropriate, collection of serum samples for biomarker analysis and relevant information should occur at HLH diagnosis, and at regular time intervals during the treatment course (not more than once a week) up to resolution of HLH. If patients present CNS involvement and lumbar puncture is being performed for diagnostic or therapeutic purposes, a CSF sample will be collected, if possible, for biomarker assessment, in particular CXCL9 and CXCL10. If feasible and consistent with the standard clinical practice at the site, genetic characterization will be performed. A specific consent for genetic testing must be given by the patient. Genetic samples

	may also be collected from existing bank of samples (frozen whole blood in EDTA or frozen extracted DNA), if the patient's consent has been previously obtained. Medical history, in particular all available information on search conducted for the identification of the potential HLH trigger needs to be collected.
Study Duration:	This study will gather information on adult HLH patients at diagnosis and, as available, during treatment of the disease up to HLH resolution, and will last until completion of the planned recruitment.
Parameters:	**1. Laboratory parameters,** at the time of HLH diagnosis, to be assessed at the site laboratory, such as: • Hemoglobin, Hematocrit, red blood cells, white blood cells and differential count, platelets • Fibrinogen • Ferritin • Fasting triglycerides • AST, ALT, Alkaline Phosphatase • BUN, serum creatinine • Albumin • Sodium (if available) • Beta2 microglobulin (if available) • Serum IgG levels (if available) • Lactate dehydrogenase • Total and conjugated Bilirubin • D-dimers • PT, aPTT • CRP • Functional tests, such as perforin expression and NK-cell activity (if performed) Results of additional tests performed for the patient's follow-up at regular time intervals during the treatment course (not more than once a week) up to resolution of HLH will be recorded, as available.

2. **Other relevant parameters,** at the time of sample collection, in particular body temperature, spleen and liver size (if available), findings in bone marrow biopsy.
3. **Inflammatory markers of disease activity.** The following assessments will include but not be limited to:
   - IFNγ
   - sCD25
   - IL-1β, IL-6, IL-10, IL-17 IL-18
   - TNFα
   - CXCL9, CXCL10, CXCL11
   - sCD163 and neopterin

   These tests will be performed at Novimmune Bioanalytical Laboratory and results will be made available to the patient's treating physician and to the patient.
4. **Medical history,** in particular any available additional information on the background disease considered to be the potential trigger of HLH, e.g.:
   - Infections (including viral load, bacterial and/or fungal search)
   - Rheumatologic diseases

Statistical Analysis:

All analyses are exploratory. Statistical analyses of the data collected in this study will be focused on providing tabular and graphical summaries of the levels of inflammatory markers and of the clinical features of the disease both at diagnosis and during the course of treatment. The degree of correlation between inflammatory markers, and between inflammatory markers and the severity of clinical manifestations, response to therapy, and survival of the patients will be assessed. Analyses may also be performed to study these relationships in various subgroups of patients, depending on the demographic, genetic and clinical characteristics observed (notably, HLH of unknown origin representing a specific subgroup of interest).

An *a posteriori* diagnostic classification of patients will be done, whenever possible, based on HLH-2004 diagnostic criteria (Henter et al., 2007) and HScore (Fardet et al., 2014).

Medications:

Any medications that are considered necessary for the patient's

	welfare are given based on the decision of the treating physician.
Informed consent:	It is the responsibility of the investigator to obtain written informed consent from each patient participating in this study, after adequate explanation of the aims, methods and potential hazards of the study. An additional signature will be requested specifically for genetic analyses. Patients may withdraw their consent at any time; it is the responsibility of the investigator to contact the sponsor for specific patient withdrawal of consent while maintaining the confidentiality by communicating only patient codes. The sponsor will proceed with the destruction of all left over patient material within 12 months. The sponsor will also inform and request confirmation from potential collaborators to destroy aliquots that may have been transferred under collaboration agreements for the purpose of the research described in this protocol. The data generated prior withdrawal of consent will be maintained.
Data collection and patient confidentiality:	Relevant clinical information including date of diagnosis, medical history and previous and current treatments will be gathered by the treating physician. The investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On Data Collection Forms or other documents or material submitted to the sponsor, patients should not be identified by their names, but by an identification code. An electronic data capture will be used for data collection in this observational study, and a specific CRF will correspond to each subject. Novimmune affirms the patient's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is more stringent).
Study administration:	**Record Retention** The investigator will ensure that essential records are kept in a secure archiving facility for the retention period stipulated in the study contract. Essential documents include, but are not limited to, the following: • Signed informed consent documents for all patients

- Subject identification codes
- Record of all communications between the investigator and the IRB/IEC
- Composition of the IRB/IEC
- Record of communications between the investigator, Novimmune and their authorised representative

These records will be held in the Investigator's archives. If the Investigator is unable to meet this obligation, the Investigator must ask Novimmune for permission to make alternative arrangements.

Financial Disclosure

Investigator is required to provide financial disclosure information to allow Novimmune to submit complete and accurate certification or disclosure statements in accordance with applicable national and local regulations upon request. In addition, investigator must provide Novimmune with a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Disclosure of Protocol and Study Results and Publication Policy

Publication or communication of results will be decided upon completion of the study or earlier if data are considered sufficiently novel and robust. NovIimune will comply with the requirements for publication of results involving human research.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements. Any formal publication of the study in which contribution of Novimmune personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Novimmune personnel.

So-called 'ghost writing' is not permitted. All contributors who do not meet the criteria for authorship should be listed in an acknowledgments section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chairperson who provided only general support.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of Novimmune, except where agreed otherwise.

Monitoring and Auditing

As the aim of this study is mainly to test blood for research purpose no specific monitoring at site is foreseen by Novimmune. However for compliance with applicable government regulations with respect to current GCP and standard operating procedures, direct access to the on-site study documentation and medical records must be ensured to any audit or inspections.

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