# Recombinant Tissue Factor Pathway Inhibitor in Severe Community-Acquired Pneumonia: A Randomized Trial

Richard G Wunderink, MD[1]; Pierre-François Laterre, MD[2]; Bruno Francois, MD[3]; Dominique Perrotin, MD[4]; Antonio Artigas, MD[5]; Luis Otero Vidal, MD[6]; Suzana M Lobo, MD[7]; Jorge San Juan, MD [8]; Sung Chul Hwang, MD [9], Thierry Dugernier, MD[10]; Steven LaRosa, MD[11]; Xavier Wittebole, MD[2]; Jean-Francois Dhainaut, MD, PhD[12], Christopher Doig, MD[13], Meryl H Mendelson, MD[14]; Christian Zwingelstein, MD[15]; Guoqin Su, PhD[14]; and Steven Opal, MD[11]; on behalf of the CAPTIVATE Trial Group*

[1]Division of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, 676 North St. Clair Street, Suite 14-044, Chicago, IL 60611, USA
[2]St Luc University Hospital, Université Catholique de Louvain, Avenue Hippocrate 10, 1200 Brussels, Belgium
[3] Service de Réanimation Polyvalente – CIC Inserm 0801, CHU Limoges, 87042 Limoges Cedex, France
[4]Centre Hospitalier Universitaire de Tours, Université François Rabelais de Tours, 37044 Tours Cedex 9, France
[5]Critical Care Center, Sabadell Hospital, CIBER Enfermedades Respiratorias, Autonomous University of Barcelona, 08208 Sabadell, Spain
[6]Intensive Care Unit Chief, Thorax Hospital "Dr. Antonio A. Cetrangolo", 1602 Buenos Aires, Argentina
[7]Division of Critical Care Medicine, Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto, SP-15090-00, Brazil
[8]Intensive Care Department of Critical Infectious Patients, Francisco J. Muñiz Hospital of Infectious Diseases, 1282 Buenos Aires, Argentina
[9]Department of Pulmonary and Critical Care Medicine, Ajou University School of Medicine, Suwon 442-749, Republic of Korea
[10]Intensive Care Department, Clinique St Pierre, 1340 Ottignies, Belgium
[11]Division of Infectious Diseases, Rhode Island Hospital, POB Suite #330, 593 Eddy Street, Providence, RI 02903, USA
[12]Université Paris Descartes, Service de réanimation Médicale, Hôpital Cochin, 75014 Paris, France
[13]Department of Community Health Sciences, University of Calgary, Calgary, Alberta T2N 2T9, Canada
[14]Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936-1080, USA
[15]Novartis Pharma AG, Forum 1, Novartis Campus, CH-4056, Basel, Switzerland
*Members of the Community-Acquired Pneumonia Tifacogin Intra-Venous Administration Trial for Efficacy (CAPTIVATE) trial group are listed in the Appendix.

Corresponding author and address for reprints: Richard G. Wunderink, Division of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, 676 North St. Clair Street, Suite 14-044, Chicago, IL 60611, USA; Tel: 312-695-1878; Fax: 312-695-1394; E-mail: r-wunderink@northwestern.edu

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Contributions:
Conception and Design: RGW, P-FL, SO
Acquisition of Data: RGW, P-FL, BF, DP, AA, LOV, SML, JSJ, SCH, TD, XW, CD, CZ
Analysis and Interpretation: RGW, P-FL, MHM, GS, SO
Initial draft and important intellectual content: RGW, P-FL, SL, MHM, CZ, GS, SO
Review and approval of manuscript revisions: RGW, P-FL, BF, DP, AA, LOV, SML, JSJ, SCH, TD, SL, XW, J-FD, CD, MHM, CZ, GS, SO

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At a Glance Commentary: Coagulation, particularly activation of tissue factor, is important in the pathogenesis of pneumonia. Recombinant tissue factor pathway inhibitor (tifacogin) infusion did not improve mortality in patients meeting IDSA/ATS criteria for severe community-acquired pneumonia.



## ABSTRACT

**Rationale**: Severe community-acquired pneumonia (sCAP) is a leading cause of death worldwide. Adjunctive therapies for sCAP are needed to further improve outcome. A systemic inhibitor of coagulation, tifacogin (recombinant human tissue factor pathway inhibitor) appeared to provide mortality benefit in the sCAP subgroup of a previous sepsis trial.

**Objective**: Evaluate the impact of adjunctive tifacogin on mortality in sCAP patients.

**Methods**: Multicenter, randomized, placebo-controlled, double-blind, three-arm study conducted from July 2005 to June 2008 at 188 centers in North and South America, Europe, South Africa, Asia, Australia, and New Zealand. Adults with sCAP were randomized to receive a continuous intravenous infusion of tifacogin 0.025 mg/kg/h, 0.075 mg/kg/h, or matching placebo over 96 h.

**Measurements**: Severity-adjusted 28-day all-cause mortality.

**Main Results**: Of 2138 randomized patients, 946, 238, and 918 received tifacogin 0.025 mg/kg/h, 0.075 mg/kg/h, and placebo, respectively. Tifacogin 0.075 mg/kg/h was discontinued

after the first interim analysis according to pre-specified futility criterion. 28-day all-cause mortality rates were similar between the 0.025 mg/kg/h (18.0%) and placebo groups (17.9%) ($p$=0.56). Greater reduction in PF1+2 and TATc levels relative to baseline throughout the first 96 hours was found with tifacogin 0.025 mg/kg/h than with placebo. The incidence of adverse events and serious adverse events were comparable between the tifacogin 0.025 mg/kg/h and placebo groups.

**Conclusions**: Tifacogin showed no mortality benefit in sCAP patients despite evidence of biological activity.

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## INTRODUCTION

Community-acquired pneumonia (CAP) is the 8$^{th}$ leading cause of death in the US, with a death rate of 18.8/100,000 (1). The annual number of hospitalized CAP cases in the US is expected to increase up to 1 million in 2020, with similar trends in many other countries, due to the disproportionate growth of the elderly population (2). Intensive care unit (ICU) mortality due to severe CAP (sCAP) is ~30% worldwide (3-5). Despite significant advancements in antimicrobial

therapy and supportive care, the mortality rate in these patients remains high**,** and newer antibiotics alone are not expected to change patient outcome (6).

sCAP progression is associated with hypercoagulation, hypotension, and alteration of microcirculation, which lead to multiple organ dysfunction (7-10). A systemic cytokine response to pathogens leads to the progression of sCAP, and the circulating cytokines in hospitalized CAP patients show elevated inflammatory markers in the majority of cases irrespective of sepsis (11).

In sepsis, coagulation activation is primarily driven by tissue factor. Tissue factor is expressed on alveolar epithelial cells, activated endothelial cells, infiltrating monocytes, and pulmonary macrophages in response to infection and tissue damage (12, 13). Excess tissue factor expression (14, 15), and the interplay of the tissue factor-initiated coagulation and inflammatory cascades may result in end-organ damage and fatal consequences (16-18). An inhibitor of coagulation, drotrecogin alfa (activated), was reported to be associated with a significant survival benefit when administered to patients with severe sepsis from sCAP (19).

Tissue factor pathway inhibitor plays a key role as an inhibitor of coagulation within the microcirculation and limits clotting in lung tissue (20-22). Recombinant tissue factor pathway inhibitor (rTFPI, tifacogin) has been shown to restore regulation of tissue factor pathways, reducing mortality, inflammation, and lung injury in a number of animal models (23-30).

The OPTIMIST Phase III trial of tifacogin in severe sepsis did not show an overall mortality benefit with rTFPI (31); however, a retrospective analysis suggested improved survival among tifacogin-treated patients with sCAP who did not receive concurrent heparin and/or had documented microbial infection (32). These findings led to this prospective study, Community-Acquired Pneumonia Tifacogin Intra-Venous Administration Trial for Efficacy (CAPTIVATE) to assess the efficacy and safety of tifacogin as adjunct therapy in sCAP.

# METHODS

## Study Design

CAPTIVATE was a Phase III, multicenter, randomized, placebo-controlled, double-blind, three-arm study (tifacogin 0.025 mg/kg/h; tifacogin 0.075 mg/kg/h; and placebo groups) to determine the efficacy and safety of tifacogin in sCAP patients admitted to the ICU. Patients were enrolled from July 2005 to June 2008 at 188 centers in North and South America, Europe, South Africa, Asia, Australia, and New Zealand. A clinical coordinating center including critical care and infectious diseases experts approved each patient after all inclusion and exclusion criteria were met. The Institutional Review Board/Independent Ethics Committee/Research Ethics Board at each participating center approved this study, and written informed consent was obtained from each patient before enrollment. The study was conducted in compliance with the current revision of the Declaration of Helsinki and Good Clinical Practice guidelines.

## Patients

Adult patients (aged ≥18 years) with a clinical diagnosis of CAP, supported by clinical and radiological signs documented within 24 h preceding hospital admission through 24-h post-admission, and satisfying the inclusion and exclusion criteria were enrolled into the study. Patients enrolled must also have met criteria for sCAP. The definition of sCAP required ICU admission and either one major severity criterion (mechanical ventilatory support or treatment with vasopressors) or at lease two minor severity criteria (systolic blood pressure <90 mm Hg or mean arterial pressure <70 mm Hg, $PaO_2/FiO_2$ ratio <250 or a respiratory rate ≥30/min, multi-lobar pneumonia, leukopenia, hypothermia, thrombocytopenia, confusion, or uremia [see Online Data Supplement for details]). Patients who were pregnant; had prior hospitalization within 14

days of current hospital admission; required long-term mechanical ventilation; suspected with aspiration pneumonitis or post-obstructive pneumonia; bone marrow or solid organ transplantation requiring ongoing immunosuppressive therapy; or currently diagnosed with acute leukemia, multiple myeloma, or lymphoma; had liver disease (Child-Pugh Grade C or esophageal varices); had intracranial bleeding within 6 months or closed head trauma or stroke within 1 month or other neurological condition with increased bleeding risk, or who were already receiving or anticipated to receive drotrecogin alfa activated were excluded from the study. Heparin administration was prohibited within 18 h (low molecular weight heparin) or 10 h (unfractionated heparin) prior to the start of study drug infusion and throughout the 96-h infusion period. Heparin at doses of 250 IU/24 h for patients with arterial lines could be administered.



**Treatment and Procedures**

Patients were randomized (1:1:1) to receive a continuous intravenous infusion of tifacogin 0.025 mg/kg/h, tifacogin 0.075 mg/kg/h, or matching placebo over 96 h. Dosing was based on the actual body weight, and the study drug was infused through a dedicated central venous catheter when feasible. Study drug infusion was initiated no longer than 36 h post-admission to the ICU or 72 h post-hospital admission. International normalized ratio (INR) and platelet count monitored during the treatment were used to guide dose reductions and dose discontinuations (see Online Data Supplement). Study drug infusion was discontinued 6 h and 2 h prior to any major and minor surgical procedures, respectively, and was resumed 6 h and 1 h after any major and minor surgical procedures, respectively. All patients received systemic antibiotic therapy and supportive treatment.

**Efficacy Endpoints**

The primary efficacy endpoint was severity-adjusted 28-day all-cause mortality. Secondary efficacy endpoint was the incidence of treatment failure (28-day all-cause mortality or administration of drotrecogin alfa on or prior to Day 10 following initiation of the study drug). Other efficacy endpoints were as follows: ICU-, hospital-, and ventilator-free days; change in $PaO_2/FiO_2$ through study Day 8; new onset respiratory failure (requiring intubation), disseminated intravascular coagulation (DIC), and acute respiratory distress syndrome (ARDS), new vasopressors; all-cause 28-day mortality in patient populations defined by the clinical evaluation committee (CEC); all-cause 28-day mortality by disease severity (acute physiology and chronic health evaluation II [APACHE II (8)], pneumonia severity index (PSI) score, and CAP severity [patient meets two major, one major, 0 major and ≥3 minor, 0 major and ≤2 minor criteria according to ATS/IDSA guidelines (3)]); all-cause 28-day mortality by baseline biomarkers: prothrombin fragment 1+2 (PF1+2), thrombin anti-thrombin complexes (TATc), D-dimer, IL-6, and procalcitonin; and relative change (post-baseline/baseline ratio) in PF1+2, TATc, D-dimer, and IL-6.

The CEC defined per-protocol (PP) and optimal cohort populations as ITT patients who had possible or confirmed CAP (PP) or confirmed CAP (optimal cohort), met CAP severity criteria at baseline in accordance with 2007 ATS/IDSA guidelines (≥1 major criterion or ≥3 minor criteria), did not have clinically significant protocol deviations (Online Data Supplement Table E1), received a minimum duration of the study drug infusion, received acceptable antimicrobial treatment (optimal cohort), and did not have microbiological evidence of only 'non-bacterial' pathogens (optimal cohort).

**Safety Assessments**

Patients were monitored for adverse events (AEs), serious adverse events (SAEs), bleeding-related AEs and SAEs, thromboembolic and ischemic AEs and SAEs both during the dosing period (during infusion and 1 day post-infusion) as well as throughout the 28-day study period. Survival status was recorded at 90 days, 6 months, and 12 months after the initiation of the study drug to assess the long-term safety (see Online Data Supplement for details).

**Statistical Methods**

For the primary efficacy endpoint, a logistic regression model was applied for mortality data with treatment group as a factor and baseline APACHE II score and patient age (years) as continuous covariates. As the tifacogin 0.025 mg/kg/h dose group alone was continued until the study end, the level of significance determined by Conditional Error Rate method (33, 34) was used to determine if the tifacogin 0.025 mg/kg/h dose group was statistically significant compared with the placebo group. The Bonferroni method to determine the level of significance was performed as a sensitivity analysis. The logistic regression analysis was repeated by substituting baseline CAP severity (meeting 2 major criteria, 1 major criterion, 0 major criterion and ≥3 minor criteria, 0 major and ≤2 minor criteria according to the 2007 ATS/IDSA guidelines) as a categorical covariate for APACHE II in the models described above. As two interim efficacy analyses were performed, statistical tests involving the primary efficacy variable were conducted using one-sided α level of 0.025–0.000002 adjusted for two interim analyses with two tifacogin dose groups. All *p*-values for the primary efficacy variable were based on one-sided tests. A data analysis plan was designed by the sponsor according to the protocol, approved by the Clinical Evaluation committee and the non-employee members of the study design committee (RGW,SO,P-FL), and filed with the FDA. All data was collected by the sponsor and analyzed independently by the contract research organization PPD. The analyses

from PPD were reviewed and accepted by the Novartis study statistician. The writing committee reviewed the data tables and requested additional analyses

## RESULTS

A total of 2138 patients were randomized. The 0.075 mg/kg/h dose group (*n*=241) was discontinued after the first interim analysis (December 2005) for lack of efficacy based on pre-specified stopping rules, and all subsequent patients were randomized to tifacogin 0.025 mg/kg/h or placebo. The number of patients randomized to tifacogin 0.025 mg/kg/h (*n*=959) or placebo (*n*=938) was balanced (Figure 1).

Patient demographics for the ITT population are presented in Table 1. No significant difference between the tifacogin 0.025 mg/kg/h group and the placebo group was found with regard to patient demographics or baseline disease characteristics such as CAP severity, APACHE II scores, and PSI. The demographics of patients enrolled in the tifacogin 0.075 mg/kg/h group were similar to those enrolled into the 0.025 mg/kg/h dose group and the placebo group prior to the discontinuation of the 0.075 mg/kg/h treatment arm (Online Data Supplement Table E2).

### Efficacy Analysis

The efficacy population included 2102 patients randomized to the treatment groups (tifacogin 0.025 mg/kg/h: n = 946; tifacogin 0.075 mg/kg/h: n = 238; placebo: n = 918). For all patients enrolled up to the time of the last patient enrolled into the 0.075 mg/kg/h group, the 28-day all-cause mortality rates were similar among the tifacogin 0.025 mg/kg/h dose group (*n*=49/243;

20.2%), tifacogin 0.075 mg/kg/h dose group (*n*=46/238; 19.3%), and the placebo group (*n*=50/246; 20.3%).

The observed 28-day all-cause mortality in the tifacogin 0.025 mg/kg/h group did not significantly differ from the placebo group after the first interim analysis (17.2% *vs.* 17%; *p*=0.61) (Online Data Supplement Figure E1A). Hence, the primary endpoint was not met using the Conditional Error Rate method. At the end of the trial, the overall 28-day all-cause mortality rates were similar between the 0.025 mg/kg/h dose group (18.0%) and placebo group (17.9%, *p*-value 0.56), and the primary study objective was not achieved (Online Data Supplement Figure E1B). The Kaplan–Meier plot of survival during the 28-day period was similar for both tifacogin 0.025 mg/kg/h group and placebo groups (Figure 2).

Analysis of 28-day all-cause mortality by disease characteristics and by CEC subpopulations also did not show any significant difference between the tifacogin (0.025 mg/kg/h) and the placebo group (Figure 3; Online Data Supplement Figure 2). Mortality rate was lower in both tifacogin and placebo groups in the per protocol population (14.8% in tifacogin 0.025 mg/kg/h *vs.* 13.4% in placebo) and in the optimal cohort (12.7% in tifacogin 0.025 mg/kg/h *vs.* 11.2% in placebo) compared with the ITT population. Analyses of the secondary endpoints including hospital-free days, ICU-free days, ventilator-free days, new onset respiratory failure, new onset ARDS or new onset DIC showed no differences between the tifacogin 0.025 mg/kg/h or placebo groups.

Baseline geometric mean of PF1+2, IL-6, and TATc were comparable between tifacogin 0.025 mg/kg/h and placebo groups in the ITT population. The change in geometric mean ratio (post baseline/baseline) for the treatment groups and placebo over time for PF1+2, and TATc are presented in Figure 4. The reduction for PF1+2 and TATc levels at 4–8 h, 24 h, 72 h and 96 h

relative to baseline was greater in tifacogin 0.025 mg/kg/h dose group compared with the placebo group, consistent with tifacogin's known anticoagulation effects.

**Safety Findings**

The incidence of AEs and SAEs were similar in both tifacogin (0.025 mg/kg/h) and placebo groups (Table 2). The incidence of any bleeding AE was similar between the tifacogin 0.025 mg/kg/h (13.8%) and placebo (11.8%) groups. Bleeding SAEs were reported in <3% patients; 22 (2.3%) in the tifacogin 0.025 mg/kg/h dose group and 19 (2.1%) in the placebo group. Gastrointestinal bleeding SAEs were slightly greater in the tifacogin 0.025 mg/kg/h (1.7%) compared with placebo (0.9%) groups. Central nervous system bleeding SAEs were reported in one tifacogin 0.025 mg/kg/h patient and three placebo patients.

Venous thromboembolic AEs and SAEs were similar between the tifacogin 0.025 mg/kg/h (3.4% AEs and 1.4% SAEs) and placebo groups (3.4% AEs and 1.5% SAEs). Ischemic AEs and SAEs were similar in the tifacogin 0.025 mg/kg/h group (4.9%) and the placebo group (5.8%).

## DISCUSSION

CAP remains the most common cause of death from infection (1). Anti-inflammatory and anti-thrombotic therapies are sought to complement antimicrobial treatment and supportive care measures existing for sCAP (35). Activation of the coagulation system is a major pathophysiological event in severe pneumonia (16). The CAP subgroup in Phase III sepsis trials of both drotrecogin alfa activated (19) and tifacogin (OPTIMIST)(32) had demonstrated mortality benefits.

Nonetheless, the present study did not confirm subgroup findings from the earlier sepsis trial (32). In addition to CAP, subgroup analysis of the OPTIMIST study suggested a benefit with tifacogin in patients with a documented microbiological etiology and/or without concurrent heparin. Heparin was excluded in CAPTIVATE and the subgroup with a defined bacterial etiology and specifically *S. pneumoniae*, the most common etiology, did not show a mortality benefit from tifacogin. Therefore, even in these more tightly defined subgroups, a benefit of tifacogin could not be confirmed.

No benefit for tifacogin was demonstrated in the patients with increasing levels of severity based on APACHE II scores or fulfilling major criteria according to IDSA/ATS guidelines (3). Findings did show a lower overall mortality rate as levels of CAP severity decreased according to IDSA/ATS guidelines. A lower overall mortality was also reported in patients in per protocol population and optimal cohorts. This finding may be due to these cohorts including only patients who met the protocol defined criteria for enrollment and in whom antibiotic treatment was consistent with standard guidelines in terms of choice of agents and administration schedule.

Biomarkers indicative of coagulation activity, did show a pharmacodynamic effect for both tifacogin doses (0.025 mg/kg/h and 0.075 mg/kg/h) confirming tifacogin's coagulation inhibitory activity. No difference in the bleeding SAEs between the tifacogin 0.025 mg/kg/h group and the placebo group (2.3% *vs.* 2.1%) was demonstrated, in contrast with the OPTIMIST study (6.5% *vs.* 4.8%, for tifacogin 0.025 mg/kg/h and placebo, respectively in the high INR group; and 6.0% and 3.0%, respectively in the low INR group) (31). Higher rates of bleeding SAEs in the OPTIMIST study may be due to the difference in patient populations between both studies.

Several potential explanations for the negative results of this study are plausible. Tissue factor activation is an early event in sepsis and the coagulation and inflammatory cascades may be

irreversibly activated before tifacogin was administered. Compartmentalization of inflammatory response occurs in CAP and local inactivation of TFPI in the alveolar space by proteases may blunt the effect (14, 18). Unequal distribution of genetic polymorphisms affecting the coagulation pathway and sepsis mortality, such as Factor V Leiden or plasminogen activation inhibitor (PAI)-1(36, 37), may have obscured a benefit in one subgroup. Consistent changes in coagulation in the experimental groups demonstrate that an inactive recombinant drug was not the cause. Nor do excessive hemorrhagic in the treatment groups or thrombotic complications in the placebo group mask a benefit from tifacogin. The most logical explanation is that tissue factor activation, while important, may not be a critical step in the pathogenesis of sCAP or sepsis mortality.

CAPTIVATE represents the largest clinical trial of severe CAP performed to date. Study design and execution demonstrates that a more homogeneous population with a single source of infection, rather than a more generic sepsis population, can be defined. Because of this, we feel that the benefit, or lack of benefit in the case of tifacogin, can be more clearly defined. This has not been true for sepsis trials with drotrecogin alfa activated (19) or the prior sepsis trial with tifacogin (31,32).

The roughly 10% mortality of sCAP with only minor IDSA/ATS criteria (3) and the >25% subsequent need for vasopressors and/or mechanical ventilation suggests that this subgroup may be important to include in future studies. Whether or not sCAP with only minor criteria are included in future studies will be based on the expected effect size and expected enrollment. The results of our study allow those decisions to be made more rationally. Epidemiologic studies can suggest a mortality for the different categories but include many patients who may be excluded or refuse participation in a clinical trial. The >11% mortality even with appropriate, timely

antibiotic therapy in the CEC-defined optimal cohort suggests that further studies of adjuvant treatment of sCAP are warranted (35). The extensive international database in over 2200 patients with sCAP may provide insight into factors that contribute to patient outcome to facilitate future study design for this common lethal medical problem.

## Conclusions

Administration of tifacogin 0.025 mg/kg/h showed no treatment benefit in this large population of patients with severe CAP. This result was consistent across a range of disease severity indices. The pharmacologic activity of tifacogin was demonstrated by the differential decrease in sensitive markers of coagulation between the tifacogin and placebo treatment arms. Although the primary end-point was not achieved, this study demonstrates the persistent unmet need for further interventions to improve mortality of sCAP and the feasibility of those studies.

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**APPENDIX**

The following investigators participated in the CAPTIVATE trial: Timothy Albertson, UC Davis Medical Center, CA, USA; Lynn Anderson, Bay Pines VA Medical Center, FL, USA; Ian Baird, Remington Davis, Inc., OH, USA; Anthony Dal Nogare, UTSW Medical Center at Dallas, TX, USA; Jane DeMatte-D'Amico, Northwestern University, IL, USA; Manuel Iregui,

St. Joseph Medical Center, WA, USA; Luis Jauregui-Peredo, ID Clinical Research, Ltd, OH, USA; Gary Kinasewitz, The University of Oklahoma Health Sciences Center, OK, USA; Luis Laos, University of Florida HSC, IL, USA; Michael Chisdak, United Health Services Hospitals, Inc., NY, USA; George Matuschak, Alta Bates Medical Center, CA, USA; Peter Morris, Wake Forest University Health Sciences, NC, USA; Maryann Park, Middletown Medical, NY, USA; Steven Simpson, University of Kansas Medical Center, KS, USA; Joseph Preston, Pulmonary Consultants and Primary Care Physicians, CA, USA; Allan Seibert, Pulmonary Associates, AL, USA; Judy Stone, Cumberland Memorial Hospital, MD, USA; Christopher Doig, Calgary Health Region - Foothills Hospital, Canada; Dean Chittock, Vancouver General Hospital, Canada; Paul Hebert, Ottawa General Hospital, Canada; John Muscedere, Kingston General Hospital, Canada; Bruce Light, St. Boniface Hospital, Canada; Michael Jacka, University of Alberta Hospital, Canada; Sangeeta Mehta, Mt. Sinai Hospital, Canada; Germain Poirier, Hopital Charles LeMoyne, Canada; Gordon Wood, Vancouver Island Health Research Centre, Canada; James Russell, St. Paul's Hospital, Canada; Peter Krumpe, VA SNHCS-Reno, NV, USA; Mark Siegel, Yale University School of Medicine, CT, USA; David Willms, Sharp Memorial Hospital, CA, USA; Sidney Tessler, Maimonides Medical Center, NY, USA; Jeffrey Hammersley, Medical University of Ohio, OH, USA; Bojan Paunovic, Grace General Hospital, Canada; Ross Stimpson, Critical Care Office, Health Sciences Center, Canada; Eugene Cheng, Kaiser Santa Teresa Hospital, CA, USA; Mitchell Levy, Rhode Island Hospital, RI, USA; Khalid Almoosa, University of Cincinnati College of Medicine, OH, USA; Gregory Hirsch, Escondido Pulmonary Medical Group, CA, USA; Roy St. John, Remington Davis, Inc, OH, USA; Niall Ferguson, Toronto General Hospital, ON, Canada; Robert Fowler, Sunnybrook & Women's College HSC, Canada; Michael Silver, Rush University Medical Center, IL, USA; Jorge Reyno, Infectious

Disease Consultations, SD, USA; Carl Shanholtz, University of Maryland Medical Center/STC, MD, USA; Paul Scheinberg, Atlanta Pulmonary Group, GA, USA; Sean Keenan, Royal Columbian Hospital, Canada; Margaret Neff, Harborview Medical Center, WA, USA; Martin Legare, Hopital Maisonneuve Rosemont, Canada; Martin Albert, Hopital du Sacre-Coeur de Montreal, Canada; Demetrios Kutsogiannis, Royal Alexandra Hospital, Canada; Jeffrey Marsh, Lehigh Valley Hospital, PA, USA; Thomas DeMarini, Atlanta Institute for Medical Research, Inc. GA, USA; Charles Bruton, Clinical Research Solutions (MMC), TN, USA; Patrick Wright, Piedmont Respiratory Research Foundation, NC, USA; Robert Barker, Kettering Medical Center, OH, USA; Jeffrey Swilley, Clinical Research Solutions, TN, USA; Guy Soo Hoo, West Los Angeles VAMC, CA, USA; Steven Conrad, Louisiana State University, LA, USA; Mehdi Kazemi, Salem Research Institute, Inc., VA, USA; Frank Lewis, Winchester Medical Center, VA, USA; Lynn Witty, Medical Consultants, IN, USA; Jonathan Martin, Clinical Research Solutions (BHW), TN, USA; David Snyder, Atlanta Institute for Medical Research, GA, USA; John Marshall, St Michael's Hospital, Canada; Michael DePietro, Christiana Care Health Services, DE, USA; Gregory Feldman, South Carolina Pharmaceutical Research/MBMH, SC, USA; John Pullman, Mercury Street Medical Group, MT, USA; Howard Klausner, Henry Ford Hospital, MI, USA; AJ Quaranta, Sentara Norfolk General Hospital, VA, USA; Joseph Boscia, South Carolina Pharmaceutical, SC, USA; Eugene C. Fletcher, Dr. Eugene Fletcher, IN, USA; Sivagini Ganesh, LAC+USC Medical Center, CA, USA; Nathan Dean, Intermountain Medical Center, UT, USA; Robert Taylor, St. Johns Mercy Medical Center, St. Louis University, MO, USA; Antonio Anzueto, University of Texas Health Care Science Center, TX, USA; Richard Hodder, The Ottawa Hospital, Canada; Devendra Amin, Bay Area Chest Physicians, IA, USA; Dan Schuller, Creighton University Medical Center Pulmonary & C., NE, USA; Warren C.

Botnick, PSS Clinical Research, GA, USA; Firas A. Koura, Kentucky Lung Clinic, KY, USA; Dr. Pedro Sepulveda, Alamo Clinical Research, TX, USA; Philip Alapat, Baylor College of Medicine Ben Taub General Hospital, TX, USA; Eric Schroeder, Consultants in Pulmonary Medicine, KS, USA; Donald Emery, The Chester County Hospital, PA, USA; Jeffrey Cohen, St Bernards Med Center Research Center, AR, USA; Steven Chang, University of Medicine & Dentistry of New Jersey, NJ, USA; Jorge Hector Gentile, Hospital Ramon Santamarina, Argentina; Jorge San Juan, Hospital de Enfermedades Infecciosas Francisco J. M, Argentina; Jorge Corral, Hospital Interzonal General de Agudos Oscar Allende, Argentina; Sergio Prieto, Hospital Zonal de Agudos "Dr. Carlos Bocalandro", Argentina; Abel Jasovich, Sanatorio Guemes, Argentina; Suzana Ajeje Margareth, Hospital de Base - Faculdade de Medicina, Brazil; Rachel Moritz, Hospital Universitário Professor Polydoro Ernani de S, Brazil; Maria Patelli Lima, PUCCAMP - Hospital Celso Pierro, Brazil; Marcelo Rocha, Santa Casa de Porto Alegre, Brazil; Jussara Fiterman, PUCRS - Hospital Sao Lucas, Brazil; Nazah Cherif Mohamad Youssef, Hospital das Clinicas da Universidade Federal do Par, Brazil; Tarcisio Cysneiros Costa Reis, Hospital Oswaldo Cruz, Brazil; Alex Gonçalves Macedo, Santa Casa de Santos- UNIMES, Brazil; Marcelo Alcantara Holanda, Hospital de Messejana, Brazil; Eanes Delgado Barros Pereira, Hospital Universitário Walter Cantídio - HU UFCe, Brazil; Wolff Reyes, Marcelo, Hospital Clinico Pontificia Universidad Catolica de C, Chile; Carolina Chahín Anania, Hospital Hernán Henriquez Aravena, Chile; Campos Barker, Maria Isabel, Hospital de Urgencia Asistencia Pública, Chile; Cesar Villaran Ferreyros, Clinica Ricardo Palma, Peru; Julio Cesar Muñoz Sanchez, Hospital Nacional Edgardo Rebagliati Martins, Peru; Aldo Vivar Mendoza, Hospital Nacional Arzobispo Loayza, Peru; Juan Genaro Sosa Paucar, PI Hospital Nacional "Dos de Mayo", Peru; Marco Antonio Camere Torrealva, Clínica San Gabriel - Complejo

Hospitalario San Pabl, Peru; Ederlon Alves de Carvalho Rezende, Hospital Servidor Público Estadual – SP, Brazil; Brent Richards, Gold Coast Hospital, Australia; Craig French, Western Hospital, Australia; Clive Woolfe, Royal Prince Alfred Hospital, Australia; Andrew Turner, Royal Hobart Hospital, Australia; Craig Hourigan, Auckland Hospital, New Zealand; John Cade, The Royal Melbourne Hospital, Australia; Sean Newell, Cairns Base Hospital, Australia; Geoffrey Dobb, Royal Perth Hospital, Australia; Isabel Anne Leditschke, The Canberra Hospital, Australia; Sandra Peake, The Queen Elizabeth Hospital, Australia; Ian Seppelt, Nepean Hospital, Australia; Seton Henderson, Christchurch Hospital, New Zealand; Anthony Williams, Middlemore Hospital, New Zealand; David Ernest, Box Hill Hospital, Australia; Peter van Heerden, Sir Charles Gairdner Hospital, Australia; Rinaldo Bellomo, Austin Hospital, Intensive Care Unit, Australia; Godfrey Wright, Launceston General Hospital, Australia; Ross Freebairn Hawkes Bay Hospital, Intensive Care Services, New Zealand; Peter Garrett, Nambour General Hospital, Australia; Lachlan Morrison, St John's Hospital, London, UK; Thierry Dugernier, Clinique St. Pierre, Belgium; Fréderic Forêt, CHR Saint Joseph, Belgium; Dominique Benoit, UZ Gent, Belgium; Alain Dive, Cliniques Universitaires UCL de Mont-Godinne, Belgium; B. Lambermont, CHU de Liège, Belgium; Laterre, St Luc University Hospital, Belgium; Manuel Quinonez, Centre Hospitlaier Bois de l'Abbaye et de Hesbaye, Belgium; H. Spapen, UZ Brussel, Belgium; Pierre van der Rest, Clinique Saint-Luc, Belgium; Manu Malbrain, Intensive Care Unit, Belgium; Claus Peckelsen, Zentrum für Internistische Akutmedizin und Präventi, Germany; Francisco Álvarez-Lerma, Hospital del Mar, Spain; Antonio Artigas, Hospital de Sabadell, Spain; Eva Tejerina, Hospital Universitario de Getafe, Spain; Jorge Ibáñez, Hospital Son Dureta, Spain; Juan Manuel Nava, Hospital Mutua Terrasa, Spain; Antonio Santos, Hospital de Santiago, Unidad de Cuidados Intensivos, Spain; Pablo Torrabadella, Hospital German Trias i

Pujol, Spain; Antonio Torres, Hospital Clinic de Barcelona, Spain; Miguel Sánchez García, Hospital Universitario Príncipe de Asturias, Spain; Arnaud Desachy, Centre Hospitalier Général d'Angoulème, Service de Réanimation Polyvalente, France; Gilles Capellier, CHU Jean Minjoz, France; Jean Carlet PI Hôpital Saint-Joseph, Paris, France; Bruno François, CHU Dupuytren, France; Georges Offenstadt, Hopital Saint-Antoine, France; Dominique Perrotin, CHU Bretonneau, France; Dr. Reignier, Centre Hospitalier Départemental, Service de Réanimation polyvalente, France; Olivier Ruyer, Centre Hospitalier, France; Jean-Pierre Sollet, Centre Hospitalier Victor Dupouy, France; Julien Bohe, CHU Lyon Sud, France; Alain Mercat, C.H.U Angers, France; Rozendaal, Jeroen Bosch Ziekenhuis, Netherlands; Pieter Stefanus van der Berg, Kimberley Hospital Complex, South Africa; Johannes Hendrick, Jansen van Rensburg, Unitas Hospital, South Africa; Umesh Lalloo, University of Kwazulu Natal, South Africa; Guy Richards, Johannesburg Hospital, South Africa; Vijo Poulose, Changi General Hospital, Singapore; Chian Min Loo, Singapore General Hospital, Singapore; Amartya Mukhopadhyay, National University Hospital, Singapore; Woo-Joo Kim, Korea University Guro Hospital, South Korea; Sung-Chul Hwang, Ajou University Hospital, South Korea; Ki-Suck Jung, Hallym University Sacred Heart Hospital, South Korea; Jang-Wook Sohn, Korea University Anam Hospital, South Korea; Yong Kyun Cho, Gachon Medical School, South Korea; Je-Hyeong Kim, Korea University Ansan Hospital, South Korea; Hyo Youl Kim, Wonju Christian Hospital, Yonsei University, South Korea; Li Ling Tai, General Hospital Kuala Lumpur, Malaysia; Laila Kamaliah, Kamalul Bahrin, Hospital Selayang, Malaysia; Mahiran Mustafa, Hospital Kota Bahru, Malaysia; Cheng Cheng Tan, Hospital Sultanah Aminah, Malaysia; Jahizah Hassan, Hospital Pulau Pinang, Malaysia; Dina Diaz, Lung Center of the Philippines, Philippines.

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## Figure Legends

Figure 1. Patient disposition.

Figure 2. Kaplan–Meier survival curves over 28-day study period.

Figure 3. 28-day all-cause mortality by disease severity. Striped bar – tifacogin 0.025 mg/kg/h dose group, black bar - tifacogin 0.075 mg/kg/h dose group, grey bar - placebo

CAP: community acquired pneumonia; APACHE II: Acute Physiology and Chronic Health Evaluation II; PSI: Pneumonia Severity Index.

Figure 4. Response of coagulation biomarkers.

TATc – thrombin anti-thrombin complexes; PF1+2: prothrombin fragment 1.2

## Table 1. Demographics and baseline characteristics (ITT population)

| | Tifacogin 0.025 mg/kg/h (*N*=946) | Placebo (*N*=918) | Total (*N*=2102) |
|---|---|---|---|
| **Age (years)** | | | |
| *N* | 946 | 918 | 2102 |
| Mean (SD) | 59.3 (16.50) | 59.5 (16.52) | 59.5 (16.51) |
| Median (min, max) | 61.0 (18, 93) | 61.0 (18, 94) | 61.0 (18, 94) |
| **Age categories, *n* (%)** | | | |
| ≤44 years | 192 (20.3) | 169 (18.4) | 403 (19.2) |
| 45–64 years | 346 (36.6) | 368 (40.1) | 796 (37.9) |
| ≥65 years | 408 (43.1) | 381 (41.5) | 903 (43.0) |
| **Sex, *n* (%)** | | | |
| Male | 387 (40.9) | 392 (42.7) | 872 (41.5) |
| Female | 559 (59.1) | 526 (57.3) | 1230 (58.5) |
| **Race/ethnic origin, *n* (%)** | | | |
| Asians | 91 (9.6) | 86 (9.4) | 198 (9.4) |
| Blacks | 55 (5.8) | 45 (4.9) | 113 (5.4) |
| Caucasians | 676 (71.5) | 664 (72.3) | 1505 (71.6) |
| Hispanics | 100 (10.6) | 104 (11.3) | 236 (11.2) |
| Others | 24 (2.5) | 19 (2.1) | 50 (2.4) |
| **Patient disease characteristics** | | | |
| **CAP severity, *n* (%)** | | | |
| Two major criteria | 339 (35.8) | 345 (37.6) | 781 (37.2) |
| One major criterion | 318 (33.6) | 278 (30.3) | 671 (31.9) |
| Vasopressor | 447 (47.3) | 433 (47.2) | 1006 (47.9) |
| Mechanical Ventilation | 549 (58.0) | 535 (58.3) | 1227 (58.4) |
| 0 major and ≥3 minor criteria | 253 (26.7) | 249 (27.1) | 557 (26.5) |
| 0 major and ≤2 minor criteria | 36 (3.8) | 46 (5.0) | 93 (4.4) |
| Confusion/disorientation | 295 (31.2) | 303 (33.0) | 696 (33.1) |
| Multilobar infiltrates | 710 (75.1) | 697 (75.9) | 1576 (75.0) |
| Renal Replacement Therapy | 12 (1.4) | 9 (1.0) | 24 (1.1) |

| | Tifacogin 0.025 mg/kg/h (*N*=946) | Placebo (*N*=918) | Total (*N*=2102) |
|---|---|---|---|
| **APACHE II** | | | |
| *N* | 936 | 908 | 2077# |
| Mean (SD) | 20.8 (7.09) | 21.0 (6.72) | 21.0 (6.91) |
| Median (min, max) | 20.0 (3, 52) | 20.5 (5, 47) | 20.0 (3, 52) |
| **APACHE II categories, *n* (%)** | | | |
| <20 | 439 (46.4) | 391 (42.6) | 916 (43.6) |
| 20 to <25 | 246 (26.0) | 251 (27.3) | 567 (27.0) |
| 25 to <30 | 142 (15.0) | 163 (17.8) | 351 (16.7) |
| ≥30 | 109 (11.5) | 103 (11.2) | 243 (11.6) |
| Missing | 10 (1.1) | 10 (1.1) | 25 (1.2) |
| **PSI** | | | |
| *N* | 889 | 860 | 1972 |
| Mean (SD) | 141.5 (41.96) | 142.7 (42.00) | 142.5 (42.19) |
| Median (min, max) | 142.0 (33, 264) | 143.0 (18, 268) | 143.0 (18, 268) |
| **PSI categories, *n* (%)** | | | |
| ≤ 90 | 105 (11.1) | 98 (10.7) | 225 (10.7) |
| >90 to 130 | 255 (27.0) | 232 (25.3) | 543 (25.8) |
| >130 | 529 (55.9) | 530 (57.7) | 1204 (57.3) |
| Missing | 57 (6.0) | 58 (6.3) | 130 (6.2) |
| **Microbiologic Evidence, n(%)*** | | | |
| Definite | 453 (47.9) | 438 (47.7) | 1005 (47.8) |
| *S. pneumoniae* | 309 (32.7) | 307 (33.4) | 694 (33.0) |
| Bacteremia | 148 (15.6) | 167 (18.2) | 349 (16.6) |
| Probable | 92 (9.7) | 95 (10.3) | 211 (10.0) |
| No positive microbiology | 338 (35.7) | 331 (36.1) | 744 (35.4) |
| No CAP | 63 (6.7) | 54 (5.9) | 142 (6.8) |
| **Subsequent Organ Failure, n/N without at randomization** | | | |
| Mechanical Ventilation | 106/397 (26.7) | 91/382 (23.8) | 230/874 (26.3) |
| Acute Respiratory Distress Syndrome | 68/821 (8.4) | 89/815 (10.9) | 185/1849 (10.0) |
| Vasopressors | 147/498 (29.5) | 125/483 (25.9) | 302/1093 (27.6) |
| New-onset Renal Failure§ | 94/943 (10.0) | 111/903 (12.3) | 234/2081 (11.2) |
| New-onset RRT | 82/937 (8.8) | 99/899 (11.0) | 209/2070 (10.1) |

| | Tifacogin 0.025 mg/kg/h (*N*=946) | Placebo (*N*=918) | Total (*N*=2102) |
|---|---|---|---|
| New-onset hepatic failure§ | 11/872 (1.3) | 3/221 (1.4) | 9/847 (1.1) |
| DIC | 36/747 (4.8) | 30/731 (4.1) | 66/1636 (4.0) |

CAP: community acquired pneumonia; APACHE II: Acute Physiology and Chronic Health Evaluation II; PSI: Pneumonia Severity Index. DIC: Disseminated Intravascular Coagulation**; RRT: Renal Replacement Therapy**,

Total includes patients randomized to the 0.075 mg/kg/h dose

* as determined by the Clinical Evaluation Committee blinded review

§ renal failure and hepatic failure defined as $\geq$ 3 points on the Sequential Organ Failure Assessment (SOFA) score: any RRT or creatinine > 3.5 mg/dl and bilirubin $\geq$ 6.0 mg/dl, respectively (38).

## Table 2. Adverse events in the safety population

| Events | Tifacogin 0.025 mg/kg/h (*N*=955) *n* (%) | Placebo (*N*=914) *n* (%) |
|---|---|---|
| Any AE | 824 (86.3) | 778 (85.1) |
| Any SAE | 226 (23.7) | 226 (24.7) |
| Deaths[1] | 185 (19.4) | 178 (19.5) |
| Any bleeding AE | 132 (13.8) | 108 (11.8) |
| Any bleeding SAE | 22 (2.3) | 19 (2.1) |
| Hemorrhagic CNS SAEs | 1 (0.1) | 3 (0.3) |
| Cerebral hemorrhage | 0 | 1 (0.1) |
| Hemorrhage intracranial | 1 (0.1) | 0 |
| Hemorrhage stroke | 0 | 1 (0.1) |
| Subarachnoid hemorrhage | 0 | 1 (0.1) |
| Any venous thrombo-embolic AE | 32 (3.4) | 31 (3.4) |
| Any venous thrombo-embolic SAE | 13 (1.4) | 14 (1.5) |
| Any ischemic AE | 47 (4.9) | 53 (5.8) |
| Any ischemic SAE | 32 (3.4) | 33 (3.6) |
| Ischemic CNS SAEs | 12 (1.3) | 17 (1.9) |
| Ischemic stroke | 6 (0.6) | 7 (0.8) |
| Cerebral infarction | 3 (0.3) | 5 (0.5) |
| Cerebral ischemia | 1 (0.1) | 1 (0.1) |
| Ischemic cerebral infarction | 0 | 2 (0.2) |
| Transient ischemic attack | 1 (0.1) | 1 (0.1) |
| Cerebral artery embolism | 1 (0.1) | 0 |

| | | |
|---|---|---|
| Hemiplegia | 0 | 1 (0.1) |
| Lacunar infarction | 0 | 1 (0.1) |
| Most frequently reported AEs* | | |
| Anemia | 81 (8.5) | 83 (9.1) |
| Hypokalemia | 48 (5.0) | 59 (6.5) |
| Atrial fibrillation | 49 (5.1) | 42 (4.6) |
| Pleural effusion | 49 (5.1) | 41 (4.5) |
| Hyperglycemia | 42 (4.4) | 37 (4.0) |
| Diarrhea | 36 (3.8) | 31 (3.4) |
| Pneumonia | 25 (2.6) | 32 (3.5) |
| Most frequently reported SAEs† | | |
| Infections and infestations | 78 (8.2) | 71 (7.8) |
| Respiratory, thoracic and mediastinal disorders | 76 (8) | 64 (7.0) |
| Cardiac disorders | 60 (6.3) | 47 (5.1) |

*****Most frequently reported AEs (at least 5% for any group) occurring during the study infusion period (from the day of first infusion initiation to the day of last infusion plus 1).

† Most frequently reported serious adverse events (at least 5% for any group) by primary system organ class.

[1] AE with outcome of death. Only deaths up to day 60 (AE resolution day) were included.

Only adverse events occurring between Days 1 to 28 were included in all AE analyses.

**Figure 1**

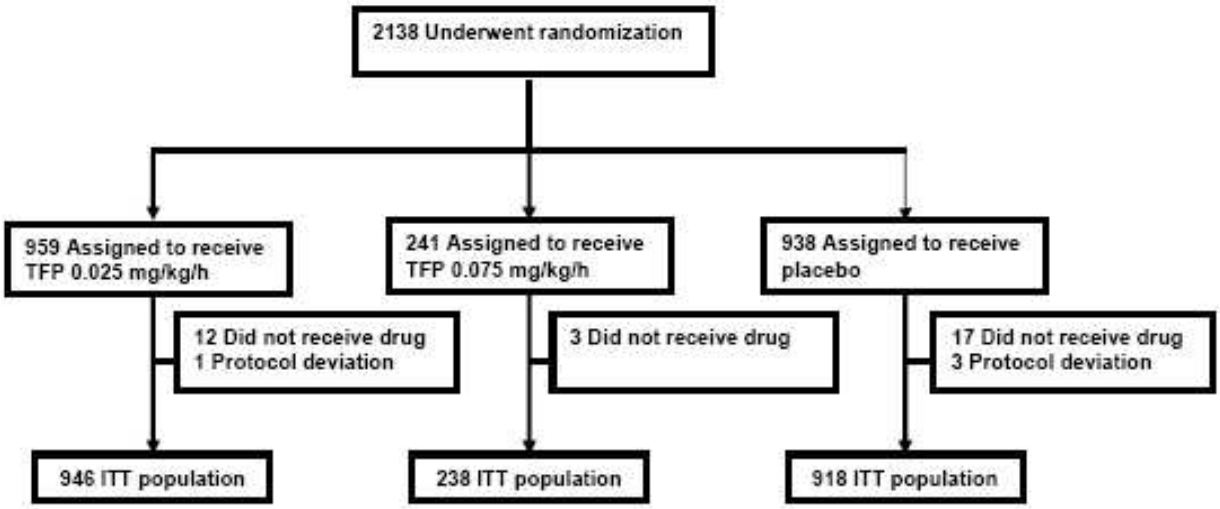


**Figure 2**

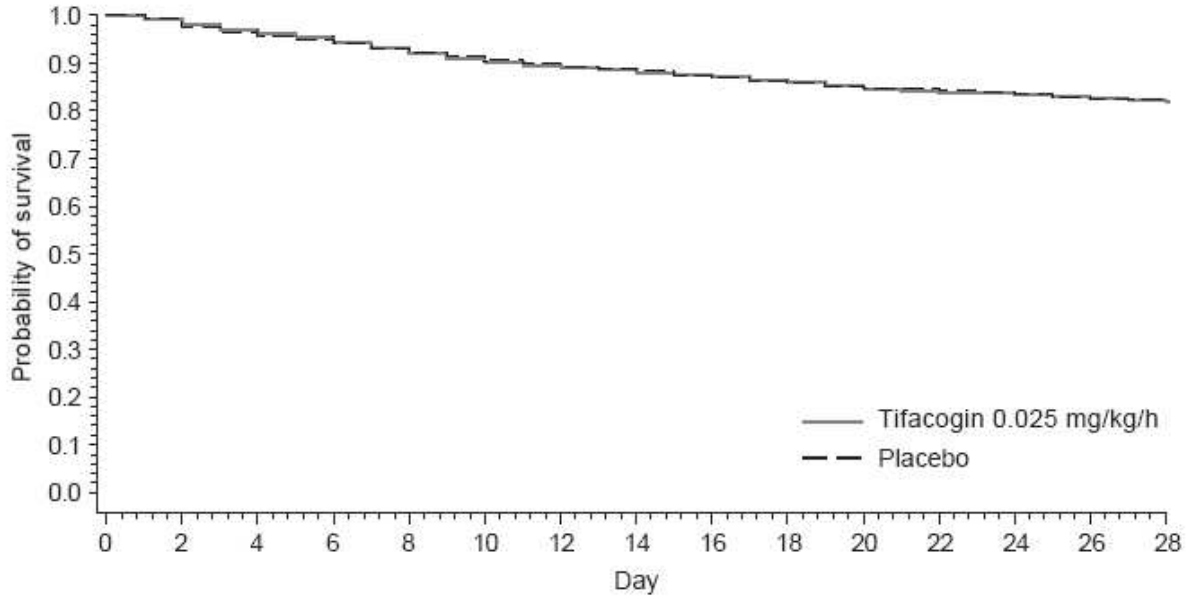
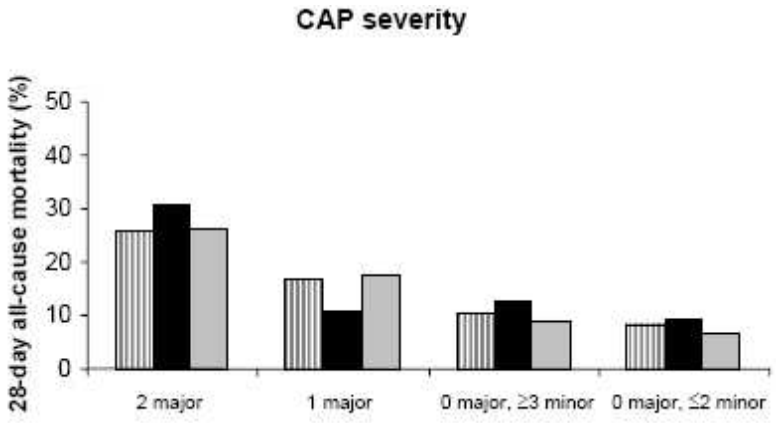


**Figure 3**

**(A)**

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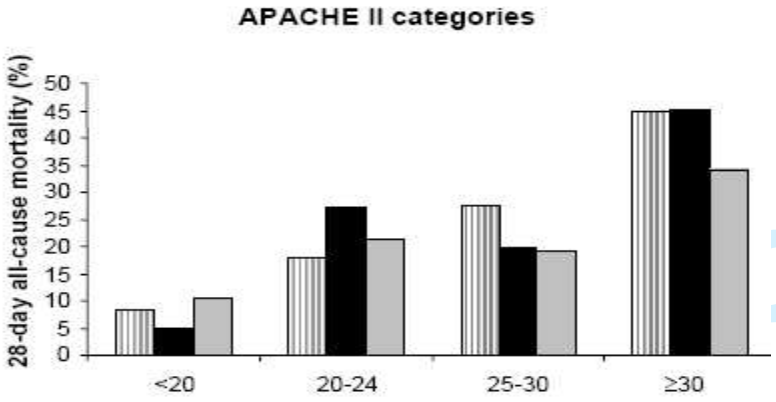

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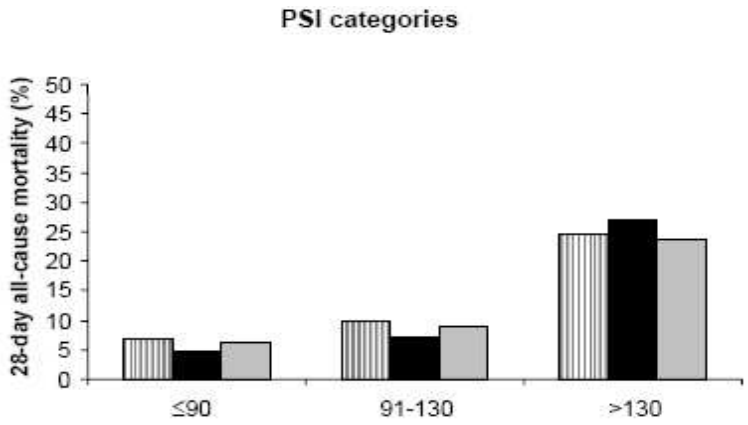
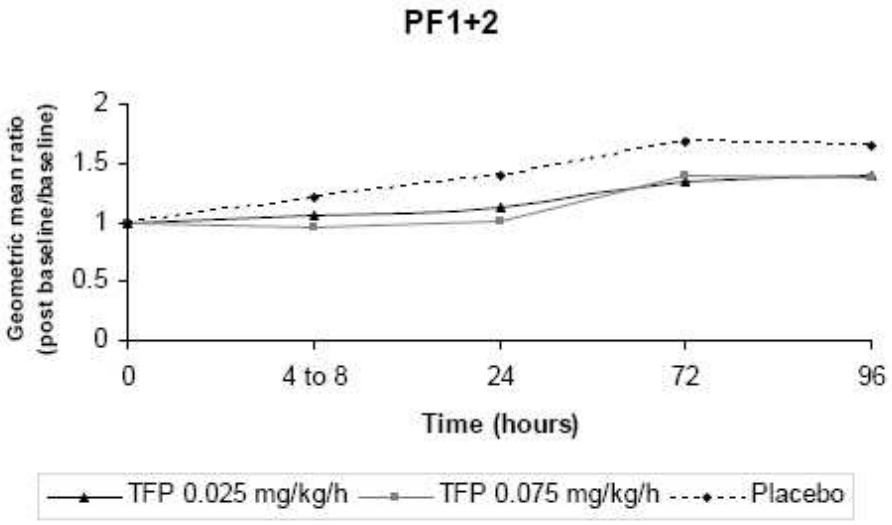
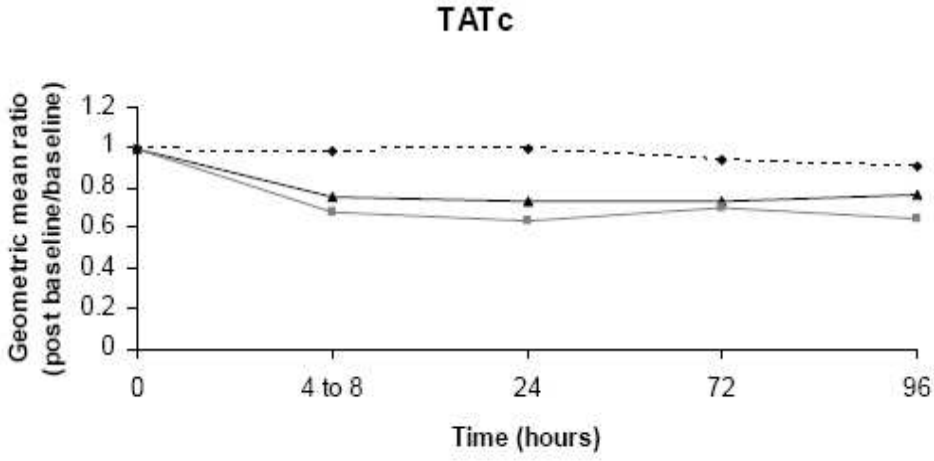


Figure 4

A.


PF1+2
Geometric mean ratio (post baseline/baseline)
2
1.5
1
0.5
0
0
4 to 8
24
72
96
Time (hours)
TFP 0.025 mg/kg/h
TFP 0.075 mg/kg/h
Placebo

B.


TATc
Geometric mean ratio (post baseline/baseline)
1.2
1
0.8
0.6
0.4
0.2
0
0
4 to 8
24
72
96
Time (hours)

# Online Data Supplement

## Recombinant Tissue Factor Pathway Inhibitor in Severe Community-Acquired Pneumonia: A Randomized Trial

Richard G Wunderink, MD[1]; Pierre-François Laterre, MD[2]; Bruno Francois, MD[3]; Dominique Perrotin, MD[4]; Antonio Artigas, MD[5]; Luis Otero Vidal, MD[6]; Suzana M Lobo, MD[7]; Jorge San Juan, MD [8]; Sung Chul Hwang, MD [9], Thierry Dugernier, MD[10]; Steven LaRosa, MD[11]; Xavier Wittebole, MD[2]; Jean-Francois Dhainaut, MD, PhD[12], Christopher Doig, MD[13], Meryl H Mendelson, MD[14]; Christian Zwingelstein, MD[15]; Guoqin Su, PhD[14]; and Steven Opal, MD[11]; on behalf of the CAPTIVATE Trial Group*



### International normalized ratio monitoring

International normalized ratio (INR) was monitored at the investigative site's hospital laboratory and INR values were available within 2 h of sample draw. If not, then INR was monitored with a commercially available bedside INR monitor provided by the Sponsor.

INR was monitored at 4 h, 8 h (±1 h) and 12 h (±1 h) after the initiation of the study-drug infusion, and thereafter every 12 h (±2 h) if the INR was not increasing steadily. Study drug infusion was interrupted for rise in INR as follows:

- With baseline INR ≤2.5, an increased INR was defined as a value of >3. A recheck value of ≤2.5 would enable resuming the infusion.
- With baseline INR >2.5 to 3.0, an increased INR was defined as a value of >3.5. A recheck value of ≤3.0 would enable resuming the infusion.

### Platelet count

Platelet count was monitored 12 h (±1 h) after study drug initiation and then daily thereafter through study day 5. If the platelet count fell below 50,000 cells/mm$^3$, the study drug infusion was interrupted. Platelet count was then monitored every 8 h (±1 h) for up to 32 h and then according to the protocol defined schedule. Study drug infusion was restarted with the platelet count ≥50,000 cells/mm$^3$ documented on two consecutive determinations during the 32 h period. Following reinstitution of the study drug infusion, the platelet count was repeated in 12 h (±2 h) and then according to the protocol defined schedule. If the platelet count again fell below 50,000 cells/mm$^3$, the study drug infusion was permanently discontinued.

### Heparin

Patients were allowed to be enrolled in the study when heparin flushes (500 IU of unfractionated heparin or equivalent to flush intravascular catheters) were used to maintain catheter patency prior to study entry. Flushing of intravascular catheters with heparin was prohibited during the 96-h infusion period. However, arterial lines might be heparinized, with the total amount per 24 h not exceeding 250 IU/24 h. If heparin therapy was required during the study drug infusion period, the study drug would be discontinued prior to initiating treatment with heparin.

### Study inclusion criteria

The study included patients presenting with at least two of these clinical signs: fever (≥38°C) or unexplained hypothermia (≤36 °C); tachypnea (≥20 breaths/min or $PaCO_2$ <32 mmHg [<4.2 kPa]); leukocytosis (WBC ≥12 x $10^9$/L), >10% immature polymorphonuclear leukocytes (bands) or relative leukopenia (WBC ≤4 x $10^9$/L) not due to other causes; and hypoxemia ($PaO_2/FiO_2$ <285 mmHg or $SaO_2$ <90%). Other inclusion criteria were radiographic findings on new pulmonary infiltrate(s) consistent with

CAP diagnosis and microbiological screening of appropriate specimens for microbiological documentation of CAP (but results were not required to determine eligibility).

Patients with pneumonia of sufficient severity requiring ICU management and meeting at least one of the severity criteria, such as receiving mechanical ventilatory support (i.e. invasive mechanical ventilation); or receiving treatment with vasopressors at therapeutic doses (i.e. dopamine >5 mg/kg/min or any dose of epinephrine, norepinephrine, phenylephrine or vasopressin) for at least 2 h to maintain or attempt to maintain systolic blood pressure (SBP) >90 mm Hg (or mean arterial pressure [MAP] >70 mm Hg) after adequate fluid resuscitation, were also included in the study.

Entry criteria also included patients who fulfilled two or more of the following criteria (documented within the previous 24 h in patients without evidence of rapid clinical improvement): SBP <90 mm Hg or MAP <70 mm Hg and received ≥40 mL/kg of fluid resuscitation over a 6 h; $PaO_2/FiO_2$ ratio <250 mmHg, or a respiratory rate ≥30/min, or the need for noninvasive mechanical ventilatory support; blood urea nitrogen (BUN) >7.0 mM (>19.6 mg/dL); new onset mental confusion (was to be documented prior to the use of sedative or other new psychotropic medication); multi-lobar pneumonia; platelet count <100,000 cells/$mm^3$ or a fall of >25% during the previous 48 h to a count of <120,000 cells/$mm^3$; leukopenia (WBC ≤4 x $10^9$/L); and hypothermia (core temperature ≤36 °C).

**Study exclusion criteria**

Patients who were pregnant; had prior hospitalization within 14 days of current hospital admission; required long-term mechanical ventilation; suspected with aspiration pneumonitis or post-obstructive pneumonia; history of bone marrow or solid organ transplantation (except for renal transplant on stable immunosuppressive regimen); or currently diagnosed with acute leukemia, multiple myeloma, non-Hodgkin's lymphoma or Hodgkin's disease, were excluded from the study. Heparin administration was prohibited within 18 h (low molecular weight heparin) or 10 h (unfractionated heparin) prior to the start of study drug infusion and throughout the 96 h infusion period.

Patients requiring deep venous thrombosis (DVT) prophylaxis, the inability to use non-pharmacologic methods, were excluded from the study. Intermittent compression devices were provided to the sites to utilize as DVT prophylaxis during the 96-h study drug infusion period as well as during the 18 h (for LMWH) or 10 h (for unfractionated heparin) pre study drug "washout period". Patients who were already receiving treatment with drotrecogin alfa activated (Xigris®, recombinant human activated Protein C) or were anticipated to need drotrecogin alfa within 24 h of study enrollment, were also excluded. Concomitant use of any other systemic anticoagulants (including antithrombin III), antiplatelet drugs (including non-steroidal anti-inflammatory drugs) or thrombolytic agents within 24 h prior to or during the study-drug infusion was not allowed, excluding aspirin up to 325 mg/day.

**Treatment**

Study drug (tifacogin or matching placebo) was continuously infused for up to 96 h by an intravenous route only, the most severe reaction being injection site necrosis. Dosing was based on actual body weight. Use of heparin through the same infusion catheter or those from which blood samples were drawn was strictly avoided because of the known interaction between heparin and tifacogin. A central line was strongly advised for study drug infusions. If a peripheral line was used, the wrist or dorsum of the hand was avoided, and the insertion site was monitored for line patency and local signs of irritation. If signs of irritation were evident, infusion of the study drug was interrupted and a central line was made for continuing study drug infusion.

**CEC defined population**

A clinical evaluation committee (CEC) performed blinded evaluation of all treated patients using pre-specified criteria to assess the diagnosis of CAP, microbiological evidence of infection, causative pathogens and acceptability of antimicrobial therapy. The CEC also assessed other clinically determined variables, including probable cause of death, clinically significant protocol deviations, and monitored the appropriateness of patient enrollment during the course of the trial.

**Per-protocol population**

The per-protocol population included all patients in the ITT population who met the following criteria:

- Had CAP or possible CAP as per the CEC assessment
- Had severe CAP (CAP severity being defined as 2 major, 1 major, or 0 major and ≥ 3 minor criteria at baseline)
- Did not have any clinically significant protocol deviations as determined by the CEC and listed in eTable 1
- Did not receive wrong study medication
- Had the minimal study medication infusion time, which was defined as follows:
    - 24 h if a patient was discharged from the initial ICU or died within 36 h after study drug infusion,
    - 2/3 of the time from the start of study drug infusion to first ICU discharge or time of death if a patient was discharged from the initial ICU or died between 36 and 96 h after the study drug infusion,
    - 64 h otherwise

All protocol deviations were identified by the site monitor and clinical trial team according to the protocol deviation list and assessed by the CEC for major protocol deviations before the database lock. Clinically significant protocol deviations were a subset of the major protocol deviations, and were also assessed by the CEC before the database lock.

All protocol deviations were classified as related to the inclusion and exclusion criteria if the deviation code was 100 series, or related to the on-study period if the deviation code was 200 series.

**Data Monitoring Committee**

An independent Data Monitoring Committee (DMC) closely monitored the safety and tolerability of the treatment throughout the trial. The DMC comprised of experienced critical care or infectious disease clinicians who were not investigators in the trial and one statistician experienced in the interim evaluation of safety and efficacy data. Prior to the start of the trial, a DMC charter was established specifying rules and guidelines for assessing safety and futility. The DMC had access to study subject treatment assignments and initially received safety updates every 4 weeks (approximately 30 patients per arm). After 300 patients were enrolled (approximately 100/group) and one day post-infusion safety and tolerability data were collected, the DMC conducted an unblinded safety evaluation. If safety and tolerability determined by the DMC were considered acceptable, the study would continue to accrue patients in all the three study arms. If safety of the 0.075 mg/kg/h arm was determined to be unacceptable, then further accrual into the 0.075 mg/kg/h arm would be terminated and accrual into the 0.025 mg/kg/h arm would be continued. If safety of both the 0.075 mg/kg/h arm and the 0.025 mg/kg/h arm were considered unacceptable, then the trial would be terminated. A second unblinded safety evaluation was conducted after 600 patients were enrolled (approximately 200/group) and 1-day post-infusion safety and tolerability data were collected. Two interim efficacy analyses and five safety reviews were performed by the DMC throughout the study. At either interim efficacy analysis or any of the safety review meetings, a tifacogin treatment group would be terminated from the study for serious safety concerns. If one of the tifacogin groups would be terminated at any safety evaluation or interim analysis, the remaining patients assigned to the terminated group would then be re-randomized at a 1:1 ratio to the remaining tifacogin or placebo groups. The information regarding whether a tifacogin treatment arm had been dropped out of the study was kept confidential to the clinical trial team until the database lock. The demographics of patients enrolled in the tifacogin 0.075 mg/kg/h, 0.025 mg/kg/h and placebo group before first interim analysis were given in eTable 2.

**Optimal cohort population**

It was defined as a subset of ITT patients who met the following criteria:

- Had confirmed CAP (Excluding No/Possible CAP) as per the CEC assessment
- Had severe CAP (as in "Per-Protocol")
- Did not have any clinically significant protocol deviations as determined by the CEC
- Did not receive wrong study medication
- Had the minimal study medication infusion time
- Did not have only non-bacterial infections (eg. fungal, viral, mycobacterial, *Pneumocystis jirovecii*, hydatid cyst by biopsy). Non-bacterial infections were identified by the clinical team before the database lock.
- Did not have either empiric or targeted antimicrobial therapy considered as unacceptable by the CEC.

A supportive analysis for the primary efficacy outcome was performed over the per-protocol population and the ideal cohort.

**Safety population**

The safety population included all patients who received the study drug, irrespective of the amount and with any available safety information. Safety analyses were performed in those patients included in the safety population.

**Statistical methods**

Treatment failure was also analyzed by a logistic-regression model with treatment group as a factor, APACHE II score and age as continuous covariates using the Bonferroni method and also the Conditional Error Rate method. The effect of tifacogin on 28-day all-cause mortality in CEC defined populations and subgroups based on disease severity were evaluated using a logistic regression model analysis with 28-day all-cause mortality as the outcome, treatment group as a factor, APACHE II and subject age (in years) as continuous covariates. Powers were estimated utilizing a simulation-based method. The study had a power of about 80% (with one-sided alpha of 0.025) to detect a 25% reduction in mortality rate for a tifacogin dosing group assuming the mortality rate to be 22% in the placebo group.

**Table E1**

Clinically significant protocol deviations (PD)

| PD Code | Description |
|---|---|
| 105 | Criteria for treatment from baseline ICU admission time window or hospital admission is not met or not verified |
| 106 | Criteria for treatment from baseline hospitalization time-window is not met or not verifiable |
| 107 | Prior hospitalization within 14 days of current hospital admission |
| 108 | INR > 3 within 4 h prior to the study drug infusion |
| 109 | Non-ambulatory resident of a long-term care facility |
| 110 | Known or suspected infective endocarditis at baseline |
| 111 | Uncontrolled hemorrhage |
| 112 | Major surgery within 12 hrs prior to start of study drug infusion |
| 113 | History of intracranial bleeding within 6 months or closed head trauma or stroke within 1 month or other neurological condition with increased bleeding risk |
| 114 | Baseline platelet count <60,000 cells/mL |
| 115 | Lumbar puncture or epidural catheter within 12 h prior to anticipated start of the study drug infusion |
| 118 | Significant liver disease (Child-Pugh Grade C) or known esophageal varices |
| 119 | Known or suspected helper/inducer T-lymphocytes (CD4+) count <200/mm$^3$ or CD4+ T-lymphocyte percentage of total lymphocytes <14 |
| 120 | For patients requiring deep venous thrombosis prophylaxis, the inability to utilize non-pharmacological methods |
| 121 | History of BMT or solid organ transplant requiring ongoing immunosuppressive therapy or with evidence of acute or chronic transplant rejection |
| 122 | Known hypersensitivity to tifacogin, other *E coli*-derived proteins or any ingredient in the final drug product |
| 123 | Clearly irreversible underlying injury that is anticipated to be fatal within 3 months or a moribund state with expected survival <24 h |
| 124 | Cardio-pulmonary arrest within 72 h pre-infusion |
| 125 | Treatment within 24 h prior to start of the study drug infusion with AT III, other systemic anticoagulants, antiplatelets* or thrombolytics |
| 128 | Subject cannot be authenticated by SDV or audit |
| 130 | Treatment with drotrecogin alfa (Xigris$^{TM}$) within 24 h prior to the study drug infusion |
| 131 | Treatment with LMWH within 18 h, unfractionated heparin within 10 h prior to start of the study drug infusion, or anticipated need for heparin within 96 h |
| 132 | Refusal of mechanical ventilation, dialysis or hemofiltration, cardioversion or required drug/fluid therapy |
| 133 | Severe neutropenia (absolute neutrophil count < 1,000 cells/mm3 due to causes other than CAP) |
| 134 | Current diagnosis of acute leukemia, multiple myeloma, non-Hodgkin's lymphoma or Hodgkin's disease |
| 135 | Post obstructive pneumonia |
| 136 | Known or suspected aspiration pneumonitis |
| 137 | Requires long-term mechanical ventilation at time of study entry |
| 199 | Other |
| 202 | Concomitant systemic anticoagulants (except citrate), or anti-platelets* (except aspirin ≤ 325 mg per day), or thrombolytics, or drotrecogin alpha |

| | |
|---|---|
| 203 | Concomitant unfractionated heparin or low-molecular-weight heparin |
| 206 | Incorrect randomization to patient enrollment sequence |
| 208 | Use of heparin flushes during study drug infusion (other than heparinization of arterial lines with a total amount per 24 h $\leq$250 IU of heparin or heparin equivalent) |
| 212 | Study drug not reduced or interrupted per INR increase algorithm |
| 213 | Study drug not permanently discontinued per INR increase algorithm |
| 214 | No follow-up confirmatory INR when INR elevated above baseline |
| 217 | Study drug resumed <6 h after surgery |
| 218 | Study drug infused despite intracranial surgery, spinal surgery, intracranial or spinal bleeding, and organ transplant |
| 223 | Study drug not interrupted for platelet counts <50000/mm$^3$ |
| 224 | Study drug not discontinued for persistent platelet counts <50000/mm$^3$ |
| 225 | Platelet counts not checked (after a decrease in count <50000/mm$^3$) |
| 230 | Study drug infusion rate errors of clinical significance |
| 231 | Significant longer infusion durations |
| 233 | Study drug resumed when INR does not return to baseline |
| 234 | INR measurement not performed within 24 h |
| 235 | Study drug resumed prior to platelet count returning to baseline |
| 236 | Study drug infusion resumed following a decrease in platelets <50000 with no follow-up platelet count showing count rising |
| 237 | Study drug stopped <6 h prior to surgical procedure |
| 299 | Others |

* Non-steroidal anti-inflammatory drugs (NSAID) were not considered as clinically significant protocol deviations

**Table E2**

Demographics and baseline disease characteristics of patients enrolled prior to interim analysis

| | Tifacogin 0.025 mg/kg/h (*n*=243) | Tifacogin 0.075 mg/kg/h (*n*=238) | Placebo (*n*=246) | Total (*N*=727) |
|---|---|---|---|---|
| **Region, *n* (%)** | | | | |
| North America | 58 (23.9) | 55 (23.1) | 55 (22.4) | 168 (23.1) |
| South America | 67 (27.6) | 73 (30.7) | 72 (29.3) | 212 (29.2) |
| Australia/NZL | 22 (9.1) | 17 (7.1) | 21 (8.5) | 60 (8.3) |
| Europe | 76 (31.3) | 73 (30.7) | 84 (34.1) | 233 (32.0) |
| South Africa | 4 (1.6) | 3 (1.3) | 3 (1.2) | 10 (1.4) |
| Asia | 16 (6.6) | 17 (7.1) | 11 (4.5) | 44 (6.1) |
| **Age (years), mean (SD)** | 60.1 (16.2) | 60.8 (16.58) | 60.8 (16.32) | 60.5 (16.35) |
| **Age categories, *n* (%)** | | | | |
| ≤44 years | 46 (18.9) | 42 (17.6) | 39 (15.9) | 127 (17.5) |
| 45 – 64 years | 85 (35) | 82 (34.5) | 96 (39) | 263 (36.2) |
| ≥ 65 years | 112 (46.1) | 114 (47.9) | 111 (45.1) | 337 (46.4) |
| **Sex, *n* (%)** | | | | |
| Women | 108 (44.4) | 93 (39.1) | 110 (44.7) | 311 (42.8) |
| Men | 135 (55.6) | 145 (60.9) | 136 (55.3) | 416 (57.2) |
| **Race, *n* (%)** | | | | |
| Asians | 17 (7) | 21 (8.8) | 14 (5.7) | 52 (7.2) |
| Blacks | 8 (3.3) | 13 (5.5) | 12 (4.9) | 33 (4.5) |
| Caucasians | 180 (74.1) | 165 (69.3) | 183 (74.4) | 528 (72.6) |
| Hispanics | 31 (12.8) | 32 (13.4) | 32 (13) | 95 (13.1) |
| Others | 7 (2.9) | 7 (2.9) | 5 (2) | 19 (2.6) |
| **Weight, kg** | | | | |
| *n* | 243 | 238 | 246 | 727 |
| Mean (SD) | 72.56 (18.18) | 70.78 (18.59) | 71.08 (17.74) | 71.48 (18.16) |
| Median (Min, Max) | 70 (36, 140) | 69 (37, 146) | 70 (31, 135) | 70 (31, 146) |
| **Height (cm)** | | | | |
| *n* | 238 | 229 | 237 | 704 |
| Mean (SD) | 167.3 (9.42) | 166.5 (10.10) | 167 (10.46) | 167 (9.99) |
| Median (Min, Max) | 167.6 (143, 197) | 165 (126, 191) | 167.6 (140, 193) | 167.6 (126, 197) |
| **BMI, kg/m$^2$** | | | | |
| *n* | 238 | 229 | 237 | 704 |
| Mean (SD) | 25.9 (6.066) | 25.59 (5.715) | 25.33 (5.52) | 25.62 (5.77) |
| Median (min, max) | 24.7 (14.2, 50.8) | 24.39 (14.7, 43.7) | 24.74 (13.5, 45.6) | 24.51 (13.5, 50.8) |
| **Patient disease characteristics** | | | | |
| CAP severity, *n* (%) | | | | |
| Two major criteria | 72 (29.6) | 97 (40.8) | 97 (39.4) | 266 (36.6) |
| One major criterion | 94 (38.7) | 75 (31.5) | 70 (28.5) | 239 (32.9) |
| 0 major and ≥3 minor criteria | 65 (26.7) | 55 (23.1) | 67 (27.2) | 187 (25.7) |
| 0 major and ≤2 minor criteria | 12 (4.9) | 11 (4.6) | 12 (4.9) | 35 (4.8) |
| APACHE II | | | | |
| *n* | 241 | 233 | 243 | 717 |
| Mean (SD) | 21.8 | 21.9 | 21.4 | 21.7 |
| Median (min, max) | 7.5 | 6.94 | 6.87 | 7.10 |

| | | | | |
|---|---|---|---|---|
| APACHE II categories, *n* (%) | | | | |
| <20 | 95 (39.1) | 86 (36.1) | 97 (39.4) | 278 (38.2) |
| 20 to <25 | 77 (31.7) | 70 (29.4) | 75 (30.5) | 222 (30.5) |
| 25 to <30 | 32 (13.2) | 46 (19.3) | 37 (15) | 115 (15.8) |
| ≥30 | 37 (15.2) | 31 (13) | 34 (13.8) | 102 (14) |
| Missing | 2 (0.8) | 5 (2.1) | 3 (1.2) | 10 (1.4) |
| PSI | | | | |
| *n* | 233 | 223 | 237 | 693 |
| Mean (SD) | 143.6 (42.8) | 145.9 (43.76) | 141.9 (41.62) | 143.8 (42.69) |
| Median (Min, Max) | 142 (38, 260) | 146 (36, 249) | 142 (43, 250) | 143 (36, 260) |
| PSI categories, *n* (%) | | | | |
| ≤90 | 23 (9.5) | 22 (9.2) | 27 (11) | 72 (9.9) |
| >90 to 130 | 71 (29.2) | 56 (23.5) | 65 (26.4) | 192 (26.4) |
| >130 | 139 (57.2) | 145 (60.9) | 145 (58.9) | 429 (59) |
| Missing | 10 (4.1) | 15 (6.3) | 9 (3.7) | 34 (4.7) |

**Figure Legends**

eFigure 1: 28-day all-cause mortality; (A) after first interim analysis (IA) and (B) overall.

After first IA: tifacogin (TFP) 0.025 mg/kg/h (121/703); Placebo (114/672).

Overall: TFP 0.025 mg/kg/h (170/946); TFP 0.075 mg/kg/h (46/238); Placebo (164/918).

eFigure 2: 28-day all-cause mortality by Clinical Evaluation Committee (CEC) subpopulations.

CAP: community acquired pneumonia; cCAP+B: confirmed community acquired pneumonia and baseline (2 major, 1 major or ≥ 3 minor severity criteria); ME: cCAP+B and definite microbiological evidence; ME+PBC: cCAP+B, definite microbiological evidence and positive blood culture; ME S.p.: cCAP+B and definite microbiological evidence of *S. pneumoniae* infection; ME-NBP: cCAP+B and definite microbiological evidence excluding patients who had only a non-bacterial pathogen.

**Figure E1**

**(A)** **(B)**

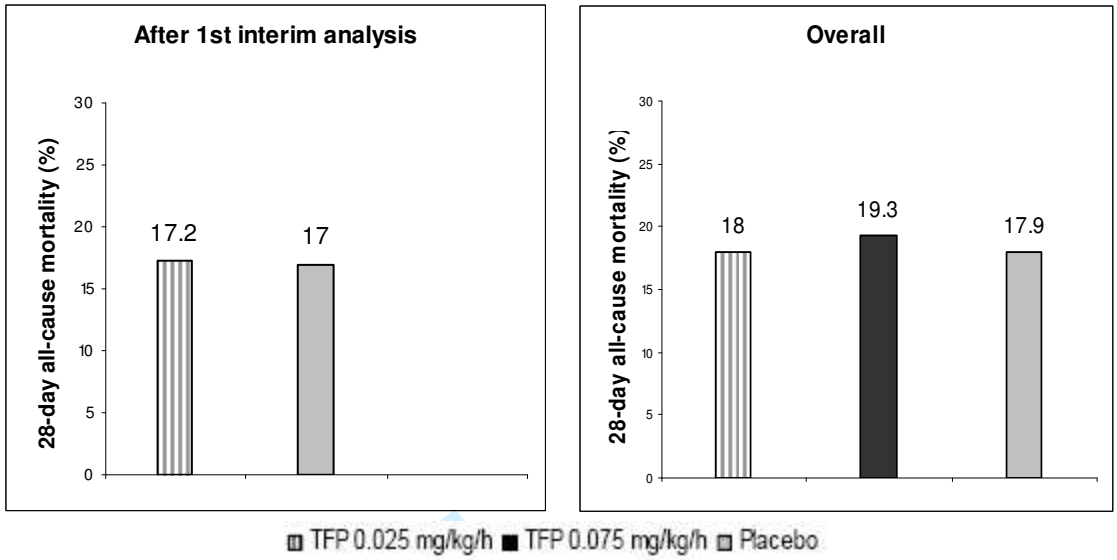



**Figure E2**