CONFIDENTIAL

Randomized prospective trial evaluating the efficacy of the antiCD38 monoclonal antibody isatuximab in the treatment of PCRA by major ABO mismatch after allogeneic hematopoietic stem cell transplantation

ErythroSIM

CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE

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SIGNATURE page for a research PROTOCOL

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Title: Randomized prospective trial evaluating the efficacy of the antiCD38 monoclonal antibody isatuximab in the treatment of PCRA by major ABO mismatch after allogeneic hematopoietic stem cell transplantation

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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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1 SUMMARY

Full title	Randomized prospective trial evaluating the efficacy of the antiCD38 monoclonal antibody isatuximab in the treatment of PCRA by major ABO mismatch after allogeneic hematopoietic stem cell transplantation.
Acronym/reference	ERYTHROSIM
Coordinating investigator	Dr XHAARD Aliénor
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	A quarter of allogeneic hematopoietic stem cell transplantation are performed in a situation of major ABO mismatch exposing patients to the risk of immunological pure red cell aplasia (PRCA) after transplant. PCRA after transplant is defined as anemia with low reticulocytes count (under 10 G/L) after day 60 despite good leucocytes and platelet engraftment, full donor chimerism, associated with the persistence of recipients hemagglutinins (anti-A or anti-B antibodies). Bone marrow evaluation when performed show erythroid hypoplasia. Red blood cells transfusions are necessary every two weeks until remission leading to impaired quality of life (anemia, repeated hospitalization), iron overload, and need for iron chelation therapy. Treatments currently used are inefficient (anti CD20 monoclonal antibodies, EPO, steroids, plasma exchanges, proteasome inhibitors) or at risk of severe acute GVHD (donor lymphocytes infusion). PRCA has been demonstrated to be associated with the persistence of recipient's plasma cells. Anti-CD38 monoclonal antibodies which targets plasma cells secreting hemagglutinins responsible of PCRA are a promising treatment: 6 cases reported in the literature support a rapid and sustain efficacy (Chapuy, NEJM, 2018 Bathini, AmJHematol, 2019, Rautenberg, BMT, 2019 Salas et al. Eur J Haematol 2019, Preethi et al. Blood Cell Mol Dis 2020, Yates et al. Transfusion 2021)) but a prospective randomized evaluation of its efficacy and safety in this context is necessary.
Main objective and primary endpoint	**Main objective:** Efficacy of the treatment of PRCA by isatuximab after allogeneic hematopoietic stem cell transplant compared to supportive care only control group (reduction in PRCA resolution time in days) **Primary endpoint:** Time to obtention of transfusion independence for patients with PRCA: time interval between randomization (corresponding to the M6 post-transplant) and resolution of PRCA (date of resolution of reticulocytopenia) treated or not by the anti-CD 38 monoclonal antibody isatuximab.
Secondary objectives and endpoints	**Secondary objectives** 1/ To evaluate the two arms in term of clinical and biological outcomes:

	- Reduction of red blood cells transfusion needs with Isatuximab - Evolution of iron overload - Adverse events related to Isatuximab in the context of allogeneic SCT (CTC-AE grade ≥ 2 in each group after M6 post-transplant) - Quality of life: functional repercussions of chronic anemia, iterative transfusions and iron overload at d29, 3, 6, 9 months after randomization - Overall survival and without relapse at M6, M9, M12 and M15 post-transplant 2/ To identify prognostic factors of spontaneous resolution of PRCA by major ABO mismatch between D60 and M6 (type of donor, cell stem cell and conditioning regimen, occurrence of acute or chronic graft versus host disease, discontinuation of immunosuppression) 3/ To evaluate the interest of follow-up of group hemagglutinins 4/ To compare both arms in term of-cost effectiveness (cost of isatuximab treatment, hospitalizations, transfusion support and chelation treatments) **Secondary Endpoints:** -Number of red blood cell transfusions after randomization -Ferritin levels at M6, M9 and M15 post-transplant -Adverse events (CTC-AE grade ≥ 2) after randomization -Quality of life questionnaire (EORTC QLQ-C30- v3) at D60, D100, M6, M9, M12, M15 post-transplant -Factors associated with spontaneous resolution of PRCA between D60 and M6 post-transplant - Antibody level (anti A and/or anti B titers) at D60, D100, M6 post-transplant then at each visit d15, d29, d45, and M3, M6, M9 post randomization, - Number of days of hospitalization, transfusions support and chelation treatments
Design of the study	Randomized prospective Phase II clinical trial assessing the efficacy and safety of the antiCD38 antibody Isatuximab in patients with persistent PRCA at 6 months after allogeneic HSCT. Including patients at day 60 after transplant will help to define the factors associated with unresolved PRCA to M6 and thus identify patients that could benefit of Isatuximab treatment earlier in the future. Interim analysis will be performed after observations of 22 events (primary endpoint) in the trial.
Category	*Cat 2: Phase 2*
Population of study participants	Allogeneic stem cell transplant recipient 15 years of age or older with PRCA
Inclusion criteria	Patients: - Aged 15 years or older - Having receiving an allogeneic hematopoietic stem cell transplantation in condition of major ABO mismatch

	- PCRA defined by persistent red blood cell transfusion dependence at day 60 post-transplant with reticulocytes count under 10 G/L despite full donor chimerism and a good leucocytes (>1 G/L) and platelet (>50G/L) recovery - No relapse or progression of underlying disease - Contraception methods must be prescribed during all the duration of the clinical trial and using effective contraceptive methods during treatment for women of childbearing age (continue abstinence from heterosexual intercourse is accepted) and for man during the study treatment period and for at least 5 months after the last dose of study treatment and refrain from donating sperm during this period - With health insurance coverage - Having signed a written informed consent (2 parents for patients aged less than 18)
Exclusion criteria	Patients: - Aged < 15 years - Relapse of underlying disease - Leucocyte chimerism < 95% - PRCA related to Parvovirus B19 infection (positive blood PCR) - Known to be HIV+ or to have hepatitis A, B, or C active infection - Active tuberculosis - Pregnancy (βHCG positive) or breast-feeding. - Patient receiving recombinant human erythropoietin. - Patient receiving proteasome inhibitor (Bortezomib for example). - Patient receiving thrombopoietin receptor agonists (ARTPO). - Patient receiving plasma or plasmapheresis exchanges after transplant. - Planned to receive any investigational drug within 14 days or 5 half-lives of the investigational drug, whichever is longer. - Any clinically significant, uncontrolled medical conditions that, in the Investigator's opinion, would expose excessive risk to the patient or may interfere with compliance or interpretation of the study results. - Hypersensitivity to the active substance or history of intolerance to steroids, mannitol, pregelatinized starch, sodium stearyl fumarate, histidine (as base and hydrochloride salt), arginine, hydrochloride, poloxamer 188, sucrose or any of the other components of study therapy that are not amenable to premedication with steroids and H2 blockers or would prohibit further treatment with these agents. - Who have any debilitating medical or psychiatric illness - Under tutorship or curatorship - Who not understand informed consent for an optimal treatment and follow-up

Experimental treatment	Isatuximab treatment at a dose of 10 mg/kg by intravenous route. The first injection of isatuximab will be performed at randomization (M6 +/- 2 days). A second injection may be performed at d15+/-2d if the reticulocytes <10 G / L, and a third at d29+/-2d if reticulocytes <10 G / L. Patients will be assessed on day 1, day 15, day 29, day 45, 2 months, 3 months, 6 months and 9 months after randomization.
Control group	No treatment, supportive care will be allowed.
Interventions added for the study	Pre-medication before each infusion of Isatuximab Follow-up of hemagglutinin antibody titers (anti A and/or anti B titers) Kinetic of immunologic reconstitution PCR for HBV if donor or recipient had a history of HBV infection
Expected benefits for the participants and for society	Early PRCA remission after first injection of isatuximab, Improvement of quality of life in the treatment group Global costs reduction in the isatuximab arm
Risks added by the clinical trial	No major risks added by the clinical trial and by the experimental treatment. The adverse events expected were the occurrence of reaction during the infusion (fever, chills, asthenia, nausea, desaturation, bronchospasm of grade 1-2, diarrheas of grade 1-2 and the occurrence of pneumonia and hypogammaglobulinemia).
Number of participants included	90 patients, 45 randomized The inclusion period will be increased to include patients (even more than the 90 expected) until to randomize the 45 patients needed, notably if less than 50% of the 90 enrolled patients are still PRCA at M6.
Number of centres	24 centers (pediatrics and adults) in France
Duration of the study	Inclusion period: 36 months Participation period (13 months post-transplant of which 9 months post-randomization) Total duration: 49 months
Number of enrolments expected per site and per month	1,2 patient/year/center (0,10 patient/month/center)
Statistical analysis	A bilateral logrank test considering a sample size of 45 randomized patients in 2:1 (30 in the experimental group with median transfusion independence under H1 of 1.5 months, 15 in the control group with median transfusion independence under H1 of 4.5 months) achieves a power of 86,4% with an alpha risk of 0.05. Considering that only 50% of patients included at D60 will be randomized at 6 months, 90 patients should be included. Interim analysis will be performed after observations of 22 events (primary endpoint) in the trial.
Funding sources	Ministry of Health (PHRC- 2019) Experimental treatment: Free supply by Sanofi Company
Study will have a Data Safety Monitoring Board	Yes

2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 Hypothesis for the study

Pure red cell aplasia (PRCA) through major ABO mismatch is observed in 10% of transplanted patients with a major ABO mismatch (donor A, B or AB and recipient have anti-A and/or anti-B isohemagglutinins). It is commonly defined as the persistence of an erythroblastopenia (reticulocytes lower than 10 G/L, despite a predominantly donor leukocyte chimerism) at 60 days from the transplant.

As patients presenting a PRCA through major ABO mismatch do not produce any red blood cells, transfusions are needed at a rate of two packs of red blood cells every 14 days on average. In 50% of patients, evolution is favorable between day 60 and day 180 due to the natural disappearance of plasma cells producing these antibodies. Other patients will be transfused for a few months to a few years in extreme cases.

Repeated transfusions are associated with an allo-immunization risk, potentially leading to a transfusional deadlock. Other side effects of repeated transfusions are a significant iron overload, requiring chelators (and phlebotomies upon resolution), sometimes with side effects, an alteration of quality of life (repeated day hospitalizations, asthenia arising from chronic anemia, liver damage, heart failure and endocrinological problems if there is a large iron overload) and extra costs.

Treatments evaluated in Anglophone literature – strong doses of corticoids, monoclonal anti-CD20 antibodies, plasmapheresis, proteasome inhibitors – have not proven their efficacy and are responsible for significant side effects, notably increased immunodeficiency. Donor lymphocytes injections may be more effective, but are associated with a risk of acute and chronic graft-versus-host disease (GVHD).

The monoclonal anti-CD38 antibody isatuximab, which targets the CD38+ plasma cells responsible for the synthesis of anti-A and Anti-B isohemagglutinins, could reduce the timeframe for red blood cell recovery in these patients.

The literature concerning the use of anti-CD38 antibodies in patients presenting post-transplant immune-mediated cytopenia (auto-immune hemolytic anemia or erythroblastopenia) that is unresponsive to other treatments supports a rapid response (median of one injection).

This study therefore aims to evaluate the efficacy of monoclonal anti-CD38 antibodies in patients with PRCA through persistent major ABO mismatch six months post-transplant, knowing that these patients, whether they have received treatment or not, have a median transfusional independence of nine months. The hypothesis is to reduce the time to resolution in the isatuximab group to six weeks.

2.2 Description of knowledge of the disease pathology

PRCA through major ABO mismatch is commonly defined as the persistence of an erythroblastopenia (reticulocytes lower than 10 G/L, despite a predominantly donor leukocyte chimerism) 60 days after a hematopoietic stem cell transplantation (HSCT) (Cornillon et al. 2016; Hirokawa et al. 2013a).

One-quarter of stem cell transplantations are carried out in a situation of major ABO mismatch: indeed, the choice of donor, when several potential donors are available, is determined by prioritizing CMV serologies of the donor and the recipient, the sex of the donor when the

recipient is male, and the weight of the donor. ABO compatibility will only be taken into consideration if several donors with identical characteristics for these factors are available, which is relatively rare.

While most studies carried out do not show any differences in terms of overall survival between transplants performed in situations of ABO mismatch or otherwise, in cases of major ABO mismatch there is a statistical delay of red blood cell engraftment. Transfusion independence is obtained later (63 days versus 41 days, p=0.001) (Blin et al. 2010) with a larger number of transfused red blood cells packs (10 versus six, p<0.001) (Mielcarek et al. 2000), whether the patient presents or not a PRCA by major ABO mismatch.

The **physiopathology** of PRCA through major ABO mismatch as part of an HSCT is not fully understood. The persistence of hemolysins related to the recipient group (anti-A or anti-B antibodies) directed against intramedullary erythroid precursors is however considered to be the main etiological factor. These antibodies are thought to inhibit the differentiation and provoke the apoptosis of erythroid precursors at the CFU-E stage, which is the first stage where surface antigens of the ABO system are expressed.

This hypothesis is supported by in vitro studies carried out using bone marrow samples from patients with PRCA through major ABO mismatch. Yasuhiro Ebihara's team has therefore shown that the recipient serum inhibited the in vitro growth of erythroblastic progenitors (using CD34+ cells collected from a recipient presenting post-transplant PRCA through major ABO mismatch) while a normal number of erythroblastic colonies was obtained using the donor serum. The inhibitor of erythropoiesis is therefore present in the recipient serum, which comforts the hypothesis of an inhibition by the hemolysins related to the recipient group.

Another team has studied the persistence of recipient B lymphocytes and plasma cells after an allogeneic HSCT with major ABO mismatch (Griffith et al. 2005). A bone marrow chimerism in plasma cells was carried out at Day 30, Day 60 and Day 100 post-transplant, after cell sorting (CD19- CD38bright CD138bright), associated with a study of myeloid (CD14/CD15+), T lymphocytes (CD3+) and B lymphocytes (CD19+) chimerism in the peripheral blood.

Of the six patients who developed PRCA through major ABO mismatch with a persistence of significant hemolysins titer (>1/8), persistence of mixed bone marrow plasma cells chimerism was observed (5 to 42% of recipient cells), while the myeloid and T lymphocytes chimerism was entirely donor. The B lymphocytes chimerism was mixed in two of the six patients. This comforts the role of the recipient persistent plasma cells in the onset of a PRCA through major ABO mismatch.

Diagnostic: PRCA through major ABO mismatch is defined as the persistence of an aregenerative anemia, with reticulocytopenia (reticulocytes < 10 G/L or 1%) associated with a satisfactory granular and platelet reconstitution and a chimerism mostly of donor origin (Hirokawa et al. 2013a; Helbig et al. 2005; Cornillon et al. 2016). The other causes of PRCA (deficiencies of vitamin B12 or folates and infection with parvovirus B19) are classically eliminated and the persistence of isohemagglutinins in the peripheral blood is sought.

Toxic causes (treatment by valgancilovir or ganciclovir or mycophenolate mofetil) and other viral infections susceptible of disrupting hematopoiesis are also looked for (particularly cytomegalovirus) (Cornillon et al. 2016). Similarly, an underlying relapse of the hemopathy is carried out three months post-transplant in all centers.

The **incidence** reported in published retrospective series varies from 1.6% (Larocca et al. 2006) to 26.4% (Wiesneth 1992; Worel et al. 2000; Zhu et al. 2007; Stussi et al. 2009; Curley et al. 2012; Hirokawa et al. 2013b; F. M. Aung et al. 2013; F. Aung et al. 2016; Wada et al. 2019; Shimuzu et al. 2019). The large disparity observed is probably linked to the

heterogeneous way in which cases are picked (registers, retrospective files studies, etc.) and the definition used by the authors. The less severe cases are probably under-diagnosed as they do not imply a particular attitude from the clinician.

Among series with more than 100 patients in the situation of major ABO mismatch, most had an incidence of 7.5%-8% (F.M. Aung et al. 2013; Stussi et al. 2009). In an exhaustive study carried out between June 2005 and December 2016 at Saint-Louis Hospital on 236 consecutive patients having received an HSCT in a situation of major mismatch, the incidence of PRCA through major ABO mismatch was 9.3% (Longval et al., oral presentation, abstract 096, Congress of the French Hematological Society (SFH), 2019).

The **risk factors** to develop or not a PRCA through major ABO mismatch 60 days post-transplantation are:

- HSCT using a geno-identical donor (Blin et al. 2010; Mielcarek et al. 2000): the median timeframe to the negativity of isohemagglutinins titer is significantly longer in cases of geno-identical transplant, independently of the occurrence of a PRCA (46 days with an unrelated donor, versus 61 days with a geno-identical donor, p=0.016).
- The occurrence of graft-versus-host disease (acute or chronic GVHD) seems to be a protective factor against the occurrence of PRCA through major ABO mismatch and encouraging the negativity of isohemagglutinins titer (patients presenting GVHD had twice as much chance of eliminating their antibodies at Day 100 post-transplant in the Mielcarek study). (Blin et al. 2010; Mielcarek et al. 2000)
- The measured rate of hemolysins pre-transplant could, in some articles, be predictive of an augmented risk of the occurrence of PRCA through major ABO mismatch (threshold >1/64) (Boland et al. 1998; Damodar et al. 2005)
- The data concerning the type of conditioning (myeloablative or otherwise) are conflicting and do not allow us to reach a conclusion.

Therapeutic management:

Despite numerous therapeutic options reported in the literature, to date there is no consensus about how PRCA through major ABO mismatch can be managed. These publications are mostly case reports or more rarely retrospective studies with small patient numbers (Hirokawa et al. 2013b; Helbig et al. 2007; F. M. Aung et al. 2013; Stussi et al. 2009; Gmur et al. 1990). There is no prospective study evaluating the interest of a specific treatment for post-HSCT PRCA through major ABO mismatch.

Preventative treatments: With the exception of the choice of donor, no validated preventative treatment exists. Carrying out plasmapheresis prior to HSCT (F.M. Aung et al. 2013) is controversial, as its impact is temporary. This has sometimes been achieved over a long period in certain centers, with controversial views of the real benefits.

The largest study carried out in Switzerland (Stussi et al. 2009) retrospectively analyzed the achievement of preventative plasmapheresis in cases of major ABO incompatible transplant but also, for some cases, transfusions of ABO-incompatible red blood cells to reduce the rate of anti-A or anti-B antibodies before transplantation. The number of cases of PRCA through major ABO mismatch observed post-transplant was 12 out of 158 patients analyzed, or 8%, which does not differ from the frequency observed without therapeutic intervention.

The techniques used allowed a pre-transplant diminution in the isohemagglutinins rate to be observed in 98 patients (64%). In patients having had a reduction in the isohemagglutinins titers pre-transplant, the frequency of PRCA through major ABO mismatch seems to have been diminished, with three cases out of 98 (3%), versus nine cases out of 55 (16%).

Transfusional support and iron chelation:

Patients presenting a PRCA, whatever its cause, have regular transfusional needs, evaluated at a rate of two packs of red blood cells every 14 days on average, until PRCA is resolved. Few studies have been undertaken into the impact of iron overload with respect to regular transfusions carried out in the post-transplant period. The majority of studies carried out have been interested in the impact of the iron overload (ferritinemia, hepatic overload on MRI scan) prior to transplantation.

A study of 290 patients transplanted between 2000 and 2009 in Switzerland showed that the peak level of ferritinemia increased until three months at most post-transplantation, before diminishing progressively to reach towards the norm five years post-transplantation: a ferritinemia superior to 1,000 µg/L post-transplantation had an adverse impact on survival, independently of usual risk factors (Meyer et al. 2013), and was all the more marked for a persistent hyperferritinemia between 12 and 60 months post-transplantation.

As transplanted patients have, in a large number of cases, iron overload prior to transplantation, attacks on organs due to this overload will be more rapidly observed and a chelation will be quickly required.

Chelation is difficult to use after allogeneic HSCT:

- Deferasirox is responsible for kidney failure (especially if the patient receives cyclosporine), abnormal liver function tests and abdominal pain, sickness and diarrhea, the interpretation of which is complex for patients at risk of GVHD.
- Deferiprone exposes patients to a risk of drug-induced agranulocytosis, so is rarely used with this population at risk.
- Deferoxamine: while it is mostly well tolerated, requires continuous administration by intravenous drip or subcutaneous injection, which is not easily accepted by patients.

In a study of 23 patients (Shimuzu et al. 2019) presenting a PRCA through major ABO mismatch post-transplantation followed for a median of two years, three patients had developed during this time organ damage related to iron overload (two isolated hepatic dysfunctions and one hepatic, cardiac and hematological dysfunction).

Among the 10 patients who received a treatment (exclusively deferasirox), six reported side effects (kidney failure 3/6, gastro-intestinal trouble 2/6 and a cutaneous rash 1/6), causing treatment to be stopped definitively in two cases. The median ferritinemia at the date of the last transfusion for non-treated patients was 2,730 µg/L, versus 1,566 µg/L for treated patients. Most prospective studies evaluating deferasirox post-transplantation have underlined side effects in 40-70% of patients, limiting the dose in most cases and requiring treatment withdrawal in a minority of cases.

The resolution of PRCA through major ABO mismatch is characterized by a rise in reticulocytes above 10 G/L in a few days, with a rapid increase to above 150 G/L.

Once PRCA through major ABO mismatch is resolved, phlebotomies can be proposed, which are most often well tolerated. The frequency is usually monthly or bimonthly for a period of six to 24 months, depending on the initial surcharge. They are most often carried out in hospital, or in exceptional cases by a home-help nurse who has been trained in this practice, if the five first treatments in hospital have been well tolerated.

Curative treatments: The main curative treatments proposed in the literature are detailed below (anti-CD20 antibodies, recombinant erythropoietin, etc.). It should be noted that in most of the cases reported, treatment was carried out relatively early (before day 180), which does not permit us to exclude a spontaneous resolution.

*** Immunotherapy by anti-CD20 antibodies – rituximab**

Rituximab and its biosimilars are used in the treatment of auto-immune cytopenias (especially adult immune thrombocytopenic purpura and auto-immune hemolytic anemia): the hypothesis is that monoclonal antibodies will permit, via the antigen CD20 present at the surface of B lymphocytes, to destroy the B lymphocytes or, according to other hypotheses, to block the maturation into plasma cells, which are responsible for the secretion of isohemagglutinins.

The treatment regime reported in publications most often involves a classic weekly administration of a dose of 375 mg/m^2 per injection for one to four weeks at most, according to response. The treatment was suspended if an increase in reticulocytes count was observed during injections. The results of these studies are summarized in the table below.

References	N	Previous treatment	Anti-A/B titer prior to anti-CD20 treatment	Time between transplantation and anti-CD20 / no. of injections	Anti-A/B titer after anti-CD20 treatment	Time between anti-CD20 and hematological recovery	Side effects
(Maschan et al. 2002)	1	Corticosteroids	1/4	+118 / 1	Not reported	+139	None reported
(Zhu et al. 2005)	1	None reported	1/256	+ 110	1/2	+140	None reported
(Sorà et al. 2005)	1	EPO	1/128	+122 / 4	Undetectable	+171	None reported
(Helbig et al. 2005)	2	(1) DLI (2) EPO	(1)* 1/2 (2) 1/4	(1) +94 / 3 (2) Not reported	Not reported	(1) +133 (2) 31 days after start of treatment	(1) Pulmonary aspergillosis (2) None reported
(Zhidong et al. 2012)	2	(1) EPO (2) EPO	(1) A 1/64 & B 1/16 (2) A 1/2	(1) +277 / 1 (2) +118 / 1	Not reported	(1) +291 (2) +126	None reported

* Concurrent infection with parvovirus B19

Treatment with anti-CD20 antibodies post-HSCT, independently of its indication (PRCA, pre-emptive or curative treatment of EBV-associated lymphoproliferation, etc.) significantly increases the risk of infections, particularly bacterial infections, due to induced deep B lymphocytopenia and hypogammaglobulinemia.

*** Recombinant human erythropoietin (rhEPO)**

Administration of recombinant erythropoietin in patients with a PRCA is intended to stimulate the proliferation and ageing of erythroblasts. In auto-immune PRCA outside of the allogeneic context, the endogenous rates of EPO are above the norm (Fu et al. 2018) and recombinant erythropoietin is not proposed as a treatment (Means 2016).

In cases reported in the literature (articles specifically designed to evaluate the efficacy of this treatment, or data figuring in therapeutic precedents of other evaluated treatments), the choice of rhEPO treatment has most often led to the administration of between 3,000 and 6,000 IU per day. There is no prospective or retrospective study supporting its efficacy.

All the responses are accompanied by a negativity of the rates of isohemagglutinins, suggesting a disappearance of the immune context inducing PRCA through major ABO mismatch and limiting the possible conclusions on the real efficacy of rhEPO in this situation. Moreover, in publications addressing other treatments, the majority of patients are in rhEPO failure.

References	N	Previous treatment	Anti-A/B titer prior to EPO	Time between transplantation and EPO / no. of injections	Anti-A/B titer after EPO	Time between transplant and hematological recovery	Side effects
(Heyll et al. 1991)	1	None reported	1/4	+260 / 15	Not reported	+296	None reported
(Paltiel et al. 1993)	1	Polyvalent immunoglobulins	Anti A 1/16 & anti B 1/4	+232 / 100 (total)	Not reported	+252	None reported
(Fujisawa et al. 1996)	1	None reported	1/16	+265 / 43	Undetectable	+282	None reported

*** Proteasome inhibitor (Bortezomib)**

Proteasome inhibitors (PI) target long-lived plasma cells of the recipient responsible for the persistence of high rates of isohemagglutinins. In the setting of monoclonal plasma cell neoplasia, the inhibitors of proteasome, led by bortezomib (an inhibitor of chymotrypsin-like activity of the proteasome 26S) have proven their efficacy as an anti-plasma cell therapy. Indeed, the inhibition of proteasome 26S prevents this targeted proteolysis and affects multiple cascades of signals inside the cell, finally leading to cancer cells apoptosis.

Most of the data published in the context of PRCA through major ABO mismatch post-transplant are case-reports where reticulocytosis, disappearance of hemolysins and withdrawal of red blood cell transfusions was observed following the introduction of bortezomib. The small number of papers published since the initial publications were made suggests reduced efficacy.

The treatment plan described in the three reported publications was a weekly subcutaneous injection of 1.3mg/m^2 for four weeks.

References	N	Previous treatment	Anti-A/B titer prior to PI	Time between transplantation and PI	Anti-A/B titer after PI	Time between transplant and hematological recovery	Side effects
(Poon et Koh 2012)	1	Rituximab, DLI	1/16	+596 / 4	Undetectable	+726	None reported
(Khan et al. 2014)	1	Corticosteroids, rituximab	1/4	Not reported / 4	Undetectable	Two months after start of treatment	None reported
(Shahan et Hildebrandt 2015)	1	Rituximab, corticosteroids	1/2	+293 / 4	Undetectable	+321	None reported

*** Donor lymphocyte infusion (DLI)**

Donor lymphocyte infusions are most often proposed post-HSCT for hematological malignancies in patients who have not had significant GVHD and present a mixed chimerism or a positive minimal residual disease (so as to prevent a relapse), or for those who are in relapse, as unique treatment or in association with specific treatment, according to the underlying hematological malignancy. Donor T CD3+ lymphocytes (harvested by cytapheresis when the initial donation was made, or most often later) are then injected at an increasing dose (from 1x10^{e5} to 10x10^{e7} CD3/kg of the recipient weight, depending on the context), so as to obtain an effect of the graft against the disease (graft-versus-leukemia effect).

The time period between each injection is at least four to six weeks, because of the GVHD risk. The efficacy of these DLIs in these indications depends on the nature of the underlying hematological malignancy, as well as the indication and occurrence of GVHD.

In the context of PRCA through major ABO mismatch, the objective is to obtain a graft-versus-recipient plasma cells-effect.

DLIs have been reported to be effective in several cases of PRCA through major ABO mismatch that have remained resistant to previous treatments. The doses of DLI were variable between centers (initially $1x10^6$ CD3+cells/kg up to $2.6x10^6$ CD3+cells/kg, depending on cases), with a rise in doses injected according to response (second dose at $5x10^6$ CD3+cells/kg), and performed at least at two month-intervals. Cases reported seem to show efficacy, with the appearance of reticulocytes, and the disappearance of PRCA following one or several DLIs, but in no case are these comparative studies.

This treatment is not free of risk, due to the danger of GHVD and induced morbidity and mortality. Most often, patients treated had a mixed indication (PRCA through major ABO mismatch and prevention of relapse). In non-malignant hematological diseases, where no graft-versus-leukemia effect is necessary; the risk of GVHD is generally considered to be a formal contra-indication to DLI.

References	N	Previous treatment	Anti-A/B titer prior to DLI	Time between transplantation and DLI / no. of injections	Anti-A/B titer after DLI	Time between transplant and hematological recovery	Side effects
(Selleri et al. 1998)	1	IVIG, danazol, corticosteroid, EPO	Anti-A 1/256 and anti-B 1/8	+195 / 2	anti-A 1/4 et anti-B 1/2	+251	Limited cGVHD
(Bavaro et al. 1999)	1	EPO, IVIG, plasmapheresis	1/8	+170 / 1	Not reported	+178	None reported
(Verholen et al. 2004)	1	EPO, plasmapheresis, rituximab	1/128	+275 / 2	Undetectable	+434	None reported
(Ebihara et al. 2007)	1	EPO, corticosteroids, cyclosporine, rituximab, IVIG	1/256	+700 / 2	1/2	+756	None reported

*** Plasma exchange or plasmapheresis**

Plasma exchange in PRCA through major ABO mismatch is designed to induce a depletion of isohemagglutinins in order to raise the inhibition of erythroblastic proliferation and maturation. They consist in achieving, via extracorporeal blood flow, a separation of different blood compartments, particularly plasma, and to remove or filter plasma and replace it with fresh frozen plasma from a healthy donor or albumin. The main risks are of infectious and vascular (one central venous line of sufficient caliber is required).

Among patients presenting a proven PRCA through major ABO mismatch, plasma exchange is most often spectacularly efficacious but temporary if the treatment is not carried on, due to the persistence of plasma cells in the recipient. Plasma exchanges are often carried out intensively (five times per week for the first two weeks, then spaced apart) by an immuno-absorption technique or by standard plasma exchange. Reported cases find that once plasma exchange is initiated, there is a diminution in the concentration of anti-A or anti-B isohemagglutinins in the recipient serum.

References	N	Previous treatment	Anti-A/B titer prior to PEX	Time between transplantation and PEX / no. of PEX	Anti-A/B titer after PEX	Time between transplant and hematological recovery	Side effects
(Or et al. 1991)	2	(1) Corticosteroids (2) None	(1) 1/1024 (2) 1/128	(1) +126 / 1 (2) +154 /	(1) Undetectable (2) Undetectable	(1) +142 (2) Not reported	(1) None reported (2) None reported
(Ohta et al. 1997)	2	(1) Corticosteroids (2) None	(1) 1/32 (2) 1/16	(1) +147 / 1 (2) + 131/ 3	(1) Undetectable (2) Undetectable	(1) +225 (2) +216	(1) None reported (2) None reported
(Worel et al. 2000)	6	(1) to (7) EPO	Median 1/16 (1/4; 1/64)	Median + 118 (+60; +264) / 3 (2;25)	Unspecified	Median +239 (+147; +333)	None reported
(Bolan et al. 2001)	1	EPO	1/32	+191 / 4	1/2	+219	None reported
(Rabitsch et al. 2003)	5	EPO	From 1/4 to 1/16	Median +130 (+62; +195) / Median 17 (9; 25)	Undetectable	+185 (+82; +316)	None reported
(Rabitsch et al. 2003)	2	(1) and (2) EPO	Unspecified	(1) +59 / 12 (2) +79 / 14	(1) and (2) Undetectable	(1) +75 (2) +100	None reported
(Tsai et al. 2004)	1	Corticosteroids	1/8	+305 / 18	1/2	+350	None reported
(Dellacasa et al. 2015)	1	EPO, corticosteroids	1/16	+204 / 5	1/4	+234	None reported
(Sackett et al. 2018)	1	Rituximab, bortezomib, EPO	1/1024	+224 / 14	1/16	+292	None reported

*** Thrombopoietin receptor agonists**

Thrombopoietin receptor agonists, especially eltrombopag, are used to treat refractory aplastic anemia in order to stimulate the proliferation and maturation of hematopoietic stem cells. In HSCT patients, efficacy was reported in patients presenting graft failure (overall bone marrow failure, despite donor chimerism). In some rare cases of genetic erythroblastopenia (Diamond-Blackfan anemia), efficacy has also been reported with an increased dose.

A recent study[42] reported on two patients treated with eltrombopag for a PRCA through major ABO mismatch that was refractory to numerous previous treatment lines. Treatment was introduced at a dose of 75mg/day, then increased to 150mg/day after one to two weeks (one of the patients presented a thrombocytosis, requiring the dose to be reduced again to 75mg/day).

For these two patients, transfusional independence was obtained one to two months after the introduction of treatment, which was then able to be suspended without a PRCA relapse. Isohemagglutinins titers of the two patients before and after the introduction of treatment with eltrombopag were not reported in this publication.

References	N	Previous treatment	Anti-A/B titer prior to aTPO-R	Time between transplantation and aTPO-R	Anti-A/B titer after aTPO-R	Time between transplant and	Side effects

						hematological recovery	
(Busca 2018)	2	(1)EPO, plasmapheresis, rituximab (2) EPO, plasmapheresis, rituximab, bortezomib, cyclophosphamide	(1) 1/64 (2) 1/64	(1)+365 (2)+900	(1) Not reported (2)	(1)+421 (2)+1050	(1) None reported (2) Transitory thrombocytosis

*** Steroids**

Corticosteroids are reported as a first-line treatment in a certain number of cases of PRCA through major ABO mismatch post-HSCT. Some teams have proposed a treatment with high doses (1.5mg/kg/day) of corticosteroids to treat secondary PRCA through major ABO mismatch in order to inhibit the production of isohemagglutinins by the recipient's residual plasma cells.

In a Japanese study describing 46 cases of PRCA through major ABO mismatch, steroids were used as a first line in half of patients. This study (detailed below) hasn't shown benefit of administering a specific treatment for PRCA through major ABO mismatch. The survival of patients who have received this treatment was even slightly reduced compared with non-treated patients.

In this context of major immunodepression, corticosteroids are associated with a risk of infectious complications (bacterial, fungal and viral), as well as severe metabolic problems.

References	N	Previous treatment	Anti-A/B titer prior to CS	Time between transplantation and CS / no. of doses	Anti-A/B titer after CS	Time between transplant and hematological recovery	Side effects
(Yang et al. 2001)	1	None	1/128	+56 / Not reported	Undetectable	+160	None reported
(Fusijawa et al 1996)	1	EPO	1/4	+167 / Not reported	Undetectable	+202	Mechanical hemolysis
$ (Deotare 2006)	1	Corticosteroids (40mg prednisone), rituximab, EPO	1/128	+348 / 4	1/2	+374	None reported

($ high doses of dexamethasone)

*** Studies conducting a comparative evaluation of the benefits of PRCA through major ABO mismatch treatments:**

The principal limits of the data presented below are in the methodology of the publications (cases reports or small series of not necessarily consecutive data, absence of reproducibility from one publication to the other), and the sometimes spontaneous favorable evolution of PRCA through major ABO mismatch, which can lead to the benefit of its resolution being erroneously attributed to a treatment.

A retrospective observational multi-centric study carried out in Japan (Hirokawa et al. 2013b) (questionnaire sent to centers concerning 145 patients having a persistent PRCA through major ABO mismatch at day 100) identified 46 patients (out of 99 questionnaires returned by

the centers) who had a PRCA through major ABO mismatch according to the definition retained below.

Out of these patients, 22 had received a treatment considered to be potentially curative of PRCA through major ABO mismatch (sometimes corticosteroids in a context of GVHD) and 24 had only transfusions. These first-line treatments were a high dose of corticosteroids (12 patients), rituximab (1), erythropoietin (1), and an abnormally rapid decrease in anti-calcineurins (8). After failure of first-line treatment, these patients received corticosteroids (3), rituximab (2), erythropoietin (2), donor lymphocyte infusion (2), cyclosporine (1), mycophenolate mofetil (1) and azathioprine (1).

The authors did not observe any difference in terms of timeframe for red blood cell reconstitution or the number of packed red blood cells transfused between the two groups of patients. Survival without relapse was significantly less good in the group of patients treated and in multivariate analysis having received treatment remained an unfavorable risk factor.

A similar study was carried out in two HSCT centers in Ile de France (Paris region) (Longval et al., 2021. It identified 38 consecutive patients who had developed PRCA through major ABO mismatch, among whom 16 received a treatment specifically designed to treat PRCA through major ABO mismatch (corticosteroids introduced to treat GVHD were not considered as a treatment) and 22 received only transfusions.

Rituximab was used as a first-line treatment in all patients (one to four injections) and donor lymphocyte infusions as a second-line treatment for six patients. The first line was administered at a median of 116 days after the transplant, while the second line was given at a median of 309 days post-transplant.

In multivariate analysis, neither the donor type, pre-transplant isohemagglutinins titer in the recipient, the occurrence of GVHD, or having received treatment were found to be associated with a reduction in terms of timeframe for red blood cell reconstitution. The median number of transfused packed red blood cells was higher in the treatment group. One patient died from GVHD following DLI. Independently of the treatment group, half of the patients had recovered an erythropoiesis at six months post-transplant. For the others, the median timeframe for resolution of PRCA through major ABO mismatch was nine months (minimum of 6.1 months and maximum of 24 months).

At least one case published in the literature reports a persistent PRCA through major ABO mismatch more than three years post-transplant (Volin et Ruutu 1990); in our experience, one patient presented a persistent PRCA through major ABO mismatch which was still persistent at 14 years post-transplant.

These two studies highlight the difficulty of evaluating the efficacy of treatments for PRCA through major ABO mismatch, given that a spontaneously favorable evolution is observed in a number of patients. They highlight the absence of efficacy of certain treatments, which are regularly the focus of positively reported individual case reports (corticosteroids, rituximab).

In the Hirokawa study (Hirokawa et al. 2013b), the rapid decline in immunosuppression was considered to be a therapeutic intervention, designed to induce an graft-versus-recipient plasma cells-effect. This strategy is similar to that used in cases of mixed chimerism in a hematological malignancy, to stimulate alloreactivity, and is similar to the principle of DLI. Immunosuppression withdrawal without GVHD is most often carried out between day 100 and day 180. As half of patients have recovered by day 180 independently of therapeutic attitude, a therapeutic intervention before this date does not seem desirable.

<u>Rational for the use of anti-CD38 monoclonal antibodies in the treatment of PRCA through major ABO mismatch</u>

All experimental and observational data presented above are in favor of a link between PRCA through major ABO mismatch after HSCT and the persistence of the recipient's plasma cells synthesizing and secreting isohemagglutinins responsible for erythropoiesis inhibition.

Anti-CD38 monoclonal antibodies, as opposed to anti-CD20 monoclonal antibodies, directly target the plasma cells, as can be seen by the efficacy of these antibodies in the treatment of plasma cell neoplasms (Lokhorst et al. 2015; Lonial et al. 2016). Unlike bortezomib, whose efficacy is also seen in the treatment of plasma cell neoplasm, the anti-CD38 monoclonal antibodies are susceptible of having a similar efficacy on normal and neoplastic plasma cells. The tolerance profile of anti-CD38 antibodies is also satisfactory, and is more favorable than bortezomib and other proteasome inhibitors that are responsible for sometimes severe neuropathies.

The Six cases reported below (Chapuy et al. 2018; Bathini et al. 2019; Rautenberg et al. 2019 Salas et al. 2019, Preethi et al. 2020, Yates et al. 2021)) suggest that efficacy is rapid (one injection of daratumumab at 16 mg/kg) and in line with the rapid decrease in isohemagglutinins titer in the recipient. The timeframes between the allograft and treatment by anti-CD38 and between the treatment by anti-CD38 and resolution of PRCA through major ABO mismatch in these two patients, as well as pre-treatment isohemagglutinins titers, do not plead for a spontaneous resolution of PRCA through major ABO mismatch.

In the six cases, no related side effect was reported. However, the onset of hypogammaglobulinemia following treatment with daratumumab was not studied in these patients.

Conclusion: PRCA through major ABO mismatch after HSCT occurs in around 10% of transplanted patients who are in a situation of major ABO mismatch. This is responsible for important transfusional needs (two packs of red blood cells every 14 days at minimum, or a median of 43 packs of red blood cells per patient) and a consequent rapid iron overload, an important deterioration in quality of life (anemia, iron overload, iron chelators treatment, repeated hospitalizations) and extra costs.

The efficacy of treatments proposed (corticosteroids, plasma exchanges or immuno-absorption, rituximab, erythropoietin (EPO), bortezomib, thrombopoietin receptor agonists) until recent times in the literature, is not supported by the rare comparative studies carried out, and these treatments are associated with potentially severe side effects.

For patients presenting a persistent PRCA through major ABO mismatch after day 180 post-transplant, a treatment with anti-CD38 monoclonal antibodies seems to be promising, seeing the three cases recently reported, but a randomized study is needed to confirm it. We therefore propose for patients presenting a persistent PRCA through major ABO mismatch after day 180 post-transplant to carry out a randomized study comparing treatment with anti-CD38 monoclonal antibody and a non-interventional arm.

Isatuximab is a monoclonal antibody presenting an efficacious and secure profile, similar to that of daratumumab. Seeing the rapidity of efficacy in the three reported cases, we propose to perform only one injection of Isatuximab at the dose ordinarily used, and to repeat these injections only in cases of failure at day 14 and then day 28 of the first injection. As the rate of reticulocytes is an objective marker of the efficacy of treatment, a placebo is not justified in this study. Potential short- and long-term side effects will be analyzed, particularly the onset of hypogammaglobulinemia.

In order to identify early patients who will not have recovered an efficacious erythropoiesis at day 180, we propose to include patients from day 60: indeed, there is no prospective study allowing us to identify persistent PRCA risk factors. In the long run, this will allow monoclonal

antibodies to be proposed earlier to high-risk patients if their efficacy is confirmed. A cost study for this treatment compared with the cost of transfusional support will be carried out.

2.3 Summary of pre-clinical experiments and clinical trials

1- Efficacy of anti-CD38 monoclonal antibodies in the treatment of PRCA through major ABO mismatch

Six cases of anti-CD38 monoclonal antibodies treatment for a PRCA through major ABO mismatch post-HSCT have been reported in the literature (Chapuy et al. 2018; Bathini et al. 2019; Rautenberg et al. 2019, Salas et al. 2019, Preethi et al. 2020, Yates et al. 2021)).

The first one was published in the New England Journal of Medicine in August 2018 (Chapuy et al. 2018). A 72-year-old man who received a transplant with ABO-major mismatch presented a persistent PRCA through major ABO mismatch at day 390 post-transplant, despite treatment with strong doses of steroids, four weekly injections of rituximab and erythropoietin (EPO).

One week after the first injection of daratumumab at a dose of 16 mg/kg, a resolution of PRCA through major ABO mismatch was observed and transfusions were stopped. Treatment was continued for six weeks in total. With a follow-up at 10 months, no relapse was observed. In this patient, anti-A titer remained high before the injection of daratumumab and went negative just afterwards. No immediate or delayed secondary effect was noted.

The second case was published in June 2019 (Bathini et al. 2019) and found similar results: PRCA through major ABO mismatch was completely resolved at day 411, despite immunosuppression treatment withdrawal and four injections of rituximab, after the first injection of daratumumab at 16 mg/kg. Isohemagglutinins titer was reported to have rapidly diminished after the injection. After four months, the patient remained in remission from PRCA through major ABO mismatch and presented no side effects.

The third case published in September 2019 (Rautenberg et al.) confirms this data with a PRCA through major ABO mismatch case that resolved after the first injection of daratumumab at day 206 post-transplant, despite previous treatment with four rituximab injections from day 77 and immunosuppression withdrawal at day 170. Reticulocytes increased rapidly from the first injection and anti-A titer went from 1/1024 to zero in a few days.

Three others patients (including two children, 17 and 8 years respectively) with nonmalignant diseases (2 with aplastic anemia and 1 with immune deficiency) experienced successful treatment with anti CD38 monoclonal antibodies for similar PRCA after allogeneic HSCT. Theirs histories and treatment details are summarized in the following table.

References	N	Previous treatment	Anti-A/B titer prior to anti-CD38	Time between transplantation and anti-CD38 / no. of doses	Anti-A/B titer after anti-CD38	Time between transplant and hematological recovery	Side effects
(Chapuy et al. 2018)	1	Corticosteroids, rituximab, darbepoetin	1/128	+390 / 6	Undetectable	+390	None reported
(Bathini et al. 2019)	1	Corticosteroids, rituximab, bortezomib	1/256	+411 / 4	1/8	+439	None reported
(Rautenberg et al. 2019)	1	Rituximab	1/1024	+206 / 2	Undetectable	+216	None reported

(Salas et al. 2019)	1	Rituximab, Plasmapheresis, Bortezomib	1/32	+ 18 months / 6	NA	30 days after anti CD39 antibody first dose	None reported
(Preethi et al. 2020)	1	Corticosteroids, Immunogloblins, Bortezomib	1/1024	+163 d	1/128	2 weeks	None reported
(Yates et al.2021)	1	None	1/16	+396 d /3	Undetectable	+426	Fever after second course

2- Another use of anti-CD38 monoclonal antibodies in immune cytopenia post-HSCT

Daratumumab was used in three patients presenting immunological hemolytic anemia post-HSCT refractory to four to nine treatment lines (including a strong dose of corticosteroid therapy, rituximab, plasmapheresis, bortezomib, mycophenolate mofetil, amongst others) (Schuetz et al. 2018). The three patients responded to daratumumab from the first injection. These patients received four to 11 weekly injections at a dose of 16 mg/kg/week. Two responded sustainably. One patient relapsed and died from this complication.

The two other patients remained in persistent remission, presenting a transient hypogammaglobulinemia requiring intravenous substitution of immunoglobulin for two to 12 months afterwards, without it being possible to confirm the exact cause of this hypogammaglobulinemia given the treatments already received. No other severe or delayed side effect was reported.

3- Potential side effects of anti-CD38 monoclonal antibodies in the specific context of an HSCT patient

There are no publications specifically reporting on the side effects of anti-CD38 monoclonal antibodies after HSCT. A certain number of transplanted patients for a multiple myeloma or a plasma-cell leukemia were nonetheless exposed to this treatment due to frequent post-transplant relapses. In order to get a better idea of the risk of specific complications in these patients, we reviewed the data for 25 patients exposed to daratumumab between 2016 and 2019 due to a post-HSCT relapse.

In most cases (24/25) it was a first exposure. The median timeframe between transplantation and treatment with daratumumab was 4.4 years (minimum of 1.1 years and maximum of 8.8 years). Two patients with severe uncontrolled steroid-resistant GVHD, together with a relapse, presented an aggravation of GVHD after the daratumumab injection without the chronology being able to determine if this aggravation was linked to the daratumumab injection. These two patients died two and four months after daratumumab, due to uncontrolled GVHD and hematological malignancy not responding to treatment.

Eleven other patients who presented GVHD, including two with an active GVHD at the time when daratumumab was begun, did not suffer from a relapse or aggravation. These data are not in favor of an increase in the GVHD risk after exposure to daratumumab. In these 25 patients, no specific complication was observed after treatment with daratumumab. Hematological tolerance was excellent.

4- Characteristics of isatuximab and clinical data

The main secondary effects of anti-CD38 monoclonal antibodies have been reported in the context of multiple myeloma treatment, in association with dexamethasone or other anti-

plasma cell therapies in patients suffering from a relapse or refractory to other therapeutic lines.

The most commonly observed side effect is the occurrence of reactions during the injection, which are prevented by a pre-medication. The link between daratumumab and CD38 is responsible for an analytical interference during the Indirect Antiglobulin Test (IAT), due to the presence of CD38 on red blood cells.

This interference with the IAT initially complicated the transfusional management of patients. Nevertheless, in order to ensure optimal care of patients under anti-CD38, complementary techniques have been developed, freeing us from this technical difficulty, while also ensuring the transfusional safety of patients. IATs are now routinely carried out on test panels of DTT-treated red blood.

Isatuximab is a new Ig-G1 kappa anti-CD38 monoclonal antibody (Deckert et al. 2014) that links selectively to a specific epitope of CD38. Pre-clinical studies suggest that Isatuximab can target plasma cells through a combination of mechanisms, including the antibody dependent cellular cytotoxicity, antibody- and complement-dependent cellular phagocytosis and cellular cytotoxicity.

As monotherapy, the main side effects observed (Martin et al. 2017) in a population of patients treated for a multiple myeloma, who had relapsed or failed prior treatment (on average five treatment lines (1 to 13), including in 81% of cases an HSCT) at doses of five to 20 mg/kg every two weeks, were, by order of frequency:

- Cytopenias: anemia, thrombocytopenia and neutropenia (98%, 64% and 45%, respectively, including 20%, 17% and 12% grade 3/4), however, no new cytopenia was described in the context of patients treated for post-HSTC PRCA through major ABO mismatch or post-HSCT immune cytopenia, suggesting a link between the underlying illness and the therapeutic precedents on the one hand, and the occurrence of side effects on the other.
- Fatigue in 37% of patients.
- Nausea in 32% of patients, diarrhea in 20% and vomiting in 17%: only diarrhea has been reported in a cohort of transplanted patients treated for an immune-mediated hemolytic anemia.
- An infection (pneumonia) in 7% of patients, which does not seem to be an increased risk given the underlying illness and neutropenia observed in this context.

These side effects are similar to those observed in patients treated with daratumumab (Salomon-Perzyński et al. 2019) in case of relapse or refractory disease.

Daratumumab seems to be associated with an increased risk of hepatitis B virus (HBV) reactivation. This risk has not been described with isatuximab but should be kept in mind at the moment of selection (pre-transplant HBV nuclear antigen testing is systematically carried out in the donor and the recipient) and randomization (HBV nuclear antigen testing and HHs antigen are systematically carried out at day 100 post-transplant in the recipient). Patients at high risk of reactivation (history of HBV infection in the donor or the recipient) should receive a specific antiviral prophylaxis in line with international and national recommendations.

2.4 Description of the population to be studied and justification of its choice

Patients will be proposed for inclusion if they have received an HSCT carried out in the condition of major or bidirectional ABO mismatch and present an immunological PRCA (defined as persistent transfusional dependence at day 60 post-transplant, with reticulocytes lower than 10 G/L, despite a predominantly donor leukocyte chimerism and a satisfactory

granular and platelet reconstitution), in the absence of relapse or progression of the subjacent hematological disease.

Patients will be included at day 60 post-transplant if they fulfill the above criteria, if they are more than 15 years old, if they have given their consent and if they don't have any exclusion criteria.

The inclusion of patients at day 60 post-transplantation means that the predictive factors of a spontaneous resolution of PRCA through major ABO mismatch six months post-transplantation can be studied, and that patients at high risk of persistent PRCA through major ABO mismatch at six months can be identified.

In the future, these patients could benefit earlier from isatuximab treatment, in order to limit the number of post-transplantation red blood cells transfusions, the number of hospitalizations, the iron overload and the need to carry out iron chelators or phlebotomies. To date, there are no prospective data in the literature that would enable us to identify patients at a high risk of prolonged PRCA through major ABO mismatch.

A spontaneous resolution of PRCA through major ABO mismatch is observed in 50% of patients between day 60 and six month in a context of decline in immunosuppression, conversion to donor plasma cell chimerism and clearance of recipient isohemagglutinins.

Patients who present a PRCA through major ABO mismatch at six months post-HSCT will be randomized between surveillance only and treatment with isatuximab.

Patients aged 15 to 18 will be included in this study given the data available in the literature on this population: 1) PRCA is as common after allogeneic transplantation as in adults and its treatment poses the same problems,(Yates et al. 2021 ; Preethi et al. 2020) 2) data regarding the efficacy and safety of antiCD38 monoclonal antibodies in post allogeneic transplantation or in autoimmune diseases concerned for half of the children (Chapuy et al. 2018, Bathini et al. 2019, Rautenberg et al. 2019, Yates et al. 2021, Preethi et al.2020, Schuetz et al. 2018, Even et al. 2020, Cooling et al. 2019) 3) efficacy and safety of monoclonal antibodies is similar in adults and childrens, 4) seven trials evaluating anti CD38 monoclonal antibodies including children are ongoing at this time according to clinical trial.

2.5 Denomination and description of experimental medication

Isatuximab is a new G1 kappa anti-CD38 monoclonal antibody that selectively links to a specific epitope of CD38. Pre-clinical studies suggest that isatuximab targets cells expressing CD38 by a combination of mechanisms, including antibody dependent cellular cytotoxicity, antibody- and complement-dependent cellular phagocytosis and cellular cytotoxicity.

For further details on isatuximab, refer to chapter seven.

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

A phase-I study has shown that isatuximab monotherapy tolerance was satisfactory up until 20 mg/kg in patients with myeloma who had received numerous previous treatments. The dose of 10 mg/kg by injection was chosen as it corresponds to the most efficacious minimum dose in the studies carried out. Unlike in a malignant disease, the plasma cells that are targeted in our study are not tumor cells and have no specific mechanism to resist apoptosis. This suggests that weaker doses should be sufficient in this context.

In the two cases already published of treatment of PRCA through major ABO mismatch by anti-CD38 monoclonal antibodies, the quick response after one injection is concordant with this hypothesis. The dose of 10 mg/kg appears to us to have the best risk/benefit ratio.

Dosage and administration procedures: The first injection of isatuximab at an intravenous dose of 10 mg/kg will be carried out at the post-transplantation six-month visit (+/- 2 days).

The injection will be carried out in day hospital. A pre-medication of:

- Dexamethasone 40 mg PO or IVL or 20mg IVL≥75 years of age, 15 to 60 minutes before the injection of Isatuximab,
- Paracetamol 1 gr, by ivl, 15 to 60 minutes before the injection of Isatuximab,
- Ranitidine 50 mg IV or equivalent, or omeprazole 15 to 60 minutes before the injection of Isatuximab,
- Dexchlorpheniramine 25 mg to 50 mg ivl or PO, 15 to 60 minutes before the injection of Isatuximab.

Nursing supervision (heart rhythm, blood pressure, temperature, oxygen saturation, chills and dyspnea) will be carried out every 30 minutes during the injection, then at 30, 60 and 90 minutes after the injection.

A second injection may be carried out 15 days after the first one if reticulocytes are lower than 10 G/L at day 14, then in a similar way a third injection may be carried out at day 29 if reticulocytes are still below 10 G/L. If a diminution in reticulocytes is observed at day 28, despite these being above 10 G/L at day 14 (so without injection), a second injection will be performed at day 29.

All injections will take place in day clinic with the same pre-medication.

2.7 Summary of the benefits and foreseeable and known risks for patients consenting to clinical trial

The benefits expected for patients receiving experimental treatment are:

- A reduction in the number of packed red blood cells received after six months post-transplant.
- A reduction in the number of day hospitalizations after six months post-transplant.
- A reduction in iron overload and consequently in the duration of chelation treatment and/or phlebotomies.
- An improvement in quality of life due to anemia resolution, diminished iron overload, and a reduction in day hospitalizations.
- A reduction in the risk of metabolic complications and organ damage linked to iron overload.

Given the data exposed above concerning transplanted patients treated with anti-CD38 monoclonal antibodies, the theoretical risks in respect to the administration of isatuximab are:

- The occurrence of a reaction during the injection (fever, asthenia, nausea, chills, desaturation, bronchospasm): with a pre-medication, this occurs in 45% of cases during the first injection and 8% of cases during subsequent injections. These reactions are all grade 1-2, resolved spontaneously or after treatment (dexchlorpheniramine and/or dexamethasone and/or paracetamol) during the day.
- The onset of diarrhea grade 1-2 in 20% of cases.
- The occurrence of pneumonitis in 7% of cases.
- The occurrence of a hypogammaglobulinemia.

- Hypersensibility to drug used for premedication could also be observed but are very exceptional.

Examinations carried out as part of the follow-up for experimental treatment are similar to those carried out for the follow-up of a transplant. Only supplementary blood samples (15 ml) will be taken at each protocol visit to follow up isohemagglutinins titers and immune reconstitution. No invasive or radiological examination will be required within the protocol.

The absence of grade 2 or more side effects reported in patients treated by anti-CD38 antibodies post-HSCT for a PRCA through major ABO mismatch or an auto-immune hemolytic anemia are in favor of a favorable benefit/risk balance for patients.

3 OBJECTIVES

3.1 Primary objective

The main objective is to demonstrate an efficacy of the treatment of PRCA by isatuximab after allogeneic hematopoietic stem cell transplant compared to supportive care only control group (reduction in PRCA resolution time in days)

3.2 Secondary objectives

The secondary objectives are to:

- Evaluate the two arms in term of clinical and biological outcomes:
  - Reduction of erythrocyte transfusion needs with Isatuximab
  - Evolution of iron overload
  - Adverse events related to Isatuximab in the context of allogeneic SCT (CTC-AE grade ≥ 2 in each group after M6 post-transplant)
  - Quality of life: functional repercussions of chronic anemia, iterative transfusions and iron overload at d29, 3, 6, 9 months of M6 post-transplant
  - Overall survival and without relapse at M6, M9, M12 and M15 post-transplant
- Identify prognostic factors of spontaneous resolution of PRCA by major ABO mismatch between D60 and M6 (type of donor, cell stem cell and conditioning regimen, occurrence of acute or chronic graft versus host disease, early withdrawal of immunosuppressive therapy)
- Evaluate the interest of follow-up of group hemagglutinins
- Compare both arms in term of-cost effectiveness (cost of isatuximab treatment, hospitalizations, transfusion support and chelation treatments)

4 STUDY DESIGN

4.1 *Study endpoints*

Primary endpoint

Time to transfusion independence for patients with PRCA: time interval between randomization (corresponding to the M6 post-transplant) and resolution of PRCA (date of resolution of reticulocytopenia) treated or not by the anti-CD 38 monoclonal antibody isatuximab.

Secondary endpoints

- Number of red blood cell transfusions after randomization in each arm
- Date of last transfusion
- Ferritin levels at M6, M9 and M15 post-transplant
- Adverse events (CTC-AE grade ≥ 2) after randomization in each arm
- Quality of life questionnaire (EORTC QLQ-C30- v3) at D60, D100, M6, M9, M12, M15 post-transplant
- Factors associated to spontaneous resolution of PRCA between D60 and M6 post-transplant
- Hemagglutinins titers (anti A and/or anti B titers) at D60, D100, M6 post-transplant then at each visit d15, d29, d45, and M3, M6, M9 post randomization,
- Number of days of hospitalization, transfusions support and chelation treatments
- Antibody level (anti A and/or anti B titers) at D60, D100, M6 post-transplant then at each visit d15, d29, d45, and M3, M6, M9 post randomization,
- Number of days of hospitalization, transfusions support and chelation treatments

4.2 *Description of clinical trial methodology*

Design of the study

A therapeutic phase II multicenter, national, open, randomized in parallel group with 2/1 ratio (experimental treatment/no treatment).

Number of participating sites

This is a national multi-center study including 22adult and pediatric transplant centers of the SFGM-TC. The arm of randomization will be assigned during the visit of randomization.

Identification of participants

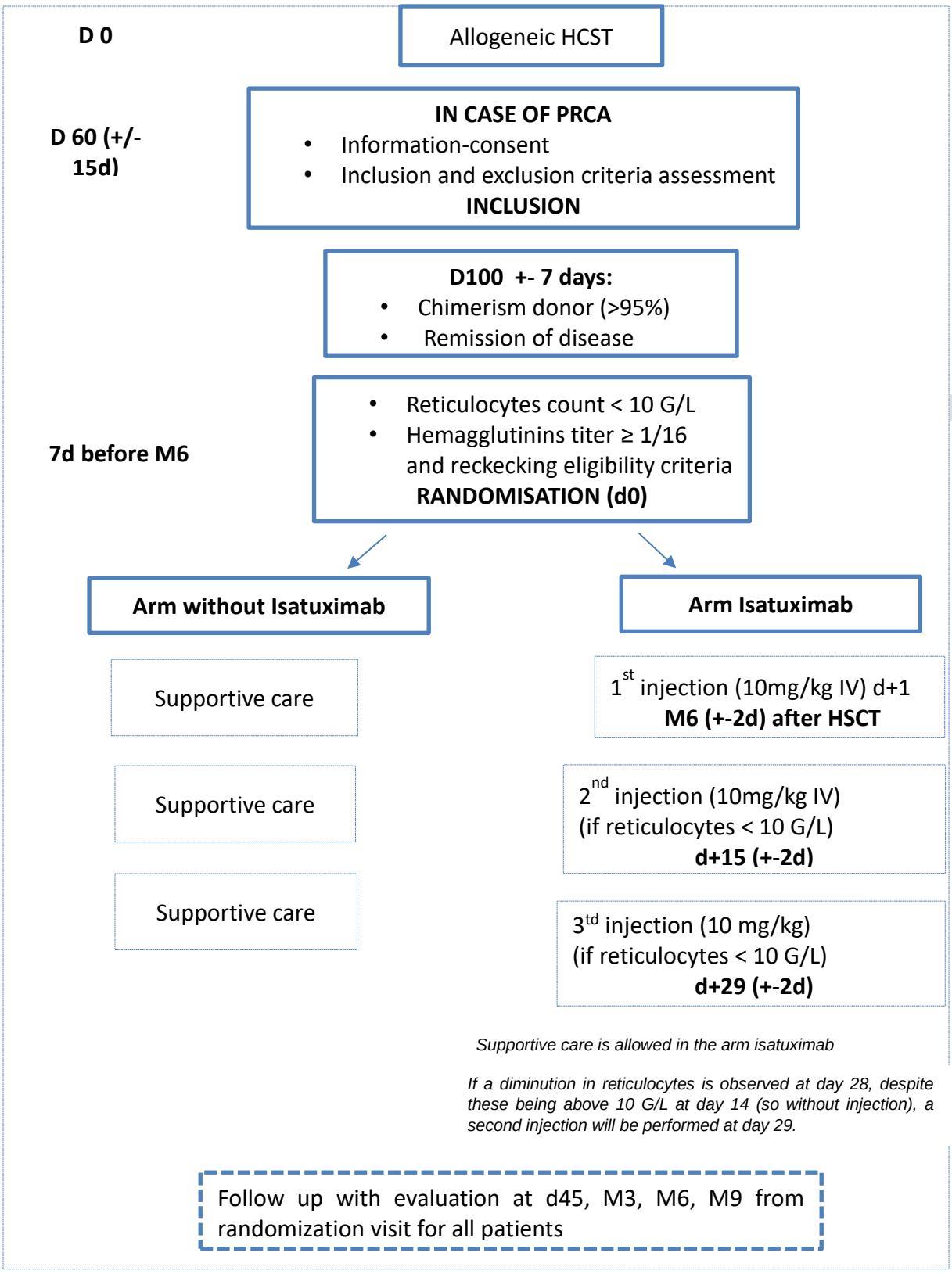
The participants in this clinical trial will be identified as follows:
Site number. (3 digits) - Sequential enrolment number for the site (4 digits) - surname initial - first name initial
This reference number is unique and will be used for the entire duration of the study.

Randomization

Randomization will be centralized (randomization 2/1 experimental group/control group), stratified by centers and performed by the physicians in charge of the patients to using eCRF-linked software for randomization process when all criteria of randomization will be verified (reticulocyte count, and isohemagglutinin titer). The result of randomization will be sent to the physician by email.

5 IMPLEMENTATION OF THE STUDY

5.1 *Clinical trial schema*



5.2 *Inclusion visit*

At D60 of transplant and in case of persistence of PCRA, the investigator checks all the inclusion/exclusion criteria and proposes the study to the patient. Information about the protocol is delivered by the transplant physician in charge of the patient (or 2 parents). The

consent of the patient will be collected after according a time of reflection (about 7 days). A Patient Information Sheet and consent form are given to the patient (or two parents) by the investigator; the original is conserved by the investigator and the third copy for the sponsor. Patients, after signing written informed consent, will be included by the investigators on eCRF CleanWebTM. The physician and project team will receive a confirmation of the inclusion by email.
If the patient can not be included, the reason will be indicated in the investigator file in each centre (identification‘s sheet patient).

It will be noted that the patient can participate to others non interventional clinical trial or be included in other interventional clinical trial (if in following period only and the experimental treatment has been stopped since 30 days).

Who consent	Who informs the individual and collects their consent	When is the individual informed	When is the individual's consent collected
Patient or 2 parents for patients aged less than 18 years. The “Non opposition” of the minor patient should be sought depending on the age of the minor.	The transplant physician (investigator of clinical trial).	At the latest within 7 days before inclusion visit (D60) if persistence of PCRA.	At the latest at the inclusion visit (D60 post-transplant) respecting the minimum reflection time of 24 hours

Collected datas

- Characteristics of patient: date of birth (month/year), age, sexe

- Personal history: hematologic, infectious, drugs allergies, cardiological, hepatological, endocrinological, iron overload

    - Complete history of malignant hemopathy and transplant modalities, serology for hepatitis B (ac antiHbS, ac antiHbc, ag HbS),

- Evolution between D0 et D60
    - Date of neutrophils recovery (PMN > 0.5 G/L3 consecutive days)
    - Date of platelets recovery (platelets > 50 G/L 3 consecutive days)
    - Chimerism at engraftment or day 30
    - Acute or chronic GVHD: date of occurence, maximal grade, steroide response, treatment(s) ,
    - Viral Infections : CMV, EBV, AdV, HHV6 and treatments (INN, dose, duration)
    - Numbers of red blood cells transfusions since the transplant
- At D60 (+/- 15 days) :
    - Clinical datas : weight, performans status, HR, BP, saturation, clinical abnormalities
    - Status of acute or chronic GVH and treatment
    - Hemoglobin (g/dL) PMN (G/L) lymphocytes (G/L) platelets (G/L)
    - Reticulocytes (G/L)
    - Ferritin (µg/l, or ng/mL)
    - Isohemagglutinins anti A et/ou anti B (IgG) titers (results not necessary for inclusion)

- Creatinine, uric acid, transaminases, alkaline phosphatase, gamma-GT and bilirubin
- Treatments ongoing
- Quality of life Questionnaire (EORTC QLQ-C30, v3.0)

5.3 Pre-randomization visit and randomization visit (M6 post-transplant)

All patients who were included at day 60 will be seen in the 7 days prior to the M6 visit (pre-randomization visit) for the randomization unless indication of study exit (see paragraph 6.4). The patient will be randomized **if the reticulocyte count is less than or equal to 10 G/L, and the isohemagglutinins titer is higher or equal to 1/16 and after verification that all the inclusion/exlusion criteria** (see paragraph 6) checked at the inclusion visit (D60) are always respected.

Collected data's:

- At D100 (+/- 7 days):
  - Evaluation of disease
  - Chimerism total blood (and cd3 if available),
  - Immune reconstitution (T, B, NK)
  - IgG, IgA, IgM levels
  - PCR HBV,
  - Hemoglobin (g/dL), PMN (G/L) , lymphocytes (G/L), platelets (G/L)
  - Reticulocytes (G/L)
  - Ferritin (µg/l, ou ng/mL)
  - TSUus, T4L
  - Isohemagglutinines anti A and/or anti B (IgG) titers at D100
  - Creatinine, uric acid, transaminases, alkaline phosphatase, gamma-GT and bilirubin
  - Treatments on going

  - At pre-randomization visit (within 7 days before M6 post-transplant visit and after checking reticulocytes count < 10 G/L, hemagglutinins titer ≥ 1/16 and reckecking eligibility criteria before randomization. Clinical datas: weight, performans status, HR, BP, saturation, T°, clinical abnormalities
  - Status of disease or hemopathy with an indication of allogenic HSCT
  - Acute GVHD: date of apparition, maximal grade, steroid response, treatment(s) ,between D60 et M6,
  - Chronic GVH date of apparition, maximal grade, steroid response, treatment(s) , between D60 et M6,
  - Viral Infections: CMV, EBV, AdV, HHV6 and treatments (INN, dose, duration)
  - Numbers of red blood cells transfusions since since d60
  - Chimerism total blood (and cd3 si available),
  - Immune reconstitution (T, B, NK)
  - IgG, IgA, IgM levels
  - PCR HBV if positive anti Hbc antibodies
  - Hemoglobin (g/dL), PMN (G/L), lymphocytes (G/L) platelets (G/L)
  - Reticulocytes (G/L)
  - Ferritin (µg/l, ou ng/mL)
  - TSUus, T4L
  - Serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL (for women of childbearing age)
  - Isohemagglutinins anti A and/oranti B (IgG) titers at D100
  - Creatinine, uric acid, transaminases, alkaline phosphatase, gamma-GT and bilirubin
  - Treatments on going

If the patient experienced an active uncontrolled infection at time of pre-randomization visit, the visit could be delayed for a maximum of 14 days.

- At randomization visit (M6 post transplants +/- 2 days): d0

- Clinical datas: weight, performans status, HR, BP, saturation, T°, clinical abnormalities
- Hemoglobin (g/dL) , PMN (G/L), lymphocytes (G/L), platelets (G/L)
- Reticulocytes (G/L)
- Creatinine, uric acid, transaminases, alkaline phosphatase, gamma-GT and bilirubin
- Pregnancy test (for women of childbearing age)
- Treatments on going

For patients of Isatuximab arm: Infusion datas and tolerance of Isatuximab perfusion performed at d1.

- Quality of life Questionnaire (EORTC QLQ-C30, v3.0)

No centralization of blood test is required. It should be noted that only the reticulocyte count determined at the investigator site hospital will be considerate. A result outside investigator site will have to be confirmed on site hospital.

5.4 Follow-up visits

- **At d15 of randomization visit (+/- 2 days)**:

- Clinical datas: weight, performans status, HR, BP, saturation, T°, clinical abnormalities
- Status of disease or hemopathy (indication of allogeneic HSCT)
- Acute GVHD: signs of GVH have occurred since the previous visit, date of apparition, maximal grade,
- Chronic GVH: signs of GVH have occurred since the previous visit, date of apparition, maximal grade,
- Viral Infections: CMV, EBV, AdV, HHV6 and treatments (INN, dose, duration)
- Numbers of red blood cells transfusions since last visit
- Hemoglobin (g/dL), PMN (G/L), lymphocytes (G/L) platelets (G/L)
- Reticulocytes (G/L)
- Ferritin (µg/l, ou ng/mL)
- Isohemagglutinins anti A and/or anti B (IgG) titers
- Creatinine, uric acid, transaminases, alkaline phosphatase, gamma-GT and bilirubin
- If infusion, serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL (for women of childbearing age)
- Treatments on going
- Adverse events since last visit

For patients of Isatuximab arm: Infusion datas and tolerance of Isatuximab perfusion

This visit will not be applicable for non-randomized patients.

- **A d29 of randomization visit**: **(+/- 2 days)**:

- Clinical datas: weight, performans status, HR, BP, saturation, T°, clinical abnormalities
- Status of disease or hemopathy (indication of allogeneic HSCT)
- Acute GVHD: signs of GVH have occurred since the previous visit, date of apparition, maximal grade,

- Chronic GVH: signs of GVH have occurred since the previous visit, date of apparition, maximal grade,
- Reticulocytes above 10 G/L since the previous visit: yes/no, if yes date and value in G/L
- Viral Infections: CMV, EBV, AdV, HHV6 and treatments (INN, dose, duration)
- Hemoglobin (g/dL), PMN (G/L), lymphocytes (G/L) platelets (G/L)
- Reticulocytes (G/L)
- Ferritin (µg/l, ou ng/mL)
- Isohemagglutinins anti A and/or anti B (IgG) titers
- Creatinine, uric acid, transaminases, alkaline phosphatase, gamma-GT and bilirubin
- If infusion, serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL (for women of childbearing age) if infusion
- Treatments on going
- Adverse events since last visit

For patients of Isatuximab arm and receiving an injection of Isatuximab: Infusion datas and tolerance of Isatuximab perfusion

This visit will not be applicable for non-randomized patients.

- **A d45 , 3, 6 and 9 months of randomization visit :**
  - **At d 45**
  - Clinical datas: weight, performans status, HR, BP, saturation, T°, clinical abnormalities
  - Status of disease or hemopathy (indication of allogeneic HSCT)
  - Acute GVHD: signs of GVH have occurred since the previous visit, date of apparition, maximal grade,
  - Chronic GVH: signs of GVH have occurred since the previous visit, date of apparition, maximal grade,
  - Reticulocytes above 10 G/L since the previous visit: yes/no, if yes date and value in G/L
  - Viral Infections: CMV, EBV, AdV, HHV6 and treatments (INN, dose, duration)
  - Numbers of red blood cells transfusions since last visit
  - Hemoglobin (g/dL), PMN (G/L), lymphocytes (G/L) platelets (G/L)
  - Reticulocytes (G/L)
  - Ferritin (µg/l, ou ng/mL)
  - Immune reconstitution (T, B, NK)
  - IgG, IgA, IgM levels
  - PCR HBV if positive anti Hbc antibodies
  - Isohemagglutinins anti A and/or anti B (IgG) titers
  - Creatinine, uric acid, transaminases, alkaline phosphatase, gamma-GT and bilirubin
  - Treatments on going
  - Adverse events since last visit
  - Quality of life Questionnaire (EORTC QLQ-C30, v3.0)

This visit will not be applicable for non-randomized patients.

For all the patients (patients in the 2 arms), the data will be collected for the following visits.

- **At 3 months:**
  - Clinical datas: weight, performans status, HR, BP, saturation, T°, clinical abnormalities
  - Status of disease or hemopathy (indication of allogeneic HSCT)
  - Acute GVHD: signs of GVH have occurred since the previous visit, date of apparition, maximal grade,
  - Chronic GVH: signs of GVH have occurred since the previous visit, date of apparition, maximal grade,

- Reticulocytes above 10 G/L since the previous visit: yes/no, if yes date and value in G/L
- Viral Infections: CMV, EBV, AdV, HHV6 and treatments (INN, dose, duration)
- Numbers of red blood cells transfusions since last visit
- Hemoglobin (g/dL), PMN (G/L), lymphocytes (G/L) platelets (G/L)
- Reticulocytes (G/L)
- Ferritin (µg/l, ou ng/mL)
- TSUus, T4L
- IgG, IgA, IgM levels
- PCR HBV if positive anti Hbc antibodies
- Isohemagglutinins anti A and/or anti B (IgG) titers
- Creatinine, uric acid, transaminases, alkaline phosphatase, gamma-GT and bilirubin
- Treatments on going
- Adverse events since last visit
- Quality of life Questionnaire (EORTC QLQ-C30, v3.0)

- **<u>At 6 and 9 months of randomization visit:</u>**
  - Clinical datas: weight, performans status, HR, BP, saturation, T°, clinical abnormalities
  - Status of disease or hemopathy (indication of allogeniec HSCT)
  - Acute GVHD: signs of GVH have occurred since the previous visit, date of apparition, maximal grade,
  - Chronic GVH: signs of GVH have occurred since the previous visit, date of apparition, maximal grade,
  - Reticulocytes above 10 G/L since the previous visit: yes/no, if yes date and value in G/L
  - Viral Infections: CMV, EBV, AdV, HHV6 and treatments (INN, dose, duration)
  - Numbers of red blood cells transfusions since last visit
  - Hemoglobin (g/dL), PMN (G/L), lymphocytes (G/L) platelets (G/L)
  - Reticulocytes (G/L)
  - Ferritin (µg/l, ou ng/mL)
  - TSUus, T4L
  - Immune reconstitution (T, B, NK)
  - IgG, IgA, IgM levels
  - PCR HBV if positive anti Hbc antibodies
  - Isohemagglutinins anti A and/or anti B (IgG) titers
  - Creatinine, uric acid, transaminases, alkaline phosphatase, gamma-GT and bilirubin
  - Treatments on going
  - Adverse events since last visit
  - Quality of life Questionnaire (EORTC QLQ-C30, v3.0)

End of follow up patient: M9 post randomization visit (M15 post allogeneic HSCT)

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

Duration of enrolment period	36 months
The length of participation for participants, of which:	13 months
Duration of treatment : Follow up included treatment period	1 to 3 non consecutive injections (d1, d15, d29 post M6 transplant) 13 months
Total study duration:	49 months

The end of the study is defined as the last visit of the last patients.

5.6 Table summarizing the chronology of the study post-transplant

	Graft (D0)	*Inclusion visit D60 +- 15d*	*D100 Post transplant (data collection, no visit)*	*Pre-randomization Visit (within 7 day before M6 post transplant)*	*Randomization visit /M6 (d0) post transplant +/- 2d*	*d15 +- 2d post randomization **	*d29+- 2d post randomization **	*d45 post randomization **	*M3 post randomization*	*M6 post randomization*	*M9 post randomization*
Patient Information (within 7 days before inclusion)		*x*									
Sign of du consent		*x*									
Check inclusion/non inclusion criteria		*x*		*X Rechecking*							
Randomization (checking randomization criteria)				*x*							
Isatuximab infusion (IV) according to the reticulocytes count		*bHCG[&]*		*bHCG[&]*	*Infusion n1(d1) bHCG[&]*	*Infusion n°2 bHCG[&]*	*Infusion n°3 bHCG[&]*				
Clinical examination		*x*		*x*	*x*	*x*	*x*	*x*	*X*	*X*	*x*
Personal history		*x*									
Transplant characteristics / disease status /chimerism / GVHD		*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Standard biological assessment (haematological, creatinine, uric acide, transaminases, GGT, PAL, Bilirubin)		*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Reticulocytes		*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
anti A et/ou anti B isohemagglutinins titers		*x*	*x*	*x*		*x*	*x*	*x*	*x*	*x*	*x*
Ferritin		*x*	*x*	*x*		*x*	*x*	*x*	*x*	*x*	*X*
T, B, NK lymphocyte phenotyping			*x*	*x*				*x*		*x*	*x*
IgG, IgA, IgM dosage			*x*	*x*				*x*		*x*	*x*
HBV PCR inclusion and if positive anti Hbc ab, hépatitis B serology (D100),			*x*	*x*				*x**		*x**	*x**
TSUus, T4			*x*	*x*					*x*	*x*	*x*
Collection of infections				*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Collection of treatments on going		*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Evaluation of treatment					*x*	*x*	*x*	*x*	*x*	*x*	*x*
QLQ (EORTC QLQ-C30-V3)		*x*			*x*			*x*	*x*	*x*	*x*
AE					*x*	*x*	*x*	*x*	*x*	*x*	*x*
SAE			*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*

&: serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL before infusion for women of childbearing age
**:examen not performed for non randomized patients and no patient's visit*
volumes authorized to be collected from children (see table &5.7)

5.7 Distinction between standard care and study

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

Acts, procedures and treatments carried out in the context of the clinical trial	**Acts, procedures and treatments related to care**	**Acts, procedures and treatments added by the clinical trial**
Treatments	All treatments related to allo -HSCT, supportive care in the two arms	Isatuximab and its pre-medication in the randomization arm "treatment"
Consultations, day hospitalization	All protocol visits or day hospitalization	*None*
Blood tests	Standard post allo-HSCT biological investigations: - Anti-A and/or anti-B (IgG) isohemagglutinin titer at D100 post-transplant - T, B, NK to D100, M6 and M12 lymphocyte phenotyping post-transplant - IgG, IgA, IgM dosage at D100, 6 ,9 and 12 months post -transplant - HBV PCR at D100 post-transplant - TSHus, T4 dosage at D100, M6, M9 post transplant	- Anti-A and/or anti-B (IgG) blood isohemagglutinin titer at D60, at pre-randomization, at d15(*+- 2d)*, d29(*+- 2d)*, d45, at 3, 6 and 9 months post-randomization, -T, B, NK lymphocyte phenotyping at d45, M9 post-randomization (i.e. M15 post-transplant) - IgG, IgA, IgM dosage at d45, and 9 months post randomization - HBV PCR if anti-Hbc antibody positive at pre-randomization, at d45, 3, 6 and 9 months post randomization Pregnancy blood or urinary test at inclusion and before each injection for women of childbearing age

TABLE: volumes authorized to be collected from children

Body weight (kg)	**Circulating total blood volume (ml)**	**Maximum allowable sample volume over 4 weeks (ml) - 3% of total blood volume**	**Maximum allowable sample volume at single time (ml) - 1% of total blood volume**
12 - 20	960 - 1600	28.8 – 48	9.6 -16
20 - 30	1600 - 2400	48 – 72	16 – 24
30 - 70	2400 - 5600	48 – 168	24 – 56

For more information, the clinical trial related blood loss as a general rule should not exceed 3% of the total blood volume over a period of four weeks, and should not exceed 1% at any single time.

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

Patients:
- Aged 15 years or older
- Having receiving an allogeneic hematopoietic stem cell transplantation in condition of major ABO mismatch
- PCRA defined by persistent red blood cell transfusion dependence at day 60 post-transplant with reticulocytes count under 10 G/L despite full donor chimerism and a good leucocytes (>1 G/L) and platelet (>50G/L) recovery
- No relapse or progression of underlying disease
- Contraception methods must be prescribed during all the duration of the clinical trial and using effective contraceptive methods during treatment for women of childbearing age (continue abstinence from heterosexual intercourse is accepted) and for man during the study treatment period and for at least 5 months after the last dose of study treatment and refrain from donating sperm during this period
- With health insurance coverage
- Having signed a written informed consent (2 parents for patients aged less than 18)

6.2 Exclusion criteria

Patients:
- Aged < 15 years
- Relapse of underlying disease
- Leucocyte chimerism < 95%
- PRCA related to Parvovirus B19 infection (positive blood PCR)
- Known to be HIV+ or to have hepatitis A, B, or C active infection
- Active tuberculosis
- Pregnant (βHCG positive) or breast-feeding
- Patient receiving recombinant human erythropoietin.
- Patient receiving proteasome inhibitor (Bortezomib for example).
- Patient receiving thrombopoietin receptor agonists (ARTPO).
- Patient receiving plasma or plasmapheresis exchanges after transplant.

- Planned to receive any investigational drug within 14 days or 5 half-lives of the investigational drug, whichever is longer.
- Any clinically significant, uncontrolled medical conditions that, in the Investigator's opinion, would expose excessive risk to the patient or may interfere with compliance or interpretation of the study results.
- Hypersensitivity to the active substance or history of intolerance to steroids, mannitol, pregelatinized starch, sodium stearyl fumarate, histidine (as base and hydrochloride salt), arginine hydrochloride, poloxamer 188, sucrose or any of the other components of study therapy that are not amenable to premedication with steroids and H2 blockers or would prohibit further treatment with these agents.
- Who have any debilitating medical or psychiatric illness
- Under tutorship or curatorship
- Who not understand informed consent for an optimal treatment and follow-up.

6.3 Recruitment procedure

Patients will be recruited from the adult and pediatric hematology departments affiliated with SFGM-TC that perform allo-HSCT. More than two thousand allo-HSCT are currently being performed in France.

	Number of subjects
Total number of subjects to be included	90
Number of sites	24
Enrolment period (months)	36
Number of subjects/site	4
Number of subjects/site/month	0.10

The inclusion period will be increased to include patients (even more than the 90 expected) until to randomize the 45 patients needed, notably if less than 50% of the 90 enrolled patients are still PRCA at M6.

6.4 Termination rules

6.4.1 Criteria and procedures for prematurely terminating the study treatment

Different situations:

- Temporary discontinuation of treatment, the investigator should document the reason for discontinuation and its recurrence in the subject's source file and the CRF
- Early discontinuation of treatment, but subject remains in clinical trial, until the end of participation, investigator should document the reason
- Early discontinuation of treatment and termination of clinical trial participation.

The investigator must:
o Document the reason(s)
o Collect the assessment criteria at the time of ending participation in the study, if the participant agrees
o Plan follow-up of the subject, especially in the event of a serious adverse event

Detailed guidelines for the management of infusion reactions for isatuximab IV are provided in paragraph 7.1.

In the case of serious adverse events, they should be reported by the investigator to the sponsor and followed up during the patient's protocol follow-up period. The notification of the serious adverse event will be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor. The serious adverse event will be tracked until it is resolved. If an independent monitoring committee has been set up, it may specify and/or validate the terms of the monitoring.

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.

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

Follow-up of subjects following a discontinuation of participation in the clinical trial

Discontinuation of a subject's participation will not change his or her usual take care to the disease.

In the event of serious adverse events during early discontinuation of treatment and participation in clinical trial by the patient: see paragraph 6.4.1.

Procedures for the replacement of these subjects

The analysis of the trial will be in intention to treat. Any patients included will be analyzed. There will therefore be no replacement procedure unless a patient's consent is withdrawn if the study inclusion period is still open.

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

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 program 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 Research 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 OF CLINICAL TRIAL SUBJECTS

7.1 Description of the investigational medicinal product

Isatuximab is an immunoglobulin (Ig) G1 monoclonal antibody (mAb) that selectively binds to the human cell surface antigen molecule classified as cluster of differentiation 38 (CD38).
Isatuximab targets CD38 expressed in hematological malignancies and is able to destroy CD38 expressing tumor cells in vitro through several mechanisms, including: Antibody-dependent cellular cytotoxicity (ADCC), Antibody-Dependent Cellular Phagocytosis (ADCP), Complement dependent cytotoxicity (CDC), and direct apoptosis. Isatuximab binding to CD38 expressed on immune cells triggers immunomodulatory functions. For instance, isatuximab can activate NK cells and increase their lytic activity. Isatuximab can also induce the polarization of monocytes to an M1 phenotype and restore the proliferative potential of conventional T cells repressed by regulatory T cells (Tregs).

Storage and handling
Vials of isatuximab concentrate for solution for infusion should be stored between 2°C and 8°C and protected from light. Do not freeze. Do not shake. The shelf life of unopened vial is 36-months.

Study intervention name	**Isatuximab**
Dosage formulation	Concentrate for solution for intravenous infusion
Unit dose strength(s)/Dosage level(s)	Concentration: 20 mg/mL Dosage presentation: 500 mg/25 mL and 100 mg/5 mL
Route of administration	Intravenous infusion
Packaging and labelling	Isatuximab will be provided in 1 glass vial per box (30 mL vial for 500 mg and 6 mL vial for 100 mg). The label contents will be in accordance with the local regulatory specifications and requirements

For details of IMP preparation and administration, refer to pharmacy documentation.

Dosage and administration modalities:

Isatuximab will be administered at a dose of 10 mg/kg intravenously. Each infusion must be performed under paramedical and medical surveillance.
Premedication should be used, 15 to 30 minutes prior to starting of isatuximab infusion, with the following medications to reduce the risk and severity of infusion reactions (IRs):

- Dexamethasone 40 mg PO or IVL or 20 mg IVL≥75 years of age,
- Paracetamol 650 mg to 1000mg, by ivl or PO,

- Montelukast 10 mg PO

- Dexchlorpheniramine preferably IV (5 mg) for the 3 injections (or 2 mg PO).

These medications are considered to be auxiliary medicinal products (treatments required to conduct the study).

According to the Regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014, an auxiliary medicinal product is a medicinal product used in the context of a clinical trial but not as investigational medicinal product.
In this clinical trial, the auxiliary medicinal products are used according to their market authorizations.

The SmPCs of the premedication products are available in annex.

Management of infusions reactions (IR)

Severity (CTCAE version 5.0)	Recommendation intervention
Mild (Grade 1) Infusion interruption or intervention not indicated	Continuation of the isatuximab infusion based on the judgment of the Investigator, following close direct monitoring of the patient's clinical status. The isatuximab infusion may be stopped at any time if deemed necessary. If the infusion is stopped, the IR will be classified as Grade ≥ 2 as per NCI-CTC-AE V5.0 and infusion will be re-started at half of the initial infusion rate.
Moderate (Grade 2) Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Stop the isatuximab infusion. Give additional medication with dexchlorpheniramine 5 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) as needed. Isatuximab may be resumed only after patient recovery, at half infusion rate and with close monitoring.
Severe or life-threatening (Grade 3 or 4) Grade 3: prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae Grade 4: life-threatening consequences; urgent intervention indicated.	Stop the isatuximab infusion. Give additional medication with dexchlorpheniramine 5 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) and/or epinephrine as needed until the resolution of the AE or until the AE improves to Grade 1. Only then, if previous Grade 3 the infusion must be restarted at the investigator's discretion; if so, the infusion rate should be half of the infusion rate before the interruption, and it may be increased subsequently at the investigator's discretion. If the severity of an infusion-related AE returns to Grade 3 after the restart of infusion, the same procedure described above my ne repeated at the Investigator's discretion. If a Grade 3 infusion-related AE occurs for a 3rd time, treatment with isatuximab will be definitively discontinued for the patient.

	In case of Grade 4, Isatuximab will be permanently discontinued.

Infusion rates of Isatuximab administration

	Dilution volume	Initial rate	Absence of infusion reaction	Rate increment	Maximum rate
1st infusion	250 mL	25 mL/hr	For 60 min	25 mL/hr every 30 min	150 mL/hr
2nd infusion	250 mL	50 mL/hr	For 30 min	100 mL/h for 30 min then increased by 200 mL/hr	200 mL/hr
3rd infusion	250 mL	200 mL/hr	-	-	200 mL/hr

Nursing monitoring (pulse, blood pressure, temperature, saturation, chills and dyspnea) will be performed every 30 minutes during the infusion and then at 30, 60 and 90 minutes after the infusion.

First Infusion:
In case of grade 2 IR during first infusion, infusion could be restarted at one-half (12.5 mL/hour) of the initial infusion rate when the IR improves to Grade ≤1. If symptoms do not recur after 30minutes, the infusion rate may be increased by 25 mL/hour increments every 30 minutes, up to a maximum of 150 mL/hour, until the total volume is infused.

Second Infusion:
In case of grade 2 IR during second infusion, infusion could be restarted at one-half (25 mL/hour) of the initial infusion rate when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 50 mL/hour increments every 30 minutes up to a maximum of 200 mL/hour, until the total volume is infused.

Third Infusion:
In case of grade 2 IR during third infusion and subsequent infusions, infusion could be restarted at one-half (100 mL/hour) of the infusion rate when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 50 mL/hour increments every 30 minutes up to a maximum of 200mL/hour, until the total volume is infused.

Supportive care: at investigator's discretion. Recommendation to consider:
- Colony-stimulating factor use as per ASCO (https://pubmed.ncbi.nlm.nih.gov/26169616/) or local guidelines
- Transfusion support (RBC, platelets) as appropriate
- Antiviral and antibiotic prophylaxis
- HBV vaccination could be considered, following investigator's discretion and according to HSCT vaccination guidelines (https://www.ncbi.nlm.nih.gov/books/NBK553979/) . In case of viral reactivation during study treatment, study treatment will be hold and specialist consulted for initiation of anti-viral treatment and monitoring of the patient. Re-start of study treatment should be agreed between sponsor, investigator and specialist (hepatologist) if controlled infection.

Close monitoring of ALAT, ASAT up to study treatment discontinuation. HBV DNA to be done as per specialist advice.

7.2 Description of the traceability elements accompanying the investigational medicinal product

The treatment, packaged in batches for clinical trials, is provided free of charge by Sanofi Laboratories. DEC AGEPS (AP-HP) will ensure the supply of PUIs to the investigation centres. A drug circuit will describe the packaging of treatments, the supply, dispensing, modalities of administration of each infusion according to investigator's brochure and destruction procedures at each site. A patient card for participation in the clinical trial will be given to the patient upon inclusion.
Treatment will be provided to the clinical department by the PUI upon presentation of a specific nominative prescription for the clinical trial.
Batch number and expiry date will be recorded on the prescription.

7.3 Treatments (drugs, surgical) authorized and prohibited, including rescue drugs

Supportive care is allowed in the two arms before randomization.

The following treatments will be prohibited throughout the patient's participation in the clinical trial and not prescribed for the medical condition subject of research:
- Recombinant human erythropoietin.
- Proteasome inhibitor (Bortezomib for example).
- Thrombopoietin receptor agonists (ARTPO).
- Plasma or plasmapheresis exchanges after transplant.
- Donor lymphocyte injections (DLI), with the exception of DLI realized to manage the risk of relapse of haematological disease and performed before and later than six weeks after the first and the last isatuximab injection respectively.
- Rituximab, with the exception of its prescription for the pre-emptive or curative treatment of EBV post-transplant lymphoproliferative disorders.

8 EFFICACY ASSESSMENT

8.1 Description of efficacy endpoints assessment parameters

The objectives regarding effectiveness are to evaluate the:
- decrease in the time to resolve the PCRA in days between the randomization date (corresponding to M6 post allo-HSCT) and the resolution date (reticulopenia resolution date) with or without treatment with Isatuximab CD38 monoclonal antibody
- reduction of erythocyte transfusion requirements with Isatuximab
- evolution of iron overload with or without Isatuximab
- quality of life: functional impact of chronic anemia, iterative transfusions and iron overload (at 1, 3, 6, 9 months from randomization) with or without specific treatment,
- overall survival and without relapse at M6, M9, M12 and M15 post-allo HSCT,
- cost of management of PCRA by major ABO mismatch with or without Isatuximab treatment (the cost of treatment, day or full hospitalizations directly related to PCRA by major ABO mismatch, transfusion of red cell transfusion support and necessary chelation treatments.

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

The parameters for assessing efficacy were collected according to the schedule in table paragraph 5.6.

No centralization of blood test is required to assess primary and secondary efficacy endpoints. However, it is imperative to consider only the reticulocyte count determined at the hospital of the investigator site. Thus, an assessment made out of hospital must be confirmed on site.

Scientific Steering Committee

Members of the committee: coordinating investigator, scientific leader, biostatistician, representatives of the sponsor appointed for this clinical trial.
Missions: The scientific steering committee will define the general organization and the conduct of the clinical trial. He will determine the initial methodology and oversee the trial.
He will propose procedures to be followed during the study, acknowledging any recommendations from the Data Monitoring Committee. The sponsor retains the decision-making authority.
Operating mode: After the start of the clinical trial, this committee will meet at least once a year.

9 SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

9.1 *Description of Safety endpoints assessment parameters*

The safety assessment shall be done by collecting all adverse events that occur at each visit during the clinical trial. All adverse event shall be graded according to CTC-AE Toxicity Grading Scale (v5.0). Adverse events shall be collected according to the schedule in table of paragraph 5.6 of the protocol.

9.2 *Recording and reporting adverse events*

9.2.1. 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) N°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.

9.2.2. 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 severity** of the adverse events by using
CTA-AE Toxicity Grading Scale, v5.0

The investigator must **assess the causal relationship** between serious adverse events and the investigational medicinal product.
The investigator uses the following terms:

- Reasonable possibility
- No reasonable possibility

9.2.2.1. 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 41of Regulation (EU) N°536/2014of, 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 hospitalization or prolongation of existing hospitalization
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.

9.2.2.2 Specific features of the protocol

9.2.2.2.1. Other events that require the investigator to notify without delay the sponsor

- Adverse events deemed "medically significant"

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.
If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be notified.

- Exposure **while breastfeeding**

Exposure while breastfeeding occurs if an infant or a child may have been exposed to a medicinal product *via* the breast milk of a mother being treated with an investigational medicinal product.
Even if it is not associated with an adverse event, the investigator must notify the sponsor without delay on the day the investigator becomes aware of the exposure while breastfeeding.

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

The following serious adverse events are only collected in the eCRF:

- *All serious adverse events occurring in non-randomized patients*

- *All serious adverse events which may occur in the 6 months after hematopoietic stem cell transplantation before randomization.*
  In case of serious adverse events of fatal outcome, an eCRF extraction of these serious adverse events will be transmitted to the Safety Department every 3 months.

- *Natural and expected evolution of the pathology:*
  - Relapse of initial hematological disease.
  - Abnormal biological value of grade ≤ 3 without any other associated symptoms.
  - Hospitalization or prolongation of hospitalization related to hematological disease, allo HSCT and unrelated to Isatuximab treatment..
  -Hospitalization for Isatuximab perfusion.

- *Special circumstances*
  - Hospitalization for a pre-existing illness or condition.
  - Transfer to the emergency ward with self-limiting event or judged as not serious by the investigator.

- *Adverse events that may be related to treatments and procedures prescribed in the context of care during the follow-up of the research*

These adverse reactions should be reported by the investigator to the applicable health authorities.

9.2.2.3. 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 randomization (d0) post transplant +/- 2d
- throughout the whole follow-up period required for the trial
- without time limitation, when the SAE is likely to be due to the investigational medicinal product (for example, serious effects that may occur at a long distance from exposure to the medicinal product, such as cancers or congenital anomalies).

9.2.2.4. Procedures and deadlines for notifying the sponsor

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, number and participant's initials.

Any adverse event will be monitored until fully resolved (stabilization 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).

For studies which use e-CRFs

- 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.

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, fetal 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.
If it was the father who was exposed, the investigator must obtain the pregnant woman's permission before collecting information about the pregnancy.

9.2.3. Role of the sponsor

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

9.2.3.1. Analysis and declaration of serious adverse events

The sponsor assesses:

- the **seriousness** of all the 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 safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorised, 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 "Isatuximab": refer to refer to the investigator's brochure enclosed in CTIS platform.
- For serious adverse events that may be related to the auxiliary drug(s): Dexamethasone, Dexchlorpheniramin, Paracetamol and Montelukast , it should be referred to the SmPC of each specialty enclosed in CTIS platform..

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), via Eudravigilance

- 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 clinical trial participants.

9.2.1.1 9.2.3.2. 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 clinical trial or of other similar trials. For trials involving the first administration or use of a health product in healthy volunteers: any serious adverse reaction.

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.

Following the initial declaration of any emerging safety issue, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 8 days after learning of the information.

9.2.3.3. 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 clinical trial 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 produce 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 authorized the trial.

9.2.3.4. Data Safety Monitoring Board (DSMB)

The Data and Safety Monitoring Board (DSMB) will be established by the sponsor. Its primary mission is to serve as a committee for monitoring safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The DSMB is mentioned in Article L. 1123-7 of the French Public Health Code.

The sponsor is responsible for justifying the creation or absence of a supervisory committee to the Competent Authority (ANSM) and to the CPP.

A DSMB will be convened for this biomedical clinical trial. The DSMB will hold its preliminary meeting before the first inclusion of the first subject.
All missions as well as the precise operating methods of the DSMB are described in the charter for the research's DSMB.

<u>General information about the DSMB</u>
The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the clinical trial. The recommendations that the DSMB can make are:

- to continue the research with no modifications
- to continue the research with a modification to the protocol and/or to the monitoring of subjects
- to temporarily halt inclusions
- to permanently terminate the clinical trial in light of:
    - safety data: serious adverse reactions
    - efficacy data: proven futility or efficacy

The DSMB is appointed by the sponsor and is made up of at least 3 people with no connection to the clinical trial, including at least one clinician specialising in the pathology being studied and one specialist in the medication being studied (or a pharmacologist/pharmacovigilance specialist), and possibly a methodologist/biostatistician,.

The DSMB has a consultative role in advising the sponsor on safety issues such as tolerance and re-assessment of the benefit-risk ratio during the clinical trial .

The DSMB must hold its preliminary meeting before the first inclusions of the first subject and ideally before the protocol is submitted to the competent authority and the CPP.

All the missions as well as the precise modalities of the DSMB's functioning are described in the study's DSMB charter.

The members of the DSMB are: Dr Charlotte Jubert (Pediatric Hematology, Bordeaux), Pr Thomas Cluzeau (Adult Hematology, Nice) and Dr Sylvain Thépot (Adult Hematology , Angers)

10 DATA MANAGEMENT

10.1 *Right to access data and source documents*

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 .

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.

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.

10.2 Data processing and storage of clinical trial documents and data

Identification of the responsible and place for the management of the data processing operations

Data Management and statistical analysis will be managed and carried out at the URC of GH Lariboisière Saint-Louis, Saint-Louis site, Pr Jérôme Lambert.

Data entry

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

10.3 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.

11 STATISTICAL ASPECTS

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

Analysis Populations

The following analysis sets will be considered:

- Intent-to-treat analysis: all included patients will be considered in their randomization arms. This will refer for all to the primary analyses.
- Analysis per protocol: it will consider patients in the arm of the effectively received treatment.

All analyses will be in ITT, per-protocol analyses will be performed as a sensitivity analysis.

As a general strategy, characteristics of patients will be presented using summary measures (median and interquartile range for quantitative characteristics and counts and percentages for categoriel characteristics)

A flow chart will summarize all patients screened, included and analysed.

Analysis of Primary Efficacy Endpoint

The delays to obtention of transfusion independence for patients with PRCA will be compared using a logrank test. The impacts of resolutions will be estimated in each arm using the Kaplan Meier estimator with their 95% confidence intervals. Patients will be censored at the end of the follow-up. In case of a competing event occurring during follow-up (death without resolution), the logrank test will be replaced by a Gray test and the Kaplan Meier estimator by the Gray cumulative incidence estimator.

Interim analysis will be performed after observations of 22 events (primary endpoint) in the trial. In case of significant logrank test at the interim analysis, trial will be stopped and final analyses performed. If the trial is still going on, the final p.value will be calculated using a combination of the p.values of the first step and of the second step using the Wassmer approach (Wassmer, Gernot. "Planning and analyzing adaptive group sequential survival trials." Biometrical Journal: Journal of Mathematical Methods in Biosciences 48.4 (2006): 714-729.). Moreover, if requested by DSMB, sample size recalculation could be performed.

Analysis of Secondary Endpoints

- Number of red blood cells received as a result of the PCRA after randomization (M6 post-transplant in each group up to M15. The number will be described per arm (Median IQR) and compared between the arms using a Wilcoxon test. In the event of death, the number of units will be considered as maximum.

- Date of last transfusion. The time to the last transfusion date will be compared between the arms using a logrank test. Patients will be censored at the end of the follow-up. In case of a competing event occurring during follow-up (death without stopping transfusions), the logrank test will be replaced by a Gray test.

- Evolution of ferritin at M6, M9, and M15 of the transplant will be modelled using a random effect general linear regression model on the patient and a time effect.

- Evaluation of adverse events of grade ≥ 2 observed in each group after randomization (M6 post-transplant). The SAE will be described in each arm and their frequencies compared using a Fisher test.

- Quality of life assessment by the EORTC -C30-v3 to D60, M6, M9, M12 and M15 post-transplant questionnaires. It will be described in each arm (Median IQR). It will be modelled using a random effect general linear regression model on the patient and a time effect.

- Overall survival and without relapse at M6, M9, M12 and M15 post-transplant will be estimated per arm using the Kaplan Meier estimator with their 95% confidence intervals. Patients will be censored at the end of the follow-up. They will be compared using Logrank test

- Factors associated with spontaneous resolution of PCRA between D60 and M6 post-transplant will be explored using Cox's model.

- Follow-up of plasma anti-A and/or anti-B antibody titers at D60, M6 post-transplant and then at each visit d15, d29, D45, and, 3, 6, 9 months after the randomization visit. They will be described in each arm (Median IQR). They will be modelled using a random effect general linear regression model on the patient and a time effect

- Assessment of the costs of PCRA with or without Isatuximab treatment (the cost of treatment), day or full hospitalizations directly related to PCRA, erythrocyte transfusion support and necessary chelation treatments. The economic evaluation will assess the costs and effectiveness and safety of the treatments. The analysis will be conducted from a health system perspective over a 9-month period. All health resources necessary for treatment will be collected prospectively. They include inpatient and outpatient treatment, testing, consultations, imaging and home care.

Health care costs will be estimated using a combination of resource and event-based methods. The total length of stay will be extracted from the hospital's information system for indexed admission and thus subsequent admissions related to the event during the 9-month follow-up period. Hospitalization costs will be allocated according to the groups related to the severity diagnosis, adjusted according to the length of the stay. The cost of each admission will be estimated from the national cost study, using the actual length of stay and the daily cost.

Non-hospital resources will be estimated from the eCRF, medical records (discharge orders) and interviews with patients during follow-up visits. In addition to the treatment, we will collect information on consultations, drugs, laboratory tests. Non-hospital resources will be assessed using the most recent price and rate schedule. The total average cost per patient will be calculated in each group; the 95% start-up interval will be estimated and costs compared using non-parametric tests).

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

A bilateral logrank test considering a sample size of 45 randomized patients in 2:1 (30 in the experimental group with median transfusion independence under H1 of 1.5 months, 15 in the control group with median transfusion independence under H1 of 4.5 months) achieves a power of 86,4% with an alpha risk of 0.05. Considering that only 50% of patients included at D60 will be randomized at 6 months, 90 patients should be included.
The inclusion period will be increased to include patients (even more than the 90 expected) until to randomize the 45 patients needed, notably if less than 50% of the 90 enrolled patients are still PRCA at M6. This will achieve the power necessary to evaluate the outcomes of the study.

Anticipated level of statistical significance

All tests will be two-sided with a type I error rate fixed at 0.05.

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

All the effort will be done to avoid missing data in the outcomes.
The analyses will be carried out on a case-by-case basis. Sensitivity analyses will be performed using a multiple imputation approach using chain equations. Patients who are lost to follow-up will be censored on the date of their last news.

11.4 Management of modifications made to the analysis plan for the initial strategy.

All the analyses will be described in a statistical analysis plan (SAP) that will be written and signed before freezing of the database. All modifications of the initial plan will be submitted to the scientific committee, the investigator and the sponsor as well as regulatories.

12 QUALITY CONTROL AND ASSURANCE

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

12.1 *General organization*

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 centers.

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 clinical trial 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

Strategy for center opening

The strategy for opening the centers established for this study is determined using the appropriate monitoring plan. In practice, the centres will be opened with a priority for the centers that will have an eligible patient or within 3 months of the start of the clinical trial .

Scope of center 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 High.

12.2 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

12.3 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.

12.4 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 days of becoming aware of that breach.

12.5 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 clinical trial. 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.

12.6 Principal Investigator's commitment to assume responsibility

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 trial and related training.
Any conditions, such as economic interests and institutional affiliations that might influence the impartiality of the investigators shall be presented (applicable after CTIS transition)

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.

12.7 Suitability of the facilities

After CTIS transition, each new 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.

12.8 Pharmacist's commitment of responsibility

Before starting the study, each pharmacist 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). The CV must include any previous involvement in clinical trial and related training.
Each pharmacist will commit to comply with legislation and to conduct the study in line with GCP, in accordance with the Declaration of Helsinki.

13 ETHICAL AND LEGAL CONSIDERATIONS

13.1 Methods for informing clinical trial 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
A reflection period of 15 days is given to the individual between the time when he or she is informed and when he or she signs the consent form.

The person's freely-given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study.

A copy of the information note and consent form, signed and dated by the clinical trial participant and by the principal investigator or the physician representing the investigator will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

In addition, the investigator will specify in the person's medical file the person's participation in the clinical trial, the procedures for obtaining his/her consent *by article European regulation N°536/2014 (art. 29 and following)* as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

Information of the holders of legal authority and its/their consent in the case of a study protocol involving a minor
In accordance with Article 32 of the European regulation , when a clinical trial is conducted on a non-emancipated minor, consent must be given by the holder(s) of its legal representative(s).

A minimal reflection period of 15 days is given to between the time when the interested person are informed and when they sign the consent form.

The freely-given written informed consent of the holders of legal authority is obtained by the investigator, or by a physician representing the investigator, before definitive inclusion of the minor in the study.

Information for minors participating in the clinical trial

Minors receive the information specified in Article,29.2 of the European regulation appropriate to their level of understanding, both from the investigator and from the holders of legall authority.
Minor's personal endorsement is sought regarding their participation in the study involving human participants. In any cases, the investigator cannot override their refusal or the revocation of their acceptance.

One copy of the signed and dated consent form is given to the holders of parental authority. The principal investigator or a physician representing him/her will keep one copy.
At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

Information recorded in the minor's medical file

The investigator will record the minor's participation in the clinical study in the minor's medical file, along with the procedure for informing and obtaining consent from the holders of legal

authority as well as the procedure for informing the minor and a record of the minor's non-rejection to take part.

Special circumstances: the minor reaches the age of majority during his or her participation in the study

According to article 32.3 of the European regulation, minors who reach the age of majority during their participation in the study will be given new, relevant information at that time. After they have been given this information, they will be asked to confirm their consent.

Information in case of pregnancy
In the event of pregnancy occurring in the partner of a study participant, an information note and consent will be offered to the expectant mother to monitor the pregnancy and the health of the child. The consent will be signed by the 2 future parents and the investigator.

13.2 Prohibition from participating in another clinical study or exclusion period set after the study.

No exclusion period of participation after the participant has finished this study is defined in the context of this clinical trial.

The participant may not enroll in another interventional study protocol involving human participants for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study.

The participants can however participate in other non-interventional studies or in minimal risk and constraint study that does not involve therapeutic strategies, but this should be reported to the physician who follows it in the present clinical trial.

13.3 Authorisation for the research location

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

13.4 Legal obligations

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 Law. 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.

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, approval from the appropriate CPP (Research Ethics Committee), within the scope of its authority and in accordance with in force legislation and regulatory requirements.

Procedures relating to data protection regulations

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

For france

- Commitment to comply with “Reference Methodology” MR-001

This clinical trial is governed by the CNIL (French Data Protection Agency) “Reference Methodology for processing personal data used within the scope of health research” (amended MR-001). AP-HP, as sponsor of the clinical trial, has signed a declaration of compliance with this “Reference Methodology”

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 authorization 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.

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 *[to be defined otherwise if this is not the case].*
The end of the recruitment of subjects for the clinical trial and the end of the clinical trial should be notified in CTIS. That notification shall be made within 15 days from the end of the clinical trial in relation to that Member State.

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.

Archiving

Specific documents for a clinical trial will be archived by the investigator and the sponsor for 25 years after the end of the clinical trial.

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 center 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 center 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 authorizations and Research Ethics Committee decisions

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

- The data collection documents

14 FUNDING AND INSURANCE

14.1 *Funding sources*

A request for funding from the PHRC 2019 has been requested. The source of funding will be indicated in the protocol.

14.2 *Insurance*

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).

15 PUBLICATION RULES

The author(s) of any publication relating to this study must include the APHP among their affiliations and name the sponsor AH-HP (DRCI) and the source of funding, if funded by a call for tenders (e.g. national or regional PHRC); a copy of the publication must be sent to the sponsor.

15.1 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

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

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

15.3 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 2019 (French Ministry of Health)"

This study has been registered on the website http://clinicaltrials.gov/ under number. ErythroSIM : NCT05559827

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17 LIST OF ADDENDA

17.1 List of investigators

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17.2 Serious Adverse Events notification form

17.3 Pregnancy notification form

17.4 Investigator's brochure

17.5 SmPC

Dexamethasone
http://agence-prd.ansm.sante.fr/php/ecodex/frames.php?specid=65822036&typedoc=R&ref=R0363424.htm

Montelukast
http://agence-prd.ansm.sante.fr/php/ecodex/frames.php?specid=67627533&typedoc=R&ref=R0373580.htm

Dexchlorpheniramine
http://agence-prd.ansm.sante.fr/php/ecodex/frames.php?specid=65227405&typedoc=R&ref=R0347578.htm

Paracétamol PO
http://agence-prd.ansm.sante.fr/php/ecodex/frames.php?specid=63107752&typedoc=R&ref=R0373333.htm

17.6 Questionnaires (EORTC QLQ-C30-V3)