English translation (May 2016)

Statistical analysis plan

MICAFUNGIN IN CANDIDA MULTICOLONIZED PATIENTS WITH ICU-ACQUIRED SEVERE SEPSIS: A RANDOMIZED CONTROLLED TRIAL

ORIGINAL PROTOCOL DATE V6 – 03 NOVEMBRE 2011

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<td>27 Mars 2014</td>
</tr>
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<td>28 Octobre 2014</td>
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SAP Version Finale 3.0: [15 Juin 2015] – english translation of the statistical analysis data

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<th>SIGNATURE</th>
<th>DATE</th>
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<tr>
<td>Statisticien</td>
<td>Stéphane RUCKLY&lt;br&gt;Université Paris Diderot / Hopital Bichat - Réanimation Médicale et des maladies infectieuses&lt;br&gt;46 rue Henri Huichard&lt;br&gt;75018 Paris</td>
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<td>16/06/2015</td>
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<tr>
<td>Coordonnateur principal</td>
<td>Pr Jean-François TIMSIT&lt;br&gt;Université Paris Diderot / Hopital Bichat - Réanimation Médicale et des maladies infectieuses&lt;br&gt;46 rue Henri Huichard&lt;br&gt;75018 Paris</td>
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<tr>
<td>Statisticien en charge du contrôle qualité</td>
<td>Adrien FRANCAIS&lt;br&gt;Responsable Biométrie&lt;br&gt;Delta Consultants&lt;br&gt;16 rue Irène Joliot Curie&lt;br&gt;38320 Eybens</td>
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**IMPORTANT:** Si l’ensemble des champs sont signés, cela confirme que cette version du Plan d’Analyse Statistique est la version finale.
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## LISTE DES ABBREVIATIONS ET DEFINITION DES TERMES

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<tr>
<td>AFSSAPS</td>
<td>Agence Française de Sécurité Sanitaire des Produits de Santé</td>
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<tr>
<td>ALAT</td>
<td>Alanine Amino Transférase</td>
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<tr>
<td>AMM</td>
<td>Autorisation de Mise sur le Marché</td>
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<tr>
<td>ARC</td>
<td>Attaché de Recherche Clinique</td>
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<tr>
<td>ASAT</td>
<td>Aspartate Amino Transférase</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomic Therapeutic Class</td>
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<tr>
<td>AUC</td>
<td>Area Under the Curve (aire sous la courbe)</td>
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<tr>
<td>BPC</td>
<td>Bonnes Pratiques Cliniques</td>
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<tr>
<td>CI</td>
<td>Candidose invasive</td>
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<tr>
<td>CNA</td>
<td>Candida non albicans</td>
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<tr>
<td>CPP</td>
<td>Comité de Protection des Personnes</td>
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<tr>
<td>CRF</td>
<td>Case Report Form (cahier d’observation)</td>
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<tr>
<td>CRO</td>
<td>Clinical Research Organization (société de recherche sous contrat)</td>
</tr>
<tr>
<td>CS</td>
<td>Candida score (score de Candida)</td>
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<tr>
<td>CSP</td>
<td>Code de la Santé Publique</td>
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<tr>
<td>DCF</td>
<td>Data Clarification Form (demande de correction complémentaire)</td>
</tr>
<tr>
<td>DSMB</td>
<td>Data Safety Monitoring Board (comité de surveillance des données de sécurité)</td>
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<tr>
<td>EI</td>
<td>Événement Indésirable</td>
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<tr>
<td>EIG</td>
<td>Événement Indésirable Grave</td>
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<tr>
<td>EIT</td>
<td>Événement Indésirable lié au Traitement (Treatment Emergent Adverse Event)</td>
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<tr>
<td>EOS</td>
<td>End of study (fin d’étude)</td>
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<td>EOT</td>
<td>End of treatment (fin de traitement)</td>
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<tr>
<td>FAS</td>
<td>Full Analysis Set</td>
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<td>FISH</td>
<td>Hybridation fluorescente in situ</td>
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<td>IC 95%</td>
<td>Intervalle de Confiance à 95%</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonisation (Conférence internationale sur l’harmonisation)</td>
</tr>
<tr>
<td>IFI</td>
<td>Infection fongique invasive</td>
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<tr>
<td>IMC</td>
<td>Indice de Masse Corporelle</td>
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<td>ITT</td>
<td>Intention-To-Treat (Intention-de-traiter)</td>
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<td>J</td>
<td>Jour</td>
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<tr>
<td>PAS</td>
<td>Plan d’Analyse Statistique</td>
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<td>PAVM</td>
<td>Pneumonies Acquises sous Ventilation Mécanique</td>
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<td>PCR</td>
<td>Polymerase chain reaction (amplification en chaine par polymérase)</td>
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<tr>
<td>PD</td>
<td>Pharmacodynamique</td>
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<td>PK</td>
<td>Pharmacocinétique</td>
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<td>PP</td>
<td>Per Protocol</td>
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<td>ProCT</td>
<td>Procalcitonine</td>
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<tr>
<td>PV</td>
<td>Pharmacovigilance</td>
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<tr>
<td>QC</td>
<td>Quality Control (Contrôle qualité)</td>
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<td>RCP</td>
<td>Résumé des Caractéristiques du Produit</td>
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<tr>
<td>SAS</td>
<td>Safety Analysis Set</td>
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<tr>
<td>SD</td>
<td>Standard Deviation (Ecart-Type)</td>
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<td>SI</td>
<td>Standard International</td>
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<tr>
<td>SOFA score</td>
<td>Septis-related Organ Failure Assessment score (score de défaillance d’organes)</td>
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<tr>
<td>TFLs</td>
<td>Tables, Figures et Listings</td>
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<tr>
<td>ULN</td>
<td>Unités internationales</td>
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<tr>
<td>V</td>
<td>Visite</td>
</tr>
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1 INFORMATIONS COMING FROM THE PROTOCOL

1.1 Study objective

1.1.1 Primary objective

See protocol and data published in trials 2013 provided in a separated sheet.

Invasive free fungal infection at day 28

1.1.2 Secondary objectives

- Impact of the study drug on:
  - D28 mortality (end of study) and D90 (3 month post randomization).
  - D28 antifungal free survival.
  - Evolutive trend of organ dysfunctions.
  - Need for mechanical ventilation during the study period.
  - Colonization index during the study period.
  - Biomarkers (1-3 β-D-glucan, antigenemia mannan, antigens and antibody, PCR Candida) during the study period,
  - (VAP) ventilatory acquired bacterial pneumonia.

- Evaluate the pharmakokinetic / pharmacodynamic (PK/PD) of micafungin chez in septic patients mechanically ventilated in ICUs,

1.2 Design of the study

Randomized double blind placebo controlled study comparing 14 days of mycafungin (100 mg a day) vs placebo in adult patients with suspicion of invasive candidasis on invasive free survival at d28.

Invasive candidasis is considered preexisting if it occurred in the first 48h after inclusion or initiation of the study drug.

Study with 2 periods:

- A treatment period between inclusion visit to d14.
  - This period should end up prematurely in case of proven invasive fungal infections diagnosed on culture of the microbiological samples.

- A post treatment evaluation period with a end-of-study visit (D28) and a long term outcome follow up visit on mortality (consultation or phone call after 3 months) in enrolled patients.

1.2.1 Study population

See the text of the article and the paper published in “Trials” provided in a separated sheet.

1.2.2 Duration of the study

See the text of the article and the paper published in “Trials” provided in a separated sheet.
Study scheme (Figure 1):
### Figure 1  Schéma de l’étude

<table>
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<th>Screening (Admission en réanimation)</th>
<th>Inclusion</th>
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<td>Calendrier théorique de</td>
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<td>J0</td>
<td>J1 à J3</td>
<td>J4 à J7</td>
<td>J9</td>
<td>J11</td>
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<tr>
<td>consultation</td>
<td></td>
<td>J14</td>
<td>J21</td>
<td>J28</td>
<td>J90</td>
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<tr>
<td>Intervalle autorisé</td>
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<td>± 1j</td>
<td>± 1j</td>
<td>± 2j</td>
<td>± 3j</td>
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<td>Traitement de l’étude</td>
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<td>Résultats des examens d’inclusions</td>
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<td>Micafungine (100 mg IV)</td>
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<td>Placebo</td>
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<td>Absence d’IFI : poursuite du traitement</td>
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<td>Présence d’IFI : fin d’étude (EOT)</td>
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</table>
1.3 Methods and procedures

1.3.1 Subject identification and treatment allocation

See the text of the article and the paper published in “Trials” refered in the manuscript.

1.3.2 Evaluation of subjects

1.3.2.1 Evaluation of primary and secondary outcomes by the adjudication committee

The adjudication committee meetings will be organized in 2015 blindly for the study group. The adjudication committee will accept or reject diagnosis of invasive fungal infection, antifungal treatment during the study period and ensure a proper documentation of all the episodes. The committee will also validate the date of occurrence of IFI (at « inclusion period » or during the study period, diagnostic methods, sources, microorgnaisms and antifungal susceptibility tests. Also the committee will validate treatment dates doses and route of administration. Adjudication committee will provide all conclusions on IFI, AFT and documentation to the CRO before database lock.

1.3.2.2 Evaluations of efficacy

(a) Evaluation of primary efficacy criteria

Invasive fungal infection free survival at day 28 (end of study EOS).

(b) Evaluation of secondary efficacy criterias

- Death all cause (Day 28 EOS ) and 3 months (Day90) post-randomization.
- Antifungal free survival at day 28.
- Organ failure free survival (measured by sofa score registered during each visit during the ICU stay. When the patients is discharged SOFA score is recorded during the study visit planned at the end of study,
- Organ dysfunction free survival at D28.
- Mechanical ventilation free survival at D28.
- ICU free survival at day 28.
- ICU survival.
- Hospital survival.
- Invasive fungal infection incidence, delay for confirmation and antifungal administration.
- Clinical and Microbiological characteristics of invasive fungal infections.
• Colonization index during treatment and follow up.
• Serum biomarkers (1-3 β-D-glucan, mannan antigen and antibodies, PCR Candida) during treatment and study periods,
• Molecular markers of resistance of recovered strains from bloodcultures (FKS1 and new markers – biotheque constitution) during treatment and study periods (will be done after the end of the study)
• Bacterial ventilatory acquired pneumonia (VAP) diagnosis.

(c) Pharmacokinetics (PK)

Pharmacokinetics (distribution volume, clearances) estimated using pharmacokinetic modelization (population analysis) will use the NONMEN software.

Area under curve (AUC), Cmax, Cmin) will be estimated and AUC/MIC and Cmax/MIC ratios calculated.

The covariables will be:
• Age.
• weight.
• Proteinemia.
• Prothrombin time.
• Weight gain between inclusion EOT and EOS.
• Evolution of proteinemia between inclusion EOT and EOS
• Evolution of fluids intakes during study.

For each patient min and max plasmatic concentrations and cumulated AUC of Mycafungin will be calculated by Bayesian estimations of PK parameters.

(d) Pharmacodynamic parameters (PD)

• Invasive fungal infection free survival at day 7.
• Biomarkers clearance:
  o PCR Candida.
  o 1,3 β-D-glucan.
  o Antigenemia mannan.
  o Antibodies anti-mannan.

1.3.2.3 Evaluation of safety

For all patients with at least one dose of the study drug:

• Adverse events reported and death during 3 months post randomization.
Survival.

Evolution of liver function (bilirubin, ALAT, ASAT, prothrombin time, alkaline phosphatases) at EOT and EOS.

Samples will be proceeded in local laboratories.

Investigator is responsible of collecting all the adverse events during the study period.

1.3.2.4 Other evaluations

(a) Descriptive data

Birth date, sex, weight height.

(b) Medical history

antecedent (HIV, corticotherapy, diabetes) and surgical (type of surgery), reason of ICU admission, Chronic diseases (Knaus), clinical characteristics on ICU admission and at inclusion (sepsis, severe sepsis, septic shock, antibiotic therapy), devices (pacemaker, electrostimulation, CPBIA, ECMO), clinical characteristics before inclusion (mechanical ventilation, corticoids, dialysis, inotropes...) and procedures at inclusion (catheter date and types, urinary cath, parenteral nutrition, drains etc)

(c) Severity Scores

Severity (SAPS II), and organ dysfunction (SOFA) scores and nurse workload (NEMS) scores will be recorded.

(d) Microbiological evaluation

Blood-cultures and results, samples of operative procedures or punctures of sterile sites, colonization index at inclusion (multiple site samples).

(e) Pregnancy tests

If non menopausal women.

(f) Concomitant drugs

Names doses reason of administration start and end dates during study periods.

1.3.2.5 Stopping rules

Subject or surrogates free of removing informed consent at any time of the study period without penalties of prosecutions. The investigator can also stop the study drug if needed by clinical judgment or

- Non randomization criteria.
- Severe adverse event.
- Protocol violation (non-respect of inclusion noninclusion criteria).
- Non-observance of the protocol.
• Use of forbidden medicationst (other antifungals: fluconazole, voriconazole, candines, amphotericine B et autres polyenes, itraconazole).

• Pregnancy.

• Consent withdrawal.

• Lost of follow up.

• Death

An early stop of the study drug occurs for any reasons.

Proven or suspected infections according to the IDSA 2009 guidelines. In case of proven invasive fungal infection an echinocandin should be given at first. If *C. parapsilosis* and *C. guilliermondii*, in stabilized patient with a candida susceptible to fluconazole the treatment should be deescalated to fluconazole IV. The recommended duration of treatment is 14 days after the last positive blood culture of decision of empirical treatment.

The study withdrawal does not change the usual care. The patients will be followed according to the protocol requirement as often as possible. In case of adverse events, he follow up will be adapted clinically according to AE severity.
### Evaluation calendar

<table>
<thead>
<tr>
<th>Evaluations</th>
<th>Screening (Admission en réanimation)</th>
<th>Inclusion</th>
<th>Treatment period</th>
<th>End of treatment (EOT)</th>
<th>End of study (EOS)</th>
<th>End of research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit</td>
<td>V1</td>
<td>V2</td>
<td>V3 V4 V5 V6 V7 V8 V9 V10 V11 V12 V13 V14 V15</td>
<td></td>
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<tr>
<td>Day</td>
<td>J-1 à J0</td>
<td>J0</td>
<td>J1 J2 J3 J4 J5 J6 J7 J9 J11 J14 J21 J28 J90</td>
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<tr>
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<td>Randomization</td>
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<td>Inclusion non inclusion criteria</td>
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<td>Poursuit of the study‡</td>
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<td>Demography</td>
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<td>Medical and surgical history</td>
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<td>Pregnancy tests† (if applicable)</td>
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<td>Vitals signs and status</td>
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<td>Catheter / drain, filling</td>
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<td>Local lab analyses†</td>
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<tr>
<td>Hématologie (3ml par prélèvement), biochimie (3ml par prélèvement), analyse d’urine (* analyse d’urine uniquement à V2, V3, V9 et V12 et procalcitonine uniquement à V2, V5, V9 et V12)*</td>
<td>X X X X X X X X X X X X X X X X X X</td>
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<td>Mycologic follow up and colonization§</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>----------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>IFI evaluations</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PK (5ml by sample)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aes follow up</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Survival</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Study Treatment**

- **Groupe MICA**
- **Groupe PB**

**Concomitant treatments**

| X | X | X | X | X | X | X | X | X | X | X | X |

---

1. Before exams informed consent is required from the patient (Annexe 2). If impossible a proxy, or a family member if available (Annexe 3). The consent is consigned by the patients when able to consent to the research. (Annexe 4), emergency procedure of consent is allowed.
2. Validation of absence of invasive fungal infection at randomization.
3. Urinary or serum test (β-HCG) for pregnancy.
4. Daily SOFA in ICU. In case of ICU discharge the SOFA score is recorded from the ward at study visit and EOS.
5. Laboratory analyses are performed at each visit and when clinically indicated.
6. **Hematology**: hémoglobine, hémocrit, leucocytes, hématies, plaquettes. **Biochimie**: sodium, potassium, calcium, glucose, aspartate aminotransférase (ASAT), alanine transaminase (ALAT), phosphatases alcalines, bilirubine totale, taux de prothrombine, albumine, créatinine sérique, procalcitonine (procalcitonin only V2, V5, V9 et V12). Urine analysis (only V2, V3, V9 et V12) : protéïnes, creatinin.
7. Blood culture in specific milieu if available in the hospital, alternately standard bottles are used.
8. Mise en culture des prélèvements de bouche, gorge, appareil respiratoire haut et bas, plaies cutanées, urines et appareil digestif bas (écouvillon rectal ou selles), et si nécessaire des drains, cathéters et aspiration postopératoire. Analyses microbiologiques selon un protocole standardisé. En cas de culture positive, une étude de la sensibilité in vitro selon la méthode standardisée par E-test était réalisée à l’inclusion sur les souches isolées si disponible.
9. Les prélèvements sanguins obligatoires pour l'analyse des biomarqueurs par PCR (polymerase chain reaction) Candida et les tests de 1,3-β-D-glucane, antigène mannan, anticorps anti-mannane, (Annexe 8) seront recueillis à l'inclusion, et si le patient a développé des signes de candidose invasive. De même, une recherche de marqueurs moléculaires de résistance (Annexe 8) dans les souches d'hémoculture ou de site profond sera effectuée et une biothèque constituée.
10. Diagnosis of proven infection will required the presence of clinical signs and appropriate diagnostic exams.
11. 5 blood samples are planned following the first dose of treatment.
12. Adverse events are collected from inclusion to EOS visit.
1.3.4 Number of subjects

A two sided log-rank test with an overall sample size of 235 subjects (118 in the micafungin group and 117 in the placebo group) would achieve to detect a difference of 18% in the primary endpoint with a 80% power at a 0.05 significance level. Our hypothesis was then to increase the proportion of patients surviving free of proven IFI from 37% to 55% in the placebo as compared to the micafungin group. In order to account for secondary drop outs, 260 patients (130 in each group) were included. Un total de 260 patients, soit 130 patients par groupe de traitement était prévu d’être inclus dans l’étude.

See paper from “trials” enclosed in a separate sheet for details of hypothesis
2 POPULATION OF ANALYSIS (ANALYSIS SETS)

2.1 Meeting of the adjudication committee
A review of data meeting will be organized in 03 March 2015 to precisely define population of analysis for each patient.

2.2 Efficacy

2.2.1 Randomized population
All population with an allocation of a randomization number and an study arm.

2.2.2 Full Analysis Set / Intention To Treat (FAS / ITT)
The FAS/ITT population is the randomized population with the exclusion of protocol violation of secondary withdrawal of informed consent.

2.2.3 Per Protocol Set (PPS)
FAS/ITT population without major protocol violation and who received at least 2 doses of the study drug. Patients that stop the study drug at day 1 because of proven IFI or death remain in the PPS population.

2.3 Safety Analysis Set (SAS)
All randomized population with at least one dose of the study drug.

2.4 Pharmacokinetic (PK)
individuals with at least one PK sample taken.

2.5 Analyses
Analysis will be conducted in the ITT FAS for the primary judgment criteria. For safety SAS population will be included in the analysis. Other population including PPS are used only in secondary objectives analyses. Qualitative variables will be described by number, percent. Quantitative variables will be described by mean, SD or median IQR according to variable distribution. Clinical characteristics will be described for FAS and PPS/ITT population per arm and in total. Other variables will be described per arm of treatment.

3 STATISTICAL METHODS

3.1 Strategy of analysis
Statistical analyses will be done according to ICH E9 specifications. PKPD analyses will be treated separately by dr Vincent Jullien
3.1.1 Primary objective

Fungal infection free survival at day 28 in the FAS/ITT population will be computed using the Kaplan Meier estimates for each arm.

A fungal infection diagnosed after inclusion but existing on admission will not be taken into account as an event. In this case, the occurrence of a new invasive fungal infection (or death) will be studied.

3.1.2 Secondary efficacy criterias

Secondary criteria are:

(a) Number rate and percent of dying patient at EOS and Day 90 post-randomisation.

(b) Survival without antifungal treatment at EOS.

(c) Number of days without organ dysfunctions at day 28 according to SOFA score.

(d) Survival without organ failures at EOS.

(e) Survival without mechanical ventilation at EOS.

(f) Survival without ICU need at day 28 (EOS).

(g) ICU survival.

(h) Hospital survival.

(i) Incidence of invasive candidiasis and delay of occurrence or administration of a new antifungal treatment for proven or suspected infections.

(j) Description of clinical and microbiological characteristics of invasive candidiasis.

(k) Colonization index during treatment and study period. This criterion will not be analyzed since colonization was performed systematically only at inclusion and according to clinical judgement during the follow up in order to respect investigator blinding.

(l) Plasma biomarkers (1-3 β-D-glucan, mannan antigenemia and antibodies, PCR Candida) during the study period.

(m) Bacteriological VAP diagnosis.

(n) Sensitivity analyses on subpopulations on the FAS/ITT population of the primary outcome: according to: SOFA score, admission category, colonization index, Candida score, β-D-glucan at inclusion.

(o) Sensitivity analyses on subpopulations on the FAS/ITT population of the d28 survival: according to: SOFA score, admission category, colonization index, Candida score, β-D-glucan at inclusion.
3.1.3 Safety

Criteria are: Adverse events (AE), vital signs, weight, temperature, clinical and biological variables.

3.1.4 Multiplicity

No correction for test multiplicity is planned.

3.1.5 Significance threshold

Results will be presented using bilateral formulation with a 5% type I error.

3.2 Methods

Individuals listings will be performed.

3.2.1 Efficacy

3.2.1.1 Analysis of the primary end point

The primary objective will be analysed in the FAS/ITT population.

Survival at day 28 (EOS) without invasive fungal infection will be analysed using survival models and Kaplan Meier estimates.

Significances of differences will be estimated using the Logrank test or other test if appropriate. If there is remaining disequilibrium between treatment arms, adjustment using a Cox model will be used.

Primary criteria will be analysed on the FAS/ITT and PP populations.

Censor occurred in case of:

- Study withdrawal before day 28 without death or IFI. (Time<28 et criteria=0)
- Study censor at EOS (d28) without death or invasive fungal infection. (time=28 et criteria=0).

Event occurs if:

- The patient died before day 28
- The patient is diagnosed with an invasive fungal infections before day 28

If a patient is diagnosed with an IFI and subsequently died the time considered with be the one of the first event.

If a patient have a proven IFI at inclusion, this IFI will not be taken into account as an event and the primary criteria will be the occurrence of a new IFI or death.

SAS codes are enclosed in separated sheets:

For the primary comparisons the SAS code will be:
PROC LIFETEST PLOTS = (S, LLS, H);
   TIME t * CRITERE (0);
   STRATA groupe;
RUN;

If necessary the codes for the Cox model will be)

PROC PHREG;
   MODEL t * CRITERE (0) = groupe covariables / options;
   STRATA centres ;
RUN;

Proportionality assumptions will be tested graphycally and by a statistical test (Lin, Wei and Ying (1993), option ASSESS of the SAS software.

In case of missing data of the covariates, a multiple imputation will be used.

3.2.1.2 Analysis of secondary efficacy criterias

Sama analysis will be done for secondary end points and in the PPS population.

All cause death at d28 (EOS) and at 3 months post randomization .

Numbers and percent will be presented for death rates.

Fisher exact tests will be used to compare d28 and d90 death.

A similar survival analysis (cf 3.2.1.1) will be used for secondary end points and subgroup analyses.

(a) Survival without antifungal treatment at day 28 (EOS).

Similar analysis will be done for this secondary end point and the primary end point.

Validation of AFT will be done by the adjudication committee.

(b) Organ failure free days at EOS using SOFA score

One organ failure is defined as an organ component of SOFA>0. Calculation of OF free days will be calculated accordingly.

Tables with descriptive statistics will be performed with SOFA score per day (N, moyenne, IC 95% de la moyenne, SD, median, minimum, 1er quartile, 3ème quartile, maximum, missing), and changes of SOFA according of the baseline value will be calculated in total and per treatment group.

Non parametric Mann-Whitney tests will be used to compare distributions between treatment groups.
(c) **Organ failure free days at EOS (d28).**

The Organ failure free days will be analysed using similar tools.

(d) **Mechanical ventilation free days at EOS (d28).**

The Mechanical ventilation free days will be analysed using similar tools.

(e) **ICU free days at EOS (d28).**

ICU free days will be analysed similarly.

(f) **Hospital free days at EOS.**

Hospital free days will be analysed similarly.

(g) **Hospital survival.**

Will be analysed as the primary criterion (survival analysis). Patients still in the hospital will be censored at the end of research (d90).

(h) **Incidence of invasive fungal infections and delays for other antifungal treatment.**

Incidence will be calculated as the ration of number of IFI and the numbers of days between inclusion and EOS.

Delay of therapy with other antifungal will only be computed for patients who will present IFI at inclusion (secondarily diagnosed) and is the time between study treatment and study withdrawal for alternative antifungal treatment (using N, mean, 95% CI, SD, median, minimum, 1st quartile, 3rd quartile, maximum, missings), in total and per study arms.

A negative binomial regression (or Poisson regression) will estimate the effect of treatment on the incidence of new invasive fungal infection.

Among patients with proven fungal infections, a non parametric test will compare the delay of confirmation of a proven fungal infection (Mann-Whitney).

(i) **Clinical and microbiological characteristics of invasive candidasis.**

A table will describe numbers clinical characteristics and frequencies (SOFA, hypotension, fever, MV) of invasive fungal infections will be performed. Chi2 test or Mann-Whitney test will be used to check comparisons between arms.

(j) **Colonization index**

Colonization index is defined as a ratio between the number of positive site with candida as compared to the number of site sampled. A corrected colonization index will only took into account site heavily colonized (excluding ‘rare’ of “Not
recorded” positive sites. Colonization index will be computed at inclusion (V2) only. A table will be done (N, mean, 95%CI, SD, median, minimum, maximum, missings).

The study design did not allow calculation of colonization index after the visit of inclusion.

(k) **Bacterial VAP diagnosis and bacteriological characteristics.**

A table will report numbers and % in total and per group as well as the delay of diagnosis (diagnostic method, numeration for quantitative samples).

A chi square will compare rates between arms.

The SAS codes for secondary criterias are presented below:

**Description d’une variable quantitative, globalement et par groupe:**

```sas
PROC UNIVARIATE;
Var QUANTI;
Class GROUP;
RUN;
```

with ‘QUANTI’ for quantitative variables and ‘GROUP’ for treatment groups.

**Analysis of variance (ANOVA) non parametric (Mann-Whitney)**

```sas
PROC NPAR1WAY;
Var QUANTI;
Class GROUP;
RUN;
```

with ‘QUANTI’ for quantitative variables and ‘GROUP’ for treatment groups.

**Analysis of variance (ANOVA) parametric (T-Test Student)**

```sas
PROC TTEST;
Class GRP;
Var QUANTI;
RUN;
```

with ‘QUANTI’ for quantitative variables and ‘GROUP’ for treatment groups.

**Check for homoscedasticity**

```sas
PROC UNIVARIATE data = xxxx normal plots;
var QUANTI;
```
RUN;

Description of quantitative variables global
PROC FREQ;
Var QUANTI;
RUN;
with ‘QUANTI’ for quantitative variables.

Comparaison of of quantitative variables global
PROC FREQ;
Var QUANTI * GROUP / CHISQ;
RUN;
with ‘QUANTI’ for quantitative variables and ‘GROUP’ fro treatment groups.

Survival
Cf primary criteria.

ANOVA for reepated measurements
PROC MIXED data = XXX METHOD=REML COVTEST;
   Class GROUP NPAT JOUR;
   Model VAR = GROUP JOUR VAR_BSL
           JOUR*GROUP /outpred = res;
   Repeated JOUR / type= UN subject = NPAT r rcorr;
   Lsmeans GROUP* JOUR / pdiff cl;
RUN;
with ‘GROUP’ for treatment allocation, ‘JOUR*GROUP’ for interaction between
day and group. If interaction non significant at a 10% threshold the tem will be
deleted of the final model.

in case of absence of convergence of the final model a covariance « Unstructured»
(UN), or ‘Exchangeable’ (EXCH), or ‘Compound symmetry structure’ (CS), or
‘autorégressive’ (AR) will be used.
The repeated observation within a patient are taken into account by the ‘Repeated’
term and patients are represented by the ‘NPAT’ term.

Negative Binomial or Poisson regression
PROC GENMOD data=table ;
CLASS GROUP;
MODEL VAR = GROUP/ offset=OFFSET  dist=NB|POISSON;
RUN;

With ‘GROUP’ for treatment, ‘VAR’ for dependent variable. OFFSET the
denominator variable of VAR in case of incidence analysis. ‘Dist=NB’ for negative
binomial (or Dist=POISSON for poisson distribution) followed by the variable of
interest. In case of overdispersion, a correction will be done using the ‘DScale’ ou
‘PSCALE’ options.

3.2.2 Tolerance
Descriptive statistics using SAS listings.

3.2.2.1 Adverse events
Descriptive statistics using SAS listings and doc files.
For adverse events
Severe adverse events.

3.2.2.2 Laboratory data
Listing of data from the first to the last visits will be produced using a SAS.
Concerning the liver toxicity (ALAT, ASAT, bilirubin, alkaline phosphatase ),
critical threshold will be determined according to the upper limit value of local
laboratories (ULN). Data will be accessible to the data safety monitoring board
DSMB (section 3.2.16) for evaluation (eDISH plot).
Change of the biological variables will also be described for each arm.

3.2.2.3 Vital signs
Vital signs and changes of the vital signs according to D0 values will be reported.
(n, mean, median, SD,) by study arm for each visit (D0 to D28).

3.2.3 Missing values
3.2.3.1 Missing values
If the primary criteria is not recorded the patient will be censored (details in section
3.1.1) for FAS ITT analysis.
Missing values for dependent variables will be imputed (if applicable). In this case
complete case and post imputation analyses will be presented. Multile imputation
will be used if needed. However for each variable, data will be reported at each visit
and for the last available visit (LVA).
If will be checked by investigators and corrected if possible. If data are obviously false the adjudication committee may decide to transform the dependent variable to a missing data.

3.2.3.2 Missing dates

Missing dates will be recorded and reported to the research monitors for corrections:

- Algorithm for date checking will be applied and corrections made accordingly using the most conservative approach.

3.2.3.3 Aberrant Datas

Will be checked by automatic data checking and corrected by the study monitors or investigators.

In case of remaining aberrant data decision of the final use will be discussed with the promoter of the study.

3.2.4 Disposition des sujets

Listings of patients included in all different population (populations FAS, PPS et SAS) will be reported. Separate listing by centers will also be reported.

Number of days of study treatment will be reported per patient.

3.2.5 Retraits / Sorties pendant l'Etude

Patients with withdrawal of informed consent or protocol violation will be reported in separated sheets.

3.2.6 Patients Characteristics

Will be reported for each population and reported in total and per study arm.

Description of data will used (n, mean, SD, median, minimum, maximum or number percentage) for the population FAS.

Wilcoxon-Mann-Whitney (quantitative) or Chi 2 (qualitative) test will be used for comparisons between arms.

3.2.7 Compliance of subject to the study drug

Compliance listing will be provided as well as protocol deviation and classify as major or minor by the adjudication committee.

3.2.8 Ongoing treatments and new treatmentTraitements

Treatment lists will be provided by patients and date.

Non authorized treatment are :

- Fluconazol
- Voriconazole
- Candines
- Amphotéricine B et autres polynes (intra-venous)
- Itraconazole
Listing will be presented and the reason of each treatment recorded. Excluded of the PPS patients because of forbidden medication will be marked by a (+).

3.2.9 Pharmacokinetics & biomarkers

See “Trials” paper enclosed for details about the PK sample and analysis.

The significance of covariables and PK parameters will be evaluated by the modification of the objective function and the impact on intra-individual variability of PK parameters. A decrease of 3.84 points (α = 5%) of the objective function will be used as a significant criteria for the ascendant phase. For the descendant phase, an increase of the objective function of at least 6.63 points (α = 1%) will be needed.

PK analysis will be done by Dr. Vincent Jullien (responsibility of the PI).

3.2.10 Pharmacodynamic

PD study will be done after the end of the study on a separate analysis.

3.2.11 Derived data

Age and BMI will be calculated.

3.2.12 Visit windows

<table>
<thead>
<tr>
<th>Visite planned</th>
<th>Delay between planned and observed date of the visit (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening (J-1 à J0)</td>
<td>-1/0</td>
</tr>
<tr>
<td>Visite 2</td>
<td>-1/0</td>
</tr>
<tr>
<td>Visite 3</td>
<td>0</td>
</tr>
<tr>
<td>Visite 4</td>
<td>1</td>
</tr>
<tr>
<td>Visite 5</td>
<td>2</td>
</tr>
<tr>
<td>Visite 6</td>
<td>3</td>
</tr>
<tr>
<td>Visite 7</td>
<td>4</td>
</tr>
<tr>
<td>Visite 8</td>
<td>5</td>
</tr>
<tr>
<td>Visite 9</td>
<td>6</td>
</tr>
<tr>
<td>Visite 10</td>
<td>8</td>
</tr>
<tr>
<td>Visite 11</td>
<td>10</td>
</tr>
<tr>
<td>Visite 12</td>
<td>13</td>
</tr>
<tr>
<td>Visite 13</td>
<td>19 à 21</td>
</tr>
<tr>
<td>Visite 14</td>
<td>27 à 29</td>
</tr>
<tr>
<td>Visite 15</td>
<td>87 à 93</td>
</tr>
</tbody>
</table>

Authorized date intervals will be checked.

3.2.13 Data formats and rules

Number of decimals will be reported according to collected variable precision.
Les P-values will be reported with a precision of 4 decimals (ex p = 0.0037). P value less than 0.0001 will be reported as '<0.0001'.

Dates format: [jj/mm/aaaa] and hours format [hh: mm].

3.2.14 Analysis per center

Analysis of the primary criteria will be performed. Heterogeneity will be tested if needed.

3.2.15 Intermediate analyses

No intermediate analysis of the primary criteria will be performed. 2 analysis of safety (liver and death) are planned after 50 et 150 patients for the data safety monitoring board. Intermediate analysis will be done by the DSMB independently and will compared blindly arm A and arm B with no other precisions. Only descriptive data will be provided.

3.2.16 Role of the Data Safety Monitoring Board (DSMB)

Safety issue and tolerance after 50 and 150 subjects.

Descriptive data of clinical and biological data.

Reported adverse event reviews

Severe adverse event will also be reported for legal use.

Liver toxicity will be reported using eDISH plot. with: ALAT, ASAT, Bilirubin, Alkaline phosphatase. Thresholds of each local labs will be used.
4 COMPUTERS SOFTWARES AND PROGRAM VALIDATION

4.1 System
SAS® version 9.2 for Microsoft® Windows XP® (ou supérieur) will be used.

4.2 Software
SAS® version 9.2

4.3 Program validation
Double check of the program script by 2 statisticians. The .Log of the SAS system will be checked for fatal errors.

4.4 Programs
Available upon request

5 CHANGE IN THE FOLLOW UP AND ANALYSES
No changes have been planned. Study was prolonged to September 2014 to reach 260 patients.

6 REFERENCES


7 OUTPUTS
SAS scripts for all the data analysis are enclosed in 4 added files
EMP_script_Efficacy.docx
EMP_script_Analyse_descriptive.docx
EMP_script_Datamanagement.docx
EMP_script_Figures.docx
7.1 Listings

16.1.7 random scheme

Listing 16.1.7: Disposition des Sujets par Groupe de Traitement – Population Randomisée

16.2 Listings
8.1 Listings Standard

Listing 16.2.4.1: Démographie - Population FAS

<table>
<thead>
<tr>
<th>N° Patient</th>
<th>Sexe</th>
<th>Age</th>
<th>Taille</th>
<th>Poids</th>
</tr>
</thead>
<tbody>
<tr>
<td>xxxx</td>
<td>Homme</td>
<td>65</td>
<td>170</td>
<td>75</td>
</tr>
<tr>
<td>xxxx</td>
<td>xxxxx</td>
<td>xx</td>
<td>xxx</td>
<td>xxx</td>
</tr>
<tr>
<td>xxxx</td>
<td>xxxxx</td>
<td>xx</td>
<td>xxx</td>
<td>xxx</td>
</tr>
<tr>
<td>xxxx</td>
<td>xxxxx</td>
<td>xx</td>
<td>xxx</td>
<td>xxx</td>
</tr>
</tbody>
</table>

Analysis Dataset : EMP_PAT
FAS / ITT, Full Analysis Set / Intention To Treat
Programme : <F:\LABOS\ACADEMIQUE\EMP\EMP_sas\EMP_prog\EMP_prog_stat>
Date et heure d’exécution : ddmmmyyyy hh:mm; Date et heure de création de l’AD : ddmmmyyyy hh:mm
## Tables Standard

### Table 14.1.4.1: Caractéristiques des patients à l’inclusion - Population FAS (1/3)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Modalité</th>
<th>Groupe X N (%)</th>
<th>Groupe Y N (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Démographie</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexe</td>
<td>Femme</td>
<td>xx (xx.x)</td>
<td>xx (xx.x)</td>
<td>xx (xx.x)</td>
</tr>
<tr>
<td></td>
<td>Homme</td>
<td>xx (xx.x)</td>
<td>xx (xx.x)</td>
<td>xx (xx.x)</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td>Age (années)</td>
<td>Mean (SD)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td></td>
<td>Median (Q1 - Q3)</td>
<td>xx.x (xx.x - xx.x)</td>
<td>xx.x (xx.x - xx.x)</td>
<td>xx.x (xx.x - xx.x)</td>
</tr>
<tr>
<td></td>
<td>(Min - Max)</td>
<td>(xx.x - xx.x)</td>
<td>(xx.x - xx.x)</td>
<td>(xx.x - xx.x)</td>
</tr>
<tr>
<td>Taille (cm)</td>
<td>N</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td></td>
<td>N Missing</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td></td>
<td>Median (Q1 - Q3)</td>
<td>xx.x (xx.x - xx.x)</td>
<td>xx.x (xx.x - xx.x)</td>
<td>xx.x (xx.x - xx.x)</td>
</tr>
<tr>
<td></td>
<td>(Min - Max)</td>
<td>(xx.x - xx.x)</td>
<td>(xx.x - xx.x)</td>
<td>(xx.x - xx.x)</td>
</tr>
<tr>
<td>Poids (kg)</td>
<td>N</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td></td>
<td>N Missing</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td></td>
<td>Median (Q1 - Q3)</td>
<td>xx.x (xx.x - xx.x)</td>
<td>xx.x (xx.x - xx.x)</td>
<td>xx.x (xx.x - xx.x)</td>
</tr>
<tr>
<td></td>
<td>(Min - Max)</td>
<td>(xx.x - xx.x)</td>
<td>(xx.x - xx.x)</td>
<td>(xx.x - xx.x)</td>
</tr>
<tr>
<td>IMC</td>
<td>N</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td></td>
<td>N Missing</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td></td>
<td>Median (Q1 - Q3)</td>
<td>xx.x (xx.x - xx.x)</td>
<td>xx.x (xx.x - xx.x)</td>
<td>xx.x (xx.x - xx.x)</td>
</tr>
<tr>
<td></td>
<td>(Min - Max)</td>
<td>(xx.x - xx.x)</td>
<td>(xx.x - xx.x)</td>
<td>(xx.x - xx.x)</td>
</tr>
</tbody>
</table>

Analysis Dataset : EMP PAT
FAS / ITT, Full Analysis Set / Intention To Treat
Programme : <F:\LABOS\ACADEMIQUE\EMP\EMP_sas\EMP_prog\EMP_prog_stat>
Date et heure d’exécution : ddmmmyyyy hh:mm; Date et heure de création de l’AD : ddmmmyyyy hh:mm
8.3 Standard Figures

PNG ou JPG.