Sponsor

Novartis

Generic Drug Name

Tifacogin

Trial Indication(s)

Community-acquired pneumonia

Protocol Number

TFP561A2308

Protocol Title

A phase 3, multicenter, randomized, placebo-controlled, double-blind, 3-arm study to evaluate the safety and efficacy of tifacogin (recombinant tissue factor pathway inhibitor) administration in patients with severe community-acquired pneumonia

Clinical Trial Phase

Phase III

Study Start/End Dates

16-May-2004 to 28-July-2008

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

A Phase 3, multicenter, randomized, placebo-controlled, double-blind, 3-arm study evaluated the safety and efficacy of TFP in patients with sCAP.

Patients were randomized in a 1:1:1 ratio to receive a continuous intravenous infusion (CIV) of either TFP at a dose of 0.025 mg/kg/h (TFP low-dose group), TFP at a dose of 0.075 mg/kg/h (TFP high-dose group), or matching placebo for up to 96 hours. After the first interim analysis, the TFP high-dose group was terminated early by an independent Data Monitoring Committee and enrollment was continued with patients randomized in a 1:1 ratio to the remaining TFP low-dose or the placebo groups.

Patients were followed for 28 days to assess survival. The incidence of treatment failure (28-day all-cause mortality or use of drotrecogin alfa within 10 days of study entry) was assessed. In addition, changes in respiratory function, ventilator requirements, and duration of ICU and hospital stay were evaluated. In addition to 28-day all-cause mortality, safety was evaluated by comparing the incidence of adverse events (AEs), serious adverse events (SAEs), and special AEs such as bleeding-related AEs and SAEs, thromboembolic and ischemic events. Survival data were also collected at 90 days, 6 months, and 1 year to assess long-term safety.

Centers

2138 patients were enrolled into the study from 68 centers in the United States (US) and 120 Ex-US centers

Objectives:

Primary objective(s)

Primary Objective: to compare the effect of tifacogin (TFP) administered at a dose of 0.025 mg/kg/h and/or 0.075 mg/kg/h versus placebo administration on 28-day all-cause mortality in patients with severe community-acquired pneumonia (sCAP).

Secondary objective(s)

To evaluate the effect of TFP on the incidence of treatment failure defined as 28-day all-cause mortality or the administration of drotrecogin alfa (Xigris®, activated recombinant protein C [aPC]) within 10 days of initiating study drug infusion.

Test Product (s), Dose(s), and Mode(s) of Administration

Tifacogin was supplied in 100 mL vials containing 100 mL of 0.15 mg/mL or 0.45 mg/mL of TFP. Tifacogin was administered as a CIV infusion (preferably via a central line) at an infusion rate of 0.025 or 0.075 mg/kg/h.

Statistical Methods

All efficacy analyses and baseline summaries were based on the ITT population. Statistical tests involving the primary efficacy variable, 28-day all-cause mortality, were performed on all treatment groups that were continued until the end of the study. To assess the treatment effect of TFP, a logistic-regression model was fitted for mortality data with treatment group as a factor and baseline APACHE II score and patient age (in years) as continuous covariates. Since only the TFP low-dose group was continued until the end of the study, the level of significance determined by Conditional Error Rate (CER) method was used to determine if the TFP low-dose group compared with the placebo group was statistically significant. This method ensured the family-wise type-1 error rate at the α level.

In addition, the Bonferroni method was performed to determine level of significance and this test was performed as a sensitivity analysis. The logistic regression analyses described above were repeated by substituting baseline CAP severity for APACHE II as a categorical covariate in the models. Since there were 2 interim efficacy analyses, statistical tests involving the primary efficacy variable was conducted using one-sided α level of 0.024998 adjusted for efficacy analysis performed in 2 interim analyses with 2 TFP dose groups. All P-values for the primary efficacy variable were based on one-sided tests.

Treatment failure was analyzed similarly to 28-day all-cause mortality. The effect of TFP on 28-day all-cause mortality in CEC-defined populations and subgroups defined based on disease severity were evaluated using a logistic -egression model analysis with 28-day all-cause mortality as the outcome, treatment group as a factor, APACHE II and patient age as continuous covariates. The effect of each disease severity on the response to TFP (28-day all-cause mortality) was evaluated by using logistic regression models with treatment group as a factor, baseline APACHE II score and patient age as continuous covariates, disease severity, and treatment by disease-severity interaction. Adverse events, SAEs and AEs during the study drug infusion period and during the 28-day study period were summarized according to primary system organ class and preferred term by treatment.

Adverse events causing discontinuation of study drug, AEs and SAEs of special interest, and AEs that occurred up to Day 28 with an outcome of death up to Day 60 were similarly summarized.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Diagnosis of community-acquired pneumonia supported by additional clinical, radiological, and microbiological evidence
- Pneumonia of sufficient severity to require ICU admission and management

Exclusion Criteria:

- Pregnancy
- Weight over 150 kg
- Patients at increased risk of bleeding
- Treatment with drotrecogin alfa or anticipated need for drotrecogin alfa
- Treatment with heparin or anticipated need for heparin

Participant Flow Table

Disposition	TFP 0.025 mg/kg/h n (%)	TFP 0.075 mg/kg/h n (%)	Placebo n (%)	Total n (%)
Randomized	**959**	**241**	**938**	**2138**
Randomized but not infused with study drug	12 (1.3)	3 (1.2)	17 (1.8)	32 (1.5)
Infused, but with the protocol deviation of 'significant deviation in execution of informed consent'	1 (0.1)	0	3 (0.3)	4 (0.2)
ITT population	946 (98.6)	238 (98.8)	918 (97.9)	2102 (98.3)
Completed the study participation (survived through Day 28)[a]	767 (81.1)	192 (80.7)	748 (81.5)	1707 (81.2)
Discontinued the study	179 (18.9)	46 (19.3)	170 (18.5)	395 (18.8)
Primary reason:				
Death	168 (17.8)	46 (19.3)	163 (17.8)	377 (17.9)
Lost to Follow-up	2 (0.2)	0	1 (0.1)	3 (0.1)
Protocol violation	0	0	1 (0.1)	1 (0.0)
Withdrawal of consent	4 (0.4)	0	4 (0.4)	8 (0.4)
Inappropriate enrollment	2 (0.2)	0	0	2 (0.1)
Unable to classify into the above reasons	3 (0.3)	0	1 (0.1)	4 (0.2)

Notes: The ITT population included all randomized patients who received any amount of study drug and did not have a protocol deviation of significant deviation in execution of informed consent.
Percentages for randomized but not infused, and ITT population were based on the total randomized for each treatment.
Percentages for completed and discontinued patients were based on the total in the ITT population for each treatment.
Patients were assigned to the treatment as randomized in the ITT population.
[a] Patients were followed up for 28-day all cause mortality and did not die on or before Day 28.
Abbreviations: ITT=intent-to-treat.

Baseline Characteristics

	TFP 0.025 mg/kg/h (N=946)	TFP 0.075 mg/kg/h (N=238)	Placebo (N=918)	Total (N=2102)
Region, n (%)				
North America	260 (27.5)	55 (23.1)	250 (27.2)	565 (26.9)
South America	199 (21.0)	73 (30.7)	190 (20.7)	462 (22.0)
Australia/NZL	92 (9.7)	17 (7.1)	87 (9.5)	196 (9.3)
Europe	304 (32.1)	73 (30.7)	304 (33.1)	681 (32.4)
South Africa	16 (1.7)	3 (1.3)	14 (1.5)	33 (1.6)
Asia	75 (7.9)	17 (7.1)	73 (8.0)	165 (7.8)
Age (years)				
n	946	238	918	2102
Mean (SD)	59.3 (16.50)	60.8 (16.58)	59.5 (16.52)	59.5 (16.51)
Age categories (years), n (%)				
≤44	192 (20.3)	42 (17.6)	169 (18.4)	403 (19.2)
45 - 64	346 (36.6)	82 (34.5)	368 (40.1)	796 (37.9)
≥65	408 (43.1)	114 (47.9)	381 (41.5)	903 (43.0)
Sex, n (%)				
Female	387 (40.9)	93 (39.1)	392 (42.7)	872 (41.5)
Male	559 (59.1)	145 (60.9)	526 (57.3)	1230 (58.5)
Race / Ethnic Origin, n (%)				
Asian	91 (9.6)	21 (8.8)	86 (9.4)	198 (9.4)
Black	55 (5.8)	13 (5.5)	45 (4.9)	113 (5.4)
Caucasian	676 (71.5)	165 (69.3)	664 (72.3)	1505 (71.6)
Hispanic	100 (10.6)	32 (13.4)	104 (11.3)	236 (11.2)
Other	24 (2.5)	7 (2.9)	19 (2.1)	50 (2.4)

Summary of Efficacy

Primary Outcome Result(s)

Logistic regression analysis of 28-day all-cause mortality using age and APACHE II score as covariates - Significance level determined by Conditional Error Rate Method (ITT population)

	TFP 0.025 mg/kg/h N=946	TFP 0.075 mg/kg/h N=238	Placebo N=918	Total N=2102
Treatment termination status	Complete	Terminated after 1st IA		
Mortality Rates at trial adaptation				
M	243	238	246	727
n (%)	49 (20.2)	46 (19.3)	50 (20.3)	145 (19.9)
Absolute difference vs placebo (%)	-0.2	-1.0		
Relative difference vs placebo (%)	0.99	0.95		
Odds Ratio for treatment (95% C.I.)[a,b]	0.972 (0.603, 1.566)	0.881 (0.544, 1.426)		
One-sided P-value from Wald test[b]	0.453080	0.302637		
Conditional type I error rate[c]	0.009688			
Mortality Rates after trial adaptation				
M	703		672	1375
n (%)	121 (17.2)		114 (17.0)	235 (17.1)
Absolute difference vs placebo (%)	0.2			
Relative difference vs placebo (%)	1.01			
Odds ratio for treatment (95% C.I.)[a,d]	1.044 (0.777, 1.402)			
One-sided P-value from Wald test[d]	0.611938			

M - Number of patients; n - Number of deaths. %=100*n/M
* significant according to the conditional Type-I error rate.
a Odds ratio <1 indicates reduced odds of mortality for the treatment versus placebo.
b Treatment was included as a 3-level factor (3 groups).
c Conditional type I error rate preserved at time of trial adaptation, maintaining an overall Type-I error of 0.024998 (1-sided).
d Treatment was included as a 2-level factor (2 groups). Missing mortality information was imputed using survival. Missing age was imputed using the mean across the ITT population. Missing APACHE II score was imputed using the mean for the ITT population.
Abbreviations: C.I.=confidence interval

Logistic regression analysis of 28-day all-cause mortality using age and APACHE II score as covariates - Significance level determined by

Bonferroni Method (ITT population)

	TFP 0.025 mg/kg/h N=946	Placebo N=918
n (%)	170 (18.0)	164 (17.9)
Absolute difference vs placebo (%)	0.1	
Relative difference vs placebo (%)	1.01	
Odds ratio for treatment (95% C.I.)[a]	1.020 (0.794, 1.309)	
One-sided P-value	0.560367	

N - Number of patients; n (%) - Number (%) of deaths
Level of significance at 0.024998 (1-sided) level using in Bonferroni procedure.
a Odds ratio <1 indicated that the treatment reduced the rate of mortality compared with placebo.
Missing mortality information was imputed as survival.
Missing age was imputed using the mean across the ITT population.
Missing APACHE II score was imputed using the mean of the ITT population.
Abbreviations: C.I. = confidence intervals

Logistic regression analysis of 28-day all-cause mortality using Age as covariate and CAP severity as a factor – Significance level determined by Conditional Error Rate Method (ITT population)

	TFP 0.025 mg/kg/h N=946	TFP 0.075 mg/kg/h N=238	Placebo N=918	Total N=2102
Treatment termination status	Complete	Terminated after 1st IA		
Mortality rates at trial adaptation:				
M	243	238	246	727
n (%)	49 (20.2)	46 (19.3)	50 (20.3)	145 (19.9)
Absolute difference vs Placebo (%)	-0.2	-1.0		
Relative risk vs Placebo	0.99	0.95		
Odds Ratio for treatment (95% C.I.)[a,d]	1.111 (0.688, 1.796)	0.886 (0.547,1.436)		
One-sided P-value from Wald test[d]	0.666699	0.311723		
Conditional type I error rate[c]	0.003096			
Mortality rates after trial adaptation:				
M	703		672	1375
n (%)	121 (17.2)		114 (17.0)	235 (17.1)
Absolute difference vs Placebo (%)	0.2			
Relative risk vs Placebo	1.01			
Odds Ratio for treatment (95% C.I.)[a,d]	1.019 (0.760, 1.366)			
One-sided P-value from Wald test[d]	0.550134			

M - Number of patients; n - Number of deaths. %=100*n/M
* significant according to the conditional type I error rate.
[a] Odds ratio <1 indicates reduced odds of mortality for the treatment versus placebo.
[b] Treatment is included as a three-level factor (three groups).
[c] Conditional type I error rate preserved at time of trial adaptation, maintaining an overall type I error of 0.024998 (one-sided).
[d] Treatment was included as a 2-level factor (2 groups).
Missing mortality information was imputed as survival.
Missing age was imputed as the mean across the ITT population.
Missing CAP severity was imputed as one major criterion.

Logistic regression analysis of 28-day all-cause mortality using Age as covariate and CAP severity as a factor – Significance level determined by Bonferroni Method (ITT population)

	TFP 0.025 mg/kg/h N=946	Placebo N=918
Number of deaths (%)	170 (18.0)	164 (17.9)
Absolute difference from placebo (%)	0.1	
Relative risk vs placebo	1.01	
Odds ratio for treatment (95% C.I.)[a]	1.027 (0.800, 1.318)	
One-sided P-value	0.582665	

* significant at 0.024998 (1-sided) level using in Bonferroni procedure.
[a] Odds ratio <1 indicated that the treatment reduced the rate of mortality compared with placebo.
Missing mortality information was imputed as survival.
Missing age was imputed as the mean across the ITT population.
Missing CAP severity was imputed as 1 major criterion.
Abbreviation: C.I.=confidence interval.

Secondary Outcome Result(s)

Not Applicable

Summary of Safety

Safety Results

Patients who died due to AEs, had serious AEs, or had other clinically significant AEs over the course of the study and before trial adaptation (Safety population)

	Over the course of the study				Stage 1 (before trial adaptation)		
	TFP low-dose N=955 n(%)	TFP high-dose N=237 n(%)	Placebo N=914 n(%)	Total N=2106 n(%)	TFP low-dose N=249 n(%)	TFP high-dose N=237 n(%)	Placebo N=243 n(%)
Total number of patients who died[a], had SAEs, discontinued the study drug due to AEs, or had AEs of special interest	**408(42.7)**	**107 (45.1)**	**388 (42.5)**	**903 (42.9)**	**127(51.0)**	**107(45.1)**	**117(48.1)**
Deaths[a]	**185(19.4)**	**55(23.2)**	**178(19.5)**	**418(19.8)**	**52(20.9)**	**55(23.2)**	**58(23.9)**
SAEs	98(10.3)	26(11.0)	94(10.3)	218(10.4)	32(12.9)	26(11.0)	25(10.3)
Non-SAEs[b]	87(9.1)	29(12.2)	84(9.2)	200(9.5)	20(8.0)	29(12.2)	33(3.6)
SAEs	**226(23.7)**	**60(25.3)**	**(24.7)**	**512(24.3)**	**72(28.9)**	**60(25.3)**	**64(26.3)**
AEs causing Discontinuation of the study drug	**70(7.3)**	**22(9.3)**	**69(7.5)**	**161(7.6)**	**12(4.8)**	**22(9.3)**	**18(7.4)**
Any Bleeding AE	**132(13.8)**	**35(14.8)**	**108(11.8)**	**275(13.1)**	**47(18.9)**	**35(14.8)**	**36(14.8)**
SAEs	22(2.3)	4(1.7)	19(2.1)	45(2.1)	6(2.4)	4(1.7)	4(1.6)
SAEs with outcome of death	4(0.4)	1(0.4)	3(0.3)	8(0.4)	1(0.4)	1(0.4)	1(0.4)
Any venous thromboembolic AE	**32(3.4)**	**4(1.7)**	**31(3.4)**	**67(3.2)**	**9(3.6)**	**4(1.7)**	**7(2.9)**
SAEs	13(1.4)	1(0.4)	14(1.5)	28(1.3)	4(1.6)	1(0.4)	2(0.8)
SAE with outcome of death	1(0.1)	0	0	1(0.0)	0	0	0
Any ischemicAE	**47(4.9)**	**13(5.5)**	**53(5.8)**	**113(5.4)**	**18(7.2)**	**13(5.5)**	**20(8.2)**
SAEs	32(3.4)	8(3.4)	33(3.6)	73(3.5)	12(4.8)	8(3.4)	11(4.5)
SAEs with outcome of death	8(0.8)	2(0.8)	9(1.0)	19(0.9)	3(1.2)	2(0.8)	4(1.6)
Any injection site reaction AE	**19(2.0)**	**3(1.3)**	**16(1.8)**	**38(1.8)**	**8(3.2)**	**3(1.3)**	**7(2.9)**
Any injection site reaction SAE	**1(0.1)**	**0**	**2(0.2)**	**3(0.1)**	**0**	**0**	**1(0.4)**

Note: Only AEs that occurred between Day 1 to Day 28 were included in all AE analyses.
[a] AE with outcome of death. The death may have occurred after Day 28 and only deaths up to Day 60 (AE resolution

day) were considered for potential outcome of AEs occurred between Day 1 to Day 28.
[b] Did not have any SAE with outcome of death. According to Section 9.5.1.5 of the study protocol, organ failures or dysfunctions which, according to the investigator were clearly secondary to sCAP, should only have been reported as SAEs if in the opinion of the Investigator the event was a clinically significant and unexpected deterioration in organ function or the organ failure or dysfunction was not a consequence of sCAP. Deaths that were considered by the investigator to be directly related to sCAP, were not reported as SAEs unless the death was thought also to be related to the administration of study drug.
Abbreviations: AEs=adverse events; SAEs=serious adverse events; and sCAP=severe community-acquired pneumonia.

Most frequently reported adverse events (at least 5% for any group) by preferred term (Safety population)

Preferred Term	TFP 0.025 mg/kg/h N=955 n (%)	TFP 0.075 mg/kg/h N=237 n (%)	Placebo N=914 n (%)	Total N=2106 n (%)
Any adverse event	**824 (86.3)**	**199 (84.0)**	**778 (85.1)**	**1801 (85.5)**
Anemia	115 (12.0)	31 (13.1)	130 (14.2)	276 (13.1)
Pneumonia	85 (8.9)	31 (13.1)	91 (10.0)	207 (9.8)
Pleural effusion	83 (8.7)	14 (5.9)	81 (8.9)	178 (8.5)
Diarrhea	77 (8.1)	24 (10.1)	71 (7.8)	172 (8.2)
Hypokalemia	67 (7.0)	16 (6.8)	73 (8.0)	156 (7.4)
Atrial fibrillation	68 (7.1)	16 (6.8)	57 (6.2)	141 (6.7)
Hypotension	64 (6.7)	14 (5.9)	58 (6.3)	136 (6.5)
Hypertension	55 (5.8)	12 (5.1)	59 (6.5)	126 (6.0)
Respiratory failure	58 (6.1)	14 (5.9)	50 (5.5)	122 (5.8)
Septic shock	50 (5.2)	10 (4.2)	53 (5.8)	113 (5.4)
Hyperglycemia	46 (4.8)	19 (8.0)	41 (4.5)	106 (5.0)
Renal failure	41 (4.3)	13 (5.5)	36 (3.9)	90 (4.3)
Acute respiratory distress syndrome	36 (3.8)	14 (5.9)	34 (3.7)	84 (4.0)
Hypernatremia	40 (4.2)	12 (5.1)	27 (3.0)	79 (3.8)
Hypoglycemia	30 (3.1)	12 (5.1)	37 (4.0)	79 (3.8)
Hyperkalemia	34 (3.6)	14 (5.9)	27 (3.0)	75 (3.6)

Only AEs occurring between Day 1 to Day 28 were included in all AE analyses.
Preferred Terms were presented by descending frequency of the Total column.
Abbreviations: AEs=adverse events.

Other Relevant Findings

Summary of INR across time (Safety population)

	TFP 0.025 mg/kg/h (N=955)	TFP 0.075 mg/kg/h (N=237)	Placebo (N=914)	Total (N=2106)
Baseline				
N	950	235	905	2090
Mean (SD)	1.27 (0.306)	1.28 (0.363)	1.28 (0.325)	1.28 (0.321)
Median (Min, Max)	1.20 (0.5 ,3.0)	1.20 (0.6 ,3.9)	1.20 (0.5 ,3.0)	1.20 (0.5 ,3.9)
Change from baseline at Day 1				
N	699	175	672	1546
Mean (SD)	0.07 (0.235)	0.20 (0.364)	-0.03 (0.184)	0.04 (0.245)
Median (Min, Max)	0.05 (-1.2 ,2.3)	0.17 (-0.6 ,3.1)	0.00 (-1.0 ,1.4)	0.01 (-1.2 ,3.1)
Change from baseline at Day 2				
N	934	233	892	2059
Mean (SD)	0.05 (0.292)	0.20 (0.505)	-0.04 (0.312)	0.03 (0.339)
Median (Min, Max)	0.03 (-0.9 ,3.0)	0.15 (-1.5 ,5.7)	-0.03 (-1.3 ,4.9)	0.00 (-1.5 ,5.7)
Change from baseline at Day 3				
N	903	226	861	1990
Mean (SD)	0.02 (0.486)	0.11 (0.401)	-0.09 (0.379)	-0.02 (0.438)
Median (Min, Max)	0.00 (-1.8 ,8.8)	0.10 (-2.4 ,2.3)	-0.09 (-1.5 ,5.6)	-0.01 (-2.4 ,8.8)
Change from baseline at Day 4				
N	863	215	826	1904
Mean (SD)	0.00 (0.380)	0.11 (0.720)	-0.08 (0.398)	-0.02 (0.443)
Median (Min, Max)	0.00 (-1.3 ,4.0)	0.10 (-2.6 ,9.1)	-0.07 (-1.6 ,6.0)	-0.01 (-2.6 ,9.1)
Change from baseline at Day 5				
N	828	207	790	1825
Mean (SD)	-0.01 (0.327)	0.06 (0.413)	-0.07 (0.456)	-0.03 (0.399)
Median (Min, Max)	0.00 (-1.7 ,2.7)	0.07 (-2.6 ,2.7)	-0.05 (-1.5 ,7.3)	-0.01 (-2.6 ,7.3)
Change from baseline at Day 8				
N	515	95	471	1081
Mean (SD)	-0.07 (0.411)	-0.05 (0.503)	-0.10 (0.356)	-0.08 (0.397)
Median (Min, Max)	-0.04 (-1.7 ,6.5)	-0.07 (-2.8 ,2.3)	-0.10 (-1.5 ,3.3)	-0.06 (-2.8 ,6.5)

Date of Clinical Trial Report

05-Aug-2009