Clinical trial results:
Comparison of teicoplanin and vancomycin in terms of efficacy and side effect profile during initial antibiotic treatment of febrile neutropenic patients at high risk for gram-positive infection: multi-center, prospective, randomized study

Summary

EudraCT number	2014-004628-23
Trial protocol	Outside EU/EEA
Global end of trial date	09 August 2007

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	M000507_6004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00454272
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi-aventis İlaçları Ltd Şti
Sponsor organisation address	Büyükdere Cad No:193 K: 3-10, Levent Istanbul, Turkey, 34394
Public contact	Trial Transparency Team, Sanofi Aventis Recherche & Developpement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi Aventis Recherche & Developpement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 June 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 August 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether or not the use of Teicoplanin containing regimen during initial empirical antibiotic treatment of febrile neutropenic subjects at high risk for gram-positive infection was at least equivalent to Vancomycin containing regimen in terms of fever remission or eradication of isolated gram-positive bacteria.
To evaluate whether or not there was any difference between the two regimens in terms of side effect profiles.

Protection of trial subjects:

Paediatric subjects:
The study was conducted by investigators experienced in the treatment of pediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimize distress and discomfort.

Adult subjects:
Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.
Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

Subjects received Amikacin and Ceftazidime throughout the study.

Evidence for comparator: -

Actual start date of recruitment	18 January 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Turkey: 190
Worldwide total number of subjects	190
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	23
Adolescents (12-17 years)	14
Adults (18-64 years)	138
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 21 sites in Turkey. A total of 190 subjects were enrolled between 18 January 2005 and 3 August 2007.

Pre-assignment

Screening details:

A total of 190 subjects were randomized and treated

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Teicoplanin

Arm description:

Ceftazidime + Amikacin + Teicoplanin with treatments duration minimum 5 days maximum 21 days.

Arm type	Experimental
Investigational medicinal product name	Teicoplanin
Investigational medicinal product code	M000507
Other name	Targocid
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Adult (400 mg) and Children aged 2-16 years (10 mg/kg): Loading dose every 12 hours for first 3 doses then maintenance dose once daily.

Arm title	Vancomycin

Arm description:

Ceftazidime + Amikacin + Vancomycin with treatments duration minimum 5 days maximum 21 days.

Arm type	Active comparator
Investigational medicinal product name	Vancomycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Children over 2 years of age: 10 mg/kg every 6 hours.
Adults: 1 gr. every 12 hours.

Number of subjects in period 1	Teicoplanin	Vancomycin
Started	97	93
Treated	97	93
Completed	89	88
Not completed	8	5
Death	7	4
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Teicoplanin
Reporting group description:	
Ceftazidime + Amikacin + Teicoplanin with treatments duration minimum 5 days maximum 21 days.	
Reporting group title	Vancomycin
Reporting group description:	
Ceftazidime + Amikacin + Vancomycin with treatments duration minimum 5 days maximum 21 days.	

Reporting group values	Teicoplanin	Vancomycin	Total
Number of subjects	97	93	190
Age categorical Units: Subjects			
Children (2-11 years)	12	11	23
Adolescents (12-17 years)	8	6	14
Adults (18-64 years)	69	69	138
From 65-84 years	8	7	15
Gender categorical Units: Subjects			
Female	42	42	84
Male	55	51	106
Diagnosis Units: Subjects			
Hematologic Malignity	86	80	166
Solid Tumor	6	3	9
Not Available	5	10	15

End points

End points reporting groups

Reporting group title	Teicoplanin
Reporting group description:	
Ceftazidime + Amikacin + Teicoplanin with treatments duration minimum 5 days maximum 21 days.	
Reporting group title	Vancomycin
Reporting group description:	
Ceftazidime + Amikacin + Vancomycin with treatments duration minimum 5 days maximum 21 days.	

Primary: Number of Subjects According to The Treatment Response

End point title	Number of Subjects According to The Treatment Response

End point description:

Success: Remission of all pre-treatment symptoms and signs without need for additional antibiotics, eradication of etiological microorganisms, no recurrence of symptoms for at least 5 days after completion of treatment and inability to isolate etiological microorganisms.
Failure: Addition of another antibacterial treatment, resistance to study drug or infection-associated death of the subject. Analysis was performed on intent-to-treat (ITT) population defined as all subjects who had satisfied the inclusion criteria and been randomized for the study. Number of subjects analyzed = subjects with data available at specified time points.

End point type	Primary

End point timeframe:

5 days after the completion of treatment maximum of 26 days

End point values	Teicoplanin	Vancomycin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	90		
Units: subjects				
Successful	54	48		
Unsuccessful	18	22		
Successful with modification	21	16		
Not evaluated	4	4		

Statistical analyses

Statistical analysis title	Teicoplanin vs Vancomycin
Comparison groups	Teicoplanin v Vancomycin
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.761
Method	Chi-squared

Secondary: Percentage of Subjects With New Infection

End point title	Percentage of Subjects With New Infection

End point description:

Presence of a new infection under treatment or 5 days after the treatment. Analysis was performed on ITT population. Number of subjects analyzed = subjects with data available at specified time points.

End point type	Secondary

End point timeframe:

At the end of treatment maximum 21 days

End point values	Teicoplanin	Vancomycin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	88		
Units: percentage of subjects				
number (not applicable)	22.6	21.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Protocol Treatment Modification or Alteration

End point title	Percentage of Subjects With Protocol Treatment Modification or Alteration

End point description:

Analysis was performed on ITT population. Number of subjects analyzed = subjects with data available at specified time points.

End point type	Secondary

End point timeframe:

At the end of treatment maximum 21 days

End point values	Teicoplanin	Vancomycin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	89		
Units: percentage of subjects				
number (not applicable)				
Addition of new drug	34.4	31.8		
Cessation of protocol drug and start of new drug	29.3	30.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Survival at 30 Days

End point title	Survival at 30 Days

End point description:

Kaplan Meier test was used for survival analyses. Analysis was performed on ITT population. Number of subjects analyzed = subjects with data available at specified time points.

End point type	Secondary

End point timeframe:

30 days

End point values	Teicoplanin	Vancomycin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	81		
Units: percentage of subjects				
number (not applicable)				
Survival (Non-infection)	84	84		
Survival (Infection)	7.4	7.4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Day 21) regardless of seriousness or relationship to investigational product

Adverse event reporting additional description:

Reported adverse events and deaths are Adverse Events that developed/worsened and deaths that occurred during the time of 1st administration of study drug until discharge.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Teicoplanin

Reporting group description:

Ceftazidime + Amikacin + Teicoplanin with treatments duration minimum 5 days maximum 21 days.

Reporting group title	Vancomycin

Reporting group description:

Ceftazidime + Amikacin + Vancomycin with treatments duration minimum 5 days maximum 21 days.

Serious adverse events	Teicoplanin	Vancomycin	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 97 (8.25%)	9 / 93 (9.68%)	
number of deaths (all causes)	7	4	
number of deaths resulting from adverse events			
Investigations			
Activated partial thromboplastin time			
subjects affected / exposed	1 / 97 (1.03%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic neoplasm			
subjects affected / exposed	1 / 97 (1.03%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Cerebral hematoma			

subjects affected / exposed	0 / 97 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
bleeding			
subjects affected / exposed	0 / 97 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhage			
subjects affected / exposed	3 / 97 (3.09%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	2 / 3	0 / 0	
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	2 / 97 (2.06%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 97 (1.03%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 97 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 97 (1.03%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	0 / 97 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 97 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 97 (1.03%)	2 / 93 (2.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephropathy toxic			
subjects affected / exposed	1 / 97 (1.03%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anuria			
subjects affected / exposed	1 / 97 (1.03%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Aspergillus infection			
subjects affected / exposed	1 / 97 (1.03%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
bacterial sepsis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infection			
subjects affected / exposed	3 / 97 (3.09%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	1 / 3	0 / 1	
Sepsis			

subjects affected / exposed	1 / 97 (1.03%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
septic schock			
subjects affected / exposed	1 / 97 (1.03%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 97 (1.03%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Teicoplanin	Vancomycin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 97 (16.49%)	16 / 93 (17.20%)	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 97 (5.15%)	5 / 93 (5.38%)	
occurrences (all)	5	5	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 97 (5.15%)	5 / 93 (5.38%)	
occurrences (all)	5	5	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	10 / 97 (10.31%)	9 / 93 (9.68%)	
occurrences (all)	11	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported