
**eAppendix.** Criteria for SIRS, Organ Dysfunction, and Key Exclusions; Clinical Evaluation Committee; and Endotoxin Substudy

**eTable 1.** Changes From Baseline in Inflammatory Markers During Treatment With Eritoran or Placebo (MITT Population)

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(added 3/29/13)

This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix. Criteria for SIRS, Organ Dysfunction, and Key Exclusions; Clinical Evaluation Committee; and Endotoxin Substudy

SIRS Criteria
• Fever (≥38°C) or hypothermia (≤36°C)
• Tachycardia (heart rate ≥90 beats/min)
• Tachypnea (respiratory rate >20/min while breathing spontaneously, or PaCO₂
  <32 mm Hg [4.3 kPa], or use of mechanical ventilation)
• Leukocytosis (≥12 x 10³/µL) or leukopenia (≤4 x 10³/µL) or >10% immature forms

Organ Dysfunction Criteria
Shock: Acute-onset systolic blood pressure <90 mm Hg or mean arterial pressure <65 mm Hg in the absence of other causes of hypotension. The decrease in blood pressure did not respond adequately to at least 1 hour of a fluid challenge (of 500 mL of a crystalloid solution or 200 mL of a colloid solution) and required the use of vasopressors (excluding dopamine <5 µg/kg/min) to maintain mean arterial pressure >65 mm Hg.
Respiratory failure: For subjects without pneumonia or other pre-existing lung disease: acute lung injury (PaO₂/FiO₂ ≤300), diffuse bilateral pulmonary infiltrates, need for endotracheal intubation with positive pressure ventilation, and absence of elevated left atrial pressure–related pulmonary edema all within a 24-hour interval). For subjects with pneumonia without shock: evidence of acute respiratory distress syndrome required a PaO₂/FiO₂ <200.
Thrombocytopenia: Acute-onset platelet count <100 x 10⁹/L or reduction by ≥50% from prior known levels, without another attributable cause of thrombocytopenia.
Acute kidney injury: Urine output of <0.5 mL/kg ideal body weight/hour for ≥2 hours despite adequate fluid
challenge (500 mL of a crystalloid solution or 200 mL of a colloid solution over 30 minutes); patients with pre-existing chronic kidney disease were excluded from using this definition of kidney injury.

**Acute lactic acidosis:** Unexplained metabolic acidosis pH <7.30, or a base deficit >5.0 mmol/L, in association with a plasma lactate level >2.2 mmol/L (>19.8 mg/dL).

**Key Exclusion Criteria**

- Expected survival <2 months or chronic vegetative state
- Pregnant or lactating
- Concurrent immunosuppressive therapy
  - Patients receiving a mean dose of >0.5 mg/kg prednisone (to a maximum of 30 mg/d) or equivalent dose of another agent in the 7 days before screening were excluded. Hydrocortisone at doses ≤300 mg/d for treatment of septic shock was acceptable.
- Third-degree burns (within the previous 7 days) covering >20% of body surface area
- APACHE score <21 or >37 within 24 hours of enrollment
- HIV+ with CD4 count ≤5 x 10⁷/L or end-stage processes
- Cancer with current chemotherapy or radiotherapy
- CPR within the previous 4 weeks
- Significant hepatic impairment, portal hypertension, or esophageal varices
- Severe heart failure
- Hemofiltration or hemodiafiltration for the indication of sepsis, use of endotoxin-removal devices, such as polymixin B columns, administration of IV polymixins, or plasma exchange for the indication of sepsis
Clinical Evaluation Committee
A clinical evaluation committee (CEC) comprised of critical care specialists, infectious disease specialists, and surgeons met regularly to perform blinded evaluations of individual patient case reports and procedures. CEC members adjudicated matters such as patient eligibility, presence of severe confounding underlying disorders, adequacy and timeliness of antimicrobial therapy and infection source control, occurrence of new infections and superinfections during the study period, and cause of death, according to a predefined CEC charter.

Endotoxin Substudy
Baseline endotoxin levels were measured using an endotoxin activity assay (EAA) (Spectral Diagnostics, Inc., Toronto, Canada) in whole blood using autologous neutrophil-dependent chemiluminescence.\textsuperscript{1} Study sites were selected to contribute EAA measurements based on high rates of enrolled patients and laboratory facilities to perform the assay. In patients with severe sepsis, an EAA level of $\geq 0.6$ is associated with higher ICU and hospital mortality compared with lower EAA levels.\textsuperscript{2}

\begin{enumerate}
\end{enumerate}

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eTable 1. Changes From Baseline in Inflammatory Markers During Treatment With Eritoran or Placebo (MITT Population)

<table>
<thead>
<tr>
<th></th>
<th>Eritoran (N = 1304) Actual</th>
<th>Change from baseline</th>
<th>Placebo (N = 657) Actual</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β (pg/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, n</td>
<td>1189</td>
<td></td>
<td>607</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>1.60</td>
<td></td>
<td>1.60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.6, 856.1)</td>
<td></td>
<td>(1.6-241.0)</td>
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</tr>
<tr>
<td>24 hr, n</td>
<td>1043</td>
<td>0</td>
<td>536</td>
<td>0</td>
</tr>
<tr>
<td>Median (range)</td>
<td>1.60</td>
<td></td>
<td>1.60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.6-1059.4)</td>
<td>(-808.5- 7.4.0)</td>
<td>(1.6-153.5)</td>
<td>(-128-143.9)</td>
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<tr>
<td>IL-6 (pg/mL)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline, n</td>
<td>1204</td>
<td></td>
<td>614</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>1346.7</td>
<td></td>
<td>1806.5</td>
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</tr>
<tr>
<td></td>
<td>(1.6-10001.0)</td>
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<td>(1.6-10001.0)</td>
<td></td>
</tr>
<tr>
<td>24 hr, n</td>
<td>1062</td>
<td>-423.1</td>
<td>545</td>
<td>-582.9</td>
</tr>
<tr>
<td>Median</td>
<td>271.5 (1.6-10001.0)</td>
<td>(-9999.4-9984.9)</td>
<td>311.6</td>
<td>(9958.8-7940.2)</td>
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<tr>
<td>IL-8 (pg/mL)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, n</td>
<td>1186</td>
<td></td>
<td>604</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>282.9</td>
<td></td>
<td>310.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.6-10001.0)</td>
<td></td>
<td>(1.6-10001.0)</td>
<td></td>
</tr>
<tr>
<td>24 hr n</td>
<td>1031</td>
<td>-127.1</td>
<td>530</td>
<td>-135.2</td>
</tr>
<tr>
<td>Median (range)</td>
<td>103.7</td>
<td></td>
<td>113.1</td>
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<table>
<thead>
<tr>
<th>Eritoran (N = 1304) Actual (1.6-10001.0)</th>
<th>Change from baseline (-9915.3-6400.7)</th>
<th>Placebo (N = 657) Actual (1.6-10001.0)</th>
<th>Change from baseline (-9776.0-9912.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IL-10 (pg/mL)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, n</td>
<td>1196</td>
<td>612</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>1082.9</td>
<td>1375.7</td>
<td>(1.6-10001.0)</td>
</tr>
<tr>
<td>(1.6-10001.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hr, n</td>
<td>1055</td>
<td>543</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>283.0</td>
<td>-524.7</td>
<td>317.9</td>
</tr>
<tr>
<td>(1.6-10001.0)</td>
<td>(-9999.4-9892.4)</td>
<td>(1.6-10001.0)</td>
<td>(9957.3-8865.2)</td>
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<tr>
<td><strong>IL-12 (pg/mL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Baseline, n</td>
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<td>584</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>1.60</td>
<td>1.60</td>
<td>(1.6-10001.0)</td>
</tr>
<tr>
<td>(1.6-10001.0)</td>
<td></td>
<td></td>
<td>(1.6-6298.3)</td>
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<tr>
<td>24 hr, n</td>
<td>982</td>
<td>502</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.60</td>
<td>0</td>
<td>1.60</td>
</tr>
<tr>
<td>(1.6-10001.0)</td>
<td>(-2775.9-3008.3)</td>
<td>(1.6-3062.0)</td>
<td>(-3236.3-808.0)</td>
</tr>
<tr>
<td><strong>TNF-α (pg/mL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, n</td>
<td>1079</td>
<td>558</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>63.8</td>
<td>71.3</td>
<td>(1.6-7840.6)</td>
</tr>
<tr>
<td>(1.6-7840.6)</td>
<td></td>
<td></td>
<td>(1.6-7873.0)</td>
</tr>
<tr>
<td>24 hr, n</td>
<td>911</td>
<td>479</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>35.8</td>
<td>-20.5</td>
<td>41.6</td>
</tr>
<tr>
<td>(1.6-7840.6)</td>
<td></td>
<td></td>
<td>(1.6-7873.0)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th></th>
<th>Eritoran (N = 1304)</th>
<th>Placebo (N = 657)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual</td>
<td>(1.6-773.2)</td>
<td>(1.6-8123.0)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>(-6257.5-321.7)</td>
<td>(-3953.8-250.0)</td>
</tr>
</tbody>
</table>

PCT values

<table>
<thead>
<tr>
<th></th>
<th>Eritoran</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, n</td>
<td>1202</td>
<td>607</td>
</tr>
<tr>
<td>Median</td>
<td>20.60</td>
<td>23.41</td>
</tr>
<tr>
<td></td>
<td>(0.04-922.66)</td>
<td>(0.06-678.40)</td>
</tr>
</tbody>
</table>

Abbreviations: IL, interleukin; TNF, tumor necrosis factor; PCT, procalcitonin. The cytokine measures were determined by the Millipore multiplex luminex cytokine assay (Billerica, MA) and the procalcitonin measurements were performed by the BRAHMS kryptor assay (Hennigsdorf, DE).
### eTable 2. Treatment-emergent Adverse Events in the Safety Population

<table>
<thead>
<tr>
<th>Eritoran (n = 1305)</th>
<th>Placebo (N = 657)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>211 (16.2)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>198 (15.2)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>175 (13.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>166 (12.7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>142 (10.9)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>133 (10.2)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>133 (10.2)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>118 (9.0)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>101 (7.7)</td>
</tr>
<tr>
<td>Agitation</td>
<td>97 (7.4)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>96 (7.4)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>95 (7.3)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>93 (7.1)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>91 (7.0)</td>
</tr>
<tr>
<td>Decubitus ulcer</td>
<td>89 (6.8)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>84 (6.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>82 (6.3)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>81 (6.2)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>80 (6.1)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Condition</th>
<th>Eritoran (n = 1305)</th>
<th>Placebo (N = 657)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypomagnesemia</td>
<td>76 (5.8)</td>
<td>31 (4.7)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>76 (5.8)</td>
<td>30 (4.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>71 (5.4)</td>
<td>36 (5.5)</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>68 (5.2)</td>
<td>35 (5.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>66 (5.1)</td>
<td>33 (5.0)</td>
</tr>
<tr>
<td>Generalized edema</td>
<td>66 (5.1)</td>
<td>27 (4.1)</td>
</tr>
</tbody>
</table>

**B. Infection TEAEs**

- Investigator-reported infection TEAE: 598 (45.8) vs. 311 (47.3)
- CEC-adjudicated new infection: 361 (27.7) vs. 183 (27.9)
- CEC-adjudicated relapse of infection: 65 (5.0) vs. 27 (4.1)
- CEC-adjudicated superinfection: 192 (14.7) vs. 93 (14.2)
**eAppendix 2.** Data and Safety Monitoring Committee Members, Clinical Evaluation Committee Members, Clinical Coordinating Center Members, and Principal Investigators

The authors would like to acknowledge the contributions made by the following individuals and thank them for their efforts to the study. We much appreciate their time and assistance in completing this study.

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Statistics assistance by Averion

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