**Empirical steroids and/or antifungals in immunocompromised patients with acute respiratory failure from undetermined etiology: a multicenter double-blind randomized controlled trial**
**EFRAIM II**

CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE

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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

| | |
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| Full title | Empirical steroids and/or antifungals in immunocompromised patients with acute respiratory failure from undetermined etiology: a multicenter double-blind randomized controlled trial |
| Acronym/reference | EFRAIM-II |
| Coordinating investigator | Prof. Elie AZOULAY<br>Service de Réanimation Médicale<br>Hôpital Saint Louis, Paris, FRANCE<br>Office phone: +33 (0) 1 42 49 34 21<br>Fax: +33 (0) 1 42 49 94 26<br>E-mail: elie.azoulay@aphp.fr |
| Sponsor | Assistance Publique – Hôpitaux de Paris |
| Scientific justification | Acute respiratory failure (ARF) is the leading reason of ICU admission in immunocompromised patients. Failure to identify the ARF etiology is associated with increased mechanical ventilation and mortality rates. This was confirmed in the large Efraim 1 study published in 2017, where undetermined ARF etiology affected 609/1611 (38%) patients at day 3, 402 (25%) patients at day 7 and 199 (12.3%) patients overall, and was associated with a case fatality of 55% (vs. 40% in other patients). In lung biopsy/autopsy findings from these patients, invasive fungal infection, steroid-sensitive affections (organized pneumonia, non-infectious interstitial involvement, drug-related pulmonary toxicity…), and lung infiltration by the underlying disease (lymphoma, carcinomatous lymphangitis, systemic vasculitis, connective tissue diseases, etc.) were the leading etiologies. No study has evaluated survival benefits from empirical steroids and/or antifungals in immunocompromised patients with ARF from undetermined etiology. |
| Main objective and primary endpoint | **Main objective**<br>To reduce the 90-day mortality in immunocompromised patients with ARF from undetermined etiology at day-3. The intervention would evaluate the impact of steroids ± isavuconazole for 14 days or until ICU discharge.<br>**Primary endpoint**<br>Mortality at day 90 |
| Secondary objectives and endpoints | **The secondary study objectives are to evaluate**<br>- how early empirical therapy can affect ICU, hospital and day-28 mortality<br>- whether steroids increase the proportion of patients with ICU acquired microbiologically documented bacterial infections within 3 months following randomization<br>- the proportion of patients with invasive fungal |

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| | infection within 3 months following randomization.<br>- the proportion of patients with HSV, VZV or CMV reactivation within 3 months following randomization<br>- whether steroids are complicated by severe hypokalemia (<2,5 meq/l), newly acquired or decompensated diabetes, or severe or newly acquired hypertension<br>- whether isavuconazole will favor the emergence of infections with Aspergillus or mucorale species with decreased sensitivity to isavuconazole<br>- Occurrence of Candida infection<br>- how steroids affect psychiatric symptoms such as Post-traumatic Stress Disorder, anxiety and depression at 6 months<br>- how this early intervention can improve quality of life at 6 months<br><br>**Secondary end points**<br>- ICU mortality<br>- hospital mortality<br>- day 28 mortality<br>- proportion of patients with ICU acquired microbiologically documented bacterial infections<br>- proportion of patients with invasive fungal infection within 3 months following randomization<br>- proportion of patients with HSV, VZV or CMV reactivation within 3 months following randomization<br>- occurrence of severe hypokalemia (<2,5 meq/l), decompensated diabetes or severe or newly acquired hypertension<br>- emergence of Aspergillus species with decreased sensitivity to isavuconazole<br>- Incidence of Candida infection<br>- incidence of post-traumatic Stress Disorder (IES-R), anxiety and depression at 6 months (HADS)<br>- quality of life at 6 months (SF36) |
| Design of the study | Multicenter double-blind randomized controlled trial, based on a 2x2 Factorial design. |
| Category | Cat. 2 |
| Population of study participants | In immune-compromised patients with Acute respiratory failure (ARF) from undetermined etiology, either intervention (steroids and/or antifungals) will be associated with improved day-90 survival. Acute respiratory failure (ARF) is the leading reason of ICU admission in immunocompromised patients' admission. |
| Inclusion criteria | 1) Age >18 years and <90 years; 2) a) immunosuppressive drug b)solid organ transplant; c) solid tumor; d) hematological malignancies; e) primary immune deficiency; 3) ICU admission for acute respiratory failure as defined by a) respiratory distress with tachypnea (respiratory rate>30/min); b) cyanosis; c) laboured breathing; d) Need for more than 6l of |

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| | standard oxygen to maintain SpO2>95%, or for high flow oxygen, non-invasive or invasive mechanical ventilation; 4) No established ARF etiology 24 hours after hospital admission; 5) Patient admitted for at least 24 hours at hospital 6) Informed consent signed:<br>- by the patient,<br>- Or informed consent signed by a family members/trustworthy person if his condition does not allow him to express his consent by written as per L. 1111-6,<br>-Or in a situation urgently and in the absence of family members/trustworthy person, the patient can be enrolled. The consent to participate to the research will be requested as soon as the condition of the patient will allow him to consent.<br>Note: Patient with Pneumocystis pneumonia can be included *given that their treatment does not require the use of neither antifungal drugs nor corticosteroids* |
| Exclusion criteria | 1) Patient who improved enough to be discharged from the ICU before inclusion; 2) Documented invasive fungal infection requiring antifungal therapy; 3) • Patient needing or receiving prophylactic or empirical antifungal treatment for clinical care 4) Patient receiving corticoid therapy; 5) Palliative care with comfort measures only (Do Not Intubate (DNI) and Do Not Resuscitate (DNR) patients can be included); 6) Pregnant or breastfeeding; 7) No social security coverage; 8) Known hypersensitivity to isavuconazole or to any of excipients of CRESEMBA® specialty; 9) Treatment with ketoconazole, ritonavir, or any CYP3A4/5 inductor; 10) Short QT syndrome and/or patient with a family history of short QT syndrome; 11) Liver insufficiency (any stage); 12) moribund patients; 13) Participation in another interventional research on acute respiratory failure. 14) Person deprived of liberty. 15) Person subject of psychiatric care. 16) Patient under enforced hospitalization. 17) Adults under legal protection or unable to give their consent 18) Isolated HI |
| Investigational medicinal products | **Methylprednisolone:** will be given once a day at a dose of 2 mg/kg/day for three days as recommended in fibrosing pneumonitis in deeply hypoxemic patients. As of day 4, the daily dose will be tapered to 1 mg/kg/day until day 7, followed by 0.5 mg/kg/day from day 8 to day 14.<br>**Isavuconazole**: will be given at a dose of 200 mg every 8 hours for 2 days (6 administrations) and then once daily until day 14 or ICU discharge, which event occurs first.<br><br><u>Patients of one of the arms will receive isavuconazole and methylprednisolone whith an established interaction. The investigator must check the SMPC</u> |

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| | where all needed information are available. |
| Comparator treatment | Placebo Methylprednisolone and Placebo Isavuconazole |
| Interventions added for the trial | None |
| Risks added by the trial | Risk C |
| Number of participants included | 420 |
| Number of centers | 19 centers in France. |
| Duration of the study | - inclusion period: 60months<br>- participation period (treatment + follow-up): 6 months<br>- total duration 66 months |
| Statistical analysis | An interim analysis will be performed after the recruitment of 120 patients (or after 50 day-90 deaths, whichever will occur first). |
| Funding sources | PHRC-N 2018 |
| Study will have a Data Safety Monitoring Board | Yes |

## 2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

### Hypothesis for the study

This PHRC project entitled Efraim 2 follows on this harmful association and relies on a large literature suggesting that patients with ARF from undetermined etiology mostly have infiltrates related to fungal infection, steroid-sensitive conditions or lung infiltration by the underlying disease. Our hypothesis is that empirical steroids and/or antifungals might reduce mortality reported in patients with ARF from unknown cause.

### Description of knowledge relating to the condition involved

A growing number of adults live with immune dysfunction.[1] Up to 5% of the general population are cancer survivors,[2] transplantation is on the rise,[3] and immunosuppressant drugs are being used in broadening indications.[4] Moreover, intensive treatments now provide higher disease-free survival rates[2] but also increase the risk of life-threatening events, many of which affect the lungs.[5–8]

Acute respiratory failure [ARF] can be defined as a triad of clinical signs, radiographic findings, and gas exchange alterations. Most patients present with newly developing or worsening respiratory symptoms over a period of 7 days. Severe ARF manifests as respiratory distress with severe tachypnoea, laboured breathing, and recruitment of accessory respiratory muscles. Various patterns of pulmonary infiltrates may be seen, the most common of which is diffuse bilateral infiltrates.[9] Patients with ARF require oxygen therapy and most studies of ARF included patients receiving ≥6 liters/minute of standard oxygen. However, depending on the country and number of available ICU beds, patients with ARF may be managed onwards, in intermediate care units, or in intensive care units [ICUs]. They may be admitted to the ICU only if they require intubation and invasive mechanical ventilation [IMV]. Overall, the need for ICU admission, need for IMV, and/or mortality increase with the required oxygen flow.[10] Thus, IMV and mortality rates of up to 40% have been reported in patients receiving ≥6 L/min of standard oxygen.[9–16] Delayed ICU admission, as indicated by respiratory symptom duration or required oxygen flow at ICU admission has been associated with mortality.[13,14,17]

Immunocompromised patients with ARF can be encountered by all clinicians in their daily practice. Diagnostic work-up is the cornerstone of initial management, with emphasis on the broad range of causes that must be considered. Invasive and non-invasive tests are both able to identify the cause of ARF, bronchoscopy being needed in selected patients[9]. However, everything must be done to avoid cases where ARF aetiology cannot be identified, leaving the patient with a high level of uncertainty and adverse outcomes. Indeed, patients with ARF from undetermined aetiology have higher intubation and mortality rates[5,18,19]. This association has recently been confirmed in the large Efraim 1 study published in 2017[13] where 199/1611 (12.3%) patients had undetermined ARF aetiology with increased need for invasive mechanical ventilation (HR 1.46 [CI 1.09-1.98]), and higher hospital mortality rate (HR 1.43 [CI 1.04-1.97]) by multivariable analyses.

**Epidemiology**

The incidence of respiratory events varies across subsets of immunocompromised patients [Table 1]. Few studies followed cohorts of patients with the main objective of collecting information about the incidence of pulmonary infiltrates or respiratory complications. Among hematological malignancies, lymphoproliferative disorders [acute lymphoblastic leukaemia and lymphoma] were associated with a moderate [8%-18%] incidence[20] compared to acute myeloid leukaemia [AML] and myelodysplastic syndromes [MDS].[21–23] Moreover, patients with prolonged neutropenia[6] and autologous or allogeneic stem-cell transplant recipients[24–27] have an up to 40% incidence of respiratory events. Solid tumours are associated with a lower incidence of respiratory events, with lung cancer producing the highest rates [up to 10%-15%], as endo-bronchial obstruction and atelectasis are risk factors for pneumonia.[28] However, in patients with breast cancer treated with radiation and paclitaxel, the crude rate of pneumonitis was 14·6% [5·6%-29·2%].[29] Of note, in cancer patients receiving immunotherapy [mostly with programmed death 1 and programmed death ligand 1 inhibitors], the incidence of pneumonitis can reach 4%.[30,31] ARF occurs in about 5% of kidney transplant recipients and 12%-14% of heart or lung transplant recipients.[32,33] Overall, mortality is about 50%, depending on the underlying condition; nature, severity, and course of the respiratory failure, need for IMV, and associated organ dysfunctions.[13]

**Table 1: Incidence of respiratory events in various types of immunocompromised patients**

| | Cumulative incidence of respiratory events | Need for ICU admission | Hospital mortality |
|---|---|---|---|
| **Hematological malignancies** | | | |
| Acute myeloid leukaemia[5,20,21,23,34–36] | 22%-84% | 66% | 45% |
| Acute lymphoblastic leukaemia[20,35,36] | 7%-18·5% | 12%-15% | 38·5% |
| Lymphoproliferative diseases [5] | 8% | 8% | 40-50% |
| Myelodysplastic syndrome [20] | 29·4% | 20% | 17% |
| Autologous HSCT [24,25] | 3%-28% | 42% | 3%-55% |
| Allogeneic HSCT [26 27] | 24%-30% | 50% | 51% |
| Prolonged neutropenia[6,37] | 8%-29·5% | 11%-16% | 5%-12% |
| **Solid tumours** | | | |
| Lung cancer [28,38] | 26%-50% | All | 11·2%-60% |
| Other solid tumours [5,28,29] | 0·7%-10·3% | All | 6·1%-55% |
| Patients on immunotherapy [30,39] | 1·3%-3·6% | 1·3% ¥ | / |
| **Solid organ transplantation** | | | |
| Lung transplantation [33] | 14% | All | 65% |
| Heart transplantation [40] | 12·5% | All | 76·5% |
| Kidney transplantation [32,41] | 3·3%-4·8% | All | 16·4%-22·5% |

**Data on patients with drug-related immunosuppression are sparse.**
**¥ Refers to grade 3-4 toxicities.**

**References for this table are:** 1 Chaoui D, Legrand O, Roche N, et al. Incidence and prognostic value of respiratory events in acute leukemia. Leukemia 2004; 18: 670–5; 2 Garcia JB, Lei X, Wierda W, et al. Pneumonia during remission induction chemotherapy in patients with acute leukemia. Ann Am Thorac Soc 2013; 10: 432–40; 3 Moreau A-S, Lengline E, Seguin A, et al. Respiratory events at the earliest phase of acute myeloid leukemia. Leuk Lymphoma 2014; 55: 2556–63 ; 4 Azoulay E, Fieux F, Moreau D, et al. Acute monocytic leukemia presenting as acute respiratory failure. Am J Respir Crit Care Med 2003; 167: 1329–33; 5 Azoulay E, Thiéry G, Chevret S, et al. The prognosis of acute respiratory failure in critically ill cancer patients. Medicine (Baltimore) 2004; 83: 360–70; 6 Specchia G, Pastore D, Carluccio P, et al. Pneumonia in acute leukemia patients during induction therapy: experience in a single institution. Leuk Lymphoma 2003; 44: 97–101 ; 7 Rossini F, Verga M, Pioltelli P, et al. Incidence and outcome of pneumonia in patients with acute leukemia receiving first induction therapy with anthracycline-containing regimens. Haematologica 2000; 85: 1255–60 ; 8 Puig N, De La Rubia J, Jarque I, et al. Characteristics of and risk factors for pneumonia in patients with hematological malignancies developing fever after autologous blood stem cell transplantation. Leuk Lymphoma 2007; 48: 2367–74; 9 Afessa B, Abdulai RM, Kremers WK, Hogan WJ, Litzow MR, Peters SG. Risk factors and outcome of pulmonary complications after autologous hematopoietic stem cell transplant. Chest 2012; 141: 442–50; 10 Bergeron A, Chevret S, Peffault de Latour R, et al. Noninfectious lung complications after allogeneic haematopoietic stem cell transplantation. Eur Respir J 2018; 51. DOI:10.1183/13993003.02617-2017; 11 Ho VT, Weller E, Lee SJ, Alyea EP, Antin JH, Soiffer RJ. Prognostic factors for early severe pulmonary complications after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant 2001; 7: 223–9; 12 Orasch C, Weisser M, Mertz D, et al. Comparison of infectious complications during induction/consolidation chemotherapy versus allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2010; 45: 521–6; 13 Meyer E, Beyersmann J, Bertz H, et al. Risk factor analysis of blood stream infection and pneumonia in neutropenic patients after peripheral blood stem-cell transplantation. Bone Marrow Transplant 2007; 39: 173–8; 14 Yadav H, Nolan ME, Bohman JK, et al. Epidemiology of Acute Respiratory Distress Syndrome Following Hematopoietic Stem Cell Transplantation. Crit Care Med 2016; 44: 1082–90; 15 Rolston KVI, Nesher L. Post-Obstructive Pneumonia in Patients with Cancer: A Review. Infect Dis Ther 2018; 7: 29–38; 16 Cupp J, Culakova E, Poniewierski MS, Dale DC, Lyman GH, Crawford J. Analysis of Factors Associated With In-hospital Mortality in Lung Cancer Chemotherapy Patients With Neutropenia. Clin Lung Cancer 2018; 19: e163–9; 17 Taghian AG, Assaad SI, Niemierko A, et al. Risk of pneumonitis in breast cancer patients treated with radiation therapy and combination chemotherapy with paclitaxel. J Natl Cancer Inst 2001; 93: 1806–11; 18 Khunger M, Rakshit S, Pasupuleti V, et al. Incidence of Pneumonitis With Use of Programmed Death 1 and Programmed Death-Ligand 1 Inhibitors in Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis of Trials. Chest 2017; 152: 271–81 ; 19 De Velasco G, Je Y, Bossé D, et al. Comprehensive Meta-analysis of Key Immune-Related Adverse Events from CTLA-4 and PD-1/PD-L1 Inhibitors in Cancer Patients. Cancer Immunol Res 2017; 5: 312–8 ; 20 Roca O, de Acilu MG, Caralt B, Sacanell J, Masclans JR, ICU collaborators. Humidified high flow nasal cannula supportive therapy improves outcomes in lung transplant recipients readmitted to the intensive care unit because of acute respiratory failure. Transplantation 2015; 99: 1092–8; 21; Komurcu O, Ozdemirkan A, Camkiran Firat A, Zeyneloglu P, Sezgin A, Pirat A. Acute Respiratory Failure in Cardiac Transplant Recipients. Exp Clin Transplant Off J Middle East Soc Organ Transplant 2015; 13 Suppl 3: 22–5; 22Canet E, Osman D, Lambert J, et al. Acute respiratory failure in kidney transplant recipients: a multicenter study. Crit Care Lond Engl 2011; 15: R91; 23 Ulas A, Kaplan S, Zeyneloglu P, Torgay A, Pirat A, Haberal M. Acute Respiratory Failure in Renal Transplant Recipients: A Single Intensive Care Unit Experience. Exp Clin Transplant Off J Middle East Soc Organ Transplant 2015; 13 Suppl 3: 44–7.

## Summary of relevant pre-clinical experiments and clinical trials

### *2.1.1 Factors associated with mortality*

Several studies have assessed risk factors for mortality in immunocompromised patients with ARF. These factors can be grouped into five categories: (1) factors reflecting the severity of the ARF and associated organ dysfunctions; (2) factors related to delayed ICU admission; (3) factors related to the underlying disease and comorbid conditions; (4) factors related to the initial oxygenation and ventilation strategy; and (5) factors related to the etiology of ARF.

Hypoxaemia is the hallmark of respiratory failure. The clinical signs and tolerance are usually a function of respiratory symptom duration. For instance, an acute hypoxemic episode can lead to respiratory distress within a few hours, whereas a subacute or non-acute lung insult of similar magnitude may result in deep hypoxaemia without signs of respiratory distress. Overall, hypoxaemia reflects the severity of the lung involvement and has been associated with various adverse outcomes. Hypoxaemia, measured directly as the $PaO_2$ on room air or assessed based on the oxygen flow needed to achieve an $SpO_2$ of 95% or on the estimated or calculated $PaO_2/FiO_2$ ratio, has been used for many years to risk-stratify patients and guide ICU admission decisions. Oxygen flow has been associated with the need for ICU admission,[10] need for IMV,[10,16] and hospital mortality.[17] Similarly, $PaO_2/FiO_2$ has been associated with mortality in patients with ARDS,[42] non-invasive ventilation [NIV],[43] or failure of high-flow nasal oxygen therapy [HFNO].[44] Finally, persistent tachypnoea has been associated with failure of standard oxygen[44] or NIV[43]. Associated organ dysfunctions are best depicted by the SOFA score, which has been consistently identified as a determinant of mortality.[5,13,45] Delayed ICU admission has been associated with increased mortality in immunocompromised patients overall[14] and, more particularly, in those with ARF.[10,13,17] This may be the result of the careful clinical assessment, optimal oxygenation strategy, avoidance of potentially harmful investigations, and selection of the least invasive diagnostic tests in ICUs. The characteristics of the underlying immunosuppressive condition are not usually associated with hospital mortality following ICU admission,[46] although variations occur depending on ICU admission policies. A higher proportion of patients admitted with do-not-resuscitate/do-not-intubate status results in stronger associations between variables reflecting disease status and mortality.[47,48] Performance status and comorbidities have been associated with mortality.[13,14,49,50] As mentioned in the introduction, several studies have assessed the relationship between the aetiology of ARF and mortality. Mortality rates are lowest in patients with cardiac pulmonary oedema and highest in those with invasive fungal infections or no identified aetiology of ARF.

### *2.3.2 Early assessment of the pre-test probability of ARF etiology*

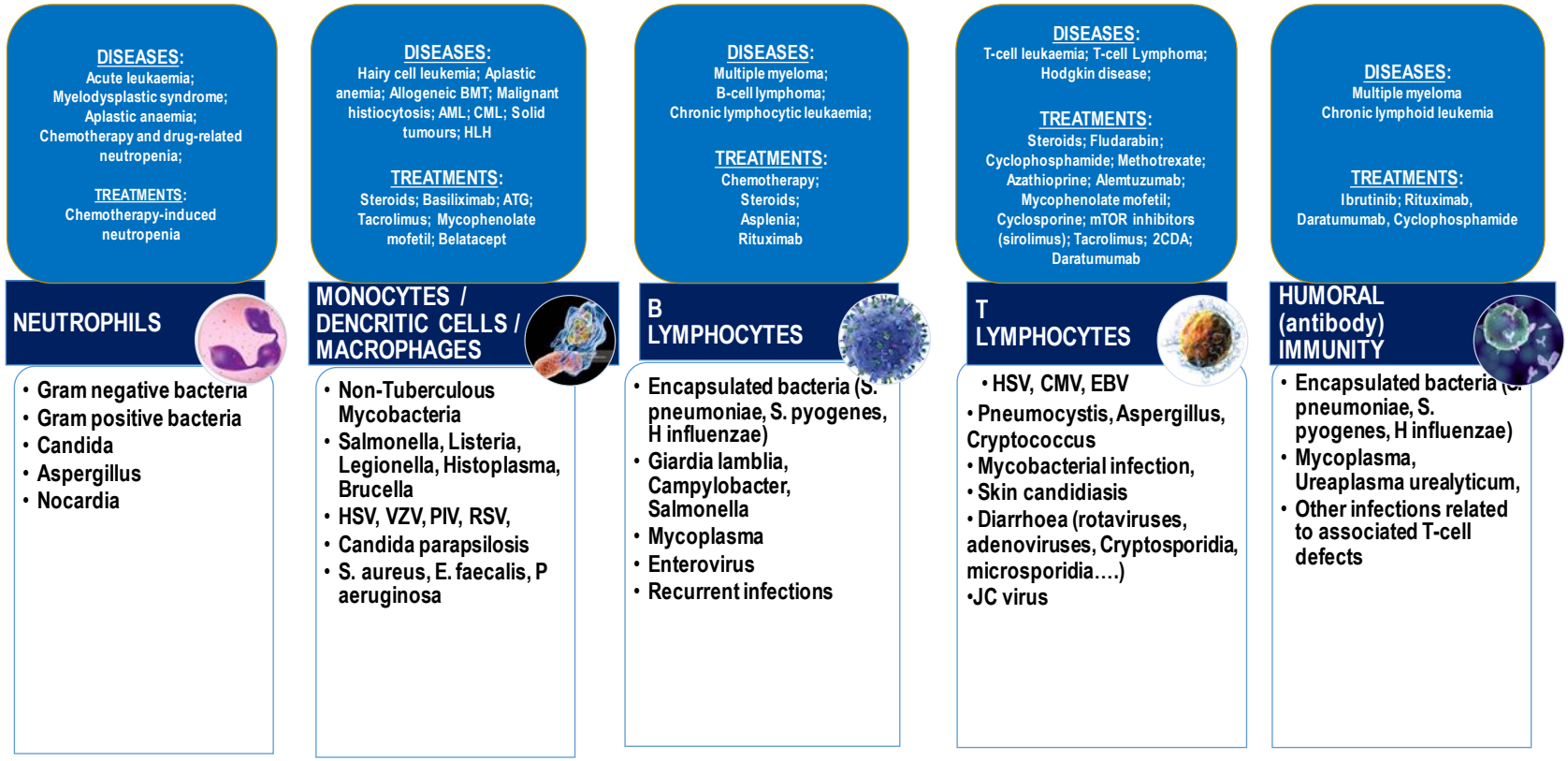
One of the first and key steps in the early management of immunocompromised patients with ARF is to establish the pre-test probability of the cause of ARF, at the bedside, based on the clinical examination. There is no standard combination therapy suitable for all patients with ARF. Each patient must be considered individually. Clinicians should not navigate in the dark with patients at high risk of intubation and mortality. Bacterial infection is the main cause of ARF and up to 90% of patients receive antibacterial agents.[9] Cardiogenic pulmonary edema must be considered in every patient. However, other diagnoses should be considered on a case-by-case basis. Thus, the basic diagnostic work-up is the same for all patients. It includes tests for cardiogenic pulmonary edema, sputum examination and blood cultures to detect bacterial or fungal infections, induced sputum examination for *Pneumocystis*, viral multiplex PCR on nasopharyngeal aspirates or swabs, viral PCR on plasma or blood, an assessment of the likelihood that the underlying condition and its treatments will affect the lungs, and an analysis of the imaging data.

When performing the first clinical examination, the mnemonic DIRECT can be used to assess the cause of ARF at the bedside.[51,52] **D** refers to respiratory symptom duration in days, **I** to the type of immunosuppression, **R** to the chest X-ray pattern, **E** to the clinician's experience of similar cases, **C** to the clinical findings, and **T** to high-resolution computed tomography (HRCT). In patients with myeloproliferative diseases such as acute myeloid leukaemia, myelodysplastic syndrome, or chronic myeloid leukaemia, most cases of ARF occurring early after disease onset are related to leukemic infiltrates, although some patients may present with pneumonia or cardiogenic pulmonary oedema.[23,34,53] ARF of infectious origin is, however, more common at the earliest phase of lymphoproliferative disorders such as acute lymphoblastic leukaemia or lymphoma.[54,55] In patients with T-cell proliferations, opportunistic infections have been reported before anti-cancer treatment initiation, underlying the role for disease-related immunosuppression.[56] Later during follow-up, infection is the main cause, although treatment-related toxicities and disease relapse can also lead to ARF. Clinicians may struggle with non-infectious etiologies whose diagnosis is believed to rely solely on biopsies, which are difficult to obtain in hypoxemic patients with thrombocytopenia and hemostatic disorders; or on bronchoscopy and bronchoalveolar lavage [BAL], which can cause respiratory deterioration requiring IMV. However, a multidisciplinary and collaborative approach allows the earlier recognition of typical patterns of clinical and laboratory findings, for which no additional diagnostic procedures are needed (lung infiltration by the underlying condition, leukemic infiltrates in patients with AML, diffuse alveolar haemorrhage, cytarabine-related pulmonary toxicity, immunotherapy-related pneumonitis, etc.). Patients with these patterns are often considered to have no known cause of ARF until a multidisciplinary team makes the appropriate diagnosis. Similarly, conditions such as neutropenia or allogeneic hematopoietic stem cell transplantation [HSCT] are associated with both a high risk of respiratory events and specific ARF etiologies such as exacerbation of previous lung injury during neutropenia recovery,[57] or non-infectious interstitial lung diseases following allogeneic HSCT.[26,58]

ARF within the first few days after solid organ transplantation is likely to be related to either a surgical complication or to decompensating chronic respiratory or cardiac comorbid condition.[32,33,40,41] Invasive candidiasis may occur quite early after transplantation.[59] However, most opportunistic infections are reported more than 3 months after transplantation and depend heavily on the prophylaxis actually used by the patient.[59,59–66] Of note, with the use of intensive immunosuppression in patients experiencing acute humoral or interstitial rejection[67] and with the use of immunosuppressant drug combinations to ensure graft tolerance, clinicians must carefully assess the individual risk for each possible etiology and perform a complete diagnostic work-up in such cases.[68]

Figure 1 illustrates the most frequently encountered types of infection according to the main disease- or treatment-related immunological deficiency. This figure focusses mainly on secondary immunosuppression in adults, as data for primary immune deficiencies are scarce. In each individual case, the type of immune deficiency must be assessed to allow appropriate adjustment of the initial anti-infectious treatment and to avoid treatment delays. Imaging studies, and more specifically HRCT, is another important bedside tool for determining the cause of ARF.[69] Patterns of lung involvement are an important piece of the puzzle but are not per se predictive of a specific etiology.[69] However, a combination of positive and negative HRCT findings suggests specific causes of lung infiltrates.[70]

**Figure 1**


DISEASES:
Acute leukaemia;
Myelodysplastic syndrome;
Aplastic anaemia;
Chemotherapy and drug-related neutropenia;
TREATMENTS:
Chemotherapy-induced neutropenia
NEUTROPHILS
• Gram negative bacteria
• Gram positive bacteria
• Candida
• Aspergillus
• Nocardia
DISEASES:
Hairy cell leukemia; Aplastic anemia; Allogeneic BMT; Malignant histiocytosis; AML; CML; Solid tumours; HLH
TREATMENTS:
Steroids; Basiliximab; ATG; Tacrolimus; Mycophenolate mofetil; Belatacept
MONOCYTES / DENCRITIC CELLS / MACROPHAGES
• Non-Tuberculous Mycobacteria
• Salmonella, Listeria, Legionella, Histoplasma, Brucella
• HSV, VZV, PIV, RSV,
• Candida parapsilosis
• S. aureus, E. faecalis, P aeruginosa
DISEASES:
Multiple myeloma;
B-cell lymphoma;
Chronic lymphocytic leukaemia;
TREATMENTS:
Chemotherapy;
Steroids;
Asplenia;
Rituximab
B LYMPHOCYTES
• Encapsulated bacteria (S. pneumoniae, S. pyogenes, H influenzae)
• Giardia lamblia, Campylobacter, Salmonella
• Mycoplasma
• Enterovirus
• Recurrent infections
DISEASES:
T-cell leukaemia; T-cell Lymphoma; Hodgkin disease;
TREATMENTS:
Steroids; Fludarabin; Cyclophosphamide; Methotrexate; Azathioprine; Alemtuzumab; Mycophenolate mofetil; Cyclosporine; mTOR inhibitors (sirolimus); Tacrolimus; 2CDA; Daratumumab
T LYMPHOCYTES
• HSV, CMV, EBV
• Pneumocystis, Aspergillus, Cryptococcus
• Mycobacterial infection,
• Skin candidiasis
• Diarrhoea (rotaviruses, adenoviruses, Cryptosporidia, microsporidia….)
•JC virus
DISEASES:
Multiple myeloma
Chronic lymphoid leukemia
TREATMENTS:
Ibrutinib; Rituximab, Daratumumab, Cyclophosphamide
HUMORAL (antibody) IMMUNITY
• Encapsulated bacteria (S. pneumoniae, S. pyogenes, H influenzae)
• Mycoplasma, Ureaplasma urealyticum,
• Other infections related to associated T-cell defects

### *2.1.2 From clinical probability to diagnostic confirmation: avoiding situations in which the ARF etiology remains undetermined*

Non-invasive diagnostic tests [NITs] offer an alternative to bronchoscopy and BAL, which carry a risk of respiratory deterioration requiring IMV[51]. Moreover, the diagnostic yield of NITs has increased since the introduction of more sensitive diagnostic tests such as PCR. In patients with cancer, the standard diagnostic work-up performed immediately at ICU admission includes a physical examination, a pre-test probability assessment using DIRECT, sputum and induced sputum examinations, nasopharyngeal aspirates or swabs, blood cultures, serum and urine antigen assays, imaging studies, and biomarker assays. These NITs perform as well as do bronchoscopy and BAL.[9,71] In solid-organ transplant recipients, however, BAL has a higher diagnostic yield,[32] although the risk/benefit ratio has not been assessed in this population. Moreover, with the advent of omics to assist in the diagnosis of infections,[72] as well as both sophisticated immunology and molecular biology methods and advances in imaging techniques to establish the diagnosis of non-infectious conditions, a reappraisal of the diagnostic yield of NITs in immunocompromised patients is warranted.

Nevertheless, as shown in Table 2 and Figure 2, despite an optimal early diagnostic workup, the etiology remains undetermined in 10% to 15% of patients with ARF. Failure to identify the etiology was independently associated with mortality in several studies.[5,13,18,19] In some patients, the etiology of ARF is identified late, and the impact of a late diagnoses and correspondingly late treatment has not been assessed. The association between absence of a documented cause and mortality raises several questions [Figure 3]. The association may be related in part to the patients who die within a few hours with intractable hypoxaemia and multiple organ dysfunctions before diagnostic tests can be performed. When providing expert opinion, careful attention should be directed to the clinical situation, underlying disease, comorbid conditions, and ongoing long-term treatments, as well as to the response to treatments given for the current ARF episode. The expert will also have the (sometimes difficult) task of determining which tests were actually performed, obtaining their exact results (as opposed to a classification as positive or negative), and potentially obtaining results that may not yet have been made available to the bedside physicians. Figure 3 depicts different situations in which failure to identify the cause of ARF translated into adverse outcomes. Figure 4 gives guidance on the first-line diagnostic strategy according to the clinical situation.

We are aware that lung biopsy is often not feasible, due to haemodynamic instability, deep hypoxaemia, or thrombocytopenia or other severe haemostatic abnormalities. Data on surgical lung biopsies in this setting are therefore scarce (Table 3). Nevertheless, valuable information can be gleaned from studies reporting surgical lung biopsy or autopsy data in immunocompromised patients with ARF of unknown cause. Overall, lung biopsy had a diagnostic yield above 60%, with complication rates of about 10% despite careful patient selection for the procedure. Lung biopsy had a lower diagnostic yield in patients receiving IMV. Invasive fungal infections and malignant or potentially steroid-sensitive lung infiltrates were the most common causes of ARF [Table 3]. The diagnostic yield of surgical lung biopsy for unexplained pulmonary infiltrates was assessed in a retrospective study of 62 haematology patients.[73] The exact diagnosis was established in 67% of patients, with invasive aspergillosis and malignancy being the main causes. The biopsy result prompted a treatment change in 40% of patients, and complications occurred in 11% of patients. The diagnostic yield was lower in patients with ARF who were receiving IMV at the time of biopsy. In a cohort of 63 haematology patients, the diagnostic yield of lung biopsy was 62% and the therapeutic yield 57%.[74] The diagnostic yield was lower in patients on IMV and in those with neutropenia but was higher in patients with focal infiltrates. Invasive aspergillosis was also a common biopsy finding in this study. The complication rate was 13%.[74] The 15% prevalence of invasive aspergillosis is in line with data on ARDS in patients with cancer[42]

and with autopsy findings in patients with ARDS.[75] In 21 haematology patients, including 10 in whom the lung biopsies were obtained post-mortem, inflammatory and malignant infiltrates were the most common diagnoses.[76] A retrospective autopsy study of 71 hematopoietic stem-cell transplant recipients showed that fungal infections, potentially steroid-responsive lung involvement, and malignant infiltrates were underdiagnosed.[77] The about 10% complication rate of lung biopsies occurred in patients who were highly selected based on platelet count, performance status, and goals of care. Given the lower diagnostic yield of lung biopsy in ICU patients, the risk/benefit ratio is not favorable, and lung biopsy is therefore rarely performed in critically ill immunocompromised patients with ARF and lung infiltrates of unknown cause. However, minimally invasive CT-guided lung biopsies and trans-bronchial cryobiopsies are being increasingly performed.[78–83] Studies to assess the timing of these minimally invasive diagnostic techniques in this setting are warranted. The diagnostic yield should be better defined as the identification of a new diagnosis that was not detected by any other less invasive technique and that translated into a change in treatment. Moreover, the risk/benefit ratio needs to be re-assessed. If these minimally invasive biopsy techniques are evaluated in a randomized controlled trial, control patients should receive empirical treatment for the most common lung-biopsy diagnoses, namely, invasive fungal infection and/or steroid-responsive lung disease.

**Table 2. Intubation and mortality rates in immunocompromised patients receiving standard oxygen ($O_2$), non-invasive ventilation (NIV) or high-flow nasal oxygen therapy (HFNO)**

Only studies published in English from 1 January 1998, to 30 April 2018 were taken into account. Studies that comprised only postoperative patients and studies on palliative NIV were not included.

¥ indicates day-90 mortality; all other studies reported hospital mortality.

**Randomized controlled trials; *post-hoc analysis of randomized controlled trials

| Author | N Patients | Immunosuppression | Intubation % | O2 | NIV | HFNO | Mortality % | O2 | NIV | HFNO | Underwent BAL | Undetermined aetiology (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Antonelli ** | 40 | Solid Organ transplants | 33·7 | 70 | 20 | / | 35 | 50 | 20 | / | 27·5 | 0 |
| Hilbert ** | 52 | All types | 61·5 | 66 | 46·1 | / | 53·8 | 80·8 | 50 | / | 32·7 | / |
| Azoulay | 203 | Oncology and haematology patients | 85·0 | / | 57 | / | 56 | 9 | 48·1 | / | 72 | 20·7 |
| Lemiale | 380 | Haematology Patients | 24·7 | 20 | 32 | / | 32 | 26 | 44 | / | / | 24·7 |
| Lemiale ** | 374 | All types | 41·4 | 45 | 38·2 | / | 25·7 | 34·4 | 30·9 | / | 38 | 4·5 |
| Mokart | 178 | Oncology and haematology patients | 48·0 | 50 | 45·9 | 75 | 46 | 55 | 56 | 25 | / | 25 |
| Frat ¥ * | 82 | All types | 46·3 | 43 | 65 | 31 | 29·3 | 27 | 46 | 15 | | 4·9 |
| Coudroy | 115 | All types | 44·0 | / | 55 | 35 | 30 | / | 40 | 20 | / | / |
| Lemiale * | 353 | All types | 40·2 | 38 | / | 45 | 22·6 | 20·7 | / | 25·9 | 38·2 | 4·5 |
| Azoulay | 1611 | All types | 40·9 | 41 | 41 | 41 | 36·5 | 32·7 | 36·9 | 38·4 | 60 | 12·9 |
| Tu | 38 | Solid Organ transplants | 34·2 | / | 50 | 20 | 22·7 | / | 22·2 | 5 | / | / |
| 11 studies | 3426 | | 45·00 | 47 | 45 | 41 | 35 | 37 | 40 | 21 | 45 | 12 |

**Figure 2**

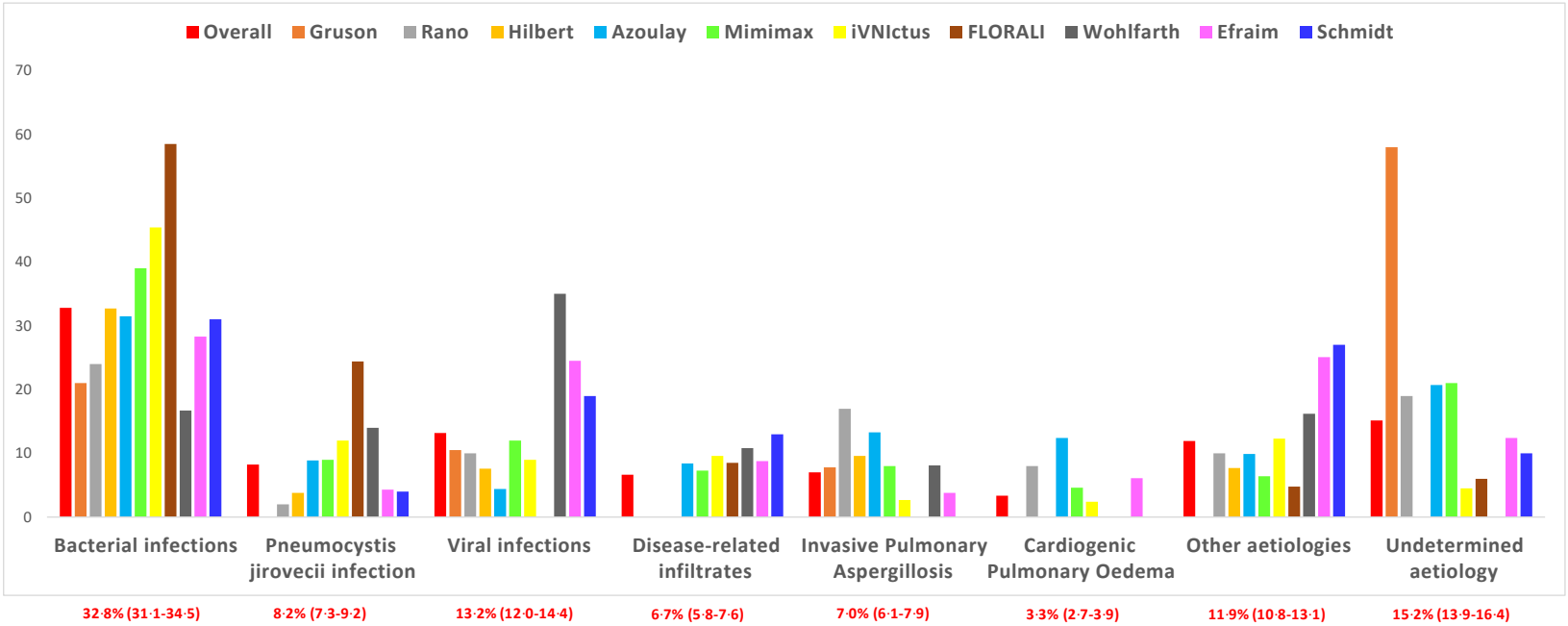
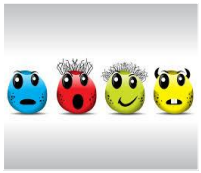


**Figure 3**

| | Unidentified, unsuspected, and untreated condition | Unidentified, suspected, but sub-optimally treated condition | Undocumented co-infection in which one pathogen remains untreated | Infectious and non-infectious condition, of which one is unidentified / untreated | Identified aetiology mistakenly considered as irrelevant finding |
|---|---|---|---|---|---|
| |  |  |  |  |  |
| **Example** | **Pneumonitis under check-point inhibitors** | **Lung infiltration by lymphoma** | **Tuberculosis in a kidney transplant recipient** | **Pneumocystis pneumonia (lung cancer patient)** | **Invasive aspergillosis** |
| **Mistakenly retained aetiology** | **Undetermined ARF aetiology**<br>Positive nasal swab (Rhinovirus) in a patient treated for melanoma<br>No clinical sign of viral infection | **Undetermined ARF aetiology**<br>Patient treated unconvincingly for bacterial infection based on high plasma CRP and PCT | **Undetermined ARF aetiology**<br>The only positive result is a positive PCR to CMV (2 logs) | **Undetermined ARF aetiology**<br>Patient receiving steroids for radiation pneumonitis without prophylaxis | **Undetermined ARF aetiology**<br>Patient believed to have an undetermined ARF aetiology |
| **Procedure that should have been performed** | - CT scan suggested hypersensitivity pneumonia. - BAL cell analysis was not performed | CT-guided lung biopsy (the diagnosis of lymphoma was made based on node and bone marrow biopsies) | CT findings suggested tuberculosis with 3 apical cavitated nodules in the right upper lobe | As hypoxemia worsened and ground-glass opacities extended, BAL should have been considered | Galactomannan at 0·50 and sputum positive for A Fumigatus, both considered irrelevant |
| **Missed treatment** | Steroids<br>Drug withdrawal | Chemotherapy | Anti-tuberculous agents | Trimethoprim sulfamethoxazole | Antifungal agents |

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

Acute respiratory failure (ARF) is the leading reason of ICU admission in immunocompromized patients. Failure to identify the ARF etiology is associated with increased mechanical ventilation and mortality rates. This was confirmed in the large Efraim 1 study published in 2017, where undetermined ARF etiology affected 609/1611 (38%) patients at day 3, 402 (25%) patients at day 7 and 199 (12.3%) patients overall, and was associated with a case fatality of 55% (vs. 40% in other patients). In lung biopsy/autopsy findings from these patients, invasive fungal infection, steroid-sensitive affections (organized pneumonia, non-infectious interstitial involvement, drug-related pulmonary toxicity…), and lung infiltration by the underlying disease (lymphoma, carcinomatous lymphangitis, systemic vasculitis, connective tissue diseases, etc.) were the leading etiologies. No study has evaluated survival benefits from empirical steroids and/or antifungals in immunocompromized patients with ARF from undetermined etiology.

## Identification and description of the investigational medication or medications

We first planned to use caspofungin because it is now in the public market. However, during our study group meeting, co-investigators shrewdly reported that as Aspergillus and mucorales were targeted, isavuconazole was the drug of choice. Also, caspofungin is not approved in these infections. Pfizer then agreed to provide isavuconazole or its placebo for this study. The steroid part of the intervention will use methylprednisolone as initially scheduled.

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

## In these high risk critically ill patients, intravenous administration is the preferred route of administration for most of the administered treatments. Moreover, gut dysfunction deprives oral access in up to one third of the patients and additional patients may be fasting. Hence, route will be intravenous for all study drugs.

Regarding treatment dosage, methylprednisolone will be given once a day at a dose of 2 mg/kg/day for three days as recommended in fibrosing pneumonitis in deeply hypoxemic patients. As of day 4, the daily dose will be tapered to 1 mg/kg/day until day 7, followed by 0,5 mg/kg/day from day 8 to day 14. Placebo will be saline with no particular masking or precaution as previously described in an ongoing trial in our group (PIC). Isavuconazole will be given at a dose of 200 mg every 8 hours for 2 days (6 administrations) and then once daily until day 14 or ICU discharge, which event occurs first. Placebo will be saline with no masking or precaution. However, both isavuconazole and placebo will be administered through a filling tubing that includes a filter, as recommended.

## Summary of the known and foreseeable benefits and risks for the clinical trial participants

Known and foreseeable benefits of steroids are improvement of the respiratory status, Pao2/FiO2 ratio and radiographic improvement as measured by the number of quadrants involved on chest X ray.

Pulsed methylprednisolone infusion been shown to be safe and effective. Known and foreseeable risks of steroids include severe hypertension, bradycardia, hypokaliemia and decompensation of diabetes.

Isavuconazole is used to treat invasive aspergillosis and invasive mucormycosis. Untreated invasive fungal infection is found in up to 20% of patients dying with acute respiratory failure.
Common adverse effects include low potassium, delirium, headache, sleepiness, vein inflammation, vomiting, diarrhea, nausea, stomach pain, elevated results in liver function tests, rash, itchy skin, and kidney failure.

# 3 OBJECTIVES

## Primary objective

The primary objective of this trial is to reduce 90-day mortality in immunocompromised patients with ARF from undetermined etiology at day-3. The intervention would evaluate the impact of steroids ± isavuconazole for 14 days or until ICU discharge.

## Secondary objectives

The secondary study objectives are to:

- Evaluate how early empirical therapy can affect ICU, hospital and day-28 mortality.
- Evaluate whether steroids increase the proportion of patients with ICU acquired microbiologically documented bacterial infections within 3 months following randomization.
- Evaluate the proportion of patients with invasive fungal infection within 3 months following randomization.
- Evaluate the proportion of patients with HSV, VZV or CMV reactivation within 3 months following randomization.
- Evaluate whether steroids are complicated by severe hypokaliemia (<2,5 meq/l), newly acquired or decompensated diabetes, or severe or newly acquired hypertension
- Evaluate whether isavuconazole will favor the emergence of infections with, Aspergillus or mucorale species with decreased sensitivity to isavuconazole
- Evaluate occurrence of Candida infection
- Evaluate how steroids affect psychiatric symptoms such as Post-traumatic Stress Disorder, anxiety and depression at 6 months
- Evaluate how this early intervention can improve quality of life at 6months

# 4 STUDY DESIGN

## Study endpoints

### *4.1.1 Primary endpoint*

All-cause day-90 mortality

### *4.1.2 Secondary endpoints*

- ICU mortality
- hospital mortality
- day 28 mortality
- proportion of patients with ICU acquired microbiologically documented bacterial infections
- proportion of patients with invasive fungal infection within 3 months following randomization
- proportion of patients with HSV, VZV or CMV reactivation within 3 months following randomization

- occurrence of severe hypokaliemia (<2,5 meq/L), decompensated diabetes or severe or newly acquired hypertension
- emergence of Aspergillus species with decreased sensitivity to isavuconazole
- Incidence of Candida infection
- incidence of psychiatric symptoms: Post traumatic Stress Disorder (IES-R), anxiety and depression at 6 months (HADS)
- quality of life at 6 months (SF36)

## Description of research methodology

### *4.1.3 Design of the trial*

➢ *Category 2 trial*

- Randomized
- Controlled
- Double blind
- 2x2 factorial design
    - **Group 1 (experimental for steroid):** 2 mg/kg/day of IV methylprednisolone for three days. As of day 4, the daily dose will be tapered to 1 mg/kg/day until day 7, followed by 0,5 mg/kg/day from day 8 to day 14 + IV placebo of isavuconazole
    - **Group 2 (experimental for antifungals):** IV placebo of methylprednisolone + IV isavuconazole (200 mg every 8 hours for 2 days followed by 200 mg per day until ICU discharge or for a total duration of 14 days)
    - **Group 3** (**experimental for steroids and antifungals):** IV methylprednisolone 2 mg/kg/day for three days. As of day 4, the daily dose will be tapered to 1 mg/kg/day until day 7, followed by 0.5 mg/kg/day from day 8 to day 14 + IV isavuconazole 200 mg every 8 hours for 2 days followed by 200 mg per day until ICU discharge or for a total duration of 14 days)
    - **Group 4 (best standard of care):** IV placebo of methylprednisolone + IV placebo of isavuconazole. This group receives the treatment that is currently recommended.

The chief advantage of a factorial design is the ability to answer two or more questions in a single experiment. The efficiency in terms of sample size of the factorial design that tests two interventions at the same time is valid under the assumption that no interaction is present between the two interventions.

### *4.1.4 Number of participating sites*

Multicenter study: several sites and hospitals in France**:** The participants will be recruited in several French hospitals, in medical or medical surgical ICU

### *4.1.5 Identification of participants*

The participants in this trial will be identified as follows:
Centre no. (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.

A randomization number will also be assigned when the participant is randomized.

When selected, the patient eligibility will be evaluated from inclusion and non-inclusion criteria. Once the consent will be signed by the patient and investigator, the patient will be

included and randomized by connecting the eCRF. The patient identification number will be allocated.

### *4.1.6 Randomization*

Randomization will be achieved using an electronic system incorporated in the eCRF and R software [http://www.R-project.org/]. The impact of the intervention will be assessed at the patient level. Randomization will be centralized on a web site to ensure allocation concealment at the trial statistical center.
Patients will be randomized into four parallel groups, in a 1:1:1:1 ratio, based on pre-specified lists.

**Stratification**: Randomization lists will be stratified on the underlying malignancy, distinguishing two groups, namely (1) haematological malignancies (Acute and chronic leukemia, lymphoma, myeloma, and others), and (2) non heamatological malignancies (solid tumors, treatment-related immunodepression, organ transplantations, and primary immunodeficiencies).

Randomization lists will be balanced through the use of permutation blocks of fixed size that will not be disclosed to the local investigators, to ensure allocation concealment and to avoid all risk of bias in patient selection.

### *4.1.7 Blinding methods and measures put in place to protect blinding*

Patients will be randomized through the eCRF and the local pharmacy will be informed of the allocated treatment. Treatment will be prepared in the local pharmacy by a team not involved at all in patient's care. Treatment will be sent to the ICU and administered IV to the patient along with a careful monitoring. Both ICU clinicians and patients will be blind from the assigned group. Preparations will not allow identifying the drugs or their placebo. Also, for isavuconazole, a filter will be added to the line of patients receiving the drug (as recommended) and to those receiving placebo (possible precipitations are invisible).

### *4.1.8 Unblinding procedures*

Unblinding will be requested by the investigator for any reason requiring:
considered essential by the investigating physician by calling upon:

- a modification of the patient's follow-up as defined in the protocol
- a medical action.

Non-emergency situation

The request must be sent to the Promotion Unit of the DRCI-APHP using the current form
By email **drc-levee-insu@aphp.fr**
**-** followed by with a phone call to 01 40 27 57 30

The investigator requesting a non-urgent unblinding must first have obtained the opinion of the coordinating investigator

**Emergency Situation**

The request should be made to the poison center at Fernand Widal Hospital, Telephone: **+33 (0)1 40 05 48 48** followed by sending the current form:

- by email to **alertes.rtu.lrb@aphp.fr**

or

- by fax to 01 40 05 48 88.

a copy will be sent simultaneously to the sponsor's Safety Department
- by email to drc-levee-insu@aphp.fr

**Specific case of infections during the blinded phase of the protocol**
In case of the occurrence of an infection (fungal or non-fungal) during the 14 days of treatment there will be a premature discontinuation of treatment, but patients will always be monitored in the trial in order to collect the corresponding data. Unblinding will be performed regarding all treatment arms (isavuconazole/placebo and corticosteroids/placebo) and a treatment adapted to the diagnosed infection, will be started.

## 5 IMPLEMENTATION OF THE STUDY

Before any examination or intervention related to the trial may be carried out, the investigator must obtain the freely given, informed and written consent of the participant, or of his/her legal representative where applicable.

| Whose consent must be obtained | Who informs the individuals and collects their consent | At what point the individuals are informed | At what point the consent is obtained |
|---|---|---|---|
| the individual participating in the study;<br>the legal representative | the PI or collaborating physician declared and trained in the study ICU | At randomization visit | At randomization visit |

### Randomization visit

If ARF etiology has not been identified 24 hours after hospital admission, eligible patients will be included and randomization will have to be performed before day 5 of ICU admission.
The randomization visit will be carried out by the physician who is responsible for the patient during the Study. During this visit, the investigator will:

- verify the eligibility criteria,
- interview the patient and record:
- medical, surgical and therapeutic histories,
- histories of undercurrent disease and current treatments,
- assess acute respiratory failure
- assess immunosuppression
- Documented invasive fungal infection that requires antifungal therapy.
- inform the patient or deferred consent by the family about the protocol, and give them the information and consent form
- If all eligibility criteria are met the investigator will complete the Study Inclusion Form listing inclusion and exclusion criteria
- Perform the randomization on CleanWeb®, an online randomization system
- Provide the first treatment.

Patients will receive the best standard of care and appropriate investigations to identify ARF etiology immediately at ICU admission.
In case no ARF etiology is documented 24 hours after hospital admission, patients will be randomized (2x2 factorial design) to one of the four following groups:

- **Group 1 (experimental for steroid):** 2 mg/kg/day of IV methylprednisolone for three days. As of day 4, the daily dose will be tapered to 1mg/kg/day until day 7, followed by 0.5 mg/kg/day from day 8 to day 14 + IV placebo of isavuconazole
- **Group 2 (experimental for antifungals):** IV placebo of methylprednisolone+ IV isavuconazole (200mg every 8 hours for 2 days followed by 200 mg per day until ICU discharge or for a total duration of 14 days)
- **Group 3** (**experimental for steroids and antifungals):** 2 mg/kg/day of IV methylprednisolone for three days. As of day 4, the daily dose will be tapered to 1mg/kg/day until day 7, followed by 0.5 mg/kg/day from day 8 to day 14 + IV isavuconazole 200 mg every 8 hours for 2 days followed by 200 mg per day until ICU discharge or for a total duration of 14 days)
- **Group 4 (best standard of care):** IV placebo of methylprednisolone + IV placebo of isavuconazole. This group receives the treatment that is recommended today.

All stakeholders will be blind of the treatment groups.

## Follow-up visits

Visits will occur following this schedule:
1/ Data will be collected on time between admission and randomization, with a special focus on diagnostic tests that have been performed to identify ARF etiology
2/ After randomization patients will be followed daily until day 7, then weekly until day 28 if they are still hospitalized, and then at day 90. Basic clinical information, SOFA score, radiographic and PaO2/FiO2 evolution, as well as all results that document ARF etiology or acquired infections.
3/ At day 180 (6 months), patients will be interviewed to assess post-ICU burden using validated questionnaires.

## Last study visit

PTSD (IES questionnaire), anxiety and depression (HADS questionnaire), and quality of life (SF36 questionnaire) will be evaluated at 6 months

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

The total duration of the Study will be 66 months.

Expected duration of inclusions: 60 months.

- Duration of participation of each patient: 6 months
  - Maximum period between screening and enrolment: 5 days
  - Treatment duration: until 14 days or ICU discharge

## Table or diagram summarizing the chronology of the study

| *Actions/*Visits | D-1/D-4 **ICU admission** | D1 (**Baseline visit) Randomization** | D2 to D7 | D14 | D 28 | D 90 | M6 |
|---|---|---|---|---|---|---|---|
| *Information* | | X | | | | | |
| *Informed consent* | | X | | | | | |
| *Inclusion and exclusion* | | X | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *criteria check* | | | | | | | |
| *BHCG* | | X | | | | | |
| *Medical History* | | X | | | | | |
| *Clinical examination* | X | X* | X* | X* | X* | X* | X* |
| *Hepatic function assessment* | X*** | X*** | X*** | X*** | | | |
| *SOFA score* | | X* | X* | X* | X* | X* | X* |
| *Randomization on CleanWeb* | | X | | | | | |
| *Dispensation of experimental treatments*** | | X | X | X | | | |
| *Substudy PKPD blood sampling* | | X** | X** | | | | |
| *Adverse events* | | X | X | X | X | X | X |
| *Questionnaires (SF36, HADS, IES-R)* | | | | | | | X |

*Dispensation of treatments**: Treatment duration= until 14 days or ICU discharge.*
*X*:* After randomization patients will be followed daily until day 7, then weekly until day 28 if they are still hospitalized.
X**: 6 PKPD blood sampling according to PKPD substudy, until D4 included.
*X***: hepatic function assessment will performed upon ICU admission then each 48h*

## Distinction between standard care and study

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

| **Interventions, procedures and treatments carried out for research purposes** | **Interventions, procedures and treatments associated with <u>standard care</u>** | **Interventions, procedures and treatments added for <u>research purposes</u>** |
|---|---|---|
| **Treatments** | Standard care at ICU admission | IV methylprednisolone<br>IV isavuconazole<br>IV placebo |
| **Visits** | | Questionnaires at M6 |
| **Blood samples** | | 6 PKPD blood samplingaccording to substudy (only for patients agreed - on substudy participants sites) |
| **Imaging** | | None |

# 6 <u>ELIGIBILITY CRITERIA</u>

## Inclusion criteria

- Age >18 years and < 90 years

- Known immunosuppression:
    a) immunosuppressive drug,
    b) solid organ transplant
    c) solid tumor
    d) hematological malignancies
    e) primary immune deficiency
- ICU admission for acute respiratory failure as defined by
    a) respiratory distress with tachypnea (respiratory rate>30/min)
    b) cyanosis
    c) laboured breathing
    d) need for more than 6L of standard oxygen to maintain SpO2>95%, or for high flow oxygen, non-invasive or invasive mechanical ventilation
- No established ARF etiology after 24 hours of hospital admission
- Patient admitted for at least 24 hours at hospital
- Informed consent signed:
  - by the patient,
  - Or informed consent signed by a family members/trustworthy person if his condition does not allow him to express his consent in written as per L1111-6,
- Or in an emergency situation and in the absence of family members/trustworthy person, the patient can be enrolled. The consent to participate to the research will be requested as soon as the condition of the patient will allow).

  Note: Patient with Pneumocystis pneumonia can be included given that their treatment does not require the use of neither antifungal drugs nor corticosteroids

## Exclusion criteria

- Patient who improved enough to be discharged from the ICU before inclusion
- Documented invasive fungal infection that requires antifungal therapy.
- Patient needing or receiving prophylactic or empirical antifungal treatment for clinical care
- Patient needing or receiving corticoid therapy
- Patient receiving palliative care with comfort measures only (Do Not Intubate (DNI) and Do Not Resuscitate (DNR) patients can be included)
- Pregnant or breastfeeding patient
- No social security coverage
- Known hypersensitivity to isavuconazole or to any of excipients of CRESEMBA® specialty
- Patient treated by ketoconazole, ritonavir, or any CYP3A4/5 inductor
- Short QT syndrome and/or patient with a family history of short QT syndrome;
- Liver insufficiency (any stage)
- Moribund patients
- Participation in another interventional research on acute respiratory failure
- Person deprived of liberty.
- Person subject of psychiatric care.
- Patient under enforced hospitalization.
- Adults under legal protection or unable to give their consent
- Isolated HIV

## Recruitment procedure

All participating centers belong to the GRRR-OH, a research network specializing in the respiratory care of critically ill immunocompromised patients. All these centers have previously taken part in observational studies, surveys, or therapeutic trials. They all have high case-volumes of patients with immune deficiencies due to immunosuppressive drugs, solid-organ transplantation, malignancies, or systemic diseases. Although they are specialized in oncology and haematology, they also admit high volumes of patients with systemic diseases, solid organ transplant and other immunosuppression. All centers are in France.

The GRRR-OH has recently completed two large trials, the iVNICTUS has been published in JAMA in 2015 and the HIGH trial has recruited 778 patients with acute respiratory failure in 14 months and is submitted for publication.

| | *Number of participants* |
|---|---|
| *Total number of participants to be included* | *420* |
| *Number of centers* | *19* |
| *Enrolment period (months)* | *60* |

| **Expected number of eligible patients in the participating centers** | | | | |
|---|---|---|---|---|
| **#** | **Investigator** | **Site** | **Expected number of patients recruited per month** | **Total in 42 months** |
| **1** | **Dr LEMIALE Virginie** | Paris Saint Louis | **2** | **35** |
| **2** | **Pr. DECAVELE Maxens** | Pitié Salpétrière | **2** | **35** |
| **3** | **Dr MOKART Djamel** | Marseille Institut Paoli Calmettes | **2** | **35** |
| **4** | **Dr KOUATCHET Achille** | CHU ANGERS | **0,5** | **11** |
| **5** | **Dr Naike BIGE** | Villejuif IGR | **0,5** | **11** |
| **7** | **Dr Jean-Herlé RAPHALEN** | Necker | **0,5** | **11** |
| **9** | **Pr ARGAUD Laurent** | CHU Lyon Edouard Herriot | **1** | **25** |
| **10** | **Dr Nicolas DE PROST** | Henri Mondor | **0,5** | **11** |
| **11** | **Dr Guillaume LACAVE** | CH Versailles André Mignot | **0,5** | **11** |
| **13** | **Dr Laure CALVET** | Clermont-Ferrand Gabriel Montpied | **0,5** | **11** |
| **15** | **Dr Emmanuel CANET** | CHU Nantes | **1** | **25** |

| | | | | |
|---|---|---|---|---|
| **16** | **Dr Florent WALLET** | CHU Lyon Sud | **1** | **25** |
| **19** | **Dr Jean Pierre QUENOT** | CHU Dijon | **0,5** | **11** |
| **21** | **Dr PICARD Muriel** | CHU Toulouse | **0,5** | **11** |
| **22** | **Dr BARBIER François** | CHR Orléans | **0,5** | **11** |
| **23** | **Dr Anne Sophie MOREAU** | CHRU Lille | **1** | **25** |
| **26** | **Dr Frederic PENE** | Cochin | **2** | **35** |
| **27** | **Dr Raphaël CLERE-JEHL** | Strasbourg | **2** | **35** |
| **29** | **Dr Alexandre LAUTRETTE** | Clermont-Ferrand Centre Jean Perrin | **0.5** | **11** |

## Termination rules

### *6.1.1 Criteria and procedures for prematurely terminating the study treatment*

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

**Specific cases of infections occurring during the first 14 days of treatment**
In case of the occurrence of an infection, fungal or not fungal, during the 14 days of treatment there will be a premature discontinuation of all experimental treatments, but patients will always be monitored in the trial in order to collect the corresponding data.

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

In the case of severe adverse events, the investigator must notify the sponsor and follow up the participant for 1 month following the premature discontinuation of treatment. Notification of a serious adverse event must be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor. The serious adverse event will be monitored until it is resolved. If a Data Safety Monitoring Board has been created, the committee can specify and/or validate the follow-up methods.

### *6.1.2 Criteria and procedure for premature withdrawal of a participant from the study*

- Participants may exit the study at any time and for any reason.

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

**Specific cases of infections occurring during the first 14 days of treatment**
In case of the occurrence of an infection (fungal or not fungal infection), during the 14 days of treatment there will be a premature discontinuation of all experimental treatments, but patients will always be monitored in the trial in order to collect the corresponding data.

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

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

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

### *6.1.3 Follow-up of participants following premature withdrawal from the study*

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

### *6.1.4 Full or partial discontinuation of the study*

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

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

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

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

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority and to the Ethics Committee without undue delay but no later than 15 days after the date of the temporary halt or early termination. It shall include the reasons fr suche action ans specify follow-up measures..

# 7 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

## Description of the investigational medicinal products

Attention:
Due to known and foreseeable interaction between isavuconazole and other treatment that might be administered to a patient as SOC in the course of his/her participation to the study the utmost attention should be given in the choice of this treatment. Each time a new treatment is considered the investigator should refer to Cresemba's summary of product characteristics (SMPC)
.
In the context of the studied treatment patient of one of the arms will receive isavuconazole and methylprednisolone with an established interaction The investigator must check the SMPC where all needed information are available.

### *7.1.1 Investigational medicinal products*

Two drugs, Methylprednisolone and CRESEMBA® (isavuconazole), and their corresponding placebo will be used as experimental treatments in this trial for a treatment period of 14 days or if less than 14 days, until ICU discharge.

Investigational medicinal products:

- CRESEMBA® (isavuconazole) 200 mg, powder for concentrate for solution for infusion, provided free of charge by PFIZER™ to the sponsor, infusion solvent: sodium chlorure (NaCl 0.9%), 250 mL (not provided, refunded in additional cost)
- Methylprednisolone 500 mg, powder for concentrate for solution for infusion and water for injection 10mL, provided by sponsor, infusion solvent: sodium chlorure (NaCl 0.9%), 50 mL (not provided, refunded in additional cost)
- Placebo of CRESEMBA® 200 mg, water for injection 10ml, provided by sponsor, infusion solvent: sodium chlorure (NaCl 0.9%), 250 mL (not provided, refunded in additional cost)
- Placebo of Methylprednisolone 500 mg, water for injection 10 ml, provided by sponsor, infusion solvent sodium chlorure (NaCl 0.9%), 50 mL (not provided, refunded in additional cost)

### *7.1.2 Storage*

#### 7.1.2.1 **CRESEMBA® or Placebo box**

Before reconstitution / dilution: Store in a refrigerator (2 °C to 8 °C).
After reconstitution / dilution: The product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the

user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

#### 7.1.2.2 **Methylprednisolone or Placebo box**

Before reconstitution / dilution: Store at a temperature between exceeding 25 ° C.
After reconstitution / dilution: the product must be used extemporaneously.

#### 7.1.2.3 **Opabag boxes for 250mL bottles**

Boxes of opabag for 250 mL bottles will be store at room temperature, protected from light and moisture.

#### 7.1.2.4 **Infusers with filter 0.2µm in polyethersulfone boxes**

Boxes of infusers with filter 0.2µm in polyethersulfone for reconstitution/dilution of CRESEMBA® will be store at room temperature, protected from light and moisture.

### *7.1.3 Posology & Dosage schedule*

Patients will receive the best standard of care and appropriate investigations to identify ARF etiology immediately at ICU admission.
In case no ARF etiology is documented after 24 hours of hospitalization, patients will be randomized to one of the four following groups:

- **Group 1 (experimental for steroid):** 2 mg/kg/day of IV methylprednisolone for three days. As of day 4, the daily dose will be tapered to 1 mg/kg/day until day 7, followed by 0.5 mg/kg/day from day 8 to day 14 + IV placebo of isavuconazole

- **Group 2 (experimental for antifungals):** IV placebo of methylprednisolone + IV isavuconazole (200 mg every 8 hours for 2 days followed by 200 mg per day until ICU discharge or for a total duration of 14 days)

- **Group 3** (**experimental for steroids and antifungals):** IV methylprednisolone 2 mg/kg/day for three days. As of day 4, the daily dose will be tapered to 1 mg/kg/day until day 7, followed by 0.5 mg/kg/day from day 8 to day 14 + IV isavuconazole 200 mg every 8 hours for 2 days followed by 200 mg per day until ICU discharge or for a total duration of 14 days)

- **Group 4 (best standard of care):** IV placebo of methylprednisolone + IV placebo of isavuconazole. This group receives the treatment that is currently recommended.

### *7.1.4 Packaging*

The clinical trial department of AGEPS will be responsible for the preparation of sealed numbered boxes according to a random list of treatment numbers (active and placebo) labelled for this study according to the Good Manufacturing Practices.

The experimental drugs will be grouped in the form of 2 types of numbered boxes:
- Boxes containing 8 vials of CRESEMBA® and/or 8 vials of Water for injections, 10mL (used for reconstitution or as placebo) and opaque bag for preparation for 6 days of treatment

- Boxes containing 8 vials of Methylprednisolone and/or Water for injections, 10mL (used for reconstitution or as placebo) and opaque bag for preparation for 8 days of treatment

The treatment of each patient requires, at least, one box of each drug.

### *7.1.5 Reconstitution and Administration*

In order to maintain the double blind, the preparation and the reconstitution of the treatments are carried out in the care service of each center by an independent manipulator of the follow-up and the evaluation of the patients. It guarantees blindness to the patient, the investigator and the rest of the health care team when preparing the treatment for the study.
The independent manipulator will record the reconstitution of the investigational medicinal product on the specified file, supplied with each box.

#### 7.1.5.1 **CRESEMBA® or Placebo**

One vial of the powder for concentrate for solution for infusion should be reconstituted by addition of **5 mL** water for injections to the vial.
The vial should be shaken to dissolve the powder completely. The reconstituted solution should be inspected visually for particulate matter and discoloration. Reconstituted concentrate should be clear and free of visible particulate.
After reconstitution, the entire content of the reconstituted concentrate should be removed from the vial and added to an infusion bag containing 250 mL of sodium chloride 9 mg/mL (0.9%) solution for injection.
After the reconstituted concentrate is further diluted, the diluted solution may show fine white-to-translucent particulates of CRESEMBA® that do not sediment (but will be removed by in-line filtration). Opabags will be provided separately from the boxes to ensure the blindness on the product.
The diluted solution should be mixed gently, or the bag should be rolled to minimise the formation of particulates. Unnecessary vibration or vigorous shaking of the solution should be avoided. The solution for infusion must be administered via an infusion set with an in-line filter (pore size 0.2 µm to 1.2 µm) made of polyether sulfone (PES) [Provided separately].
CRESEMBA® should not be infused into the same line or cannula concomitantly with other intravenous products.

#### 7.1.5.2 **Methylprednisolone or Placebo**

For the active boxes: One vial of the powder for concentrate for solution for infusion should be reconstituted by addition of **7.8 ml** of water for injections.
In order to avoid a coring phenomenon of plugs, it is recommended to perform the reconstitution using a syringe equipped with an external diameter needle of 0.8 mm (equivalent to 21 gauges)

Placebo boxes: vial of 10 ml water for injection
Once reconstituted, the solution should be administered by I.V. infusion with an infusion bag containing 50 mL of sodium chloride 9 mg/mL (0.9%) solution for injection.

## Management of the investigational medicinal products

### *7.1.6 Supply*

#### 7.1.6.1 **First Supply**

Numbered patient boxes of CRESEMBA®/placebo and Methylprednisolone/placebo will be sent after the opening visit.

#### 7.1.6.2 **Re Supply**

Re-supplies of patient boxes will be ordered via the eCRF: boxes will be automatically sent to the centers' pharmacies according to their remaining stock.
The hospital pharmacist (with respect to domestic procedures) will confirm receipt in writing of all batches of the study medications and maintain an accurate accounting of them.

### *7.1.7 Dispensing*

Pharmacies will dispense boxes to the care unit on the basis of a specific prescription.

### *7.1.8 Destruction*

At the end of the study, accountability must be ensured by the CRA. After completion, boxes (unused, returned…) will be destructed by the local hospital pharmacy only with the promoter's authorization.

## Traceability information for the investigational medicinal products

The traceability will be insured by the prescription with the first peel-off label.
The second peel off label will be affixed on the patient/nurse booklet by the independent manipulator.

## Authorised and prohibited treatments (medicinal, non-medicinal, surgical), including emergency medications

### *7.1.9 Standard of care*

Patients in the four groups will receive the best standard of care, according to the usual practice of the local intensivists and primary-care physicians in the GRRR-OH. We want to emphasize the five elements of the standard of care that have been put forward by multinational experts[84]:

1. Early admission should be the rule for every patient as to avoid losing the chance for performing non-invasive diagnostic and therapeutic strategy;
2. The goals of care need to be assessed at admission as to allow to treat at best the patients, respect their preferences but also maintain the treatments for a certain time period (time-limited trials);
3. As the recent iVNIctus and HIGH trials in immunocompromised ICU patients showed no difference in terms of mortality or intubation rates between standard oxygen and NIV, or standard oxygen and HFNC[11,85], these treatments should be used at clinician's discretion as long as they allow to alleviate the signs of respiratory distress and reach a $SpO_2 \geq 95$;
4. As mentioned above, immediately after ICU admission, patients need to have a clinical examination, clinicians establish at the bedside the pre-test probability of the ARF aetiology and the basic non-invasive diagnostic tests. Bronchoscopy and BAL should be left for specific cases. Investigators of this trial do not discourage to perform a bronchoscopy, and do not consider that the procedure is mandatory for all patients. Hence, patients eligible to be randomized for this trial will not need to

undergo a bronchoscopy and BAL prior to randomization. However, when patients are intubated, investigators of this trial encourage clinicians to perform bronchoscopy and BAL, but this is not mandatory.

5. Patients who need an antifungal therapy for a documented fungal infection and patients needing or receiving prophylactic or empirical antifungal treatment for clinical care are not eligible for this trial. The same applies for steroids. If patients have a mandatory indication for steroids, then, they are not eligible for this trial

Once patients are stabilized and have reached oxygenation targets, a diagnostic workup is performed ideally within a short time after ICU admission. As the Minimax trial published in 2010 suggested that diagnostic and therapeutic yields of non-invasive tests are overall not inferior to this of bronchoscopy and BAL,[9] we do not recommend mandatory bronchoscopy for all the patients. Instead, we do recommend a personalized approach that selects the most appropriate investigation based on the type of immunosuppression, the clinical picture and CT findings. As shown in Figure 4, for some patients, bronchoscopy and BAL still remain indicated for several cases.

The basic package is non-invasive and is performed in every patient. This include a blood culture, sputa examination for bacteria, sputa examination for fungi and mycobacteria when appropriate, induced sputa for the search of Pneumocystis when appropriate, nasal swab for multiplex PCRs, serum and urines antigens, serum PCRs for herpes viruses, pleural and cardiac echography, and a CT scan when feasible.

The following question is whether this patient would actually benefit from a bronchoscopy and BAL. In other words, clinicians need to assess whether a) bronchoscopy and BAL can provide a diagnosis that none of the non-invasive test can make; and b) what is the risk for respiratory deterioration following the procedure in these hypoxemic patients. This assessment of the risk/benefit ratio of bronchoscopy and BAL is the cornerstone of initial management. The procedure is still needed as a frontline strategy in some situations:

a) when patients are unable to produce sputa
b) when drug toxicity is suspected
c) when *pneumocystis jirovecii* pneumonia is suspected
d) when lung infiltrates might be related to the underlying disease (except leukemic infiltrates that do not usually require any procedure).

Figure 4 illustrates this strategy based on clinical and imaging findings.

Indications for surgical lung biopsy are not standardized and remain performed in less than 1% of the cases when patients are hypoxemic and critically ill. The place of minimally invasive CT-guided lung biopsies is not yet established and depends on the availability of trained radiologists. Hence, lung biopsy is not part of the standard diagnostic workup in this setting. Centers that are used to perform trans-bronchial biopsies, cryobiopsies or CT-guided biopsies will not change their practice.

### *7.1.10 Authorized treatments*

All treatments are allowed in the context of inclusion and non-inclusion criteria.

### *7.1.11 Prohibited treatments*

Co-administration with ketoconazole.

Co-administration with high-dose ritonavir (>200 mg every 12 hours).

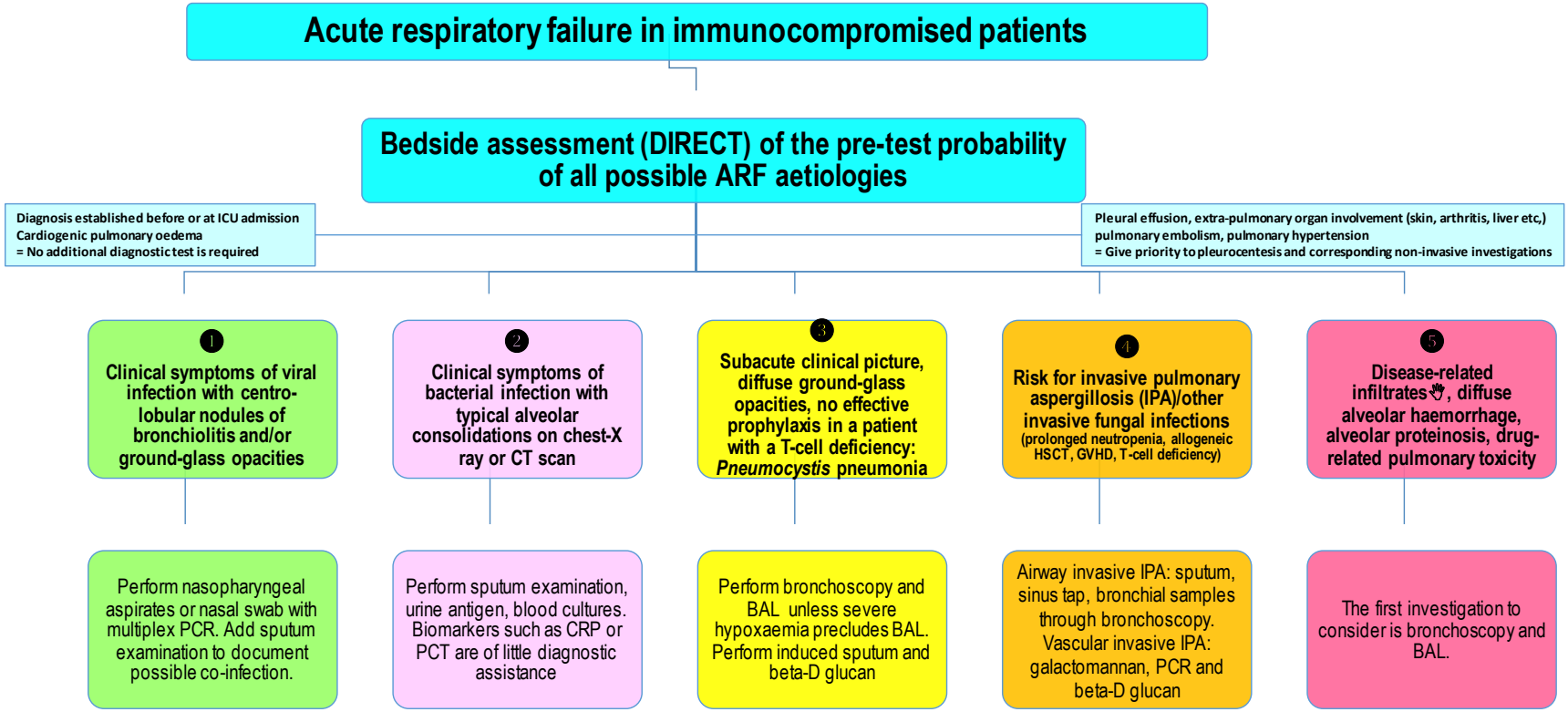
Co-administration with strong CYP3A4/5 inducers such as rifampicin, rifabutin, carbamazepine, long acting barbiturates (e.g. phenobarbital), phenytoin and St. John's wort or with moderate CYP3A4/5 inducers such as efavirenz, nafcillin and etravirine.

Administration of live vaccines, or live attenuated vaccines.

## Methods for monitoring compliance with the treatments

Treatment administration will be done during hospitalization and compliance will be monitored.
Nurses will complete a booklet to record administration. In the booklet, the nurses will note every injection during 14 days (or if less than 14 days, until ICU discharge) and it will be kept in the patient's medical records + eCRF.

Figure 4



# 8 EFFICACY ASSESSMENT

## Description of efficacy endpoints assessment parameters

### *8.1.1 Primary endpoint*

All-cause day-90 mortality

### *8.1.2 Secondary endpoints*

- ICU mortality
- hospital mortality
- day 28 mortality
- proportion of patients with ICU acquired microbiologically documented bacterial infections
- proportion of patients with invasive fungal infection within 3 months following randomization
- proportion of patients with HSV, VZV or CMV reactivation within 3 months following randomization
- occurrence of severe hypokaliemia (< 2.5 meq/L), decompensated diabetes or severe or newly acquired hypertension
- emergence of Aspergillus species with decreased sensitivity to isavuconazole
- Incidence of Candida infection
- incidence of psychiatric symptoms: Post traumatic Stress Disorder (IES-R), anxiety and depression at 6 months (HADS)
- quality of life at 6 months (SF36)

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

| | ICU Discharge | Hospital Discharge | D28 | D90 | M3 | M6 |
|---|---|---|---|---|---|---|
| Mortality | A | A | A | A | | |
| ICU acquired microbiologically documented bacterial infections | A | A | | | | |
| invasive fungal infection | | A | | | | |
| HSV, VZV or CMV reactivation | | | | | A | |
| severe hypokaliemia (<2,5 meq/L), decompensated diabetes or severe or newly acquired hypertension | A | | | | | |
| Aspergillus species with decreased sensitivity to | A | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| isavuconazole | | | | | | |
| Candida infection | A | | | | | |
| Questionnaires SF36, HADS, IES-R | | | | | | B |

A: Medical records regarding standard of care.
B: Sites will contact patients by phone or mail.

# 9 SPECIFIC STUDY COMMITTEES

**Members of the committee:**

- Pr Elie AZOULAY,
- Pr Sylvie CHEVRET,
- Didier BOUTON,
- Lakhdar MAMERI

# 10 SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

## Recording and reporting adverse events

### *10.1.1 Definitions*

According to Article 2 of the Regulation (EU) N° 536/2014::

- **Adverse event**

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

- **Serious adverse event**

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

- **Unexpected serious adverse reaction**

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

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

- **Unexpected event**

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

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

- **Urgent safety measure**

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects.

The sponsor shall notify the Member States concerned, through the EU portal, of the event and the measures taken.
That notification shall be made without undue delay but no later than seven days from the date the measures have been taken.

### *10.1.2 The role of the investigator*

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

The investigator must **assess the severity** of the adverse events:
- either by using general terms:
    - *Mild: tolerated by the patient, does not interfere with daily activities*
    - *Moderate: sufficiently uncomfortable to affect daily activities*
    - *Serious: prevents daily activities*
- or by using a rating scale for adverse events appended to the protocol (WHO)

The investigator must **assess the causal relationship** between serious adverse events and the investigational medicinal products.

The method used by the investigator is based on the2 causality terms (EVCTM method)::
- Related
- Not related

#### 10.1.2.1 **Serious adverse events that require a notification without delay by the investigator to the sponsor**

The investigator notifies the sponsor **without undue delay but no later than within 24hours on the day the investigator becomes aware** of any serious adverse event which occurs during a trial that meets the description in Article 41of Regulation EU) N°536/2014, except those which are listed in the protocol (see corresponding section) and, if applicable, in the investigator's brochure as not requiring a notification

A serious adverse event is any untoward medical occurrence that:

1- results in death
2- is life-threatening
3- requires inpatient 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.

#### 10.1.2.2 **Specific features of the protocol**

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

- Adverse events judged as "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 when the investigator becomes aware** of any pregnancy that occurs during the trial, even if not associated with an adverse event.
  If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be reported to the sponsor.

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

These serious adverse events are simply recorded in the case report forms**.**

*Special rules for trials with a high mortality rate*
The primary objective of the trial is to reduce the 90-day mortality in immunocompromised patients with ARF from undetermined etiology at day-3. The intervention would evaluate the impact of steroids ± isavuconazole for 14 days or until ICU discharge. The primary endpoint is the mortality at day 90. The expected number of participants included in the "EFRAIM II" research is 420.
The mortality rate of the condition under investigation is 55 % at 90 days.

Taking account of the particular context of the research, the sponsor will regularly monitor the balance of deaths and ICU-acquired infection in randomization groups.
All these data will be sent to the Data Safety Monitoring Board members.

If there is any imbalance between the randomization groups or the mortality rate is higher than expected affecting the safety of trial subjects and which requires the sponsor to take urgent safety measures, the ANSM will be informed about the emerging safety issue without delay.

- ***Serious adverse events related to normal and natural course of the condition including:***
  - Admission in ICU or reanimation department
  - Intubations and re-intubations
  - Progression disease with fatal issue

- ***Other serious adverse events:***
  - ICU-acquired infection

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

The investigator notifies the sponsor without delay of all serious adverse events listed in the corresponding section:
- starting from the date on which the subject begins treatment with an investigational medicinal product
- throughout the whole follow-up period intended by the trial
- until 4 weeks or more after the end of the subject's treatment with the investigational medicinal product.

- indefinitely, if the SAE is likely to be due to the investigational medicinal product or to the study interventions (e.g. serious reactions that could appear long after exposure to the medication, such as cancers or congenital abnormalities)

#### 10.1.2.4 **Procedures and deadlines for notifying the sponsor**

The investigator should initially complete a SAE reporting form (contained in the case report form). This report must be signed by the investigator.

The investigator must complete every section of the SAE form so that the sponsor can carry out the appropriate assessment.

The initial report sent to the sponsor must be rapidly followed up by one or more additional written reports describing the course of the event and any complementary information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful for medical assessment of the case (medical reports, laboratory test results, results from additional examinations, etc.). These documents must be anonymized. In addition, the investigator must state the study acronym and the number and initials of the study participant on each paper of the attached document.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the subject has terminated his participation in the trial.

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

For trials which use e-CRF:
- the investigator completes the SAE report form in the e-CRF, then validates, prints, and signs the form before sending it by email;
- In case of failure 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 report form in the e-CRF.

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 “Follow-up form for reporting a pregnancy occurring in a clinical trial”.
The investigator must monitor the pregnant woman until delivery or until premature interruption, 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, termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure as for reporting SAEs.
The initial pregnancy report form, the SAE follow-up forms and any other documents will be sent to the sponsor using the same modalities as described in this section.
If it was the father who was exposed, the investigator must obtain the mother's permission before collecting information about the pregnancy.

### *10.1.3 Role of the sponsor*

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

#### 10.1.3.1 **Analysis and declaration of serious adverse events**

The sponsor assesses:

- the **seriousness** of all reported adverse events
- 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 suspect a causal relationship with the investigational medicinal product are considered as suspected serious adverse reactions.
- the **expectedness assessment** 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 authorized, is considered unexpected.
  The sponsor, acting through its Safety Department, assesses the expectedness of the serious adverse reaction based on the information described below**.**

❖ For serious adverse events likely to be related to the investigational medicinal products:

- refer to the SmPC for **CRESEMBA® (isavuconazole)** and the SmPC **for Méthylprednisolone MYLAN®** enclosed in CTIS platform.

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

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

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

**Special rules for double-blind trials**
After unblinding, if the administered product is the investigational medicinal product, the case will be reported within the regulatory time frame as suspected unexpected serious adverse reaction (SUSAR). however, if the administered product is the comparator, the unexpected nature of the adverse reaction will be re-assessed according to the reference document for the comparator found in the protocol.
In the exceptional case of a clinical study about a disease with high mortality or morbidity, the sponsor may request the Competent Authority a readjustment of the conditions for unblinding and reporting suspected adverse reaction. These conditions should be thoroughly defined in the study protocol

#### 10.1.3.2 **Analysis and declaration of other safety data**

This relates to any emerging safety issue that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials.

The sponsor will report to the competent authority and the Ethics Committee without delay upon knowledge any emerging safety issues and, if applicable, describe what urgent safety measures have been taken by the sponsor.
Following the initial declaration of any emerging safety issue, the sponsor will report to ANSM and the Ethics committee 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 upon knowledge of the sponsor.

If the suspected unexpected serious adverse reaction meets the definition of an emerging safety issue, the sponsor will report both the SUSAR and the emerging safety issue to the ANSM according to the appropriate modalities and within the regulatory timelines as previously described.

#### 10.1.3.3 **Annual safety report**

The sponsor must prepare once yearly throughout the trial duration an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- an analysis of safety data concerning trial subjects,
- a description of the patients included in the trial (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- cumulative summary tables of all the serious adverse events that have occurred since the beginning of the clinical trial.

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 date corresponding to the date of authorization of the clinical trial by Competent Authority.

### *10.1.4 Independent Data Safety Monitoring Board (DSMB)*

An independent Data Safety Monitoring Board (DSMB) can be set up by the sponsor. Its primary mission is to monitor safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).

The sponsor is responsible for justifying the creation or absence of a DSMB to the Competent Authority and to the Ethics committee.

A DSMB will be set up for this trial. The DSMB must hold its first meeting before the first subject's enrollment.

**The DSMB members are:**
Pr Tattevin, Infectious Diseases, Rennes
Pr Dominique Benoit, hematology, Ghent,
Pr A de Jong, Methodologist, Montpellier

All missions as well as the precise operating procedures of the DSMB are described in the DSMB charter of the clinical trial.

The DSMB has a consultative role. The final decision concerning the conduct of the clinical trial relies on the sponsor.

# 11 DATA MANAGEMENT

## Right to access data and source documents

### *11.1.1 Data access*

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

### *11.1.2 Source documents*

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

### *11.1.3 Data confidentiality*

The persons responsible for the quality control of clinical trials 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 the identity of the participants and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy.
During and after the research involving human participants, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered anonymous.
Under no circumstances shall the names and addresses of the participants involved be shown.
Only the participant's initials will be recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.

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.

## Data processing and storage of research documents and data

### *11.1.4 Identification of the data processing manager and location(s)*

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

### *11.1.5 Data entry*

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

## Data ownership

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

# 12 STATISTICAL ASPECTS

## Description of statistical methods to be used

According to the intention-to-treat principle, the full analysis set, that is, the set of patients whose data are included in the main primary analysis, is composed of all randomized patients except those who withdraw consent, who are analyzed in the arm thy were allocated to.

**Primary outcome**

The main comparison based on the intention-to-treat principle will compare the intervention arm to the control arm on the full-set of randomized patients. The primary hypothesis is superiority of steroids and/or antifungals in terms of 90-day mortality (primary outcome, binary, as all patients will be followed until day 90, at which time they will be classified as alive or dead) and for all secondary outcomes, with two-sided p-values for comparison tests.

The relative risk of death within the first 90 days in each experimental versus the control arm, stratified on the other randomization arm, will be estimated to assess the effectiveness of the intervention, with 95% confidence interval

The main analysis will compute only main effects of each intervention using all patients (testing the benefit of treatment A using the stratified Mantel-Haenszel statistic by stratifying subjects as to whether they received treatment B or not, and vice versa) (Peto 1978). Analyses adjusted on potential confounders will be performed using multivariable logistic regression models.

Check for the absence of interaction between intervention B on the effect of intervention A on the main outcome measure (and vice versa) will be assessed using the Gail and Simon interaction test statistics (Gail, 1985).

Secondary and exploratory comparisons of the primary endpoint will look for treatment-by-covariate interactions according to the subsets defined above.

Finally, a per-protocol analysis will be performed.

**Secondary outcomes**
Competing-risk endpoints (ICU-acquired events including intubation, etc.) will be analyzed using competing-risk methods. Specifically, cumulative incidences of the event of interest will be estimated, taking into account the competition between death or discharge alive from the ICU and the event of interest, then compared using the Gray test (1989). Adjustment for potential confounders will be based on cause-specific Cox models (1972).
ICU length of stay will be analyzed overall and in survivors and dead patients, separately. The former analysis will be based on Kaplan Meier estimate while the later on the competing-risk estimator, as described above.
Analyses of longitudinal outcomes will be based on joint models, taking into account the right censoring of the data.

All statistical analyses will be performed using SAS (SAS Inc, Cary, NC, USA) and R (http://www.R-project.org/) software.

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

Factorial designs provide an efficient method of evaluating more than one intervention in absence of interactions. Actually, the general approach to the analysis of a factorial trial is through 'retrospective stratification'; the main analysis computes only main effects of each intervention using all patients (testing the benefit of treatment A using the stratified Mantel-Haenszel statistic by stratifying subjects as to whether they received treatment B or not, and vice versa), and if the two interventions have no effect on one another's action, the analysis is efficient and straightforward.

We thus performed a separate calculation based on target effect sizes for each of the interventions compared with their respective controls. The proportion of death at day 90 in each intervention group is assumed to be 0.40 while the proportion in each control group is 0.55: accordingly, 344 patients are needed for this trial. Group sample sizes of 86 in each group (172 per intervention) achieve indeed a 80.2% power to detect a difference between group proportions of 0.15. An interim analysis will be performed as recommended by the PHRC experts. Therefore, the sample size computation handled the two scheduled analyses and controlling for a type I error rate at 5% overall; this type I error correction results in a required sample of 420 patients overall (thus, based on 105 patients in each of the four arms, 210 for each intervention group).

## Anticipated level of statistical significance

When dealing with interim analyses (see below), in order to handle multiplicity in analyses, only p-values below 0.025 will be considered as statistically significant.

At the time of terminal analyses, all p-values of 0.05 or less will be considered as statistically significant.

## Statistical criteria for termination of the study

As suggested by the PHRC experts, an interim analysis will be performed after the recruitment of 120 patients (or after 50 day-90 deaths, whichever will occur first).

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

Missing values for the main outcome measure are not expected to be observed; nevertheless, in case of occurrence, they will be handled using time-to-event methods in

which each patient contributes to the estimate of failure time distribution until he/she is lost-to-follow up or withdrawn from the study using competing-risks estimates.

Missing values for predictors will be imputed using multiple imputation techniques.

# 13 QUALITY CONTROL AND ASSURANCE

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

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

### *13.1.1 Strategy for site opening*

The strategy for opening the sites is determined using the tailored monitoring plan. It will be performed by the CRA from the URC-DRC from Saint Louis hospital.

### *13.1.2 Scope of center monitoring*

In the case of this risk study **which is considered level C risk,** the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Thus, the sponsor and the coordinating investigator have agreed on the logistic score and impact, resulting in a research monitoring level to be implemented: level « High »

## 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

## 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.

## 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.

## 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 who are not associated with the study managers. 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.

## 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 research and related training.
Any conditions, such as economic interests and institutional affiliations that might influence the impartiality of the investigators shall be presented.

Each investigator will agree 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.

## Suitability of the facilities

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

# 14 ETHICAL AND LEGAL CONSIDERATIONS

## Methods for informing research participants and obtaining their consent

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

- **Who is informed**? The participant, or if applicable: family members/trustworthy person
- **Who is providing consent**? The participant, or if applicable: family members/trustworthy person
- **When**? Before the person is enrolled in the study
- **How**? Information note given to the participant and oral explanation emergency situation, or if applicable: family members/trustworthy person
- **Who informs and obtains the consent**? The principal investigator or a physician representing the investigator before the person is enrolled in the study.

When the patient was enrolled in emergency situation and he stay not able to give his consent, family members/trustworthy person must sign a pursuit consent as soon as possible after inclusion.

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

The person will be granted a reflection period between the time when the subject receives the information and the time when he or she signs the consent form at inclusion visit
In addition, the investigator will specify in the research participant's medical file the methods used for obtaining their consent [or the consent of any other person, in the cases described in *article European regulation N°536/2014 (art. 29 and following)* as well as the methods used for providing information with a view to obtaining consent.

A copy of the information note and consent form, signed and dated by the research 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 research participant's medical file the methods used for obtaining their consent [or consent from any other person in the cases stipulated in Articles L. 1122-1-1 to L. 1122-2 of the Code de la Santé Publique (French Public Health Code) as well as the methods used for providing information with a view to obtaining their consent. The investigator will retain one copy of the signed and dated consent form.

Special circumstances: If the person is unable to give his or her written consent, consent may be witnessed, in descending order of priority, from a trustworthy person, a family member or a close relative. These persons must be fully independent of the investigator and of the sponsor

**Special circumstances: Mention of the possibility for the investigator of withholding certain information relating to the diagnosis, as applicable,**

- *Studies in emergency situations: Article 35 of the European regulation N°536/2014*

## Legal obligations

### *14.1.1 Role of the sponsor*

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

### *14.1.2 Request for approval from the CPP (Research Ethics Committee)*

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

### *14.1.3 Start of the Clinical Trial*

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

### *14.1.4 Procedures relating to data protection regulations*

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

#### 14.1.4.1 **Request for approval from the CNIL**

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

### *14.1.5 Amendments to the clinical trial*

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

### *14.1.6 End of the Clinical Trial*

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

### *14.1.7 Summary of the resultas 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 lay persons.

### *14.1.8 Archiving*

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

This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the site who participated in the study;
- A sealed envelope for the sponsor, containing one copy of all information notes and consent forms signed by all individuals at the site who participated in the research;
- "Study" binders for the Investigator and the sponsor, containing:

- the successive versions of the protocol (identified by the version no. and 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 research
- final study report

- The data collection documents

## 15 FUNDING AND INSURANCE

### Funding sources

PHRC (Hospital Funding for Clinical Research),2018

### Insurance

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

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

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

## 16 PUBLICATION RULES

### 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

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

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

## 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 2018 (French Ministry of Health)"

**This study is registered on the website** http://clinicaltrials.gov NTCxxxxx.

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## 18 ADDENDA

### 18.1 List of principal investigators and sites

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## 18.2 Safety Forms for notification of Serious Adverse Events or Pregnancy

### *18.2.1 Serious Adverse Event (SAE) form for a clinical trial conducted on an investigational medicinal product or a related product involving human subject*

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

**Please return this form (3 pages) completed and signed as soon as the investigator becomes aware of the SAE without delay to the Safety Department of the DRCI by email to eig-vigilance.drc@aphp.fr**
***(email object: P180584_EFRAIM2_yyyymmdd)***
**It is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99 only in case of unsuccessful attempt to send the SAE report by email (in order to avoid duplication).**

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

**1. Clinical trial information**

Acronym: EFRAIM II

Sponsor study number: APHP180584 / EUDRACT no: 2019-002569-37

Risk: C

Date of report: |__|__| |__|__| |2|0|__|__| (dd / mm / yyyy)

Date the investigator became aware of the SAE: |__|__| |__|__| |2|0|__|__| (dd / mm / yyyy)

**Full title of the clinical trial: Empirical steroids and/or antifungals in immunocompromised patients with acute respiratory failure from undetermined etiology: a multicenter double-blind randomized controlled trial»**

**2. Clinical investigation center information**

Center name: .....
City and address: .....
Department: .....

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

**3. Identification and medical history of the subject**

Subject identification number: |__|__|__| - |__|__|__|__|__|__| - |__| - |__| (Center No. – Selection order No. – Initial last name – Initial name)

Sex: ☐ M ☐ F

Date of birth: |__|__||__|__|__|__| (mm yyyy)

Weight: |__|__|__| kg
Height: |__|__|__| cm

Age: |__|__|__|years

Informed consent signature date: |__|__| |__|__| |2|0|__|__| (dd mm yyyy)

Randomization date: |__|__| |__|__| |2|0|__|__| (dd mm yyyy)

**Please provide any medical, surgical or family history which may impact the assessment of the case (medical anonymized documentation to be attached as appropriate):**
.....
.....
.....
.....
.....
.....
.....

Randomization No. (as appropriate):
Treatment No. (all delivered boxes):

**4. Investigational Medicinal Product(s) (IMP) or related product(s) [to be specified] administered prior the occurring of the SAE**
*(cross out the box if the treatment has not started yet)*

| Brand name (preferably) or International Nonproprietary Name | Route (1) | Dosage (specify the dosing unit ex: mg/d) | Start date *(dd/mm/yyyy)* | Ongoing (2) | End date *(dd/mm/yyyy)* |
|---|---|---|---|---|---|
| methylprednisolone / placebo of methylprednisolone | IV | ---- | \|_\|_\| \|_\|_\| \|2\|0\|_\|_\| | ☐ | \|_\|_\| \|_\|_\| \|2\|0\|_\|_\| |
| Isavuconazole / placebo of isavuconazole | IV | ---- | \|_\|_\| \|_\|_\| \|2\|0\|_\|_\| | ☐ | \|_\|_\| \|_\|_\| \|2\|0\|_\|_\| |

| **5. Additional procedures or medical cares performed during the clinical trial** *(ex.: biopsies, MRI ...)*<br>*(cross out the box if no additional procedure has been performed)* | Date *(dd/mm/yyyy)* | Chronology: Before the SAE onset | Chronology: After the SAE onset |
|---|---|---|---|
| ..... | \|_\|_\| \|_\|_\| \|2\|0\|_\|_\| | ☐ | ☐ |
| ..... | \|_\|_\| \|_\|_\| \|2\|0\|_\|_\| | ☐ | ☐ |

Acronym: EFRAIM II

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

**SECTION FOR THE SPONSOR USE ONLY**
INTERNAL SAFETY REFERENCE:

GED Reference: REC-DTYP-0385

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

⇨ Annex attached to this form: ☐ Yes ☐ No

| Brand name (preferred) or International Nonproprietary Name | Route (1) | Dosage (specify the dosing unit ex: mg/d ) | Administration of the medicinal product date *(from dd/mm/yy to dd/mm/yy)* | Ongoing (2) | Indication | *Action undertaken 0: dosage remained unchanged 1: drug withdrawal 2: dosage reduction 3: dosage increasing 4: unknown* | *Causality of the SAE 0: not related to the drug 1: related to the drug 2: unknown* |
|---|---|---|---|---|---|---|---|
| | | | from \|__\|__\| \|__\|__\| \|__\|__\| to \|__\|__\| \|__\|__\| \|__\|__\| | ☐ | | | |
| | | | from \|__\|__\| \|__\|__\| \|__\|__\| to \|__\|__\| \|__\|__\| \|__\|__\| | ☐ | | | |

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

**7. Serious Adverse Event [SAE]**

Diagnosis: ☐ Definitive ☐ Provisional
.....
.....
.....

Date first symptoms occurred: |__|__| |__|__| |2|0|__|__|
Describe the symptoms:
.....

Organ(s) affected:
.....
.....
.....
.....
.....
.....

Date of start of SAE:
|__|__| |__|__| |2|0|__|__|
dd mm yyyy
Onset time: |__|__| hh |__|__| min
☐ *missing data*

Time interval between the last treatment dose intake/absorption of the product or the date of the additional procedures or medical cares performed during the clinical trial and the start of the SAE:
|__|__| / |__|__| / |__|__|
dd hh min

Seriousness criteria:

☐ Hospitalization or prolongation of existing hospitalization:

*from* |__|__| |__|__| |2|0|__|__|

*to* |__|__| |__|__| |2|0|__|__| ☐ *ongoing*

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

Severity:
☐ Mild ☐ Moderate ☐ Severe

The occurrence of the SAE led to:
☐ no action undertaken regarding the IMP
☐ IMP dosage reduction ☐ IMP dosage increasing
☐ definitive withdrawal of the IMP
☐ temporary withdrawal of the IMP, resumption date: |__|__| |__|__| |2|0|__|__|
☐ unknown

Recurrence of the SAE after resumption: ○ No ○ Yes, Date: |__|__| |__|__| |2|0|__|__|
○ Not applicable

Has any symptomatic measure been taken?

☐ No ☐ Yes Date: |__|__| |__|__| |2|0|__|__| Specify: .....

Did the event require unblinding?

☐ No ☐ Yes Date: |__|__| |__|__| |2|0|__|__| ☐ Not applicable

If yes, result of the unblinding: .....
☐ Group1 (experimental for steroid)
☐ Group2 (experimental for antifungals)
☐ Group3 (experimental for steroids and antifungals)
☐ Group4 (best standard of care)

Please specify if the SAE is the outcome of:

| | | |
|---|---|---|
| - A medication error? | ☐ No | ☐ Yes Date: \|__\|__\| \|__\|__\| \|2\|0\|__\|__\| |
| - An overdose? | ☐ No | ☐ Yes Date: \|__\|__\| \|__\|__\| \|2\|0\|__\|__\| |
| - A misuse? | ☐ No | ☐ Yes Date: \|__\|__\| \|__\|__\| \|2\|0\|__\|__\| |
| - Other (specify): ..... | ☐ No | ☐ Yes Date: \|__\|__\| \|__\|__\| \|2\|0\|__\|__\| |

Acronym: EFRAIM II
Subject identification number: |__|__|__| - |__|__|__|__|__| - |__| - |__|
Center No. - selection order No. - Initial last name - Initial name

**SECTION FOR THE SPONSOR USE ONLY**
**INTERNAL SAFETY REFERENCE:**
GED Reference: Erreur ! Source du renvoi introuvable.

**Outcome of the SAE**

☐ **Death**
○ unrelated to the SAE
○ related to the SAE
Date: |__|__| |__|__| |2|0|__|__| (dd mm yyyy)

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

☐ **Resolved:**
○ without sequelae
○ with sequelae, specify the sequelae: .....
Date: |__|__| |__|__| |2|0|__|__| (dd mm yyyy)
|__|__| |__|__| (hh min)

☐ **Unknown outcome**

**8. Other etiology(ies) considered**

☐ No ☐ Yes Specify: .....

**9. Additional test(s) performed**

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

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

Related to the clinical trial:

☐ **Yes:**

☐ to the investigational medicinal product(s): which one(s)?

Specify: methylprednisolone/placebo ☐ Certain relationship ☐ Probable/Likely relationship ☐ Possible relationship ☐ Unlikely relationship
Specify: isavuconazole/placebo ☐ Certain relationship ☐ Probable/Likely relationship ☐ Possible relationship ☐ Unlikely relationship
Specify: ..... ☐ Certain relationship ☐ Probable/Likely relationship ☐ Possible relationship ☐ Unlikely relationship

☐ to the additional procedures/care: which one(s)?

Specify: ..... ☐ Certain relationship ☐ Probable/Likely relationship ☐ Possible relationship ☐ Unlikely relationship
Specify: ..... ☐ Certain relationship ☐ Probable/Likely relationship ☐ Possible relationship ☐ Unlikely relationship

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

| Reporter: | Investigator: | Department stamp: |
|---|---|---|
| Name and function:<br>Signature: | Name:<br>Signature: | |

### *18.2.2 Follow-up form for reporting a pregnancy occurring in a clinical trial*

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

**Please return this form (3 pages) completed and signed as soon as the investigator becomes aware of the SAE without delay to the Safety Department of the DRCI by email to eig-vigilance.drc@aphp.fr (email object: P180584_EFRAIM2_yyyymmdd)**

***It is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99 only in case of unsuccessful attempt to send the SAE report by email (in order to avoid duplication).***

**1. Clinical trial identification**

Acronym: EFRAIM II

Sponsor study number: APHP180584 / EUDRACT no: 2019-002569-37

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

Date of report: |__|__| |__|__| |2|0|__|__| (dd mm yyyy)

Date the investigator became aware of pregnancy: |__|__| |__|__| |2|0|__|__| (dd mm yyyy)

**Full title of the clinical trial: Empirical steroids and/or antifungals in immunocompromised patients with acute respiratory failure from undetermined etiology: a multicenter double-blind randomized controlled trial»**

**2. Identification of the clinical investigation center**

Center name: .....

City and address:

.....

Country: .....

Department: .....

Investigator (last name/name): .....

.....

Phone number: Fax:

**3. Identification of subject presenting pregnancy**

Subject reference: |__|__|__| - |__|__|__|__|__| - |__| - |__| (center n° - selection order n° - surname initial - first name initial)

Date of birth: |__|__| |__|__| |__|__|__|__|

Inclusion date: |__|__| |__|__| |2|0|__|__|

Randomization date: |__|__| |__|__| |2|0|__|__| (dd mm yyyy)

Randomization No. (as appropriate):.....

Treatment No. (all delivered boxes): .....

Date of last menstrual period: |__|__| |__|__| |2|0|__|__|

And/or pregnancy start date: |__|__| |__|__| |2|0|__|__| (dd mm yyyy)

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

Subject reference: |__|__|__| - |__|__|__|__|__| - |__| - |__| (center n° - selection order n° - surname initial - first name initial)

Date of birth: |__|__| |__|__| |__|__|__|__|

Inclusion date: |__|__| |__|__| |2|0|__|__|

Randomization date: |__|__| |__|__| |2|0|__|__| (dd mm yyyy)

Randomization No. (as appropriate):.....

Treatment No. (all delivered boxes): .....

**Exposures during pregnancy:**

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

Other substances (specify):

**4. Maternal history**

**Medical:**

**Surgical:**

**Obstetrical:** |__|__| gravida |__|__| para

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

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

| Brand name (preferred) or International Nonproprietary Name | Date of first administration or not administered | Date of last administration Or ongoing | Route of administration(1) | Dose / 24h |
|---|---|---|---|---|
| methylprednisolone / placebo of methylprednisolone | \|__\|__\| \|__\|__\| \|2\|0\|__\|__\| ☐ Not administered | \|__\|__\| \|__\|__\| \|2\|0\|__\|__\| ☐ Ongoing | IV | |
| Isavuconazole / placebo of isavuconazole | \|__\|__\| \|__\|__\| \|2\|0\|__\|__\| ☐ Not administered | \|__\|__\| \|__\|__\| \|2\|0\|__\|__\| ☐ Ongoing | IV | |

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

 

Acronym: EFRAIM II

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

SECTION FOR THE SPONSOR USE ONLY

INTERNAL SAFETY REFERENCE:

GED Reference: REC-DTYP-0288

**Did the event require unblinding?**

☐ No ☐ Yes Date: |__|__| |__|__| |_2_|_0_|__|__| ☐ Not applicable

If yes, result of the unblinding: .....

☐ Group1 (experimental for steroid)
☐ Group2 (experimental for antifungals)
☐ Group3 (experimental for steroids and antifungals)
☐ Group4 (best standard of care)

| **6. Procedures and care added by the research** *(cross out the box if procedures and care have not been performed )* | Date *(dd/mm/yyyy)* | Chronology | |
|---|---|---|---|
| | | Before pregnancy | During pregnancy |
| | |_|_| |_|_| |_2_|0_|_|_| | | |
| | |_|_| |_|_| |_2_|0_|_|_| | | |

**7. Concomitant medication(s)**

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

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

**8. Pregnancy follow-up**

☐ Ultrasounds. Specify date(s) and results:

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

**9. Current pregnancy** ☐ (fax another completed form on outcome of pregnancy)
**or Outcome of pregnancy** ☐ (complete the box below)

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

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

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

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

☐ Delivery: ☐ Spontaneous ☐ Induced ☐ Vaginal ☐ Caesarean

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

 

| 10. Newborn information (for multiple births, please complete sections 1, 2, 3, 9 and 10 on a different form and send by fax) | | |
|---|---|---|
| Sex: ☐ Male ☐ Female<br>Weight: \|__\|__\|__\|__\| grams Height: \|__\|__\|__\| cm Head circumference: \|__\|__\|__\| cm<br>APGAR: 1 minute: _____ 5 minutes: _____ 10 minutes: _____ | | |
| Congenital malformation(s): ☐ No ☐ Yes, please specify: | | |
| Non-malformative(s) congenial(s)/neonatal(s) pathology(ies): ☐ No ☐ Yes, please specify: | | |
| Did the newborn receive any specific treatment at birth: ☐ No ☐ Yes, please specify: | | |
| **Reporter** | **Investigator** | **Department stamp:** |
| Name and function: | Name: | |
| Signature: | Signature: | |

## 18.3 SMPCs

### *18.3.1 SMPC CRESEMBA© (isavuconazole)*

SMPC for Cresemba was obtained from ANSM website:
http://agence-prd.ansm.sante.fr/php/ecodex/extrait.php?specid=60184590

### *18.3.2 SMPC Méthylprednisolone MYLAN*

SMPC for Méthylpredisolone Mylan was obtained from ANSM website:
http://agence-prd.ansm.sante.fr/php/ecodex/extrait.php?specid=67672560

### *18.3.3 SMPC for Physiological saline solution*

SMPC for Physiological saline solution was obtained from ANSM website:
http://agence-prd.ansm.sante.fr/php/ecodex/rcp/R0224963.htm

## 18.4 SOFA score

| SOFA score | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| Respiration | | | | | |
| $PaO_2/FIO_2$ (mmHg) | > 400 | 301–400 | 201–300 | 101–200 | ≤ 100 |
| (kPa) | > 5.3) | (4.1–5.3) | (2.8–4.0) | (1.4–2.7) | ≤ 1.3) |
| Coagulation | | | | | |
| Platelets ($x10^3/mm^3$) | > 150 | 101–150 | 51–100 | 21–50 | ≤ 20 |
| Liver | | | | | |
| Bilirubin (mg/dl) | < 1.2 | 1.2–1.9 | 2.0–5.9 | 6.0–11.9 | ≥ 12.0 |
| (µmol/l) | < 20) | (20–32) | (33–101) | (102–204) | ≥ 204) |
| Cardiovascular | | | | | |
| Hypotension | No hypotension | MAP < 70 mmHg | Dopamine ≤ 5 or dobutamine (any dose)* | Dopamine > 5 | Dopamine > 15 |
| Central nervous system | | | | | |
| Glasgow coma score | 15 | 13–14 | 10–12 | 6–9 | < 6 |
| Renal | | | | | |
| Creatinine (mg/dl) | < 1.2 | 1.2–1.9 | 2.0–3.4 | 3.5–4.9 | > 5.0 |
| (µmol/l) | < 110) | (110–170) | (171–299) | (300–440) | > 440) |
| or urine output | | | | < 500 ml/day | < 200 ml/day |

* adrenergic agents administered for at least 1 h (doses given are in µg/kg/min)

## 18.5 Conversion tables for eCRF completion

### *18.5.1 Estimating PaO2 from a given SO2*

**1 Estimating $PaO_2$ from a given $SO_2$**

| $SO_2$ (%) | $PaO_2$ (mmHg) |
|---|---|
| 80 | 44 |
| 81 | 45 |
| 82 | 46 |
| 83 | 47 |
| 84 | 49 |
| 85 | 50 |
| 86 | 52 |
| 87 | 53 |
| 88 | 55 |
| 89 | 57 |
| 90 | 60 |
| 91 | 62 |
| 92 | 65 |
| 93 | 69 |
| 94 | 73 |
| 95 | 79 |
| 96 | 86 |
| 97 | 96 |
| 98 | 112 |
| 99 | 145 |

*Table to be used to complete the eCRF only if arterial blood gases are not available, in order to estimate the P/F ratio in the daily SOFA score.*
*Use the lowest SpO2 then select the highest FIO2 of the day.*

### *18.5.2 Estimating FiO2 according to the ventilation mode*

**2 Estimating $FiO_2$**

| Method | $O_2$ flow (l/min) | Estimated FiO2 (%) |
|---|---|---|
| Nasel cannula | 1 | 24 |
| | 2 | 28 |
| | 3 | 32 |
| | 4 | 36 |
| | 5 | 40 |
| | 6 | 44 |
| Nasopharyngeal catheter | 4 | 40 |
| | 5 | 50 |
| | 6 | 60 |
| Face mask | 5 | 40 |
| | 6-7 | 50 |
| | 7-8 | 60 |
| Face mask with reservoir | 6 | 60 |
| | 7 | 70 |
| | 8 | 80 |
| | 9 | 90 |
| | 10 | 95 |

*Table to be used to complete the eCRF, in order to estimate the P/F ratio in the daily SOFA score only if the patient is not intubated and mechanically ventilated.*

*Note: Ambient air respiration : FiO2=21%.*

## 18.6 Questionnaires

### *18.6.1 IES-R questionnaire for M6 visit*

**IES-R version française**

***Nom patient :*** ***Date passation :***

***Instructions***. Voici une liste de difficultés que les gens éprouvent parfois à la suite d'un événement stressant. Veuillez lire chaque item et indiquer à quel point vous avez été bouleversé(e) par chacune de ces difficultés *au cours des 7 derniers jours* en ce qui concerne l'événement :

……

…

Dans quelle mesure avez-vous été affecté(e) ou bouleversé(e) par ces difficultés ?

| | Pas du tout | Un peu | Moyen-nement | Passa-blement | Extrême-ment |
|---|---|---|---|---|---|
| 1. Tout rappel de l'événement ravivait mes sentiments face à l'événement | 0 | 1 | 2 | 3 | 4 |
| 2. Je me réveillais la nuit | 0 | 1 | 2 | 3 | 4 |
| 3. Différentes choses m'y faisait penser | 0 | 1 | 2 | 3 | 4 |
| 4. Je me sentais irritable et en colère | 0 | 1 | 2 | 3 | 4 |
| 5. Quand j'y repensais ou qu'on me le rappelait, j'évitais de me laisser bouleverser | 0 | 1 | 2 | 3 | 4 |
| 6. Sans le vouloir, j'y repensais | 0 | 1 | 2 | 3 | 4 |
| 7. J'ai eu l'impression que l'événement n'était jamais arrivé ou n'était pas réel | 0 | 1 | 2 | 3 | 4 |
| 8. Je me suis tenu loin de ce qui m'y faisait penser | 0 | 1 | 2 | 3 | 4 |
| 9. Des images de l'événement surgissaient dans ma tête | 0 | 1 | 2 | 3 | 4 |
| 10. J'étais nerveux (nerveuse) et je sursautais facilement | 0 | 1 | 2 | 3 | 4 |
| 11. J'essayais de ne pas y penser | 0 | 1 | 2 | 3 | 4 |
| 12. J'étais conscient(e) d'avoir encore beaucoup d'émotions à propos de l'événement, mais je n'y ai pas fait face | 0 | 1 | 2 | 3 | 4 |
| 13. Mes sentiments à propos de l'événement étaient comme figés | 0 | 1 | 2 | 3 | 4 |
| 14. Je me sentais et je réagissais comme si j'étais encore dans l'événement | 0 | 1 | 2 | 3 | 4 |
| 15. J'avais du mal à m'endormir | 0 | 1 | 2 | 3 | 4 |
| 16. J'ai ressenti des vagues de sentiments intenses à propos de l'événement | 0 | 1 | 2 | 3 | 4 |
| 17. J'ai essayé de l'effacer de ma mémoire | 0 | 1 | 2 | 3 | 4 |
| 18. J'avais du mal à me concentrer | 0 | 1 | 2 | 3 | 4 |
| 19. Ce qui me rappelait l'événement me causait des réactions physiques telles que des sueurs, des difficultés à respirer, des nausées ou des palpitations | 0 | 1 | 2 | 3 | 4 |

| | | | | | |
|---|---|---|---|---|---|
| 20. J'ai rêvé à l'événement | 0 | 1 | 2 | 3 | 4 |
| 21. J'étais aux aguets et sur mes gardes | 0 | 1 | 2 | 3 | 4 |
| 22. J'ai essayé de ne pas en parler | 0 | 1 | 2 | 3 | 4 |

**Score** :

- *un score au-dessus de 22 moins d'1 mois après l'évènement : indice pour un stress aigü (surveiller)*
- *score au-dessus de 36 plus d'1 mois après l'événement : indice pour un état de stress post-traumatique (consulter)*

### *18.6.2 SF36 questionnaire for M6 visit*

# Questionnaire de santé SF-36

1. **Dans l'ensemble, pensez-vous que votre santé est** : (entourez la bonne réponse)

| | |
|---|---|
| Excellente | 1 |
| Très bonne | 2 |
| Bonne | 3 |
| Médiocre | 4 |
| Mauvaise | 5 |

2. **Par rapport à l'année dernière à la même époque, comment trouvez-vous votre état de santé en ce moment** ? (entourez la réponse de votre choix)

| | |
|---|---|
| Bien meilleur que l'an dernier | 1 |
| Plutôt meilleur | 2 |
| A peu près pareil | 3 |
| Plutôt moins bon | 4 |
| Beaucoup moins bon | 5 |

3. **Au cours de ces 4 dernières semaines, et en raison de votre état physique**
(Entourez la réponse de votre choix, une par ligne)

| | Oui | Non |
|---|---|---|
| a. Avez-vous réduit le temps passé à votre travail ou à vos activités habituelles | 1 | 2 |
| b. Avez-vous accompli moins de choses que vous auriez souhaité ? | 1 | 2 |
| c. Avez-vous du arrêter de faire certaines choses ? | 1 | 2 |
| d. Avez-vous eu des difficultés à faire votre travail ou toute autre activité ? (par exemple, cela vous a demandé un effort supplémentaire) | 1 | 2 |

4. **Au cours de ces 4 dernières semaines, et en raison de votre état émotionnel (comme vous sentir triste, nerveux(se) ou déprimé(e))**
(Entourez la réponse de votre choix, une par ligne)

| | Oui | Non |
|---|---|---|
| a. Avez-vous réduit le temps passé à votre travail ou à vos activités habituelles | 1 | 2 |
| b. Avez-vous accompli moins de choses que vous auriez souhaité ? | 1 | 2 |
| c. Avez-vous eu des difficultés à faire votre travail ou toute autre activité ? (par exemple, cela vous a demandé un effort supplémentaire) | 1 | 2 |

5. **Au cours de ces 4 dernières semaines dans quelle mesure votre état de santé, physique ou émotionnel, vous a-t-il gênée dans votre vie sociale et vos relations avec les autres, votre famille, vos connaissances**
(Entourez la réponse de votre choix)

| | |
|---|---|
| Pas du tout | 1 |
| Un petit peu | 2 |
| Moyennement | 3 |
| Beaucoup | 4 |
| Enormément | 5 |

6. **Au cours de ces 4 dernières semaines, quelle a été l'intensité de vos douleurs (physiques) ?** (Entourez la réponse de votre choix)

| | |
|---|---|
| Nulle | 1 |
| Très faible | 2 |
| Faible | 3 |
| Moyenne | 4 |
| Grande | 5 |
| Très grande | 6 |

7. **Au cours de ces 4 dernières semaines, dans quelle mesure vos douleurs physiques vous ont-elles limité(e) dans votre travail ou vos activités domestiques ?** (Entourez la réponse de votre choix)

| | |
|---|---|
| Pas du tout | 1 |
| Un petit peu | 2 |
| Moyennement | 3 |
| Beaucoup | 4 |
| Enormément | 5 |

8. **Au cours de ces 4 dernières semaines ; y a-t-il eu des moments où votre état de santé ou émotionnel, vous a gêné dans votre vie et vos relations avec les autres, votre famille, vos amis, vos connaissances ?** (Entourez la réponse de votre choix)

| | |
|---|---|
| En permanence | 1 |
| Une bonne partie du temps | 2 |
| De temps en temps | 3 |
| Rarement | 4 |
| Jamais | 5 |

9. **Voici une liste d'activités que vous pouvez avoir à faire dans votre vie de tous les jours. Pour chacune d'entre elles indiquez si vous êtes limit(é) en raison de votre état de santé actuel.** (Entourez la réponse de votre choix, une par ligne)

| Liste d'activités | Oui, beaucoup limité(e) | Oui, un peu limité(e) | Non, pas du tout limité(e) |
|---|---|---|---|
| a. Efforts physiques importants tels que courir, soulever un objet lourd, faire du sport | 1 | 2 | 3 |
| b. Efforts physiques modérés tels que déplacer une table, passer l'aspirateur, jouer aux boules | 1 | 2 | 3 |
| c. Soulever et porter des courses | 1 | 2 | 3 |
| d. Monter plusieurs étages par l'escalier | 1 | 2 | 3 |
| e. Monter un étage par escalier | 1 | 2 | 3 |
| f. se pencher en avant, se mettre à genoux, s'accroupir | 1 | 2 | 3 |
| g. Marcher plus d'un km à pied | 1 | 2 | 3 |
| h. Marcher plusieurs centaines de mètres | 1 | 2 | 3 |
| i. Marcher une centaine de mètres | 1 | 2 | 3 |
| j. Prendre un bain, une douche ou s'habiller | 1 | 2 | 3 |

10. **Les questions qui suivent portent sur comment vous vous êtes senti(e) au cours de ces 4 dernières semaines. Pour chaque question, veuillez indiquer la réponse qui vous semble la plus appropriée. Au cours de ces 4 dernières semaines, y a-t-il eu des moments où :** (Entourez la réponse de votre choix, une par ligne)

| Liste d'activités | En permanence | Très souvent | Souvent | Quelques fois | Rarement | Jamais |
|---|---|---|---|---|---|---|
| a. vous vous êtes senti(e) dynamique ? | 1 | 2 | 3 | 4 | 5 | 6 |
| b. vous vous êtes senti(e) très nerveux(se) ? | 1 | 2 | 3 | 4 | 5 | 6 |
| c. Vous vous êtes senti(e) si découragé(e) que rien ne pouvait vous remonter le moral | 1 | 2 | 3 | 4 | 5 | 6 |
| d. vous vous êtes senti(e) calme et détendu(e) ? | 1 | 2 | 3 | 4 | 5 | 6 |
| e. vous vous êtes senti(e) débordant(e) d'énergie? | 1 | 2 | 3 | 4 | 5 | 6 |
| f. vous vous êtes senti(e) triste et abattu(e) ? | 1 | 2 | 3 | 4 | 5 | 6 |
| g. vous vous êtes senti(e) épuisé(e) ? | 1 | 2 | 3 | 4 | 5 | |
| h. vous vous êtes senti(e) heureux(e) | 1 | 2 | 3 | 4 | 5 | 6 |
| i. vous vous êtes senti(e) fatigué(e) ? | 1 | 2 | 3 | 4 | 5 | 6 |

**11. Indiquez pour chacune des phrases suivantes dans quelle mesure elles sont vraies ou fausses dans votre cas :**
(Entourez la réponse de votre choix, une par ligne)

| Liste d'activités | Totalement vrai | Plutôt vrai | Je ne sais pas | Plutôt fausse | Totalement fausse |
|---|---|---|---|---|---|
| a. je tombe malade plus facilement que les autres | 1 | 2 | 3 | 4 | 5 |
| b. je me porte aussi bien que n'importe qui | 1 | 2 | 3 | 4 | 5 |
| c. je m'attends à ce que ma santé se dégrade | 1 | 2 | 3 | 4 | 5 |
| d. je suis en excellent santé | 1 | 2 | 3 | 4 | 5 |

**→ Score (0 à 100) : l__l__l__l**

### *18.6.3 HADS questionnaire for M6 visit*

**Le questionnaire HADS (de l'anglais *Hospital Anxiety and Depression Scale*)**

Dans la série de questions ci-dessous, cochez la réponse qui exprime le mieux ce que vous avez éprouvé au cours de la semaine qui vient de s'écouler. Ne vous attardez pas sur la réponse à faire : votre réaction immédiate à chaque question fournira probablement une meilleure indication de ce que vous éprouvez, qu'une réponse longuement méditée.

| Score | Anxiété | Score | Dépression |
|---|---|---|---|
| | Je me sens tendu ou énervé : | | Je prends plaisir aux mêmes choses qu'autrefois |
| 3 | ❒ la plupart du temps | 0 | ❒ oui, tout autant |
| 2 | ❒ souvent | 1 | ❒ pas autant |
| 1 | ❒ de temps en temps | 2 | ❒ un peu seulement |
| 0 | ❒ jamais | 3 | ❒ presque plus |
| | J'ai une sensation de peur comme si quelque chose d'horrible allait m'arriver | | Je ris facilement et vois le bon côté des choses |
| 3 | ❒ oui, très nettement | 0 | ❒ autant que par le passé |
| 2 | ❒ oui, mais ce n'est pas grave | 1 | ❒ plus autant qu'avant |
| 1 | ❒ un peu, mais cela ne m'inquiète pas | 2 | ❒ vraiment moins qu'avant |
| 0 | ❒ pas du tout | 3 | ❒ plus du tout |
| | Je me fais du souci : | | Je suis de bonne humeur : |
| 3 | ❒ très souvent | 3 | ❒ jamais |
| 2 | ❒ assez souvent | 2 | ❒ rarement |
| 1 | ❒ occasionnellement | 1 | ❒ assez souvent |
| 0 | ❒ très occasionnellement | 0 | ❒ la plupart du temps |
| | Je peux rester tranquillement assis à ne rien faire et me sentir décontracté : | | J'ai l'impression de fonctionner au ralenti : |
| 0 | ❒ oui, quoi qu'il arrive | 3 | ❒ presque toujours |
| 1 | ❒ oui, en général | 2 | ❒ très souvent |
| 2 | ❒ rarement | 1 | ❒ parfois |
| 3 | ❒ jamais | 0 | ❒ jamais |
| | J'éprouve des sensations de peur et j'ai l'estomac noué : | | Je ne m'intéresse plus à mon apparence : |
| 0 | ❒ jamais | 3 | ❒ plus du tout |
| 1 | ❒ parfois | 2 | ❒ je n'y accorde pas autant d'attention que je le devrais |
| 2 | ❒ assez souvent | | ❒ il se peut que je n'y fasse plus autant attention |
| 3 | ❒ très souvent | 1 | ❒ j'y prête autant d'attention que par le passé |
| | | 0 | |
| | J'ai la bougeotte et n'arrive pas à tenir en place : | | Je me réjouis d'avance à l'idée de faire certaines choses : |
| | ❒ oui, c'est tout à fait le cas | | ❒ autant qu'auparavant |
| 3 | ❒ un peu | 0 | ❒ un peu moins qu'avant |
| 2 | ❒ pas tellement | 1 | ❒ bien moins qu'avant |
| 1 | ❒ pas du tout | 2 | ❒ presque jamais |
| 0 | | 3 | |
| | J'éprouve des sensations soudaines de panique : | | Je peux prendre plaisir à un bon livre ou à une bonne émission radio ou de télévision : |
| | ❒ vraiment très souvent | | |
| 3 | ❒ assez souvent | 0 | ❒ souvent |
| 2 | ❒ pas très souvent | 1 | ❒ parfois |
| 1 | ❒ jamais | 2 | ❒ rarement |
| 0 | | 3 | ❒ très rarement |
| | ☜ **Total du score pour l'anxiété** | | ☜ **Total du score pour la dépression** |

Chaque réponse correspond à un chiffre. En additionnant ces chiffres, on obtient un score total par colonne (anxiété et dépression). Si le score d'une colonne est supérieur ou égal à 11, cela signifie que vous souffrez d'anxiété ou de dépression (selon la colonne concernée).

## 18.7. Etude Ancillaire

# Etude Ancillaire PK/PD Efraim-II

**Etude PK/PD de l'isavuconazole**

### I. Objectifs:

- Décrire la pharmacocinétique de l'isavusonazole chez les patients de réanimation en IRA
- Evaluer l'éventuelle relation entre les paramètres pharmacocinétiques de l'isavuconazole et le risque d'infection fongique invasive dans cette population

### II. Prélèvements :

II.1. PK de l'isavuconazole
Les prélèvements seront réalisés à J3, soit dans les 24h suivant la première dose d'entretien d'isavuconazole :

- T0 (avant administration)
- fin de perfusion
- entre 30 et 60 minutes après la fin de la perfusion
- entre 2 et 4h après la fin de la perfusion
- entre 8 et 16 h après la fin de la perfusion
- juste avant la perfusion suivante

2 ml de sang sera prélevé à chaque point en tube sec hépariné (bouchon vert) soit un total de 12 ml de sang pour chaque patient acceptant de participer.
Les tubes seront centrifugés 10 min à 2200 g.
Le plasma sera prélevé et aliquoté puis congelé à -80°C.
Les échantillons seront détruits une fois les mesures réalisées.

### III. Mesure des concentrations

Les prélèvements seront envoyés tous les 3 mois au laboratoire pour dosage.
Les concentrations plasmatiques d'isavuconazole seront mesurées par LC-MS/MS selon une méthode publiée (Toussain et al, J Chrom B 2017)

### IV. Analyse pharmacocinétique

Les données seront analysées selon une approche de Population avec le logiciel NONMEM.
Les paramètres pharmacocinétiques moyens de l'isavuconazole, ainsi que leur variabilité interindividuelle seront estimés. L'impact des covariables suivantes sur la variabilité pharmacocinétique interindividuelle sera évalué : âge, taille, poids, sexe, CLcr, albuminémie, TP, ASAT, ALAT, GGT, Bilirubinémie, épuration extracorporelle
Le coût global sera de 3570€

### V. Patients et Centre participants

Cette étude sera réalisée sur un échantillon de 100 patients recrutés dans les centres de l'hôpital Saint Louis (Paris), de la Pitié-Salpêtrière (Paris) et de l'institut Paoli Calmette (Marseille).
Une note d'information et un consentement spécifique leur sera proposé
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