Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
### eBox. Inclusion and Noninclusion Criteria

#### Main inclusion criteria

- **Age ≥ 18 years**
- **Hospitalization in ICU ≥ 5 days (120 hours) before randomization**
- **Suspected but unproven candidiasis:**
  
  - Systemic Inflammatory Response Syndrome (SIRS) manifested by 2 signs among 4 (body temperature < 36°C or > 38°C; heart rate > 90/min; respiratory rate > 20/min or PaCO₂ < 32 mmHg; White Blood Cells > 12,000/mm³, < 4,000/mm³ or > 10% of circulating immature forms)
  - Mechanical ventilation ≥ 4 days
  - Presence of a central vein catheter and/or an arterial line
  - Use of broad spectrum antibacterial agents (i.e. co-amoxiclav, ticarcillin, piperacillin, piperacillin-tazobactam, carbapenems, third generation cephalosporins, ceftazidime, cefepime, ciprofloxacin, ofloxacin, amikacin, tobramycin, gentamicin) ≥ 4 days during the last seven days
  - At least one extra-digestive site of *Candida* spp. colonization (urine, mouth, throat, upper and lower respiratory system, skin folds and drains and postoperative aspiration…); positive samples of rectal swab and/or stool culture are not taken into account although they are collected at randomization visit.
  - No evidence of bacterial infections that explain the symptoms.
  - No evidence of invasive fungal infections (positive blood culture, direct examination or positive culture of surgery site, deep biopsy with mycosis) or mould infection according to the criteria of the “fungal infection cooperative group of EORTC”
Organ failure defined as a SOFA score ≥ 3.

**Main non inclusion criteria**

- Proven invasive infection (positive blood culture with yeast, positive culture of surgery site (only samples taken during surgery or by percutaneous puncture), deep biopsy with mycosis) including aspergillosis requiring antifungal treatment at the time of randomization
- Moribund status, i.e. Patients status considered by the investigator to inevitably lead to death or to withdrawal of life support within 48 hours
- Antifungal treatment with an echinocandin > 1 day or with any other antifungal agent > 72 hours the week preceding the inclusion
- Allergy, hypersensitivity or known intolerance to antifungal echinocandins or to any excipient composing the study drug
- Neutropenia (neutrophils count < 500/mm³)
- Previous marrow or organ transplantation
- Recent chemotherapy (since less than 6 months)

Ongoing systemic immunosuppressant agents therapy, other than corticosteroids at doses < 2 mg/kg/d of prednisolone or equivalent
eFigure 1. Survival Without Invasive Fungal Infections

(*) p=0.20 (Wald test stratified by centers)
eFigure 2. Time-to-Event Curves for Day-28 Death or Invasive Fungal Infection (IFI)*

Cumulative Incidence
day–28 death or IFI probabilities

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Days after randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micafungin</td>
<td>128 123 111 105 100 95 90 88</td>
</tr>
<tr>
<td>Placebo</td>
<td>123 118 111 100 91 85 78 73</td>
</tr>
</tbody>
</table>

(*) p=0.20 (Wald test stratified by centers)
eFigure 3. Survival Curves Censored at Day 28*

(*) p=0.95 (Wald test stratified by centers)

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Figure 4. Time-to-Event Curves for Day-28 Death*

Cumulative Incidence
day-28 death probabilities

No. at risk
Micafungin  128  123  111  106  102  97  92  89
Placebo    123  118  115  106  101  94  89  85

(*) p=0.95 (Wald test stratified by centers)
eFigure 5. Survival Curves Censored at Day 90 *

(*) $p=0.95$ (Wald test stratified by centers)
eFigure 6. Survival Without Antifungal Treatment*

(*) p=0.60 (Wald test stratified by centers)

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eFigure 7. Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH Plot)

Legend: Upper Limit of Normal value (ULN) of randomized patients.
In this figure, the peak values of alanine aminotransferase (ALT: x axis) and total bilirubin (TB: y axis) are plotted as a planar (x-y graph), with ALT abscissa values and ordinate TB values, each point representing a single patient.
For conservative purposes, to preserve sensitivity of detecting nearly all cases, low cut-off levels were employed: 3×ULN for ALT and 2×ULN for TB.
The lower left quadrant contains most patients with normal or near normal peak values for both variables.
Upper left quadrant (Cholestasis quadrant) contains patients with elevated bilirubin levels but not marked ALT elevation.
Lower right quadrant (Temple’s Corollary quadrant) show patient with elevated ALT levels but not TB levels, indicating hepatocellular injury without whole liver dysfunction.
Right upper quadrant (Hy’s Law Range) showed clinically significant hepatocellular injury AND whole liver dysfunction by elevations of both. See reference 1 for details.
eFigure 8. Evolution of 1-3 β-D-Glucan Plasma Levels in the Placebo and the Micafungin Group*

(*) p=0.97, given by the generalized estimating equation model for comparisons between groups.
Table 1. *Candida* spp. Colonization of Patients at Inclusion: Type and Number of Body Sites

<table>
<thead>
<tr>
<th>Body sites</th>
<th>Placebo N=123</th>
<th>Micafungin N=128</th>
<th>Total N=251</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of sites sampled (max 7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>4.7 (1.2)</td>
<td>4.7 (1.3)</td>
<td>4.7 (1.2)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>5 (4 ; 5)</td>
<td>5 (4 ; 5)</td>
<td>5 (4 ; 5)</td>
</tr>
<tr>
<td>(Min ; Max)</td>
<td>(1 ; 7)</td>
<td>(1 ; 7)</td>
<td>(1 ; 7)</td>
</tr>
<tr>
<td>Number of sites colonized (max 7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.3 (1.4)</td>
<td>3.1 (1.3)</td>
<td>3.2 (1.4)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>3 (2 ; 4)</td>
<td>3 (2 ; 4)</td>
<td>3 (2 ; 4)</td>
</tr>
<tr>
<td>(Min ; Max)</td>
<td>(1 ; 7)</td>
<td>(1 ; 5)</td>
<td>(1 ; 7)</td>
</tr>
<tr>
<td>Tracheal (n (%))</td>
<td>99 (80.5)</td>
<td>102 (79.7)</td>
<td>201 (80.1)</td>
</tr>
<tr>
<td>Oropharyngeal (n (%))</td>
<td>101 (82.1)</td>
<td>98 (76.6)</td>
<td>199 (79.3)</td>
</tr>
<tr>
<td>Rectal (n (%))</td>
<td>74 (60.2)</td>
<td>81 (63.3)</td>
<td>155 (61.8)</td>
</tr>
<tr>
<td>Skin (n (%))</td>
<td>62 (50.4)</td>
<td>58 (45.3)</td>
<td>120 (47.8)</td>
</tr>
<tr>
<td>Urine (n (%))</td>
<td>40 (32.5)</td>
<td>41 (32)</td>
<td>81 (32.3)</td>
</tr>
<tr>
<td>Other sites (n (%))</td>
<td>22 (17.9)</td>
<td>16 (12.5)</td>
<td>38 (15.1)</td>
</tr>
<tr>
<td>Population</td>
<td>Unadjusted Hazard Ratios for day-28 IFI–free survival</td>
<td>Unadjusted* Hazard Ratios for day-28 survival</td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------------------------------------------</td>
<td>---------------------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>Entire population</td>
<td>1.32</td>
<td>(0.86-2.00)</td>
<td>0.20</td>
</tr>
<tr>
<td>SOFA ≤ 8</td>
<td>1.10</td>
<td>(0.53-2.22)</td>
<td>0.80</td>
</tr>
<tr>
<td>SOFA &gt; 8</td>
<td>1.67</td>
<td>(0.97-2.86)</td>
<td>0.06</td>
</tr>
<tr>
<td>Surgical</td>
<td>1.54</td>
<td>(0.67-3.57)</td>
<td>0.31</td>
</tr>
<tr>
<td>Medical</td>
<td>1.37</td>
<td>(0.82-2.33)</td>
<td>0.23</td>
</tr>
<tr>
<td>Colonization index ≥ 0.5</td>
<td>1.35</td>
<td>(0.85-2.17)</td>
<td>0.20</td>
</tr>
<tr>
<td>Corrected colonization index ≥ 0.4</td>
<td>1.54</td>
<td>(0.90-2.63)</td>
<td>0.11</td>
</tr>
<tr>
<td>Candida score ≥ 3</td>
<td>1.39</td>
<td>(0.86-2.22)</td>
<td>0.18</td>
</tr>
<tr>
<td>(1-3)-B-D-glucan &gt; 250 pg/mL</td>
<td>1.54</td>
<td>(0.52-4.55)</td>
<td>0.43</td>
</tr>
<tr>
<td>(1-3)-B-D-glucan &gt; 80 pg/mL</td>
<td>1.41</td>
<td>(0.86-2.27)</td>
<td>0.18</td>
</tr>
<tr>
<td>(1-3)-B-D-glucan ≤ 80 pg/mL</td>
<td>1.33</td>
<td>(0.53-3.33)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

(*) The analyses were stratified by centers.
<table>
<thead>
<tr>
<th>End Point</th>
<th>Total</th>
<th>Placebo</th>
<th>Micafungin</th>
<th>p</th>
<th>Absolute difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of days without organ failure at day 28</td>
<td>8 (0;23)</td>
<td>6 (0;22)</td>
<td>14 (0;24)</td>
<td>0.42</td>
<td>8.0 (-1.5;17.5)</td>
</tr>
<tr>
<td>(IQR) (Days)</td>
<td>(n=251)</td>
<td>(n=123)</td>
<td>(n=128)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one day without organ failure</td>
<td>50 (20)</td>
<td>21 (17)</td>
<td>29 (23)</td>
<td>0.27</td>
<td>5.6% (-4.4;15.4)</td>
</tr>
<tr>
<td>- no. (%)</td>
<td>(n=251)</td>
<td>(n=123)</td>
<td>(n=128)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFA score day 28*</td>
<td>4 (2-12)</td>
<td>4 (2-13)</td>
<td>4 (1-12)</td>
<td>0.61</td>
<td>0 (-2.1;2.1)</td>
</tr>
<tr>
<td>- median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evolution of the SOFA score between 0 and day 28</td>
<td>-3 (-6;3)</td>
<td>-2 (-6;3)</td>
<td>-4 (-7;1)</td>
<td>0.16</td>
<td>-1.5 (-3.35;0.3)</td>
</tr>
<tr>
<td>- median (IQR)**</td>
<td>(n=251)</td>
<td>(n=123)</td>
<td>(n=128)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilatory-acquired pneumonia - no (%)</td>
<td>86 (34)</td>
<td>39 (32)</td>
<td>47 (37)</td>
<td>0.43</td>
<td>5.0% (-6.7;16.5)</td>
</tr>
<tr>
<td>Day-28 survival - no (%)</td>
<td>176 (70)</td>
<td>86 (70)</td>
<td>90 (70)</td>
<td>0.95</td>
<td>-0.39% (-11.6;10.8)</td>
</tr>
<tr>
<td>Day-90 survival - no (%)</td>
<td>140 (56)</td>
<td>68 (55)</td>
<td>72 (56)</td>
<td>0.90</td>
<td>-0.97% (-13.6;11.2)</td>
</tr>
</tbody>
</table>

( * ) considered to be equal to the SOFA at ICU discharge for patients censored before Day28 (=maximum SOFA, 24 points)

( ** ) indicate the difference between the SOFA at day 28 (or ICU discharge) and the SOFA at inclusion.
**Table 4. Summary of the Clinical Adverse Events Recorded**

<table>
<thead>
<tr>
<th></th>
<th>Micafungin (n= 131)</th>
<th>Placebo (n=129)</th>
<th>Total (n= 260)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of adverse events (serious and not serious)</td>
<td>175</td>
<td>188</td>
<td>363</td>
</tr>
<tr>
<td>Number of patients with adverse event</td>
<td>82</td>
<td>81</td>
<td>163</td>
</tr>
<tr>
<td>Number of serious adverse events</td>
<td>124</td>
<td>140</td>
<td>264</td>
</tr>
<tr>
<td>Number of patients with serious adverse event</td>
<td>77</td>
<td>77</td>
<td>154</td>
</tr>
<tr>
<td>Number of serious adverse events related to study drug*</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Study discontinuation related to study drug</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death before the end of study (Day28)</td>
<td>38</td>
<td>37</td>
<td>75</td>
</tr>
</tbody>
</table>

Data are presented as number (%).

(*) i.e. one patient had cholestasis on the 8th day of treatment leading to terminate the study drug administration. One patient had toxidermal reaction on the 2nd day of treatment that resolved within 3 days. One patient had delirium on the 3rd day of treatment that resolved after 12 days.
eTable 5. Evolution of Liver Function in the Micafungin and Placebo Groups

<table>
<thead>
<tr>
<th></th>
<th>Total (n=251)</th>
<th>Placebo (n=123)</th>
<th>Micafungin (n=128)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AST (UI/l) level - median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>inclusion</td>
<td>47 (27 - 78)</td>
<td>42 (25 - 96)</td>
<td>50 (33 - 78)</td>
<td>0.23</td>
</tr>
<tr>
<td>day 1</td>
<td>44 (28 - 70)</td>
<td>40 (25 - 69)</td>
<td>48 (30 - 70)</td>
<td>0.27</td>
</tr>
<tr>
<td>day 2</td>
<td>42 (28 - 71)</td>
<td>38 (27 - 70)</td>
<td>45 (28 - 72)</td>
<td>0.36</td>
</tr>
<tr>
<td>day 3</td>
<td>42 (28 - 68.5)</td>
<td>41 (26 - 68)</td>
<td>46 (31 - 69)</td>
<td>0.4</td>
</tr>
<tr>
<td>day 5</td>
<td>42 (27 - 66)</td>
<td>39 (26 - 66)</td>
<td>46 (30 - 67)</td>
<td>0.13</td>
</tr>
<tr>
<td>day 7</td>
<td>35 (24.5 - 53.5)</td>
<td>34 (24 - 56)</td>
<td>39.5 (25 - 52)</td>
<td>0.37</td>
</tr>
<tr>
<td>day 9</td>
<td>35 (26 - 61)</td>
<td>32 (25.5 - 73.5)</td>
<td>37.5 (27 - 58.5)</td>
<td>0.66</td>
</tr>
<tr>
<td>day 11</td>
<td>34 (22 - 52)</td>
<td>26 (21 - 51)</td>
<td>38 (26 - 59)</td>
<td>0.06</td>
</tr>
<tr>
<td>day 14</td>
<td>30 (22 - 48.5)</td>
<td>30 (20 - 43)</td>
<td>30 (26 - 54)</td>
<td>0.22</td>
</tr>
<tr>
<td>day 21</td>
<td>28 (21 - 40.5)</td>
<td>25 (18 - 38)</td>
<td>32 (22 - 44)</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>ALT (UI/l) level - median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>inclusion</td>
<td>38 (24 - 79)</td>
<td>38 (23 - 87)</td>
<td>37 (24 - 64)</td>
<td>0.72</td>
</tr>
<tr>
<td>day 1</td>
<td>38 (22.5 - 71)</td>
<td>37 (23 - 72)</td>
<td>39 (22 - 64)</td>
<td>0.79</td>
</tr>
<tr>
<td>day 2</td>
<td>38 (23 - 74)</td>
<td>34.5 (21 - 76)</td>
<td>39 (25 - 70)</td>
<td>0.9</td>
</tr>
<tr>
<td>day 3</td>
<td>40 (24 - 74)</td>
<td>41 (23.5 - 76.5)</td>
<td>39 (28 - 67)</td>
<td>0.8</td>
</tr>
<tr>
<td>day 5</td>
<td>39 (25 - 70)</td>
<td>44 (25 - 71)</td>
<td>36 (24 - 70)</td>
<td>0.6</td>
</tr>
<tr>
<td>day 7</td>
<td>35 (24 - 61)</td>
<td>35.5 (24 - 60)</td>
<td>33 (24 - 70)</td>
<td>0.94</td>
</tr>
<tr>
<td>day 9</td>
<td>36 (23 - 68)</td>
<td>37 (23 - 61)</td>
<td>36 (22 - 68)</td>
<td>0.6</td>
</tr>
<tr>
<td>day 11</td>
<td>36 (21 - 62)</td>
<td>34.5 (21 - 65)</td>
<td>39.5 (21 - 60)</td>
<td>0.6</td>
</tr>
<tr>
<td>day 14</td>
<td>30 (20 - 49)</td>
<td>30.5 (19 - 50)</td>
<td>30 (20 - 45)</td>
<td>0.78</td>
</tr>
<tr>
<td>day 21</td>
<td>31.5 (21 - 46)</td>
<td>30.5 (23 - 47)</td>
<td>32.5 (20.5 - 46)</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>Alkaline phosphatase (UI/l) level - median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>inclusion</td>
<td>129 (93 - 202)</td>
<td>132 (87 - 186)</td>
<td>128 (97 - 220)</td>
<td>0.33</td>
</tr>
<tr>
<td>day 1</td>
<td>127.5 (91.5 - 185)</td>
<td>127 (88 - 180)</td>
<td>127.5 (96 - 199)</td>
<td>0.48</td>
</tr>
<tr>
<td>day 2</td>
<td>128 (91.5 - 182)</td>
<td>133 (92 - 178)</td>
<td>124 (91 - 196)</td>
<td>0.99</td>
</tr>
<tr>
<td>day 3</td>
<td>132 (92 - 184)</td>
<td>133.5 (95 - 182)</td>
<td>125 (91 - 193)</td>
<td>0.76</td>
</tr>
<tr>
<td>day 5</td>
<td>149 (99 - 210)</td>
<td>149 (98 - 203)</td>
<td>139.5 (100 - 212)</td>
<td>0.81</td>
</tr>
<tr>
<td>day 7</td>
<td>130 (94 - 192)</td>
<td>131 (91 - 198)</td>
<td>129.5 (98 - 177)</td>
<td>0.98</td>
</tr>
<tr>
<td>day 9</td>
<td>137 (93 - 193.5)</td>
<td>137 (93 - 209)</td>
<td>137 (91 - 181)</td>
<td>0.6</td>
</tr>
<tr>
<td>day 11</td>
<td>144.5 (103 - 210)</td>
<td>144.5 (85 - 207)</td>
<td>142.5 (106 - 215)</td>
<td>0.45</td>
</tr>
<tr>
<td>day 14</td>
<td>134.5 (94 - 188)</td>
<td>131 (91 - 186)</td>
<td>144.5 (95 - 188)</td>
<td>0.75</td>
</tr>
<tr>
<td>day 21</td>
<td>138 (102 - 209)</td>
<td>137 (100 - 199)</td>
<td>138.5 (106 - 241)</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Bilirubin (µmol/l) level - median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>inclusion</td>
<td>11 (7 - 24)</td>
<td>11 (7 - 21)</td>
<td>12 (7.5 - 26)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

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<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>day 1</td>
<td>11.3 (7 - 23)</td>
<td>11 (7 - 20)</td>
<td>12 (8 - 26)</td>
<td>0.33</td>
</tr>
<tr>
<td>day 2</td>
<td>11 (7 - 21)</td>
<td>12 (6 - 18)</td>
<td>10 (7 - 28)</td>
<td>0.41</td>
</tr>
<tr>
<td>day 3</td>
<td>11 (7 - 22)</td>
<td>10 (7 - 18)</td>
<td>11.4 (8 - 28)</td>
<td>0.29</td>
</tr>
<tr>
<td>day 5</td>
<td>11 (6 - 20)</td>
<td>10 (6 - 17)</td>
<td>12 (7 - 27.7)</td>
<td>0.26</td>
</tr>
<tr>
<td>day 7</td>
<td>11 (6 - 20)</td>
<td>11 (6 - 19)</td>
<td>11 (6.9 - 22.5)</td>
<td>0.58</td>
</tr>
<tr>
<td>day 9</td>
<td>11 (6 - 23)</td>
<td>10.5 (5 - 21)</td>
<td>12 (6.7 - 26)</td>
<td>0.42</td>
</tr>
<tr>
<td>day 11</td>
<td>9 (6 - 18)</td>
<td>9 (5.8 - 14)</td>
<td>9.5 (6 - 20)</td>
<td>0.56</td>
</tr>
<tr>
<td>day 14</td>
<td>10 (6 - 17)</td>
<td>9 (6 - 15)</td>
<td>11 (6 - 19)</td>
<td>0.32</td>
</tr>
<tr>
<td>day 21</td>
<td>9 (5.5 - 15.4)</td>
<td>8 (5.3 - 12)</td>
<td>10 (6 - 20)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

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