“JAK inhibitor in Acquired Hemophagocytic synDrome in the Intensive care unit”

JAKAHDI

CLINICAL TRIAL ON MEDICINAL PRODUCT FOR HUMAN USE

Version N°1-1 dated 2023/09/12
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SIGNATURE page for a research PROTOCOL

Research code number: APHP220919

Title: JAK inhibitor in Acquired Hemophagocytic synDrome in the Intensive care unit

Version no.1-1 dated: 2023/09/12

The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

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"JAKAHDI" protocol, version 1-1 of 2023/09/12

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1 SUMMARY

Full title	**JAK** inhibitor in **A**cquired **H**emophagocytic syn**D**rome in the **I**ntensive care unit
Acronym/reference	**JAKAHDI**
Coordinating investigator	**Dr Sandrine VALADE**
Scientific Director	Dr Eric MARIOTTE
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Hemophagocytic syndrome (HS) is a rare condition that can be responsible for severe organ failure. Therapeutic guidelines are mainly based on observational studies and expert opinions: no therapeutic advance has been developed for years, explaining why mortality in HS remains high (ICU mortality ranging from 40 to 70%). If etoposide remains the gold standard in critically ill HS patients, nearly 20% of patients are refractory to this therapy: treatment escalation is common, most often requiring the administration of intensive treatments generating high toxicity. Ruxolitinib is the first approved JAK inhibitor. It has been associated with improvement of HS manifestations and survival in a pre-clinical murine model. Data in humans are scarce but promising.
Main objective and primary endpoint	We aim to demonstrate that ruxolitinib, in association with standard of care, may reverse organ failure (as represented by SOFA score) better than standard of care alone in critically ill patients with acquired HS The primary end point will be survival with a decrease in SOFA score ≥ 3 points at day 7.
Secondary objectives and endpoints	- To demonstrate that ruxolitinib may improve overall survival in HS critically ill patients - To demonstrate that ruxolitinib may reverse clinical (temperature, SOFA score) and biological (ferritin level, CD25 soluble receptor dosage, fibrinogen level, triglycerides level, hemoglobin level, white blood cells count, platelets count) manifestations related to HS - To analyse the impact of ruxolitinib on biological inflammatory markers (IL2, IL6, IL10, IL12, GM-CSF, IFN gamma, TNF alpha) - To demonstrate the safety of ruxolitinib in critically ill HS patients
Design of the study	This will be a multicenter, national, uncontrolled, phase II trial, based on a Fleming 2-stage design
Category	Cat 2 (phase 2)
Population of study participants	Adult patients older than 18 years
Inclusion criteria	- adult patients older than 18 years - acquired hemophagocytic syndrome, regardless of etiology, defined by the presence of 5 or 6 HLH-2004 criteria or HScore ≥ 200 - admission in the ICU - need for symptomatic treatment of HS in relation with organ failure, as defined by SOFA score ≥ 4 - Informed consent signed: • by the patient, • Or informed consent signed by a family members/trustworthy person if his condition does not allow him to express his consent in written as per L1111-6,

	- Or in an emergency situation and in the absence of family members/trustworthy person, the patient can be enrolled. The consent to participate to the research will be requested as soon as the condition of the patient will allow). - The inclusion of women of childbearing potential requires the use of a highly effective contraceptive measure. Contraception should be maintained during treatment and one day after.
Exclusion criteria	- Moribund, defined by a life expectancy < 48 hours; - Pregnant or lactating patients (women of childbearing potential must have a negative urine or blood Human Chorionic Gonadotropin pregnancy test prior to trial entry); - No affiliation to health insurance; - Known hypersensitivity to ruxolitinib; - Lactose intolerance; - Hypersensitivity to cellulose, microcrystalline; magnesium stearate; silica, colloidal anhydrous; sodium starch glycolate (Type A); povidone K30; hydroxypropylcellulose 300 to 600 cps, - Pre-existing decisions of withholding/withdrawing care, - History of progressive multifocal leukoencephalopathy - Uncontrolled cutaneous cancer - Persons under psychiatric care that would impede understanding of informed consent and optimal treatment and follow-up - Adults subject to a legal protection measure (guardianship, curatorship and safeguard of justice) - Patients deprived of their liberty by a judicial or administrative decision - Participation in another interventional research
Investigational medicinal product(s)	Patients will receive oral ruxolitinib twice a day (10 mg x 2 during 28 days) in association with standard of care in HS.
Comparator treatment	*None*
Interventions added for the study	Ruxolitinib Cytokines dosage: 1 sampling tube at D1, D7, D14 and D28 CD25 soluble dosage: 1 sampling tube at D1, D7, D14 and D28
Expected benefits for the participants and for society	For the patient: rapid improvement in organ failures and improved survival. The use of ruxolitinib may avoid treatment escalation in refractory patients, thereby reducing treatment-related toxicities. For the society: improving the survival of those patients
Practical implementation	Patients admitted to the participating ICUs will be included in this study if the meet eligibility criteria. Patient consultation will be performed by study investigator, and data collection by the investigator or research assistant (clinical research technicians, CRTs).
Number of participants included	42 (maximal sample size)
Number of centres	9
Duration of the study	inclusion period: 18 months participation period (treatment + follow-up): 6 months total duration 24 months
Number of enrolments expected per site and per month	0.26

Statistical analysis	Based on the 2-stage Fleming design, an interim analysis will be performed once Day 7 status of the 21th consecutively enrolled patient has been observed. Terminal analysis, based on the intention-to-treat population, will be performed once all patients have been recruited unless early stopping.
Funding sources	Ministry of Health
Study will have a Data Safety Monitoring Board	Yes

1 SUMMARY (IN FENCH)

Titre complet	**JAK** inhibitor in **A**cquired **H**emophagocytic syn**D**rome in the **I**ntensive care unit
Acronyme/référence	**JAKAHDI**
Investigateur Coordonnateur	**Dr Sandrine VALADE**
Directeur Scientifique	Dr Eric MARIOTTE
Promoteur	Assistance Publique – Hôpitaux de Paris
Justification Scientifique	Le syndrome hémophagocytaire (SH) est une affection rare qui peut être responsable d'une défaillance organique sévère. Les recommandations thérapeutiques reposent principalement sur des études observationnelles et des avis d'experts : aucune avancée thérapeutique n'a été développée depuis des années, expliquant pourquoi la mortalité dans l'HS reste élevée (mortalité en réanimation allant de 40 à 70 %). Si l'étoposide reste le gold standard chez les patients gravement atteints de SH, près de 20 % des patients sont réfractaires à cette thérapie : l'escalade de traitement est fréquente, nécessitant le plus souvent l'administration de traitements intensifs générant une forte toxicité. Le ruxolitinib est le premier inhibiteur de JAK approuvé. Il a été associé à une amélioration des manifestations de SH et de la survie dans un modèle murin préclinique. Les données chez l'homme sont rares mais prometteuses.
Objectif principal et critère principal	Notre objectif est de démontrer que le ruxolitinib, en association avec la norme de soins, peut mieux inverser la défaillance d'organe (représentée par le score SOFA) que la norme de soins seule chez les patients gravement malades atteints d'HS acquise. Le critère de jugement principal sera la survie avec une diminution du score SOFA ≥ 3 points au jour 7.
Objectifs secondaires et critères d'évaluation	- Survie à 6 mois - Mesure de la température, du taux de ferritine, du dosage du récepteur soluble CD25, du taux de fibrinogène, du taux de triglycérides, du taux d'hémoglobine, de la numération des globules blancs, de la numération des plaquettes (J1, J7, J14 et J28) - Dosages d'IL2, IL6, IL10, IL12, GM-CSF, IFN gamma, TNF alpha (J1, J7, J14 et J28) - Incidence des infections nosocomiales (virales et bactériennes) jusqu'à J28 - Score SOFA à J1, J7, J14 et J28 - Durée de séjour en réanimation - Durée du séjour à l'hôpital - Incidence des événements indésirables dans les 28 jours

Conception de l'étude	Il s'agira d'un essai de phase II multicentrique, national, non contrôlé, basé sur une conception en deux étapes de Flemin
Catégorie	Cat 2 (phase 2)
Population des participants à l'étude	Patients adultes de plus de 18 ans
Critères d'Inclusion	- patients adultes de plus de 18 ans - syndrome hémophagocytaire (SH) acquis, quelle qu'en soit l'étiologie, défini par la présence de 5 ou 6 critères HLH-2004 ou HScore ≥ 200 - admission aux soins intensifs - nécessité d'un traitement symptomatique du SH en rapport avec une défaillance d'organe, tel que défini par un score SOFA ≥ 4 - Consentement éclairé signé : • par le patient, • Soit consentement éclairé signé par un membre de la famille/personne de confiance si son état ne lui permet pas d'exprimer son consentement par écrit au sens de L1111-6, - Soit en situation d'urgence et en l'absence des membres de la famille/personne de confiance, le patient peut être inscrit. Le consentement à participer à la recherche sera demandé dès que l'état du patient le permettra). - L'inclusion des femmes en âge de procréer nécessite l'utilisation d'une mesure contraceptive très efficace. La contraception doit être maintenue pendant le traitement et un jour après.
Critères d'exclusion	- Moribond, défini par une espérance de vie < 48 heures ; - Patientes enceintes ou allaitantes (les femmes en âge de procréer doivent avoir un test de grossesse urinaire ou sanguin à la gonadotrophine chorionique humaine négatif avant l'inscription à l'essai (soin courant)); - Pas d'affiliation à l'assurance maladie ; - Hypersensibilité connue au ruxolitinib ; - Intolérance au lactose; - Hypersensibilité à la cellulose, microcristalline ; stéarate de magnésium; silice colloïdale anhydre; glycolate d'amidon sodique (Type A); povidone K30; hydroxypropylcellulose 300 à 600 cps, - Décisions préexistantes de refus/retrait de soins, - Antécédents de leucoencéphalopathie multifocale progressive - Cancer cutané non contrôlé - Personnes sous soins psychiatriques qui entraveraient la compréhension du consentement éclairé et d'un traitement et d'un suivi optimaux - Les majeurs faisant l'objet d'une mesure légale de protection (tutelle, curatelle et sauvegarde de justice) - Patients privés de liberté par décision judiciaire ou administrative - Participation à une autre recherche interventionnelle
Médicament(s) expérimental(s)	Les patients recevront du ruxolitinib par voie orale deux fois par jour (10 mg x 2 pendant 28 jours) en association avec la norme de soins dans l'HS.
Traitement comparateur	*Aucun*
Interventions ajoutées pour l'étude	Ruxolitinib Dosage des cytokines : 1 tube de prélèvement à J1, J7, J14 et J28 Dosage CD25 soluble : 1 tube de prélèvement à J1, J7, J14 et J28

Bénéfices attendus pour les participants et pour la société	Pour le patient : amélioration rapide des défaillances d'organes et amélioration de la survie. L'utilisation du ruxolitinib peut éviter l'escalade du traitement chez les patients réfractaires, réduisant ainsi les toxicités liées au traitement. Pour la société : améliorer la survie de ces patients
Mise en œuvre pratique	Les patients admis dans les unités de soins intensifs participantes seront inclus dans cette étude s'ils répondent aux critères d'éligibilité. La consultation des patients sera effectuée par l'investigateur de l'étude et la collecte des données par l'investigateur ou l'assistant de recherche (techniciens de recherche clinique, CRT).
Nombre de participants inclus	42 (taille maximale de l'échantillon)
Nombre de centres	9
Durée de l'étude	Période d'inclusion period: 18 mois Période de participation (traitement + suivi): 6 months Durée totale : 24 months
Nombre d'inscriptions attendues par site et par mois	0,26
Analyses statistiques	Sur la base de la conception Fleming en 2 étapes, une analyse intermédiaire sera effectuée une fois que le statut au jour 7 du 21e patient inscrit consécutivement aura été observé. L'analyse terminale, basée sur la population en intention de traiter, sera réalisée une fois tous les patients recrutés sauf arrêt précoce.
Funding sources	Ministère de la Santé, PHRC-K 2022
L'étude aura un Comité de Surveillance Indépendant (CSI) des données	Oui

2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 Hypothesis for the study

Our hypothesis, based on animal studies and preliminary data in humans, is that the use of ruxolitinib in severe forms of hemophagocytic syndrome (HS), in association with standard of care, will improve organ failure and reduce mortality.

2.2 Description of knowledge relating to the condition involved

Hemophagocytic syndrome (HS) or hemophagocytic lymphohistiocytosis (HLH) is a rare condition that can be responsible of severe organ failures [1]. This syndrome can be congenital or acquired, the latter being seen mostly in adult patients. Since the first description of this syndrome in 1939, a growing number of patients are reported, mostly in small series. The annual incidence of HLH is low, estimated at 1 per 800,000 people in the general population, but this syndrome is probably under-diagnosed.

The typical presentation associates a pancytopenia with a high fever. Two sets of criteria are routinely used to help with the diagnosis of HLH: the HLH 2004 criteria [2], and most recently the HScore [3]. The two classifications can be used in ICU patients, as HScore and HLH criteria are both highly sensitive and specific in severely ill patients [4].

HLH 2004 criteria:

Diagnostic criteria for HLH fulfilled (5 out of the 8 criteria below)

- (A) Initial diagnostic criteria
  - Fever
  - Splenomegaly
  - Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood)
    - Hemoglobin < 9g/dL; Platelets < 100x 109/L; Neutrophils < 1.0 x 109/L
  - Hypertriglyceridemia and/or hypofibrinogenemia:
    - Fasting triglycerides ≥ 3.0 mmol/L (i.e., ≥ 2.65 g/L)
    - Fibrinogen ≤ 1.5 g/L
  - Hemophagocytosis in bone marrow or spleen or lymph nodes
- (B) New diagnostic criteria
  - Low or absent NK-cell activity (according to local laboratory reference)
  - Ferritin ≥ 500 µg/L
  - Soluble CD25 (i.e., soluble IL-2 receptor) ≥ 2,400 U/ml

HScore:

Parameter	No. of points (criteria for scoring)
Known underlying immunosuppression*	0 (no) or 18 (yes)
Temperature (°C)	0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)
Organomegaly	0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
No. of cytopenias†	0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)
Ferritin (ng/ml)	0 (<2,000), 35 (2,000–6,000), or 50 (>6,000)
Triglyceride (mmoles/liter)	0 (<1.5), 44 (1.5–4), or 64 (>4)
Fibrinogen (gm/liter)	0 (>2.5) or 30 (≤2.5)
Serum glutamic oxaloacetic transaminase (IU/liter)	0 (<30) or 19 (≥30)
Hemophagocytosis features on bone marrow aspirate	0 (no) or 35 (yes)

The pathophysiology of this condition remains incompletely understood. However, based on the physiology of inherited HS, a defect of cytotoxicity regarding the NK cells and CD8 lymphocytes is suspected. In the presence of a trigger, the impaired function of these immune cells leads to a prolonged and persistent exposure to the pathogen. As a result, they proliferate

and secrete cytokines (IFN gamma, MCSF) that activate the macrophages. In response, the macrophages also release a large number of cytokines (including IL6, IL10, TNF alpha..). This cytokine storm is responsible for a loop of immune over-activation between CD8/NK cells and macrophages and may explain the different symptoms of HS [5].
The triggers/underlying conditions responsible of HS can be classified in three main categories: infections, neoplasms and systemic rheumatic diseases [5]. Unknown etiology concerns only a few patients (<10%). Infections are mostly caused by viruses (EBV, CMV, HSV, VZV, HHV6, HHV8…) but also bacteria (mycobacteria are predominant) or parasites/fungi (leishmania, histoplasma, toxoplasma…etc.). The most frequent neoplasms associated with HS are lymphomas and multicentric Castleman disease. In adults, systemic rheumatic diseases are less frequently associated with HS and are mostly represented by systemic lupus erythematosus and adult-onset Still's disease. An extensive diagnostic work-up must always be performed in order to find and treat the underlying condition.

2.3 Description of the population to be studied and justification for this choice of participants

Several organ failures can lead the patient to ICU admission, mostly respiratory distress and shock [1]. Mortality remains high in HS, reported around 40% in the entire population of HS patients, with large variations according to the underlying condition and the severity of presentation [1,5,6]. In fact ICU mortality is higher as the patients often present with life-threatening organ failures, ranging between 40% and 80% [1,7]. Patients with HS related to hematological malignancies have the worst survival, especially in case of T cell lymphoma where mortality rates can reach 80% [6].

2.4 Summary of relevant pre-clinical experiments and clinical trials

Given the low incidence of reactive HS, no randomized clinical trials have been conducted in adult patients with this condition. Therapeutic guidelines are mainly based on observational studies and expert opinions [8,9]. The first step in the management of patients with HS consists in the prompt administration of broad-spectrum antibiotics in case of organ failures, as these patients are immunocompromised, in addition with supportive care of organ dysfunctions. The last consensus-based guidelines for the management of HS in critically ill adults recommend that "early and aggressive intensive interventions, such as broad-spectrum antibiotics, vasopressors, renal replacement therapy, mechanical ventilation, blood product replacement, and management of coagulopathy, are often required in HS (strong consensus)" [8].
Then, the treatment always relies on the treatment of the underlying condition once it has been identified. In patients with severe organ failure, it may sometimes be necessary to initiate urgent probabilistic treatments targeting the main suspected diseases [9].
In the most severe forms of HS with life-threatening organ failures, a symptomatic treatment should also be given [8,9]: etoposide, which remains a corner stone in familial HS [2], is effective in decreasing the cytokine storm since it significantly reduces the level of activated T lymphocytes [10]. Its early use is correlated with a better outcome in a study conducted in children with EBV-associated HS [11]. In adult patients, the use of etoposide as a first-line treatment tended to be associated with increased survival in a retrospective study [6]. It remains an emergency treatment in order to control the organ failures, and its use is recommended in severe forms of HS (SOFA score ≥ 3) [8] in order to dampen the inflammatory state. Corticosteroids and IV immunoglobulins are also widely used, particularly in infections-related HS or auto-immune diseases and in moderate forms of HS. Nevertheless, etoposide induces cytopenias and increases the risk of secondary infections. Moreover, if etoposide remains the gold standard in critically ill HS patients, nearly 20% of patients fail to respond to this therapy, leaving very few therapeutic options at clinicians' disposal. Despite adequate therapeutic management, ICU mortality remains high in HS patients, being reported between 40 and 70%.

Since several decades to present time, there has been and there is still no alternative to etoposide in the most severe patients.

The Janus kinases (JAKs) and the signal transducers and activators of transcriptions (STATs) represent a major signalling pathway, which promotes the cytokine-mediated cell activation. JAKs are unique tyrosine kinases that are associated with cytokines receptors. Their activation through a trans-phosphorylation leads to the STATs recruitment, dimerization and translocation to the nucleus, where they promote transcription of cytokine-responsive genes [12]. Many signals are transmitted by these receptors (anti-apoptotic, proliferation and differentiation signals) and their expression and functions are critical for the formation of all hematological lineages.
Several cancers have been associated with constitutive activation of members of the STAT family. In myeloproliferative neoplasms, such as polycythemia vera and in many essential thrombocythemia or idiopathic myelofibrosis, mutations in the *JAK2* gene were found to play key roles in inducing an aberrant activation of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signalling pathway [13]. Therefore, JAK inhibition represents an attractive therapeutic strategy for these disorders.
Several JAK inhibitors have entered clinical trials, including ruxolitinib, the first JAK1/2 inhibitor to become commercially available. In France, ruxolitinib is approved for the treatment of myelofibrosis, and for the treatment of adults with polycythemia vera who are resistant or intolerant to hydroxyurea. A randomized, phase 3 study has shown the superiority of ruxolitinib over the best available therapy in patients with myelofibrosis, although it has no curative effect. Ruxolitinib resulted in a rapid reduction in splenomegaly and was associated with an improved quality of life [14]. Promising effects of JAK inhibitors are expected in the future in solid cancers and auto immune disorders. Recently, ruxolitinib has also been evaluated in the setting of allograft patients with steroids-refractory acute graft-versus-host disease. Ruxolitinib led to significantly greater overall response, failure-free survival, and symptom response in these patients with a poor prognosis [15].

Ruxolitinib has been associated with improvement of HS manifestations and survival in a pre-clinical animal model. Ruxolitinib was used in murine models of primary or secondary HS: in both models, treatment with the JAK1/2 inhibitor ruxolitinib significantly decreased the clinical features of HS, including weight loss and organomegaly. It was also found to be associated with an improvement of cytopenias (anemia, thrombocytopenia), a decrease in pro inflammatory cytokines levels (IL-6, TNF) and tissue inflammation. Importantly, in this study the use of ruxolitinib was also associated with an improved survival [16]. Maschalidi et al. also demonstrated that ruxolitinib reversed HS clinical manifestations and liver tissue damages, concomitantly with a decrease in the number of infiltrating inflammatory macrophages in two HS murine models [17]. To further understand the mechanisms of action of ruxolitinib, which targets both JAK 1 and JAK 2, Albeituni et al. compared the effects of ruxolitinib and anti-interferon gamma antibodies in mice. Both treatments improved hemoglobin level, but only ruxolitinib was associated with a decrease in the number of activated immune cells (T-CD8 lymphocytes) and tissue infiltration [18]. Data in humans are scarce but promising, ruxolitinib being used as a salvage therapy in case reports, and more recently front-line in small pilot studies. Ruxolitinib was administered as front-line therapy in 12 pediatric patients with secondary HS (8 having EBV-associated HS). Patients received ruxolitinib twice daily (2.5mg, 5mg or 10mg depending on body weight) during 28 consecutive days. The overall response rate at day 28 was 83% with a majority of complete and sustained response [19]. In adult patients, a recent single centre, open-label, pilot trial, evaluated ruxolitinib administration in 5 patients with secondary HS. Corticosteroids were allowed and ruxolitinib dosage was 15mg twice per day during a continuous 28-day cycle. The resolution of HS-related symptoms (complete or partial) was obtained in all patients and survival at 2 months was 100%. Cytopenias improved in all patients in the first week of treatment, pro-inflammatory markers decreased (soluble IL-2 receptor) and ruxolitinib was well tolerated [20].

2.5 Identification and description of the investigational medication or medications

Ruxolitinib (Jakavi®) tablets, commercialized by Novartis Pharma will be used for this study.

2.6 Description and justification of the dosage, route of administration, administration schedule and treatment duration

The pharmaceutical form consists of white round tablets of 5 mg. Excipient with known effect: each tablet contains 285.80 mg lactose monohydrate. This medicine contains less than 1 mmol sodium (23 mg) per tablet.
Ruxolitinib is to be taken orally. After oral administration, ruxolitinib is rapidly absorbed and can be given without regard to meals. Ruxolitinib should be then taken every day at the same time, with or without food. In patients unable to ingest tablets (mechanical ventilated patients), ruxolitinib can be administered through a gastric tube: the tablet is suspended in 40 mL of water, stirred for approximately 10 minutes, and then administered. The tube is flushed and rinsed with 75 mL of sterile water to ensure that the patient receive the full dose [21].

2.7 Summary of the known and foreseeable benefits and risks for the Clinical Trial participants

HS remains a life-threatening condition in which the ideal immune suppression/anti-inflammatory therapy regimen remains unknown. The excessive inflammatory state is responsible for various organ failure that can lead to death if not promptly treated. No therapeutic advance has been developed for years, explaining why mortality in HS remains high, especially in the most severe forms. In refractory HS, treatment escalation is common, most often requiring the administration of intensive treatments generating high toxicity, such as alemtuzumab, antithymocyte globulin or liposomal doxorubicin.

Ruxolitinib is a drug used and approved for the treatment of hematological malignancies, such as myelofibrosis and polycythemia vera. In animal studies, ruxolitinib lessens inflammation in HS models both via interferon gamma-dependent and –independent mechanisms. Moreover, it reduces the number of activated T cells and their infiltration of tissues. Additionally, ruxolitinib seems well tolerated, as no serious adverse effect has been reported. In our study, the expected benefits for patients, more than half of whom have cancer, are a rapid improvement in organ failures and improved survival. The use of ruxolitinib may avoid treatment escalation in refractory patients, thereby reducing treatment-related toxicities.

This is the first study evaluating the benefit of ruxolitinib in critically ill patients with secondary hemophagocytic syndrome. Ruxolitinib has the advantage of not targeting a single cytokine, like some drugs that have been previously used in hemophagocytic syndrome, for example tocilizumab or anakinra. Ruxolitinib inhibits a signalling pathway involving several cytokines responsible for inflammation in HS.
If etoposide remains the gold standard in critically ill HS patients, some patients are refractory to this therapy and few therapeutic options are available with a high mortality rate. Recently, several publications have reported the successful use of ruxolitinib in HS patients, alone or in association with steroids or chemotherapy. Ruxolitinib was found to reverse clinical and biological features related to the inflammatory state, even in critically ill patients. However, data were mostly obtained from case report or very small series with large heterogeneity regarding HS etiology, the population of interest and the initial severity.

Risks, very common adverse events of ruxolitinib

Hematological toxicity is frequent in patients receiving ruxolitinib. However, in the phase III clinical studies, the median time to onset of cytopenias was approximately 8 to12 weeks, that is far longer than the duration of the treatment in our study. Adverse events are described from phase III clinical studies in myelofibrosis (MF) patients [14], polycythemia vera (PV) patients [22] and patients with refractory Graft Versus Host Disease (GVHD) [15,23].

In the pilot study conducted by Ahmed et al. in HS patients, a single serious adverse event (ie, grade 4 febrile neutropenia) was reported. One patient discontinued treatment because of grade 2 extremity pain and no treatment-related deaths were observed.

- *Anemia*
  In phase 3 clinical studies in patients with refractory GVHD (REACH 1 and REACH 3), anemia is reported between 29 to 35% of patients receiving ruxolitinib (13-28% grade 3-4).

- *Thrombocytopenia*
  In the REACH 3 study, 15.2% of patients receiving ruxolitinib presented grade 3 or higher thrombocytopenia (versus 10.1% of patients who received control therapies). Both thrombocytopenia and anemia were reversible and managed with doses reductions and supportive care.
  In the phase 3 clinical studies in myelofibrosis patients (COMFORT-I and COMFORT-II), thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50,000/mm^3 was 14 days. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving ruxolitinib and 0.9% of patients receiving control regimens.

- *Neutropenia*
  In COMFORT-I and COMFORT-II studies, dose holding or reductions due to neutropenia were reported in 1.0% of patients, and 0.3% of patients discontinued treatment because of neutropenia.
  In phase 3 clinical studies in patients with refractory GVHD (REACH1 and REACH 3), severe neutropenia (grade 3 or higher) was reported between 8.5 to 21% of patients receiving ruxolitinib.

- *Bleeding*
  No bleeding was reported in patients with refractory GVH receiving ruxolitinib.
  In the phase 3 pivotal studies in myelofibrosis, incidence of grade 3-4 bleeding events was similar for patients treated with ruxolitinib or reference treatments (4.7% versus 3.1%). In RESPONSE 2 study, no intracranial bleeding or gastrointestinal haemorrhage events were reported in patients receiving ruxolitinib.

- *Infections*
  In the REACH III study, infections of any type occurred in 63.6% of patients who received ruxolitinib as compared with 56.3% of patients who received control therapy (grade 3 infections 19.4% vs. 18.4%). Viral infections were the most common (33.9%of patients, especially HSV and CMV related infections), followed by bacterial (27.9%) and fungal infections (11.5%). 11% of patients experienced pneumonia in the ruxolitinib group and 12.7% in the control group: it was the only adverse event leading to discontinuation of treatment by 2% or more of patients in the ruxolitinib group (4.8%). One patient (0.6%) developed septic shock.

- *Elevated lipase*
  In the randomised period of the RESPONSE study, the worsening of lipase values was higher in the ruxolitinib arm compared to the control arm (mainly grade 1 elevation, 18.2% vs 8.1%).

In myelofibrosis patients, high lipase values were reported in 18.7% and 19.3% of patients in the ruxolitinib arms compared to 16.6% and 14.0% in the control arms in COMFORT-I and COMFORT-II studies, respectively. In patients with elevated lipase values, no concurrent signs and symptoms of pancreatitis were reported.

- *Increased systolic blood pressure*
  In the phase 3 pivotal clinical studies in MF an increase in systolic blood pressure of 20 mmHg or more from baseline was recorded in 31.5% of patients on at least one visit compared with 19.5% of the control-treated patients. In COMFORT-II study mean values showed little difference between the ruxolitinib-treated and the control-treated MF patients.

Other adverse events ≥ grade 3 in 5% or more of patients in the ruxolitinib arm up to week 24 (from the REACH II study, Zeiser et al)

Adverse event	**Ruxolitinib n = 165**	**Control n = 158**
Gastrointestinal event		
- diarrhea	1 (0.6%)	2 (1.3%)
- nausea	0	2 (1.3%)
- vomiting	0	2 (1.3%)
Laboratory abnormalities		
- alanine aminotransferase increase	7 (4.2%)	0
- creatinine increase	0	1 (0.6%)
- aspartate aminotransferase increase	3 (1.8%)	1 (0.6%)
- hypertriglyceridemia	8 (4.8%)	6 (3.8%)
- gamma glutamyl transferase increase	11 (6.7%)	3 (1.9%)
- hyperglycemia	8 (4.8%)	3 (1.9%)
- hypokalaemia	3 (1.8%)	7 (4.4%)
- cholesterol increase	4 (2.4%)	3 (1.9%)
- hyperkaliemia	9 (5.5%)	1 (0.6%)
Other		
- pyrexia	3 (1.8%)	2 (1.3%)
- cough	0	0
- fatigue	1 (0.6%)	3 (1.9%)
- dyspnea	3 (1.8%)	2 (1.3%)
- headache	2 (1.2%)	1 (0.6%)
- peripheral edema	1 (0.6%)	0
- back pain	1 (0.6%)	0

3 OBJECTIVES

3.1 Primary objective

To demonstrate that ruxolitinib, in association with standard of care, may reverse organ failure (as represented by SOFA score) [24] better than standard of care alone in critically ill patients with acquired hemophagocytic syndrome.

Variables	SOFA score				
	0	1	2	3	4
Respiratory PaO_2/FiO_2, mmHg	>400	≤400	≤300	≤200*	≤100*
Coagulation platelets×$10^3/\mu l$†	>150	≤150	≤100	≤50	≤20
Liver bilirubin, mg/dl†	<1.2	1.2~1.9	2.0~5.9	6.0~11.9	>12.0
Cardiovascular hypotension	No hypotension	MAP‖ <70 mmHg	Dop¶≤5 or Dob** (any dose)†	Dop>5, Epi††≤0.1, or Norepi††≤0.1†	Dop>15, Epi>0.1, or Norepi>0.1†
Central nervous system GCS§§ scale	15	13~14	10~12	6~9	<6
Renal creatinine, mg/dl or urine output, ml/dl§	<1.2	1.2~1.9	2.0~3.4	3.4~4.9 or <500	>5.0 or <200

*values are with respiratory support; †to convert bilirubin from mg/dl to μmol/L, multiply by 17.1; ‡adrenergic agents administered for at least 1 hour (dose given are in μg/kg per minute); §to convert creatnine from mg/dl to μmol/L, multiply by 88.4; ‖MAP = mean arterial pressure; ¶Dop = dopamine; **Dob = dobutamine; ††Epi = epinephrine; ††Norepi = norepinephrine; §§GCS = Glasgow Coma Score.

3.2 Secondary objectives

- To demonstrate that ruxolitinib may improve overall survival in HS critically ill patients
- To demonstrate that ruxolitinib may reverse clinical and biological manifestations related to HS
- To analyse the impact of ruxolitinib on biological inflammatory markers
- To demonstrate the safety of ruxolitinib in critically ill HS patients

4 STUDY DESIGN

4.1 Study endpoints

4.1.1 Primary endpoint

Survival with a decrease in SOFA score ≥ 3 points at day 7.

The main endpoint was defined at day 7 first given the effect of ruxolitinib is expected to be rather quick, as observed in acute respiratory distress syndromes in COVID-19 disease with improvement within 48h [25]

We used the survival status together with an improved SOFA score to better delineate the early effect of the treatment, not only on the survival but also on the clinical improvement. Indeed, a rapid resolution of symptoms is expected with ruxolitinib, as previously reported in small clinical pilot studies [19,20].

We based the clinical improvement on the improvement of the SOFA score. since it is commonly as an endpoint in ICU clinical trials and has been reported significantly associated with mortality [26], with a reported earliest time point where ΔSOFA score predicted mortality at day 7 [27]. We set the cut-off of improvement at 3 points, given the expected distribution of SOFA at enrolment and the reported mean decrease of 0.5 point per day in a large cohort of 20,007 ICU patients [28].

4.1.2 Secondary endpoints

- **Overall survival in HS critically ill patients :**

Survival within 6 months (by medical file)

- **Reverse clinical and biological manifestations related to HS :**

- Organ Failure : SOFA score at day 1, day 7, day 14 and day 28
- ICU length of stay (number of days in the ICU from inclusion to ICU discharge or death)
- Hospital length of stay (number of days in the hospital from inclusion to hospital discharge or death)
- Measurements of temperature, ferritin level, CD25 soluble receptor dosage, fibrinogen level, triglycerides level, haemoglobin level, white blood cells count, platelets count (at day 1, 7, 14 and 28)
- Dosages of IL2, IL6, IL10, IL12, GM-CSF, IFN gamma, TNF alpha (at day 1, day 7, day 14 and day 28)

- **Impact of ruxolitinib on biological inflammatory markers :**

- Measurements of temperature, ferritin level, CD25 soluble receptor dosage, fibrinogen level, triglycerides level, haemoglobin level, white blood cells count, platelets count (at day 1, 7, 14 and 28)
- Dosages of IL2, IL6, IL10, IL12, GM-CSF, IFN gamma, TNF alpha (at day 1, day 7, day 14 and day 28)

- **Safety of ruxolitinib in critically ill HS patients :**

- Incidence of nosocomial infections (viral and bacterial) until day 28
- Incidence of adverse event, severe adverse event within 28 days. Intensity and frequency of adverse event and severe adverse event according to the CTCAE Toxicity Grading Scale for Determining The Severity of Adverse Events [29]

4.2 Description of research methodology

4.2.1 Design of the study

This is an uncontrolled phase II trial based on a Fleming 2-stage design [30]. The primary objective of such a phase II clinical trial of a new drug is to determine whether it has sufficient activity against the disease under study to warrant more extensive development. Moreover, the use of a sequential design allows avoiding the exposure of too many patients to an inefficacious therapy, based on an early assessment of benefit or futility. The first study period will end after the inclusion of 21 patients, when day 7-response will have been recorded for all patients. The decision to stop or continue the inclusions after this interim analysis will be based on the observed number of responses (see sample size computation below). The DSMB may recommend termination of the trial because of « futility », i.e. in absence of a reasonable probability that the trial may reach a conclusion within its planned frame. The final decision comes from the Sponsor.

Patients will receive oral ruxolitinib 10mg twice a day for 28 days, unless they have unacceptable side effects or progression of the disease, in association with standard of care.

For patients unable to ingest tablets, ruxolitinib can be suspended in water and administered through a nasogastric tube.

Dose reductions for renal insufficiency or toxicity are planned (see section VIII).

Once the clinical condition triggering HS is identified, additional etiological treatment will be administered.

4.2.2 Number of participating sites

Multicenter study, there will be 9 recruiting centres across France (see appendix 17.1): Paris = 3 centres, Toulouse = 2 centres, Villejuif = 1 centre, Marseille = 1 centre, Nantes = 1 centre, Lille = 1 centre.

4.2.3 Identification of participants

The participants in this Clinical Trial will be identified as follows:
Site number (3 digits) - Sequential enrolment number for the site (4 digits) - surname initial - first name initial
This reference number is unique and will be used for the entire duration of the study.

5 IMPLEMENTATION OF THE STUDY

The start of the clinical trial is the inclusion of the first patient.

5.1 Screening visit

Screening will start at ICU admission. Eligibility of critically ill patients will be systematically assessed.
The screening visit takes place in ICU departments. Patient history and laboratory tests usually carried out for patient's care are sufficient to assess eligibility of the patients.

Informed consent will be searched for eligible patients. Information note will be given by the investigators to the patient (when his/her condition will allow) or to family member or a close relative for patients. Study investigator will inform competent patients of the study, its purpose, its potential benefits and risks. Patients who consent to participate will be included after a reflection period of 1 to 6 hours for individual participating in the study and/or relatives.

For patients who fulfil inclusion criteria and are unable to consent, investigators will try to obtain consent from their legal representative. Patients unable to consent in whom legal representative consent will be included. Deferred consent of the patients will be obtained as soon as patient regain competency.

According to French law specifications for emergency inclusion, when the close relative or family member is absent, a waiver of consent will be asked to the Ethical Committee to include the patient. As soon as possible, family member or close relative will be asked to give his or her consent for continuation of the trial, and the patient's himself when his or her condition will allow it.

Whose consent must be obtained	**Who informs the individuals and collects their consent**	**At what point the individuals are informed**	**At what point the consent is obtained**
• *the individual participating in the study;* • *the appointed legal representative;*	• *the principal investigator or collaborating physician declared and trained in the study, ICU*	• *screening visit*	• *screening visit, after a reflection period of 1 to 6 hours for individual participating in the study and/or relatives*

5.2 Baseline visit

Baseline visit will collect:
Standard of care :
- Patients medical history, comorbidities, reason for ICU admission, organ failure and organ support at ICU admission, etiology of HS (hematological malignancy, infectious or auto-immune disease), physical exam, standard laboratory tests (including blood cell count, hemostasis parameters, creatinine level, livers tests, ferritin level, triglycerides level, urine or blood Human Chorionic Gonadotropin pregnancy test)
- Severity according to SOFA score (and including SOFA score per organ)
- Standard of care in HS: treatments (etoposide, steroids), timing and dosages

Research :
- Cytokines and CD25 soluble dosages (IL2, IL6, IL10, IL12, GM-CSF, IFN gamma, TNF alpha)

5.3 Follow-up visits

Standard of care :
Follow-up visits will be performed at day 7, day 14 and day 28. They will report:
- Patient condition (vital status)
- Severity according to SOFA score, organ support
- Physical exam, temperature, standard laboratory tests (including blood cell count, hemostasis parameters, creatinine level, livers tests, ferritin level, triglycerides level)
- Standard of care in HS: treatments (etoposide, steroids), timing and dosages
- Additional treatments for HS (chemotherapy, anti-infectious agents, immunosuppressive drugs)
- Occurrence of nosocomial infections
- Occurrence of opportunistic infections (PCR EBV, CMV)

Research :
- Cytokines and CD25 soluble dosages (IL2, IL6, IL10, IL12, GM-CSF, IFN gamma, TNF alpha)
- Adverse events

Status at day 90
Standard of care :
The visit will record patient condition (vital status) and adverse events, physically if the patient is still in the hospital or by phone if the patient is discharged from hospital.
Additional etiological treatments for HS (chemotherapy, anti-infectious agents, immunosuppressive drugs) will also be recorded.

5.4 Last study visit

Status at day 180
It will record patient condition (vital status) and adverse events, physically if the patient is still in the hospital or by phone if the patient is discharged from hospital.
Additional etiological treatments for HS (chemotherapy, anti-infectious agents, immunosuppressive drugs) will also be recorded.

5.5 Expected length of participation and description of the chronology and duration of the study.

Patients admitted to the participating ICUs will be included in this study if the meet eligibility criteria.
Anticipated duration of recruitment: 18 months
Planned number of patients to be recruited: 42 patients
Duration of participation of each patient: 6 months

Duration of enrolment period	18 months
The length of participation for participants, of which:	
• Maximum period between screening and enrolment:	4 days
• Treatment duration:	28 days
• Duration of follow-up period:	6 months
Total study duration:	24 months

5.6 Table or diagram summarising the chronology of the study

Patient consultation will be performed by study investigator, and data collection by the investigator or research assistant (clinical research technicians, CRTs).

Actions	***Screening phase***	***Inclusion Visit D1***	***Treatment period D1 to D28***	***Follow-up period D90 and D180***
Information		*X*		
Informed consent		*X*		
Verification of inclusion and exclusion criteria	*X*	*X*		
Urine or blood Human Chorionic Gonadotropin pregnancy test prior to trial entry);		*X*		
SOFA score		*X*	*D1, D7, D14, D28*	
Standard blood tests (including blood cell count, hemostasis parameters, creatinine level, livers tests, ferritin level, triglycerides level)	*X*	*X*	*X*	
Opportunistic infections (EBV, CMV)		*X*	*X*	
Cytokines and CD25 soluble dosages (IL2, IL6, IL10, IL12, GM-CSF, IFN gamma, TNF alpha)		*X*	*D1, D7, D14, D28*	
Adverse events		*X*	*X*	*X*
Vital status, ICU/hospital discharge		*X*	*X*	*X*

5.7 Distinction between standard care and study

TABLE: "Standard care" vs. "additional interventions" required specifically for the study

Procedures and treatments carried out as part of the research	**Procedures and treatments associated with <u>care</u>**	**Procedures and treatments added because of <u>the research</u>**
Treatments	Standard of care	Ruxolitinib*
Consultations	Standard of care	None
Blood samples	Standard of care	Cytokines dosage**: 1 sampling tube at D1, D7, D14 and D28 CD25 soluble dosage: 1 sampling tube at D1, D7, D14 and D28

*Provision of Ruxolitinib by Sponsor AP-HP
**The DGOS considers these procedures reimbursed. Therefore the dosage of cytokines above is not to be considered as additional costs for the centers

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- Adult patients older than 18 years
- Acquired hemophagocytic syndrome, regardless of etiology, defined by the presence of 5 or 6 HLH-2004 criteria or HScore ≥ 200
- Admission in the ICU
- Need for symptomatic treatment of HS in relation with organ failure, as defined by SOFA score ≥ 4
- Informed consent signed:
  - by the patient,
  - Or informed consent signed by a family members/trustworthy person if his condition does not allow him to express his consent in written as per L1111-6,
- Or in an emergency situation and in the absence of family members/trustworthy person, the patient can be enrolled. The consent to participate to the research will be requested as soon as the condition of the patient will allow).
- The inclusion of women of childbearing potential requires the use of a highly effective contraceptive measure. Contraception should be maintained during treatment and one day after.

6.2 Exclusion criteria

- Moribund, defined by a life expectancy < 48 hours;
- Pregnant or lactating patients (Women of childbearing potential must have a negative urine or blood Human Chorionic Gonadotropin pregnancy test prior to trial entry);
- No affiliation to health insurance;
- Known hypersensitivity to ruxolitinib;
- Lactose intolerance;
  Hypersensitivity to cellulose, microcrystalline; magnesium stearate; silica, colloidal anhydrous; sodium starch glycolate (Type A); povidone K30; hydroxypropylcellulose 300 to 600 cps,
- Pre-existing decisions of withholding/withdrawing care,
- History of progressive multifocal leukoencephalopathy
- Uncontrolled cutaneous cancer
- Persons under psychiatric care that would impede understanding of informed consent and optimal treatment and follow-up
- Adults subject to a legal protection measure (guardianship, curatorship and safeguard of justice)
- Patients deprived of their liberty by a judicial or administrative decision
- Participation in another interventional research

6.3 Recruitment procedure

The department of intensive care in Saint Louis hospital (Pr Azoulay) coordinates the GRRROH (Groupe de Recherche en Réanimation du patient d'Onco Hématologie), a research network that performs clinical studies focusing on the critically ill patient with onco-haematological diseases and solid tumors.
All the participating centres are located in France and belong to the GRRROH. They have previously taken part in observational studies, surveys, and/or therapeutic trials in the field. They all have high case-volumes of patients with onco-haematological diseases.

All study sites have medical and paramedical teams who are experienced in the field of immunocompromised patients and hemophagocytic syndrome.
According to previous studies conducted by our group, 1000 onco-haematology patients are admitted annually in the participating centres. The proportion of HS patients in the coordination centre of the study is 1.5% of admitted patients (12 patients per year). In the other participating centres, around 5 patients per year are admitted for HS.

	Number of participants
Total number of participants to be included	42
Number of centres	9
Enrolment period (months)	18
Number of participants/centre	4.7
Number of participants/centre/month	0.26

6.4 Termination rules

6.4.1 Criteria and procedures for prematurely terminating the study treatment

Several situations are possible
- Temporary suspension of treatment: the investigator must document the reason for suspending and resuming the treatment in the participant's source file and the case report form (CRF)
- Premature discontinuation of treatment, but the participant remains enrolled in the study until the end of their participation
- Premature discontinuation of treatment and withdrawal from the study

The investigator must:
- Document the reason(s)
- Collect the assessment criteria at the time of ending participation in the study, if the participant agrees
- Schedule a follow-up for the participant, particularly in case of a serious adverse event.

In the case of a serious adverse event that led to premature and permanent termination of the study treatment, the investigator must notify the sponsor immediately. Notification of a serious adverse event must be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor (see appropriate section related to serious adverse event reporting). The serious adverse event will be monitored until it is resolved. As a Data Safety Monitoring Board has been created, the committee can specify and/or validate the follow-up methods.

If, during the course of his/her participation in the study, the participant presents one of the following exclusion criteria, then the study product/procedure must be discontinued but the participant will continue to be monitored for the study.

Exclusion criteria:
- Moribund, defined by a life expectancy < 48 hours;
- Pregnant or lactating patients (Women of childbearing potential must have a negative urine or blood Human Chorionic Gonadotropin pregnancy test prior to trial entry);
- No affiliation to health insurance;
- Known hypersensitivity to ruxolitinib;
- Lactose intolerance;
- Hypersensitivity to cellulose, microcrystalline; magnesium stearate; silica, colloidal anhydrous; sodium starch glycolate (Type A); povidone K30; hydroxypropylcellulose 300 to 600 cps,
- Pre-existing decisions of withholding/withdrawing care,
- History of progressive multifocal leukoencephalopathy
- Uncontrolled cutaneous cancer
- Persons under psychiatric care that would impede understanding of informed consent and optimal treatment and follow-up
- Adults subject to a legal protection measure (guardianship, curatorship and safeguard of justice)
- Patients deprived of their liberty by a judicial or administrative decision

6.4.2 Criteria and procedure for premature withdrawal of a participant from the study

- Participants may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead

If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.

- If a participant exits the study prematurely, and if the participant agrees, state the procedure and schedule for collecting the data required by the protocol (primary endpoint, secondary endpoints, safety assessment) (NB: this must be stated in the information and consent form)
- State how premature exit from the study will affect the participant's ongoing care (state exactly what the participant will be offered).
- In case of serious adverse events, see the corresponding section on vigilance

The case report form must list the various reasons why the participant has discontinued the study:

- ☐ Lack of efficacy
- ☐ Adverse reaction
- ☐ Another medical issue
- ☐ Personal reasons of the participant
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

6.4.3 Follow-up of participants following premature withdrawal from the study

If a participant discontinues the study, this will in no way affect their usual care for their condition.
In the event of serious adverse events following premature and permanent discontinuation of treatment and participation of the patient in the study; see section 6.4.1

6.4.4 Full or partial discontinuation of the study

AP-HP as sponsor or the Competent Authority can prematurely discontinue all or part of the study, temporarily or permanently, further to the recommendations of the Data Safety Monitoring Board in the following situations:

- first of all, if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the treatment arms or if there is a discrepancy in the serious adverse reactions between the treatment arms, requiring a reassessment of the benefit-risk ratio for the study
- if an interim analysis confirms the efficacy of one of the treatment arms or, alternatively, the lack of efficacy

Similarly, AP-HP, as the sponsor, or the Competent Authority may decide to prematurely discontinue the study due to unforeseen issues or new information about the product, in light of which the objectives of the study or clinical programme are unlikely to be achieved.

AP-HP as sponsor reserves the right to permanently suspend enrolment at any time if it appears that the inclusion objectives are not met.

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority and to the Ethics Committee without undue delay but not later than in 15 days of the date of the temporary halt or early termination. It shall include the reasons for such action and specify follow-up measures, along with recommendations from the Data Safety Monitoring Board in the case of substantial modification.

7 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

7.1 Description of the investigational medicinal product(s)

Ruxolitinib (Jakavi®) tablets, commercialized by Novartis Pharma will be used for this study.
Patients will receive oral ruxolitinib twice a day (10 mg x 2 during 28 days) in association with standard of care in HS.

Presentation
The pharmaceutical form consists of white round tablets of 5 or 10mg. Excipient with known effect: each tablet contains 285.80 mg lactose monohydrate. This medicine contains less than 1 mmol sodium (23 mg) per tablet.

Mechanism of action
Ruxolitinib is a selective inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2. These mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function.

Pharmacodynamic effects
Ruxolitinib inhibits cytokine-induced STAT3 phosphorylation in whole blood from healthy subjects and patients with myelofibrosis or polycythemia vera. Ruxolitinib resulted in maximal inhibition of STAT3 phosphorylation 2 hours after dosing which returned to near baseline by 8 hours in both healthy subjects and MF patients, indicating no accumulation of either parent or active metabolites.
Ruxolitinib is mainly metabolised by CYP3A4 (>50%), with additional contribution from CYP2C9.

Pharmacokinetics
In clinical studies, ruxolitinib is rapidly absorbed after oral administration with maximal plasma concentration (Cmax) achieved approximately 1 hour post-dose.
The mean volume of distribution at steady state is approximately 75 litres. At clinically relevant concentrations of ruxolitinib, binding to plasma proteins in vitro is approximately 97%, mostly to albumin.
Ruxolitinib is mainly eliminated through metabolism. The mean elimination half-life of ruxolitinib is approximately 3 hours.

Administration
Ruxolitinib is to be taken orally. After oral administration, ruxolitinib is rapidly absorbed and can be given without regard to meals. Ruxolitinib should be then taken every day at the same time, with or without food.
For patients that can't swallow tablets (mechanical ventilated patients), ruxolitinib can be administered through a gastric tube: the tablet is suspended in 40 mL of water, stirred for approximately 10 minutes, and then administered. The tube is flushed and rinsed with 75 mL of sterile water to ensure that the patient receive the full dose [21].
As necessary, tablets could also be crushed and mixed with apple sauce/ yogurt/ grenadine juice or water.

The tablet can be crushed but toxicity still exist therefore precautionary measures of protection are necessary for handler.

7.2 Description of dose modifications

A. Adjusting dosages in specific populations

Renal insufficiency
No specific dose adjustment is needed in patients with mild or moderate renal impairment.
In patients with severe renal impairment (creatinine clearance less than 30 ml/min) the recommended starting dose should be reduced by 50% to be administered twice daily.
Per manufacturer, ruxolitinib is not removed by dialysis; however, the removal of active metabolite is possible. Therefore, the dose was administered immediately after dialysis sessions on dialysis days [31]. The starting dose for patients with end-stage renal disease on haemodialysis is a single dose of 20 mg or two doses of 10 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis

Hepatic impairment
In patients with any hepatic impairment the recommended starting dose should be reduced by 50% to be administered twice daily.

Elderly patients (≥65 years)
No additional dose adjustments are recommended for elderly patients.

B. Dose reduction for adverse events

Organ toxicities are relatively common in HS patients: liver tests, hemostasis parameters and kidney function are frequently disturbed.
Any adverse event must be assessed to determine whether it is suspected to be related to ruxolitinib treatment. Ruxolitinib dose adjustments are only required for adverse events that are suspected to be related to the study drug. This has particular relevance in evaluation of blood cells count, as cytopenias are often seen in HS and may be related to macrophage activation in the bone marrow or to etoposide-induced toxicity.

In addition to the investigator responsible for the participant, an adjudication committee, made of two independent experts, will review all severe adverse events (grade ≥3) to assess whether they are related to ruxolitinib or adjunctive treatments (etoposide, chemotherapy…).

Dose reductions or interruptions for toxicity are permitted in order to allow the subject to continue on the study treatment. Dose adjustments for different ranges of toxicity are described in the table below.

Table: criteria for dose reduction/interruption of ruxolitinib for adverse events suspected to be drug-related *(adapted from Zeiser et al, NEJM 2021)*

Toxicity	**Recommendations**
Neutropenia (attributed to ruxolitinib), ANC = absolute neutrophils count	
Grade 1 (ANC < 1500/mm^3)	Maintain dose level
Grade 2 (ANC < 1000/mm^3)	Maintain dose level
Grade 3 (ANC < 750/mm^3)	Decrease one level until resolution ≤ grade 2, then resume initial dose level
Grade 4 (ANC < 500/mm^3)	Hold dose, restart and decrease one level until resolution to ≤ grade 3, then resume initial dose level if ≤ grade 2
Thrombocytopenia (despite adequate transfusional support)	

Grade 1 (platelets < 75000/ mm^3) Grade 2 (platelets < 50000/ mm^3) Grade 3 (platelets < 25000/ mm^3) Grade 4 (platelets < 20000/ mm^3) Grade 4 (platelets < 15000/ mm^3)	Maintain dose level Maintain dose level Maintain dose level Decrease one level until platelets ≥20000/ mm^3, then resume initial dose level Hold dose until platelets ≥20000/mm^3, then restart and decrease one dose level. Resume initial dose level when platelets ≥25000/mm^3
Serum creatinine (see paragraph "dose adjustment in specific populations")	
Grade 1 (creatinine ≤ 1.5 x ULN or baseline) Grade 2 (creatinine > 1.5 x ULN or baseline) Grade 3 (creatinine > 3 x ULN or baseline) Grade 4 (creatinine > 6 x ULN or baseline)	Maintain dose level Decrease one dose level until resolution to ≤ grade 1 Hold dose until resolution to ≤ grade 2, then restart and decrease one dose level. Resume initial dose level when resolution to ≤ grade 1 Hold dose and discontinue patient from study
Bilirubin elevation	
Grade 1 (> 1.5 x ULN or baseline) Grade 2 (> 3 x ULN or baseline) Grade 3 (> 5 x ULN or baseline) Grade 4 (> 10 x ULN)	Maintain dose level Decrease one level until resolution ≤ grade 1, then resume initial dose level Hold dose until resolution ≤ grade 1, then restart initial dose level Hold dose until resolution to ≤ grade 1 and decrease one level
Transaminases elevation	
AST or ALT ≤ 3 x ULN AST or ALT > 3 x ULN AST or ALT > 5 x ULN AST or ALT > 10 x ULN	Maintain dose level Maintain dose level Hold dose until resolution to ≤ grade 2, then resume initial dose level Hold dose until resolution to ≤ grade 2, then restart and decrease one dose level
Asymptomatic lipase elevation	
Grade 1 (≤ 1.5 x ULN) Grade 2 (> 1.5 x ULN) Grade 3 (> 2 x ULN) Grade 4 (> 5 x ULN)	Maintain dose level Maintain dose level Hold dose until resolution to ≤ grade 2, then resume initial dose level (if resolved > 7 days, decrease one dose level) Hold dose and discontinue patient from study
Other adverse events	
Grade 1 or grade 2 Grade 3 Grade 4	Maintain dose level Decrease one dose level until resolution to ≤ grade 2 then resume initial dose level Hold dose and discontinue study treatment

Table: dose reduction steps for ruxolitinib

Current dose	First dose reduction	Second dose reduction
10mg BID	**5mg BID**	**5mg QD**
5mg BID	**5mg QD**	**discontinue**

Reminder: In the case of a serious adverse event that led to dose reduction of the study treatment, the investigator must report it to the sponsor immediately. Notification of a serious adverse event must be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor (Safety Department) (*see appropriate section related to serious adverse event reporting*). As a Data

Safety Monitoring Board has been created, the committee could be referred to specify and/or validate the follow-up methods by the sponsor (Safety Department).

7.3 Description of Additional medicinal product(s) (treatments required to conduct the study)

7.3.1 Etoposide

Etoposide will be used for this study, according to the current recommendations in the most severe patients with hemophagocytic syndrome.
In the most severe forms of HS with life-threatening organ failures the administration of etoposide is recommended by experts opinion [8,9]: "a clear indication for immediate administration of etoposide is severe HLH presenting with imminent organ failure". Etoposide, which remains a corner stone in familial HS [2], is effective in decreasing the cytokine storm since it significantly reduces the level of activated T lymphocytes [10]. Its early use is correlated with a better outcome in a study conducted in children with EBV-associated HS [11]. In adult patients, the use of etoposide as a first-line treatment tended to be associated with increased survival in a retrospective study [6].

Posology and administration
In adult patients with secondary hemophagocytic syndrome, the experts recommend that "a reduced etoposide frequency, from twice weekly to once a week, with or without a reduction in dose from 150 mg/m^2 to 50-100 mg/m^2, should be considered". "Because etoposide is primarily cleared by the kidneys, dose reduction is recommended if renal function is impaired based on age-specific norms" [9].

In our study, etoposide should be used at a dosage of 150 mg/m^2, with dose adjustment in case of renal/liver failure or low albumin level. Etoposide is administered by slow intravenous infusion (usually over at least a 60 minutes period). The intravenous infusion will be administered very slowly, over a 2 hours period, to facilitate hemodynamic tolerance in critically-ill patients since hypotension has been reported as a possible side effect of rapid intravenous injection.
However, as no national or European recommendations have been issued regarding treatment of secondary hemophagocytic syndrome, administration (or not), dosage and duration of administration of etoposide should be performed according to each centre's practices.

<u>Renal Impairment</u>
In patients with impaired renal function, the following initial dose modification should be considered based on measured creatinine clearance.
- >50 mL/min 100% of dose
- 15-50 mL/min 75% of dose
- In patients with creatinine clearance less than 15 mL/min and on dialysis, further dose reduction is likely to be required as etoposide clearance is further reduced in these patients. Since etoposide and its metabolites are not dialyzable, it can be administered pre- and post-haemodialysis.

Contra-indications
- Hypersensitivity to the active substance or to any of the excipients (Acide citrique anhydre, polysorbate 80, éthanol, macrogol 300)

- Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy during etoposide therapy. Etoposide has been shown to be teratogenic in mice and rats
(see Summary of Products Characteristics of the medicinal product for exhaustive information)

7.3.2 Methylprednisolone

Presentation
Methylprednisolone, is available as a powder to be made into a solution for intravenous or administration.

Posology and administration
Methylprednisolone is administered by slow intravenous infusion (over 30 minutes).
In secondary hemophagocytic syndrome, current experts opinion recommend the administration of corticosteroids, with or without etoposide, depending on the severity of the patient and the suspected etiology of hemophagocytic syndrome. The most commonly used and recommended dosages are : Méthylprednisolone 1-2 mg/kg or dexamethasone 5-10 mg/m^2 per day in adults patients [8,9].
In our study, methylprednisolone should be used at a dosage of 1-2mg/kg per day, by slow intravenous infusion.
However, as no national or European recommendations have been issued regarding treatment of secondary hemophagocytic syndrome, administration (or not), dosage and duration of administration of methylprednisolone in this indication should be performed according to each centre's practices.

Contra-indications
Methylprednisolone is generally contraindicated in the following situations (there is, however, no absolute contraindication for corticosteroid therapy for life-saving indications):
- any infectious condition excluding the previous specified indications
- certain progressive viruses (including hepatitis, herpes, varicella, shingles),
- psychotic states not yet controlled by treatment,
- live vaccines, or live attenuated vaccines (yellow fever, tuberculosis, rotavirus, measles, mumps, rubella, varicella, shingles, influenza) in patients receiving doses greater than 10 mg/d of Méthylprednisolone equivalent
- hypersensitivity to the active substance or to any of the excipients (phosphate monosodique dihydraté, phosphate disodique dodécahydraté, hydroxyde de sodium, glucose monohydrate)
- in intrathecal or epidural administration
- haemostasis disorders or ongoing anticoagulant treatment, in case of intramuscular injection.

7.4 Authorised and prohibited treatments (medicinal, additional medicinal, surgical), including rescue medications

Ruxolitinib is primarily metabolized by the cytochrome P-450 (CYP) 3A4 isoenzyme system; therefore, the collective PK/PD data suggest that starting doses of ruxolitinib should be reduced by 50% if co-administered with a strong CYP3A4 inhibitor (such as ketoconazole, high-doses ritonavir, rifampicin, rifabutin, carbamazepine, phenobarbital, phenytoin), whereas adjustments in ruxolitinib starting doses may not be needed when co-administered with inducers or mild/moderate inhibitors of CYP3A4 [32]**.**

The concomitant use of ruxolitinib with fluconazole doses greater than 200 mg daily should be avoided.
More frequent monitoring (e.g., twice a week) of haematology parameters and of clinical signs and symptoms of ruxolitinib-related adverse drug reactions is recommended while on strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzyme.

7.5 Methods for monitoring compliance with the treatment

No blood or urine drug testing is scheduled.

Treatment administration will be done during hospitalization and compliance will be monitored.

Nurses will complete a booklet to record administration and it will be kept in the patient's medical records + eCRF.

In case of patients discharged from hospital before the end of treatment, a patient notebook will be given for the follow-up of observance. The patient must return to D28 for the end-of-treatment visit with the rest of the treatments / blisters and the notebook.

8 EFFICACY ASSESSMENT

8.1 Description of efficacy endpoints assessment parameters

Primary endpoint
Survival with a decrease in SOFA score ≥ 3 points at day 7.

Secondary endpoints
- Survival within 6 months
- Measurements of temperature, ferritin level, CD25 soluble receptor dosage, fibrinogen level, triglycerides level, hemoglobin level, white blood cells count, platelets count (at day 1, 7, 14 and 28)
- Dosages of IL2, IL6, IL10, IL12, GM-CSF, IFN gamma, TNF alpha (at day 1, day 7, day 14 and day 28)
- Incidence of nosocomial infections (viral and bacterial) until day 28
- SOFA score at day 1, day 7, day 14 and day 28
- ICU length of stay (number of days in the ICU from inclusion to ICU discharge or death)
- Hospital length of stay (number of days in the hospital from inclusion to hospital discharge or death)
- Incidence of adverse event, severe adverse event within 28 days. Intensity and frequency of adverse event and severe adverse event according to the WHO Toxicity Grading Scale for Determining The Severity of Adverse Events

8.2 Anticipated methods and timetable for measuring, collecting and analysing the efficacy data

	D1	D7	D14	D28	D90	D180
Survival	X	X	X	X	X	X
Measurements of temperature, ferritin level, CD25 soluble receptor dosage, fibrinogen level, triglycerides level, hemoglobin level, white blood cells count, platelets count	X	X	X	X		
Dosages of IL2, IL6, IL10, IL12, GM-CSF, IFN gamma, TNF alpha	X	X	X	X		
Incidence of nosocomial infections	X	X	X	X		
SOFA score	X	X	X	X		
Intensity and frequency of adverse event and severe adverse event according to the WHO Toxicity Grading Scale for Determining The Severity of Adverse Events	X	X	X	X		

9 SPECIFIC STUDY COMMITTEES

9.1 Steering Committee

- Committee members: Sandrine Valade, Eric Mariotte, Jehane Fadlallah, Sylvie Chevret, Lakhdar Mameri (Chef de projet URC), Sio Audrey (Gestionnaire financière de la DRCI), Chaix Clotilde (PH URC aide projet), Pong Stéphany (Chargé de vigilance), Empana Florence (Pharmacienne de l'AGEPS), Lemadre Elodie (chef de projet du pôle promotion de la DRCI)
- Roles: Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the study. Propose procedures to be followed during the study, acknowledging any recommendations from the Data Safety Monitoring Board, if applicable.
- Operating procedures: meetings at the start, at the intermediate analyses and at the end of the project and possibly on request of the promoter and/or the scientific committee.

9.2 Scientific Committee

- Committee members: Sandrine Valade, Eric Mariotte, Jehane Fadlallah, Sylvie Chevret
- Roles: to define the purpose, to draft the protocol, to suggest modifications to the protocol during the study.
- Operating procedures: regular meetings during protocol writing and analysis.

9.3 Adjudication Committee

- Committee members: Etienne Lengliné (Paris), Ygal Benhamou (Rouen), Ludovic Suner (Paris)
- Roles: to review all severe adverse events (grade ≥3) to assess whether they are related to ruxolitinib or adjunctive treatments (etoposide, chemotherapy…).
- Operating procedures: regular meetings during protocol

10 SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

10.1 Recording and reporting adverse events

10.1.1 Definitions

According to Article 2 of the Regulation (EU) No 536/2014:

- **Adverse event**

Any untoward medical occurrence in a subject, to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

- **Serious adverse event**

Any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death.

- **Unexpected serious adverse reaction**

A serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information.

According to Article 53 of the Regulation (EU) No 536/2014:

- **Unexpected event**

An unexpected event which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions as referred to in Article 42. That notification shall be made without undue delay but no later than 15 days from the date the sponsor became aware of this event.

According to Article 54 of the Regulation (EU) No 536/2014:

- **Urgent safety measure**

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects. The sponsor shall notify the Member States concerned, through the EU portal, of the event and the measures taken.
That notification shall be made without undue delay but no later than seven days from the date the measures have been taken.

10.1.2 The role of the investigator

The investigator must **assess the seriousness of each adverse event** and record all serious and non-serious adverse events in the case report form (eCRF).
The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the intensity** of the adverse events by using a rating scale for adverse events appended to the protocol, i.e., the Common Terminology Criteria for Adverse Events [National Cancer Institute] (CTCAE) version 5.0.

The investigator must **assess the causal relationship** between serious adverse events and the investigational medicinal product, or interventions/procedures added by the study (blood samples).

The method used by the investigator is based on 2 causality terms (EVCTM method):

- Related ("Reasonable possibility")
- Not related ("No reasonable possibility")

10.1.2.1 Serious adverse events that require the investigator to notify the sponsor without delay

The investigator notifies the sponsor without undue delay but not later than within 24 hours on the day the investigator becomes aware of any serious adverse event which occurs during a study that meets the description in article 41 of Regulation (EU) N°536/2014, with the exception of any event which is listed in the protocol and, if applicable, in the investigator's brochure as not requiring notification.

A serious adverse event is any untoward medical occurrence that:

1- results in death
2- is life-threatening to the participant enrolled in the study
3- requires hospitalisation or prolongation of existing hospitalisation
4- results in persistent or significant disability/incapacity
5- is a congenital anomaly/birth defect

Medication errors, pregnancies and uses outside what is foreseen in the protocol, including misuse and abuse of the product, require the investigator to notify the sponsor without delay.

10.1.2.2 Specific features of the protocol

10.1.2.2.1 Other events that require the investigator to notify without delay the sponsor

- **Adverse events deemed "medically significant"**

- Brain haemorrhage
- Severe haemorrhage with shock
- Malignant hypertension, defined as a severe elevation in blood pressure (systolic blood pressure greater than 180 mmHg and diastolic blood pressure greater than 120 mmHg) associated with end-organ damage
- Abnormal liver function test results (> 20 x ULN)
- Increased blood creatine phosphokinase (> 20 x ULN)
- Hypertriglyceridemia > 11.4mmol/L
- Major adverse cardiovascular events such as ischaemic stroke or myocardial infarction, death from a cardiovascular origin
- Pulmonary embolism

The investigator must notify the sponsor without delay on the day the investigator becomes aware of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above).

- ***In utero* exposure**

The investigator must notify the sponsor without delay on the day the investigator becomes aware of any pregnancy that occurs during the study, even if it is not associated with an adverse event.

10.1.2.2.2 Serious adverse events that do not require the investigator to notify the sponsor without delay

These following serious adverse events are only recorded in the case report forms.

A data retrieval of the case report forms (of these serious adverse events) will be performed by the Clinical Research Unit for each Data Safety Monitoring Board (DSMB) meeting and/or every six months and addressed in a reasonably comprehensive manner to DSMB members by email and in copy, to Safety Department (vigilance.drc@aphp.fr).

- Normal and natural course of the condition except events leading to death of the participant :
  - ICU complications : intubation and mechanical ventilation, aspiration pneumonia
  - Anemia, thrombocytopenia, leucopenia, neutropenia ≤ grade 3 (CTCAE)
  - Bleeding, hemorrhages ≤ grade 3 (CTCAE) (except brain hemorrhages and severe haemorrhage with shock)
  - Infections ≤ grade 3 (CTCAE)
  - Lipase increase ≤ grade 3 (CTCAE)
  - ALT, AST increase ≤ grade 3 (CTCAE)
  - Cholesterol, triglycerides increase ≤ grade 3 (CTCAE)

10.1.2.3 Period during which SAEs must be notified without delay by the investigator to the sponsor

The investigator must notify the sponsor without delay of any serious adverse events as defined in the corresponding section:
- from the date on which the participant begins treatment with ruxolitinib,
- throughout the whole follow-up period required for the trial (6 months),
- indefinitely, if the SAE is likely to be due to ruxolitinib (e.g. serious reactions that could appear long after exposure to the medication, such as cancers or congenital abnormalities)

10.1.2.4 Procedures and deadlines for notifying the sponsor

- **Serious adverse events**

The initial notification of an SAE must be provided in a written report signed by the investigator using a SAE notification form specific to the study and intended for this purpose (in the case report form).

Each item in this form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department or to provide further information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results from additional examinations, etc.). These documents must be non-identifying. In addition, the documents must include the following: study acronym, participant's identification number and initials.

Any adverse event will be monitored until fully resolved (or stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the participant has left the study.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department by email (eig-vigilance.drc@aphp.fr). It should be noted that it is

possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99 only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

- the investigator completes the SAE notification form in the e-CRF, then validates, prints, and signs the form before sending it by email;
- if it is not possible to connect to the e-CRF, the investigator should complete, sign, and send the SAE notification form to the Safety Department. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must respond to all requests from the sponsor for additional information.
For all questions relating to the notification of an adverse event, the Safety Department can be contacted via email: vigilance.drc@aphp.fr.

- ***In utero* exposure**

For cases of *in utero* exposure, the investigator will complete the "Notification and Follow-up form for a pregnancy occurring during participation in a study".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy notification, the SAE follow-up reports, and any other documents will be sent to the sponsor according to the same procedures specified herein.

10.1.3 Role of the sponsor

The sponsor, represented by its Safety Department, shall continuously, throughout the trial, assess the safety of the investigational medicinal product throughout the study.

10.1.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- the **seriousness** of all the serious adverse events reported,
- the **causal relationship** between these events and each investigational medicinal product and any other treatments,
  All serious adverse events which the investigator and/or the sponsor reasonably believe may have a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.
- the **expected or unexpected nature** of the serious adverse reactions
  Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the reference safety information is considered unexpected.
  The sponsor, represented by its Safety Department assesses the expected/unexpected nature of a serious adverse reaction based on the information described below**.**

For serious adverse events likely to be related to the investigational medicinal product ruxolitinib and considered expected:

- **refer to SmPC and arguments enclosed in CTIS platform**

For serious adverse events likely to be related to the auxiliary medicinal products etoposide and corticosteroids used in Standard of Care and considered expected:

- refer to SmPC Etoposide Teva® 100 mg/5 ml, solution injectable pour perfusion and the SmPC Solumedrol® 120 mg/2 ml, lyophilisat et solution pour usage parenteral.

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs) via Eudravigilance, within the regulatory time frame, to the competent authority:

- in the case of fatal or life-threatening suspected unexpected serious adverse reactions, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction;
- in the case of non-fatal or non-life-threatening suspected unexpected serious adverse reactions, not later than 15 days after the sponsor became aware of the reaction;
- in the case of a suspected unexpected serious adverse reaction which was initially considered to be non-fatal or nonlife threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction being fatal or life-threatening
- in the uncompleted case of fatal or life-threatening suspected unexpected serious adverse reactions, all additional information to complete this case have to be reported as soon as possible and in any event not later than eight days after the initial report
- All additional, relevant information must be declared by the sponsor in the form of follow-up reports within a period of 15 days starting from when the sponsor had this information.

The sponsor must notify all the investigators involved about any information that could adversely affect the safety of the research participants.

10.1.3.2 Analysis and declaration of other safety data

This means any new information that prompts a reassessment of the risk/benefit ratio of the trial or of the product under investigation, or which could be sufficient to consider changes to the use of the product, the trial procedures or trial documentation, or the suspension, cancellation or amendment of the research trial or of other similar trials.

The sponsor will report in CTIS platform and to ANSM without delay upon knowledge of any emerging safety issue and, if applicable, describe what measures have been taken.

10.1.3.3 Annual safety report

Once a year for the duration of the clinical study, the sponsor must produce an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- a safety analysis for the research participants,
- a description of the patients included in the study (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- summary tables of all the serious adverse events that have occurred since the start of the study.

The sponsor produces one annual safety report (Development Safety Update Report - DSUR) for one clinical trial.

The report must be submitted in CTIS no later than 60 days after the anniversary of the date on which the competent authority authorised the trial.

10.1.4 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) may be established by the sponsor. Its primary mission is to monitor safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The sponsor is responsible for justifying the creation or absence of such a committee to the Competent Authority and to the Ethics Committee).

A DSMB will be established for this trial. The DSMB must hold its first meeting before the first participant is enrolled and ideally before the protocol is submitted to the competent authority and the Ethics Committee.
All missions as well as the specific operating procedures of the DSMB are described in the study's DSMB charter (see below) :

- Safety: To analyse vigilance data (serious adverse events, events of special interest, etc.);
- Efficacy/futility: To provide an opinion on the results of the planned interim statistical analyses in the protocol;
- To provide an opinion on new events;
- To provide an opinion on substantial modifications impacting safety.

The DSMB members are:

- Jean Daniel Chiche (Lausanne),
- Paul Coppo (Paris),
- Audrey De Jong (Montpellier)

The DSMB will operate in accordance with the sponsor's procedures. The DSMB works in an advisory capacity only and the sponsor retains all decision-making authority.

11 DATA MANAGEMENT

11.1 Data collection procedures

During and after the clinical study, all data will be collected by the investigators of each participating centres and clinical research technicians (CRTs). The coordinating centre will conduct an on-site visit and audit of data collection at each ICU during the trial.
The investigators will ensure the persons in charge of monitoring, quality control and auditing or inspecting the interventional study involving human participants have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code).
CRTs will assess the process-of-care indicators for all patients in all ICUs, using handheld wireless electronic devices connected to a central database via a local server (CleanWeb™).
The central coordinating team (Clinical Research Unit Hôpital Saint Louis, INCa Data center – Centre de Traitement des Données INCa) will provide all CRTs with specific data collection training for this study.

11.2 Identification of data recorded directly in the CRFs which will be considered as source data

Data will be encrypted to ensure confidentiality. The persons responsible for the quality control of clinical studies (Article L.1121-3 of the Code de la Santé Publique [French Public Health Code]) will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular their identity and the results obtained.
During and after the research involving human participants, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-identifiable.

11.3 Right to access data and source documents

11.3.1 Data access

In accordance with GCPs and appendix 1 of the European Regulation N°536-2014:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority
- the Sponsor declares that investigators and participating institution will ensure the persons in charge of monitoring, quality control and auditing or inspecting the clinical trial have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force

11.3.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in accordance with the regulations in force by the investigator or by the hospital in the case of a hospital medical file.

11.3.3 Data confidentiality

The persons responsible for the quality control of clinical studies will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy.

During and after the clinical trial, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-identifying.
Under no circumstances shall the names and addresses of the participants involved be shown. The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.4 Data processing and storage of research documents and data

11.4.1 Identification of the data processing manager and location(s)

The database will be handled by, and only by, Pr Sylvie Chevret, who will be responsible for data storage, the statistical analysis, and the tables and figures for the study report. She will be in close contact with the Data Safety and Monitoring Board and with the statistical editors of the journal to which the study report will be submitted for publication.

11.4.2 Data entry

Non-identifying data will be entered electronically via a web browser.

11.5 Data ownership

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

12 STATISTICAL ASPECTS

12.1 Description of statistical methods to be used including the timetable for the planned interim analyses

All primary analyses will be based on an intent-to-treat principle. A flowchart of the study will be reported, with summary statistics at enrolment, treatment received, and protocol deviations.

Primary endpoint. Interim analysis will be based on the first 21 enrolled patients, at day 7 after the 21th inclusion. Based on these 21 patients, if there are 11 responses or less, the trial ends with the conclusion of futility; if there are 17 responses or higher, it ends with the conclusion of efficacy; otherwise, it continues with 21 additional subjects; efficacy will be demonstrated if there are at least 27 responses overall.

Secondary endpoints. Terminal analysis will present point estimates of secondary outcome measures, with 95% confidence intervals, based on statistical estimators adapted to the type of endpoints:
Overall survival curves will be estimated by the Kaplan Meier method; incidence of nosocomial infection and of adverse event (AE) will use a competing framework where ICU death or discharge treated as competing risks; cumulative hazard of nosocomial infection and AE based on Andersen-Gill approach will allow to model all repeated events per patient if any; longitudinal measures of SOFA, temperature, ferritin level, CD25 soluble receptor dosage, fibrinogen level, triglycerides level, hemoglobin level, white blood cells count, platelets count (at day 1, 7, 14 and 28) and of dosages of IL2, IL6, IL10, IL12, GM-CSF, IFN gamma, TNF alpha will be analyzed in joint models for longitudinal and survival data.

12.2 Calculation hypotheses for the number of participants required and the result

A Fleming 2-stage design with 42 patients tests the null hypothesis that response rate is $\leq$ 0.50 versus the alternative that it is $\geq$ 0.75 with a 80%-power, and a 5% two-sided type I error rate.
The hypotheses were set based on the literature on the prognosis of those patients, as well as from our series of 186 patients admitted to our ICU from 2007 to 2021. These data allowed to set the null hypothesis of no treatment benefit (that is, an improved rate at most of 0.50 in the control arm). The alternate hypothesis of treatment potential effect (that is, at least an absolute 0.25 difference in the rate of success- that is a survival status with improved SOFA of at least 3 points on day 7-, increased up to 0.75). Such a large improvement was derived from the literature on the effect of ruxolitinib, which has been shown successfully used to treat severe immune-mediated disease such as graft vs host disease [33] or secondary HS [20].

12.3 Anticipated level of statistical significance

Two-sided type I error rate at 0.05.

12.4 Statistical criteria for termination of the study.

See interim analysis above.

12.5 Method for taking into account missing, unused or invalid data

No missing data is expected in the main endpoint.
Missing data on secondary endpoints will be handled by methods adapted to censoring (Kaplan-Meier estimator, competing risks analyses, joint models). If no possible, sensitivity analyses to the imputed outcomes will be performed.

13 QUALITY CONTROL AND ASSURANCES

Every clinical trial sponsored by AP-HP is ranked according to the projected risk incurred by study participants using the classification system specific to AP-HP sponsored clinical trial.

13.1 General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation centres.

For this purpose, the sponsor shall assign Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study locations, after having carried out the initial visits.
The purpose of monitoring the study, as defined in Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the rights, safety and protection of the research participants are met
- the data reported are exact, complete and consistent with the source documents
- the study is carried out in accordance with the protocol in force, the GCPs and the statutory and regulatory provisions in force

13.1.1 Strategy for centre opening

The strategy for opening the centres established for this study is determined using the appropriate monitoring plan.

13.1.2 Scope of centre monitoring

In the case of this **D** risk study the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore, in agreement with the coordinating investigator, the sponsor has determined the logistical score and impact, resulting in a study monitoring level to be implemented: level D.

13.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI (Clinical Research and Innovation Department) and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits carried out by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the monitoring level:

- written consent
- compliance with the study protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used
- primary outcome measure

13.3 Case report forms

All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.
When the investigators complete the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
The investigator must archive a copy of the authenticated document that was issued to the sponsor.

13.4 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

These non-compliances will be managed in accordance with the sponsor's procedures.

The sponsor shall notify the Member States concerned about a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach through the EU portal without undue delay but not later than seven (07) days of becoming aware of that breach.

13.5 Audits/inspections

The investigators agree to consent to the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the grounds of medical secrecy.

An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

13.6 Principal Investigator's commitment to assume responsibility

The investigators will have three main responsibilities:

a) Before starting the study in the ICU, the local investigator must inform all members of the ICU team (physicians and nurses) and referring physicians in the hospital about the study,

in particular by showing them a set of slides provided by the principal investigator to describe the study;

b) The local investigator must screen all patients admitted to the ICU with HS to determine whether the study inclusion and exclusion criteria are met. Then, the local investigators must collect written informed consent from the patient. Patients who are incompetent at the time of study inclusion will be asked whether they consent to continued participation in the study as soon as they regain competence.

c) The local investigator must guide the CRT in matters of data entry and collection of all relevant information, check the accuracy of collected data, and alert the principal investigator and sponsor about any unexpected outcomes or adverse event.

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (*Répertoire Partagé des Professionnels de Santé*, Collective Database of Health Professionals, for France). The CV must include any previous involvement in clinical research and related training.
Any conditions, such as economic interests and institutional affiliations that might influence the impartiality of the investigators shall be presented.

Each investigator will commit to comply with legislation and to conduct the study in line with GCP, in accordance with the Declaration of Helsinki. Each investigator will give the sponsor's representative a GCP certificate dated fewer than three years ago.

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

13.7 Suitability of the facilities

Before starting the study, each clinical trial sites will give the sponsor's representative a duly justified written statement on the suitability adapted to the nature and use of the investigational medicinal product and including a description of the suitability of facilities, equipment, human resources and description of expertise.

13.8 Pharmacist's commitment of responsibility

Not applicable

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing research participants and obtaining their consent

According to article 29 of European regulation N°536/2014, No clinical trials on medicinal products for human use can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in article 29.2 of the European Regulation.

Special circumstances *(Studies in emergency situations: Article 35 of the European regulation N°536/2014):* if the person is physically unable to give his or her written consent, consent may be witnessed, in descending order of priority, from a trustworthy person, a family member or a close relative. These persons must be fully independent of the investigator and of the sponsor.

Informed consent will be searched for eligible patients. Information note will be given by the investigators to the patient (when his/her condition will allow) or to family member or a close relative for patients. Study investigator will inform competent patients of the study, its purpose, its potential benefits and risks. Patients who consent to participate will be included.
For patients who fulfill inclusion criteria and are unable to consent, investigators will try to obtain consent from their legal representative. Patients unable to consent in whom legal representative consent will be included. Deferred consent of the patients will be obtained as soon as patient regain competency.
According to French law specifications for emergency inclusion, when the close relative or family member is absent, a waiver of consent will be asked to the Ethical Committee to include the patient. As soon as possible, family member or close relative will be asked to give his or her consent for continuation of the trial, and the patient's himself when his or her condition will allow it.

14.2 Authorisation for the research location

In France, the study will be carried out in treatment units on individuals presenting a clinical condition for which the units are specialised and who require interventions that are routinely performed at those units. Therefore, the research location does not require specific authorisation.

14.3 Legal obligations

14.3.1 Role of the sponsor

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 and all national Laws. Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

14.3.2 Request for authorisation

Prior to starting the study, AP-HP, as sponsor, must obtain authorisation from the Competent Authority and the Research Committee for this clinical trial on medicinal product for human use within the scope of its authority and in accordance with in force legislation and regulatory requirements.

14.3.3 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended "Informatique et Libertés" law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

- Request for authorisation by the CNIL (French Data Protection Agency)

This research is not governed by the CNIL "Reference Method" (MR-001) because

As the processing of personal data for this study is not governed by the MR 001 Reference Method, the sponsor must obtain approval from the CNIL, because of emergency situation enrolment in accordance with Article L.1122-1-2 can be carried out in the case where the patient could not consent and family members/trustworthy person is not be present.

14.3.4 Start of the Clinical Trial

The sponsor shall notify each Member State concerned of the start of a clinical trial and the start of the recruitment through the EU portal. That notification shall be made within 15 days from the start of the clinical trial.

14.3.5 Amendments to the Clinical Trial

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain approval from the Ethics Committee) and authorisation from the competent authority within the scope of their respective authorities, before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

14.3.6 End of the Clinical Trial

The end of the Clinical Trial corresponds to the end of the participation of the last person who participate to the Clinical Investigation.

14.3.7 Summary of the results of the clinical trial

According to article 37.4 of the European regulation n°536/2014, irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the CTIS a summary of the results of the clinical trial. This summary shall be accompanied by a summary written in a manner that is understandable to laypersons.

14.3.8 Archiving

Specific documents for a clinical trial on medicinal product for human use will be archived by the investigator and the sponsor for 25 years after the end of the research.

This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- A sealed envelope for the sponsor, containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- "Study" binders for the Investigator and the sponsor, including (non-exhaustive list) :
  - the successive versions of the protocol (identified by the version number and its date), and any appendices
  - the competent authority authorisations and Research Ethics Committee decisions

- any correspondence
- the enrolment list or register
- the appendices specific to the research
- final study report

- The data collection documents

15 FUNDING AND INSURANCE

15.1 Funding sources

PHRC-K 2022 (Hospital Funding for Clinical Research).

15.2 Insurance

Pursuant to Article L.1121-10 of the Code de la Santé Publique (French Public Health Code), insurance policies must guarantee the civil liability of the sponsor and that of any contributor and cover pecuniary consequences of damages arising from the study involving human participants.

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GLOBAL SE through the insurance broker BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article 76(1) of regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 and Article L.1121-10 of the *Code de la Santé Publique* (French Public Health Code).

16 PUBLICATION RULES

16.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is unimportant
- However, if the study is funded in the context of an internal AP-HP call for tender, the first affiliation must be "AP-HP"
- Each of these affiliations must be identified by an address and separated by a semicolon (;)
- The AP-HP institution must feature under the acronym "**AP-HP**" first in the address, specifically followed by: **AP-HP**, hospital, department, city, postcode, France.

16.2 Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

- "The sponsor was Assistance Publique – Hôpitaux de Paris (Direction de la Recherche Clinique et de l'Innovation)"

16.3 Mention of the financial backer in the acknowledgements of the text

"The study was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC K 2022 (French Ministry of Health)"

This study has been registered on the website http://clinicaltrials.gov/ under number *(add the registration number when the study is registered)*.

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List of addenda

17.1 List of investigators

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17.2 Serious Adverse Events notification form

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Serious Adverse Event (SAE) form for a clinical trial conducted on an investigational medicinal product or a related product involving human subjects**	**SECTION FOR THE SPONSOR USE ONLY** **INTERNAL SAFETY REFERENCE:** GED Reference: REC-DTYP-0385

Please return this form (4 pages) completed and signed as soon as the investigator becomes aware of the SAE without delay to the Safety Department of the DRCI by mail (eig-vigilance.drc@aphp.fr)
It is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99 only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

Initial report ☐ **Follow-up report** ☐ **Follow-up number** |__|__|

1. Clinical trial information	
Acronym: JAKAHDI	**Date of report:** |__|__| |__|__| |2|0|__|__| dd mm yyyy
Sponsor study number: APHP 220919	**Date the investigator became aware of the SAE:** |__|__| |__|__| |2|0|__|__| dd mm yyyy
Risk: D	

Full title of the clinical trial: **JAK inhibitor in Acquired Hemophagocytic synDrome in the Intensive care unit**

2. Clinical investigation center information	
Center name:	Investigator (last name/name): .....
City and address:	
Department:	Phone: ..... Mail: .....

3. Identification and medical history of the subject	
Subject identification number: |__|__|__| - |__|__|__|__| - |__| -|__| Center No. - Selection order No. - initial last name - initial name	**Please provide any medical, surgical or family history which may impact the assessment of the case (medical anonymized documentation to provided as appropriate):** .....
Sex: ☐ M ☐ F Date of birth: |__|__||__|__|__|__| mm yyyy	
Weight: |__|__|__| kg Height: |__|__|__| cm Age: |__|__|__|years	**Principal etiology(ies) identified for the acquired hemophagocytic syndrome:** ☐ No etiology found (yet) ☐ See below: .....
Inclusion date: |__|__| |__|__| |2|0|__|__| dd mm yyyy	

4. Investigational Medicinal Product (IMP) administered prior SAE onset

Brand name (preferably) or International Nonproprietary Name	Route (1)	Dosage (specify the dosing unit ex: mg/d)	Start date *(dd/mm/yyyy)*	*Ongoing at the time of the SAE*	End date *(dd/mm/yyyy)*
Ruxolitinib (Jakavi®)	Oral	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|

5. Other medicinal product(s) used to treat the acquired hemophagocytic syndrome

Brand name (preferably) or International Nonproprietary Name	Route (1)	Dosage (specify the dosing unit ex: mg/d)	Start date *(dd/mm/yyyy)*	*Ongoing at the time of the SAE*	End date *(dd/mm/yyyy)*
☐Etoposide ☐Etoposide not administered	IV	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|

☐Methylprednisolone ☐Methylprednisolone not administered	IV	.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

Acronym: JAKAHDI

Patient identification number: |__|__|__| - |__|__|__|__| - |__| - |__|
Center No. - selection order No. - initial last name - initial name

6. Concomitant Medication(s) at the time of the SAE, excluding those used to treat the SAE ***(please fill the table below and the related annex on the concomitant medication(s) as appropriate. Cross out the box if not applicable.)***

➪ **Annex attached to this form:** ☐ Yes ☐ No

Brand name (preferred) or International Nonproprietary Name	Route (1)	Dosage (specify the dosing unit ex: mg/d)	Administration of the medicinal product date *(from dd/mm/yy to dd/mm/yy)*	Ongoing *at the time of the SAE(2)*	Indication	***Action undertaken following SAE onset*** *0: dosage remained unchanged 1: drug withdrawal 2: dosage reduction 3: dosage increasing*	***Causality to the SAE*** *0: not related to the drug 1: related to the drug*
			from |__|__| |__|__| |__|__| to |__|__| |__|__| |__|__|	☐			
			from |__|__| |__|__| |__|__| to |__|__| |__|__| |__|__|	☐			

(1) Route of administration: PO=oral route; IM=intramuscular; IV=intravenous; SC=subcutaneous or other (specify) (2) Ongoing at the time of the SAE

7. Serious Adverse Event [SAE]

Diagnosis: ☐ Definitive ☐ Provisional

.....

Organ(s) affected:

.....

Date first symptoms occurred: |__|__| |__|__| |_2_|_0_|__|__|

Describe the symptoms:

.....

Date of start of SAE:

|__|__| |__|__| |_2_|_0_|__|__|
dd mm yyyy

Onset time: |__||__| hh |__||__| min

☐ *missing data*

Time interval between the last administration of the IMP performed during the clinical trial and the start of the SAE:

|__||__| / |__||__| / |__||__|
dd hh min

Seriousness criteria:

☐ Hospitalization or prolongation of existing hospitalization:

from |__|__| |__|__| |_2_|_0_|__|__|

to |__|__| |__|__| |_2_|_0_|__|__| ☐ *ongoing*

☐ Death
☐ Life threatening
☐ Persistent or significant disability or incapacity
☐ Congenital anomaly/birth defect
☐ Other significant medical event, specify:

.....

The occurrence of the SAE led to:

☐ no action undertaken regarding the IMP
☐ dose reduction to ..... mg/d
☐ permanent withdrawal of the IMP, date of withdrawal: |__|__| |__|__| |_2_|_0_|__|__|
☐ temporary withdrawal of the IMP, date of withdrawal: |__|__| |__|__| |_2_|_0_|__|__|
  ☐ Administration was not resumed yet
  ☐ Resumption date: |__|__| |__|__| |_2_|_0_|__|__|, dose : ..... mg/d

  Recurrence of the SAE after resumption: ○ No ○ Yes, see new SAE form
☐ not applicable (IMP administration was not ongoing at SAE onset)

Has any symptomatic measure been taken?

☐ No ☐ Yes Date: |__|__| |__|__| |_2_|_0_|__|__| Specify: .....

.....

Severity: CTCAE grade: .....

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INTERNAL SAFETY REFERENCE:

GED Reference: **Erreur ! Source du renvoi introuvable.**

Please specify if the SAE is the outcome of:

- A medication error? ☐ No ☐ Yes Date: |__|__| |__|__| |_2_|_0_|__|__|
- An overdose? ☐ No ☐ Yes Date: |__|__| |__|__| |_2_|_0_|__|__|
- A misuse? ☐ No ☐ Yes Date: |__|__| |__|__| |_2_|_0_|__|__|
- Other (specify): ..... ☐ No ☐ Yes Date: |__|__| |__|__| |_2_|_0_|__|__|

Acronym: **JAKAHDI**

Subject identification number: |__|__|__| - |__|__|__|__| - |__| - |__|
Center No. - selection order No. - initial last name - initial name

Outcome of the SAE

☐ **Death** Date: |__|__| |__|__| |_2_|_0_|__|__|
dd mm yyyy
○ unrelated to the SAE
○ related to the SAE

☐ **Not recovered yet**, specify:
○ Stable condition ○ Improvement ○ Worsening

☐ **Resolved:** Date: |__|__| |__|__| |_2_|_0_|__|__|
dd mm yyyy
○ without sequelae
○ with sequelae, specify the sequelae: .....
|__|__| |__|__|
hh min

☐ **Unknown outcome**

8. Other etiology(ies) for the SAE considered by the investigator

☐ No ☐ Yes Specify: .....
.....
.....

9. Additional test(s) performed

☐ No ☐ Yes Please specify date, type and results: [please attach the anonymized reports where
.....
.....
.....

10. According to the investigator, the SAE is (multiple choice allowed)

RELATED to the clinical trial:

☐ **Yes:** ☐ **to the investigational medicinal product: ruxolitinib (Jakavi®)**

NOT related to the clinical trial:

☐ **No:** ☐ **to the disease progression**
☐ **to one (or more) concomitant medicinal product(s) administered, specify: .....**
☐ **to an intercurrent disease, specify: .....**
☐ **other, specify: .....**

Reporter:	**Investigator:**	Department stamp:
Name and function: Signature:	Name: Signature:	

17.3 Pregnancy notification form

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Follow-up form for reporting a pregnancy occurring in a clinical trial**	SECTION FOR THE SPONSOR USE ONLY INTERNAL SAFETY REFERENCE: GED Reference: REC-DTYP-0288

Please return this form (4 pages) completed and signed as soon as the investigator becomes aware of the SAE without delay to the Safety Department of the DRCI by mail (eig-vigilance.drc@aphp.fr)
It is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99 only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

1. Clinical trial identification

Acronym: **JAKAHDI**
Sponsor study number: **APHP 220919**

Initial report ☐ **Follow-up report** ☐ **Follow-up N°** |__|__|

Date of report: |__|__| |__|__| |_2_|_0_|__|__|
dd mm yyyy

Date the investigator became aware of pregnancy: |__|__| |__|__| |_2_|_0_|__|__|
dd mm yyyy

Full title of the clinical trial: **JAK inhibitor in Acquired Hemophagocytic synDrome in the Intensive care unit**

2. Identification of the clinical investigation center

Center name: .....
City and adress: .....
Country: .....
Department: .....

Investigator (last name/name): .....
Phone number: Fax:

3. Identification of subject presenting pregnancy

Subject reference: |__|__|__| - |__|__|__|__| - |__| - |__|
centre n° - selection order n° - surname initial - first name initial

Date of birth: |__|__| |___|___|__|__| mm-aaaa
Inclusion date: |__|__| |__|__| |_2_|_0_|__|__|

Date of last menstrual period: |__|__| |__|__| |_2_|_0_|__|__|
And/or pregnancy start date: |__|__| |__|__| |_2_|_0_|__|__|
dd mm yyyy

Specific case of exposure involving the father: ☐ No ☐ Yes

Subject reference: |__|__|__| - |__|__|__|__| - |__| - |__|
centre n° - selection order n° - surname Initial - first name initial

Date of birth: |__|__| |___|___|__|__| mm-aaaa
Inclusion date: |__|__| |__|__| |_2_|_0_|__|__|
Randomisation date: |__|__| |__|__| |_2_|_0_|__|__|
dd mm yyyy

Randomisation number: .....Treatment number: .....

Exposures during pregnancy:

Tobacco:	☐ no	☐ yes (specify number) :	☐ stopped on (specify date):	☐ ongoing
Alcohol:	☐ no	☐ yes (specify OH units) :	☐ stopped on (specify date):	☐ ongoing
Drug:	☐ no	☐ yes (specify substance) :	☐ stopped on (specify date):	☐ ongoing

Other substances (specify):

4. Maternal history

Medical:	**Surgical:**

Obstetrical: |__|__| gravida |__|__| para
Specify any miscarriages, ectopic pregnancies, abortions, medical termination of pregnancy, stillbirths, congenital malformations (birth defects), non-malformative congenital/neonatal pathologies, etc. *(number, date and nature/reason, if applicable).*

5. Investigational drug administered or not during pregnancy or exposure involving the father ***(delete as appropriate)***

Brand name (preferred) or International Nonproprietary Name	Date of first administration or not administered	Date of last administration Or ongoing	Route of administration(1)	Dose / 24h
Glenzocimab/placebo	|__|__| |__|__| |_2_|_0_|__|__| ☐ Not administered	|__|__| |__|__| |_2_|_0_|__|__| ☐ Ongoing		

(1) Route of administration: O=orally; IM=Intramuscular; IV=intravenous; SC=subcutaneous or other (please specify)

6. Procedures and care added by the research ***(cross out the box if procedures and care have not been performed)***	Date *(dd/mm/yyyy)*	Chronology	
		Before pregnancy	During pregnancy
MRI ☐with contrast agent ☐without contrast agent	|__|__| |__|__| |_2_|_0_|__|__|		
Scanner ☐with contrast agent ☐without contrast agent	|__|__| |__|__| |_2_|_0_|__|__|		
MRA ☐with contrast agent ☐without contrast agent	|__|__| |__|__| |_2_|_0_|__|__|		
ECG	|__|__| |__|__| |_2_|_0_|__|__|		
Endovascular thrombectomie	|__|__| |__|__| |_2_|_0_|__|__|		

Acronym*:*

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INTERNAL SAFETY REFERENCE:

GED Reference: REC-DTYP-0288

Subject reference: \|__\|__\|__\| - \|__\|__\|__\|__\| - \|__\| - \|__\|
n°centre - selection order n° - surname initial - first name initial

7. Concomitant medication(s)				
Commercial name (preferred) or International Non-proprietary Name	Date of first administration	Date of last administration Or ongoing	Route of administration(1)	Dose / 24h
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ Ongoing		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ Ongoing		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ Ongoing		

(1) Route of administration: O=orally; IM=Intramuscular; IV=intravenous; SC=subcutaneous or other (please specify)

8. Pregnancy follow-up

☐ Ultrasounds. Specify date(s) and results:

☐ Other exams. Specify date(s) and results *(attach reports)*:

9. Current pregnancy ☐ (transmit by mail another completed form on outcome of pregnancy)
or Outcome of pregnancy ☐ (complete the box below)

Date: \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\| Term: \|__\|__\| WA \|__\|__\| D

☐ Miscarriage
→ Anatomopathological exams available: ☐ No ☐ Yes, please specify result:

☐ Ectopic pregnancy
→ Anatomopathological exams available: ☐ No ☐ Yes, please specify result:

☐ Abortion → Reason:
→ Anatomopathological exams available: ☐ No ☐ Yes, please specify result:

☐ Delivery: ☐ Spontaneous ☐ Induced ☐ Vaginal ☐ Caesarean

Multiple birth: ☐ No ☐ Yes, please specify number:
Foetal distress: ☐ No ☐ Yes, please specify:
Stillbirth: ☐ No ☐ Yes, please specify:
Placenta normal: ☐ Yes ☐ No, please specify:
Amniotic fluid: ☐ Clear ☐ Other, please specify:
Anaesthesia: ☐ General ☐ Epidural ☐ Spinal anaesthesia ☐ None

10. Newborn information (for multiple births, please complete sections 1, 2, 3, 9 and 10 on a different form and send by mail)

Sex: ☐ Male ☐ Female

Weight: \|__\|__\|__\|__\| grams Height: \|__\|__\|__\| cm Head circumference: \|__\|__\|__\| cm

APGAR: 1 minute: _____ 5 minutes: _____ 10 minutes: _____

Congenital malformation(s): ☐ No ☐ Yes, please specify:		
Non-malformative(s) congenial(s)/neonatal(s) pathology(ies): ☐ No ☐ Yes, please specify:		
Did the newborn receive any specific treatment at birth: ☐ No ☐ Yes, please specify:		
Reporter	**Investigator**	Department stamp:
Name and function:	Name:	
Signature:	Signature:	

17.4 SmPC or Investigator's Brochure

Specify here that the SmPC must have been obtained from the EMA website (http://www.ema.europa.eu/ema/), if absent from this site, the SmPC must have been obtained from the ANSM website (http://agence-prd.ansm.sante.fr/php/ecodex/index.php) and if absent from the ANSM website, use the SmPC from the Vidal compendium.

17.5 Questionnaire or scale

Not applicable.

17.6 Description of the Clinical Trial in the AP-HP Trials Register

Le syndrome hémophagocytaire (SH) est une pathologie rare qui peut être responsable de défaillances d'organes sévères. La physiopathologie repose sur un défaut de cytotoxicité des lymphocytes NK et CD8, conduisant à une activation secondaire incontrôlée des macrophages qui va induire la production excessive de cytokines pro-inflammatoire (ou orage cytokinique). Le SH acquis chez l'adulte est principalement d'origine tumorale (le plus souvent causé par une hémopathie maligne ou induit par une immunothérapie) ou infectieuse. Les recommandations thérapeutiques actuelles reposent principalement sur des études observationnelles et des avis d'experts : aucune avancée thérapeutique n'a été faite depuis des années, expliquant pourquoi la mortalité dans le SH reste élevée, notamment dans les formes les plus sévères (la mortalité en réanimation est rapportée entre 40 et 70 %). Dans les formes de SH réfractaires, l'escalade thérapeutique est inévitable, nécessitant le plus souvent l'administration de traitements lourds et générant une toxicité importante.
Le ruxolitinib est le premier inhibiteur de JAK développé, qui a l'AMM en France au cours du traitement de la myélofibrose et de la maladie de Vaquez. Dans un modèle murin pré-clinique, son utilisation au cours du SH était associée à une réduction des manifestations hémophagocytaires, ainsi qu'à une amélioration de la survie. Les données chez l'Homme sont encore rares mais encourageantes. Récemment, le ruxolitinib a été administré avec succès chez des patients ayant un SH acquis, seul ou en association avec des corticoïdes ou une chimiothérapie. Les inhibiteurs de JAK ont en effet permis une amélioration des manifestations cliniques et biologiques liées au SH, y compris chez les patients les plus sévères. Cependant, les données sont principalement issues de case reports ou de petites séries avec une grande hétérogénéité concernant l'étiologie du SH, la population étudiée et la gravité initiale des patients. Par ailleurs, le profil de tolérance de cette molécule était acceptable, aucun effet secondaire grave n'ayant été rapporté.
Nous souhaitons démontrer que le ruxolitinib, en association avec le traitement de référence du SH, peut améliorer plus rapidement les défaillances d'organes (représentées par le score

SOFA) que le traitement de référence seul, chez les patients ayant une forme grave de syndrome hémophagocytaire acquis.
Les patients âgés de plus de 18 ans, admis en réanimation, avec un diagnostic de syndrome hémophagocytaire acquis (défini par la présence de 5 ou 6 critères de l'HLH-2004 ou un HScore > 200), nécessitant un traitement symptomatique du SH en rapport avec une défaillance d'organe (définie par un score SOFA ≥ 4) seront inclus après information et consentement éclairé. Seront exclus les patients moribonds, non affiliés à la Sécurité sociale et les femmes enceintes.
Il s'agit d'un essai multicentrique de phase II, non contrôlé, basé sur un schéma de Fleming en 2 étapes, avec 42 patients (la première étape se terminera après l'inclusion de 21 patients, et la décision d'arrêter ou de poursuivre les inclusions se fera après une analyse intermédiaire). Le critère de jugement principal est la survie avec une diminution du score SOFA d'au moins 3 points à J7. Les patients recevront du ruxolitinib par voie orale deux fois par jour (10 mg x 2 pendant 28 jours) en association avec le traitement de référence du SH. Lorsque la pathologie responsable du SH sera identifiée, un traitement étiologique sera alors administré à tous les patients.
Les bénéfices attendus pour les patients, dont plus de la moitié ont un cancer, sont une amélioration rapide des défaillances d'organes et de la survie. L'utilisation du ruxolitinib pourrait permettre d'éviter l'escalade thérapeutique chez les patients réfractaires, réduisant ainsi les toxicités liées au traitement. Le syndrome hémophagocytaire, bien que rare, reste un challenge diagnostique et thérapeutique avec une mortalité et une morbidité élevées, pour lequel de nouvelles armes thérapeutiques ayant une faible toxicité sont nécessaires.