Clinical trial results:
A prospective randomized pilot study to evaluate the effect of preoperative antithrombin supplementation on postoperative levels of antithrombin in patients undergoing cardiac surgery with cardiopulmonary bypass.

Summary

EudraCT number	2008-007313-68
Trial protocol	IT
Global end of trial date	10 June 2011

Results information

Result version number	v1 (current)
This version publication date	26 January 2017
First version publication date	26 January 2017

Trial information

Trial identification

Sponsor protocol code	IG0801

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00823082
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Instituto Grifols SA
Sponsor organisation address	Can Guasch, 2, Parets del Vallès, Spain, 08150
Public contact	Michael K. Woodward, Grifols Therapeutics Inc, michael.woodward@grifols.com
Scientific contact	Michael K. Woodward, Grifols Therapeutics Inc, michael.woodward@grifols.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 June 2011
Global end of trial reached?	Yes
Global end of trial date	10 June 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare postoperative ATIII levels at the ICU admission between two groups of subjects randomly allocated to receive (ATIII treatment group) or not to receive (control group) ATIII supplementation preoperatively

Protection of trial subjects:

The Investigator (or designee) obtained a freely given written informed consent from each subject participating in this study, after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards and any other aspect of the study relevant to the subject's decision to participate prior to initiating any study-related procedure to the subject. Subjects were informed of the advantages, risks and constrains of the study. The informed consent form was signed, with name and date noted by the subject, before the subject was exposed to any study-related procedure, including screening tests for eligibility.
The Investigator ensured that the subject's anonymity was preserved. On CRFs or any other documents submitted to the Sponsor, the subjects were not identified by their names, but by an identification code, consisting of their randomization number. Documents not for submission to the Sponsor, i.e. the confidential subject identification code, original consent forms and source records were maintained by the Investigator in strict confidence.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 June 2009
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	Italy: 200
Worldwide total number of subjects	200
EEA total number of subjects	200

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	69
From 65 to 84 years	128
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

206 subjects were screened, six were screen failures. 100 subjects in the ATIII treatment group and 100 subjects in the control group were randomized.
First subject enrolled was 08 June 2009 and Last subject completed on 10 June 2011

Pre-assignment

Screening details:

Subjects undergoing elective cardiac surgery with cardiopulmonary bypass were considered for enrollment at a single institution (IRCCS Policlinico San Donato, Milan, Italy).

Period 1

Period 1 title	Overall trial
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	ATIII treatment group

Arm description:

Preoperative ATIII supplementation administered after anesthesia induction.

Arm type	Experimental
Investigational medicinal product name	antithrombin III
Investigational medicinal product code	
Other name	Anbinex
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single dose of antithrombin III sufficient to achieve a preoperative level of 120%

Arm title	Control group

Arm description:

No preoperative ATIII supplementation administered

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	ATIII treatment group	Control group
Started	100	100
Completed	100	94
Not completed	0	6
Missing postoperative AT activity	-	5
Non-compliant	-	1

Period 2	
Period 2 title	ICU admission
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms	
Are arms mutually exclusive?	Yes
Arm title	ATIII treatment group

Arm description:

Preoperative ATIII supplementation administered after anesthesia induction.

Arm type	Experimental
Investigational medicinal product name	antithrombin III
Investigational medicinal product code	
Other name	Anbinex
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single dose of antithrombin III sufficient to achieve a preoperative level of 120%

Arm title	Control group

Arm description:

No preoperative ATIII supplementation administered

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	ATIII treatment group	Control group
Started	100	94
Completed	100	94

Period 3	
Period 3 title	ICU discharge
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms	
Are arms mutually exclusive?	Yes
Arm title	ATIII treatment group

Arm description:

Preoperative ATIII supplementation administered after anesthesia induction.

Arm type	Experimental
Investigational medicinal product name	antithrombin III
Investigational medicinal product code	
Other name	Anbinex
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single dose of antithrombin III sufficient to achieve a preoperative level of 120%

Arm title	Control group

Arm description:

No preoperative ATIII supplementation administered

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 3	ATIII treatment group	Control group
Started	100	94
Completed	99	93
Not completed	1	1
Adverse event, serious fatal	1	1

Period 4	
Period 4 title	Follow-up visit
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms	
Are arms mutually exclusive?	Yes
Arm title	ATIII treatment group

Arm description:

Preoperative ATIII supplementation administered after anesthesia induction.

Arm type	Experimental

Investigational medicinal product name	antithrombin III
Investigational medicinal product code	
Other name	Anbinex
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single dose of antithrombin III sufficient to achieve a preoperative level of 120%

Arm title	Control group

Arm description:

No preoperative ATIII supplementation administered

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 4	ATIII treatment group	Control group
Started	99	93
Completed	64	61
Not completed	35	32
Adverse event, serious fatal	11	8
Lost to follow-up	3	2
Protocol deviation	21	22

Baseline characteristics

Reporting groups	
Reporting group title	ATIII treatment group
Reporting group description:	
Preoperative ATIII supplementation administered after anesthesia induction.	
Reporting group title	Control group
Reporting group description:	
No preoperative ATIII supplementation administered	

Reporting group values	ATIII treatment group	Control group	Total
Number of subjects	100	100	200
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	34	35	69
From 65-84 years	65	63	128
85 years and over	1	2	3
Age continuous Units: years			
arithmetic mean	66.51	67.38	
standard deviation	± 10.48	± 11.45	-
Gender categorical Units: Subjects			
Female	17	25	42
Male	83	75	158

Subject analysis sets	
Subject analysis set title	ATIII treatment ITT set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intent-to-Treat (ITT) population was defined as all randomized subjects who met the selection criteria, received study medication, and had evaluation of AT levels at the ICU admission.	
Subject analysis set title	ATIII treatment Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety population was defined as all randomized subjects who took at least one dose of the study medication	
Subject analysis set title	Control group ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intent-to-Treat (ITT) population was defined as all randomized subjects who met the selection	

criteria, received study medication, and had evaluation of AT levels at the ICU admission.

Subject analysis set title	Control Group safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety population was defined as all randomized subjects who took at least one dose of the study medication.

Reporting group values	ATIII treatment ITT set	ATIII treatment Safety	Control group ITT
Number of subjects	100	100	94
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	34	34	30
From 65-84 years	65	65	62
85 years and over	1	1	2
Age continuous Units: years			
arithmetic mean	66.51	66.51	67.63
standard deviation	± 10.48	± 10.48	± 11.18
Gender categorical Units: Subjects			
Female	17	17	24
Male	83	83	70

Reporting group values	Control Group safety		
Number of subjects	99		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	34		
From 65-84 years	63		
85 years and over	2		
Age continuous Units: years			
arithmetic mean	67.46		
standard deviation	± 11.47		

Gender categorical Units: Subjects			
Female	25		
Male	74		

End points

End points reporting groups

Reporting group title	ATIII treatment group
Reporting group description:	
Preoperative ATIII supplementation administered after anesthesia induction.	
Reporting group title	Control group
Reporting group description:	
No preoperative ATIII supplementation administered	
Reporting group title	ATIII treatment group
Reporting group description:	
Preoperative ATIII supplementation administered after anesthesia induction.	
Reporting group title	Control group
Reporting group description:	
No preoperative ATIII supplementation administered	
Reporting group title	ATIII treatment group
Reporting group description:	
Preoperative ATIII supplementation administered after anesthesia induction.	
Reporting group title	Control group
Reporting group description:	
No preoperative ATIII supplementation administered	
Reporting group title	ATIII treatment group
Reporting group description:	
Preoperative ATIII supplementation administered after anesthesia induction.	
Reporting group title	Control group
Reporting group description:	
No preoperative ATIII supplementation administered	
Subject analysis set title	ATIII treatment ITT set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intent-to-Treat (ITT) population was defined as all randomized subjects who met the selection criteria, received study medication, and had evaluation of AT levels at the ICU admission.	
Subject analysis set title	ATIII treatment Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety population was defined as all randomized subjects who took at least one dose of the study medication	
Subject analysis set title	Control group ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intent-to-Treat (ITT) population was defined as all randomized subjects who met the selection criteria, received study medication, and had evaluation of AT levels at the ICU admission.	
Subject analysis set title	Control Group safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety population was defined as all randomized subjects who took at least one dose of the study medication.	

Primary: Postoperative ATIII levels at the ICU admission	
End point title	Postoperative ATIII levels at the ICU admission
End point description: Measurement of postoperative ATIII functional activity at ICU admission	
End point type	Primary
End point timeframe: ICU admission (day 0)	

End point values	ATIII treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	94		
Units: IU				
arithmetic mean (standard deviation)	94.06 (± 13.74)	64.7 (± 9.89)		

Statistical analyses

Statistical analysis title	ANCOVA
Statistical analysis description: The AT levels were analyzed by means of an Analysis of Covariance (ANCOVA) model by time-point with the baseline value as a covariate and, if statistical significant at the adjusted alpha level for the analysis (α=0.049), the percentage of subjects with AT levels of 58% or higher were assessed using the Fisher exact test at the same alpha level.	
Comparison groups	ATIII treatment group v Control group
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA

Primary: Subjects with ATIII levels of 58% or higher at ICU admission	
End point title	Subjects with ATIII levels of 58% or higher at ICU admission
End point description: Subjects with ATIII levels of 58% functional activity or higher at ICU admission	
End point type	Primary
End point timeframe: ICU admission (day 0)	

End point values	ATIII treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	94		
Units: Subjects	100	70		

Statistical analyses

Statistical analysis title	Fisher Exact

Statistical analysis description:

The AT levels were analyzed by means of an Analysis of Covariance (ANCOVA) model by time-point with the baseline value as a covariate and, if statistical significant at the adjusted alpha level for the analysis (α=0.049), the percentage of subjects with AT levels of 58% or higher were assessed using the Fisher exact test at the same alpha level.

Comparison groups	ATIII treatment group v Control group
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Fisher exact

Secondary: Subjects with postoperative myocardial infarction at ICU discharge

End point title	Subjects with postoperative myocardial infarction at ICU discharge

End point description:

Subjects with postoperative myocardial infarction defined through enzymatic criteria plus new Q-waves at the electrocardiogram

End point type	Secondary

End point timeframe:

ICU discharge

End point values	ATIII treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	93		
Units: Subjects	1	2		

Statistical analyses

Statistical analysis title	Fisher exact ICU discharge
Comparison groups	ATIII treatment group v Control group

Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6115
Method	Fisher exact

Secondary: Subjects with adverse neurologic outcome at ICU discharge

End point title	Subjects with adverse neurologic outcome at ICU discharge

End point description:

Subjects with adverse neurologic outcome defined as: coma, stroke or psychotic behaviors lasting >12 hours after extubation

End point type	Secondary

End point timeframe:

At ICU discharge

End point values	ATIII treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	93		
Units: Subjects	1	0		

Statistical analyses

Statistical analysis title	Fisher Exact ICU discharge

Statistical analysis description:

For categorical secondary efficacy variables, the Fisher’s Exact Test was used to perform the between treatment comparisons, by time-point when applicable.

Comparison groups	Control group v ATIII treatment group
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Fisher exact

Secondary: Subjects with thromboembolic events at ICU discharge

End point title	Subjects with thromboembolic events at ICU discharge

End point description:

Subjects with thromboembolic events defined as perioperative myocardial infarction, stroke, mesenteric infarction, peripheral thromboembolism and pulmonary embolism

End point type	Secondary

End point timeframe:

At ICU discharge

End point values	ATIII treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	94		
Units: Subjects	0	1		

Statistical analyses

Statistical analysis title	Fisher exact ICU discharge
Comparison groups	ATIII treatment group v Control group
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.487
Method	Fisher exact

Secondary: ICU stay duration

End point title	ICU stay duration

End point description:

End point type	Secondary

End point timeframe:

During ICU stay (maximum 70 days)

End point values	ATIII treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	93[1]		
Units: days				
median (inter-quartile range (Q1-Q3))	2 (1 to 4)	2 (1 to 3)		

Notes:

[1] - One subject in the control group was missing this data

Statistical analyses

Statistical analysis title	Hodges-Lehmann test ICU stay
Comparison groups	ATIII treatment group v Control group

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3897
Method	Hodges-Lehmann test

Secondary: In-hospital postoperative mortality

End point title	In-hospital postoperative mortality

End point description:

End point type	Secondary

End point timeframe:

Until ICU discharge

End point values	ATIII treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	93[2]		
Units: subjects	1	1		

Notes:

[2] - One subject in the control group was missing this data

Statistical analyses

Statistical analysis title	Fisher exact
Comparison groups	ATIII treatment group v Control group
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Fisher exact

Secondary: Heparin Resistance

End point title	Heparin Resistance

End point description:

Subjects with heparin resistance defined as failure to reach an activated clotting time >450 seconds after a dose of up to 400 IU/kg of heparin, or failure to maintain this activated clotting time value despite heparin supplementations of 100 IU/kg per each dose with an interval of at least 30 minutes between doses

End point type	Secondary

End point timeframe:

Immediately after anesthesia induction

End point values	ATIII treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99[3]	94		
Units: Subjects	17	38		

Notes:

[3] - One subject in the ATIII treatment group was missing this data

Statistical analyses

Statistical analysis title	Fisher exact
Comparison groups	ATIII treatment group v Control group
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0004
Method	Fisher exact

Secondary: Postoperative blood loss in first 12 hours

End point title	Postoperative blood loss in first 12 hours

End point description:

Blood loss defined as the amount of blood collected in the cardiotomy reservoir from ICU admission through the following 12 hours

End point type	Secondary

End point timeframe:

ICU admission through 12 hours post-operative

End point values	ATIII treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	94		
Units: mililiters				
least squares mean (standard error)	516.11 (± 30.292)	415 (± 31.087)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	ATIII treatment group v Control group

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0209
Method	ANCOVA

Secondary: Need for blood products

End point title	Need for blood products

End point description:

Number of units of packed red blood cells, fresh frozen plasma, and/or platelets needed

End point type	Secondary

End point timeframe:

During the ICU stay (máximum 70 days)

End point values	ATIII treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100[4]	94[5]		
Units: Units				
arithmetic mean (standard error)				
packed red blood cells	43.711 (± 3.551)	41.987 (± 3.864)		
fresh frozen plasma	12.188 (± 1.646)	13.125 (± 2.327)		
platelet	8.5 (± 1.564)	6.188 (± 1.236)		

Notes:

[4] - Packed red blood cells (n = 45)
Fresh Frozen Plasma (n=16)
Platelets (n=5)
[5] - Packed red blood cells (n = 38)
Fresh Frozen Plasma (n=8)
Platelets (n=8)

Statistical analyses

Statistical analysis title	ANCOVA - Packed red blood cells
Comparison groups	ATIII treatment group v Control group
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7433
Method	ANCOVA

Statistical analysis title	ANCOVA Fresh frozen plasma
Comparison groups	ATIII treatment group v Control group

Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7453
Method	ANCOVA

Statistical analysis title	ANCOVA platelet
Comparison groups	ATIII treatment group v Control group
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2705
Method	ANCOVA

Secondary: Subjects needing surgical re-exploration	
End point title	Subjects needing surgical re-exploration
End point description: Subjects needing surgical re-exploration resulting from bleeding	
End point type	Secondary
End point timeframe: ICU discharge	

End point values	ATIII treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98[6]	92[7]		
Units: Subjects	5	2		

Notes:

[6] - Two subjects in the ATIII treatment group were missing this data

[7] - Two subjects in the control group were missing this data

Statistical analyses

Statistical analysis title	Fisher exact
Comparison groups	ATIII treatment group v Control group
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.446
Method	Fisher exact

Secondary: Subjects with low cardiac syndrome	
End point title	Subjects with low cardiac syndrome
End point description:	
Subjects with low cardiac sindrome defined as the need for major inotropic support or intra-aortic balloon pump	
End point type	Secondary
End point timeframe:	
ICU discharge	

End point values	ATIII treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97[8]	93[9]		
Units: Subjects	24	19		

Notes:

[8] - Three subjects in the ATIII treatment group were missing this data

[9] - One subject in the control group was missing this data

Statistical analyses

Statistical analysis title	Fisher exact
Comparison groups	ATIII treatment group v Control group
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4936
Method	Fisher exact

Secondary: Subjects with renal dysfunction at ICU discharge	
End point title	Subjects with renal dysfunction at ICU discharge
End point description:	
Subjects with renal dysfunction defined as an increase of serum creatinine levels to > 2.0 and twice the baseline level or need for renal replacement therapy	
End point type	Secondary
End point timeframe:	
At ICU discharge	

End point values	ATIII treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	93		
Units: Subjects	3	1		

Statistical analyses

Statistical analysis title	Fisher Exact ICU discharge
Comparison groups	ATIII treatment group v Control group
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6218
Method	Fisher exact

Secondary: Mechanical Ventilation Duration

End point title	Mechanical Ventilation Duration
End point description:	
End point type	Secondary
End point timeframe:	
During ICU stay (maximum 70 days)	

End point values	ATIII treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	94		
Units: days				
median (inter-quartile range (Q1-Q3))	1 (1 to 1)	1 (1 to 1)		

Statistical analyses

Statistical analysis title	Hodges-Lehmann
Comparison groups	ATIII treatment group v Control group
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9574
Method	Hodges-Lehmann

Secondary: Length of Hospital stay

End point title	Length of Hospital stay

End point description:

Length of hospital stay (days) in both groups was defined as the discharge date minus the surgery date plus 1 day, during a máximum of 70 days after ICU admission

End point type	Secondary

End point timeframe:

During ICU stay (maximum 70 days)

End point values	ATIII treatment ITT set	Control group ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	100	94		
Units: days				
median (inter-quartile range (Q1-Q3))	10 (8 to 13.5)	10 (8 to 13)		

Statistical analyses

Statistical analysis title	Hodges-Lehmann
Comparison groups	ATIII treatment ITT set v Control group ITT
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7489
Method	Hodges-Lehmann

Secondary: Subjects with postoperative myocardial infarction at Follow-up visit

End point title	Subjects with postoperative myocardial infarction at Follow-up visit

End point description:

Subjects with postoperative myocardial infarction defined through enzymatic criteria plus new Q-waves at electrocardiogram

End point type	Secondary

End point timeframe:

During ICU stay (maximum 70 days)

End point values	ATIII treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	69		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects with adverse neurologic outcome at Follow-up visit

End point title	Subjects with adverse neurologic outcome at Follow-up visit

End point description:

Subjects with adverse neurologic outcome defined as: coma, stroke or psychotic behaviors lasting >12 hours after extubation

End point type	Secondary

End point timeframe:

During ICU stay (maximum 70 days)

End point values	ATIII treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	69		
Units: subjects	4	0		

Statistical analyses

Statistical analysis title	Fisher Exact (Follow-up Visit)
Comparison groups	ATIII treatment group v Control group
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1211
Method	Fisher exact

Secondary: Subjects with thromboembolic events

End point title	Subjects with thromboembolic events

End point description:

Subjects with thromboembolic events defined as perioperative myocardial infarction, stroke, mesenteric infarction, peripheral thromboembolism and pulmonary embolism

End point type	Secondary

End point timeframe:

During ICU stay (maximum 70 days)

End point values	ATIII treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	69		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects with renal dysfunction at Follow-up visit

End point title	Subjects with renal dysfunction at Follow-up visit

End point description:

Subjects with renal dysfunction defined as an increase of serum creatinine levels to > 2.0 and twice the baseline level or need for renal replacement therapy

End point type	Secondary

End point timeframe:

During ICU stay (maximum 70 days)

End point values	ATIII treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	69		
Units: Subjects	1	0		

Statistical analyses

Statistical analysis title	Fisher Exact (Follow-up visit)
Comparison groups	ATIII treatment group v Control group
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Fisher exact
Parameter estimate	Cox proportional hazard

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of the recruitment visit (day-14) to the follow-up visit (day 50 +/- 20 days)

Adverse event reporting additional description:

206 subjects were randomized, six were screen failures. 199 subjects were included in the Safety population (100 Anbinex and 99 control). One subject in the control group was excluded from the Safety population as Anbinex was administered during the ICU stay

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	ATIII treatment group

Reporting group description:

preoperative ATIII supplementation administered after anesthesia induction.

Reporting group title	Control group

Reporting group description:

No preoperative ATIII supplementation administered

Serious adverse events	ATIII treatment group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 100 (32.00%)	29 / 99 (29.29%)	
number of deaths (all causes)	11	8	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Haemodynamic instability			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhage			
subjects affected / exposed	2 / 100 (2.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	1 / 100 (1.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Evidence based treatment			
subjects affected / exposed	0 / 100 (0.00%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospitalisation			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tricuspid valve repair			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Device occlusion			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperpyrexia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
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			
Acute pulmonary oedema			

subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 100 (2.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 100 (0.00%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 100 (1.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 100 (1.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychotic behaviour			

subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Electrocardiogram ST segment elevation			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcus test positive			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Seroconversion test			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcus test positive			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Graft thrombosis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Post procedural haemorrhage			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasoplegia syndrome			
subjects affected / exposed	2 / 100 (2.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Wound secretion			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	22 / 100 (22.00%)	17 / 99 (17.17%)	
occurrences causally related to treatment / all	0 / 22	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 100 (0.00%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 100 (2.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 100 (1.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 100 (0.00%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Low cardiac output syndrome			
subjects affected / exposed	1 / 100 (1.00%)	3 / 99 (3.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			

subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular fibrillation			
subjects affected / exposed	0 / 100 (0.00%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular hypokinesia			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haematoma			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coma			
subjects affected / exposed	2 / 100 (2.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Oliguria			
subjects affected / exposed	2 / 100 (2.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscle necrosis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (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			
Acinetobacter infection			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	2 / 100 (2.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pseudomonas infection			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Septic shock			
subjects affected / exposed	2 / 100 (2.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Serratia infection			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Wound infection staphylococcal			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ATIII treatment group	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 100 (96.00%)	96 / 99 (96.97%)	
Investigations			
Electrocardiogram ST segment elevation			
subjects affected / exposed	5 / 100 (5.00%)	4 / 99 (4.04%)	
occurrences (all)	5	4	
Haematocrit decreased			
subjects affected / exposed	22 / 100 (22.00%)	6 / 99 (6.06%)	
occurrences (all)	22	7	
Vascular disorders			
Haemorrhage			
subjects affected / exposed	27 / 100 (27.00%)	23 / 99 (23.23%)	
occurrences (all)	27	23	
Hypertension			

subjects affected / exposed	8 / 100 (8.00%)	10 / 99 (10.10%)	
occurrences (all)	8	11	
Hypotension			
subjects affected / exposed	11 / 100 (11.00%)	13 / 99 (13.13%)	
occurrences (all)	11	13	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	24 / 100 (24.00%)	17 / 99 (17.17%)	
occurrences (all)	24	17	
Atrioventricular block			
subjects affected / exposed	5 / 100 (5.00%)	2 / 99 (2.02%)	
occurrences (all)	5	2	
Bradycardia			
subjects affected / exposed	23 / 100 (23.00%)	12 / 99 (12.12%)	
occurrences (all)	23	12	
Pericardial effusion			
subjects affected / exposed	5 / 100 (5.00%)	5 / 99 (5.05%)	
occurrences (all)	5	5	
Sinus bradycardia			
subjects affected / exposed	0 / 100 (0.00%)	7 / 99 (7.07%)	
occurrences (all)	0	7	
Sinus tachycardia			
subjects affected / exposed	4 / 100 (4.00%)	5 / 99 (5.05%)	
occurrences (all)	4	5	
Supraventricular extrasystoles			
subjects affected / exposed	8 / 100 (8.00%)	6 / 99 (6.06%)	
occurrences (all)	8	6	
Tachycardia			
subjects affected / exposed	21 / 100 (21.00%)	17 / 99 (17.17%)	
occurrences (all)	21	17	
Surgical and medical procedures			
Diuretic therapy			
subjects affected / exposed	15 / 100 (15.00%)	15 / 99 (15.15%)	
occurrences (all)	15	15	
Blood and lymphatic system disorders			

Leukocytosis			
subjects affected / exposed	12 / 100 (12.00%)	11 / 99 (11.11%)	
occurrences (all)	12	11	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	16 / 100 (16.00%)	15 / 99 (15.15%)	
occurrences (all)	16	15	
Pyrexia			
subjects affected / exposed	38 / 100 (38.00%)	42 / 99 (42.42%)	
occurrences (all)	38	45	
Serositis			
subjects affected / exposed	6 / 100 (6.00%)	5 / 99 (5.05%)	
occurrences (all)	6	5	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	3 / 100 (3.00%)	6 / 99 (6.06%)	
occurrences (all)	3	6	
Dyspnoea			
subjects affected / exposed	6 / 100 (6.00%)	3 / 99 (3.03%)	
occurrences (all)	6	3	
Hypoxia			
subjects affected / exposed	10 / 100 (10.00%)	10 / 99 (10.10%)	
occurrences (all)	10	10	
Increased bronchial secretion			
subjects affected / exposed	9 / 100 (9.00%)	5 / 99 (5.05%)	
occurrences (all)	9	5	
Pleural effusion			
subjects affected / exposed	47 / 100 (47.00%)	45 / 99 (45.45%)	
occurrences (all)	47	45	
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	5 / 100 (5.00%)	0 / 99 (0.00%)	
occurrences (all)	5	0	
Psychiatric disorders			
Disorientation			

subjects affected / exposed occurrences (all)	6 / 100 (6.00%) 6	1 / 99 (1.01%) 1	
Renal and urinary disorders Oliguria subjects affected / exposed occurrences (all)	 7 / 100 (7.00%) 7	 2 / 99 (2.02%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2009	Amendment 1 was generated to adapt the study design to changed operational aspects of the Study, including: 1. Deletion of the clinical research organization (CRO) Pharmacovigilance signature and replacement with the Serious or Unexpected Adverse Drug Reaction report form in attachment B 2. Clarification of the randomization process, adding essentially that the study was single-blinded 3. Modification of laboratory tests to be performed, adding international normalized ratio (INR) to the pre-operative assessments, lowest ACT during surgery, as well as heparin sensitivity index at baseline and after infusion before the heparin dose and heparin resistance, and INR to the post-operative assessments 4. Deletion of central laboratory participation 5. Modification of heparin resistance criteria, one of the secondary efficacy endpoints, and assessment as noted in number 3. Heparin resistance definition was modified to: failure to reach an ACT > 450 seconds after a dose of up to 400 IU/kg of heparin, or failure to maintain this ACT value despite heparin supplementations of 100 IU/kg per each dose with an interval of at least 30 minutes between doses. As noted above in number 3, heparin resistance was measured once, immediately after anesthesia induction.
20 July 2009	Amendment 2 was generated to adapt the study design to be compatible with both the standard cardiac surgery schedule and to changed operational aspects of the study. This amendment reflects mainly the following changes: 1. Deletion of inclusion criteria number 5 2. Modification of laboratory tests to be performed 3. Adaptation of study visits to the center's standard operating schedule. Specifically, the modification of inclusion criteria number 5, "human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis A virus (HAV), and PARVO B19 status known prior to entry", was cancelled or removed, because the Ethics Committee determined adherence to this criterion may have required some patients to wait several days until the tests results were available which may have been incompatible with the cardiac surgery schedule. Rather, it was determined to be sufficient that the subject have a blood sample drawn and stored before the first administration of the study product in case further viral serological investigations were needed. Inclusion criteria number 6, 'signed the consent sheet' in "subject has read the patient information and consent form and has agreed to participate in the trial and signed the consent sheet", was modified for clarity, to "signed informed consent form." Subject participation (since enrollment) was also extended from at least 1 month to 1.65 months (40 ± 10 days).

07 January 2010	Amendment 3 was generated to adapt the study design to be compatible with both the standard cardiac surgery schedule and to changed operational aspects of the study. This amendment reflects: 1. Extension of enrollment period from 8 to 18 months, follow-up period, and total study duration with the total subject participation since enrollment of at least 1 month to 1.65 month (40 ± 10 days) extended to at least 1 month to 2.3 months (50 ± 20 days) and total study duration extended from 9 to 12 months to 18 to 20 months 2. Use of prescreening laboratory values routinely taken 24 hours prior to the informed consent signature which would lessen the burden on participating subjects; more exactly, avoiding unnecessary blood draws though the use of pre-screening laboratory values taken routinely 24 or 48 hours prior to the recruitment visit and preoperative visit, respectively 3. Modification of laboratory tests to be performed, including deletion of hepatitis B surface antigen (HBsAg) from the viral panel 4. Adaptation of study visits to center's standard operating schedule. 5. Establishment of phone call follow-up visit for patients unable to return to the site during the scheduled follow-up period. Improvement of patient follow-up though the establishment of a phone call follow-up visit. 6. Modification of concomitant medication reporting in order to facilitate its documentation. 7. Adjustment of the definition of pre- and post-operative significant clinical chemistry (including hematology) laboratory values and vital signs to the particularities of the cardiac surgery setting.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23102903