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Name of Finished Product: <ATG-Fresenius® (Grafalon®) >		
Name of Active Ingredient: <Anti-T-lymphocyte Immune Globulin.>		

SYNOPSIS

Title of Study:

Efficacy and Safety of two Anti-T-lymphocyte Immune Globulin (ATG-F) Induction Regimens in de novo Kidney Transplant Patients – a multicenter, randomized, parallel group study

Investigators/Coordinating Investigator:

[redacted]

Study Center(s) (19 centers):

[redacted]

Publication Based on the Study: One manuscript in Chinese based on the study is planned to submit in FY2017.

Study Period: From July 2012 to Nov 2016;

Study Initiation Date (Date of First Enrollment): 2013-05-16

Study Completion Date (Date of Last Evaluation): 2015-12-28

Phase of Development: Phase 4

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Objectives:

Primary objective:

Compare the efficacy and safety of ATG-F based two induction therapy protocols (ATG-F single high dose and five low dose administration) in de novo renal transplant recipients.

The main analysis is to carry out non-inferiority evaluation of the two treatment regimens based on treatment failure rate.

Secondary objective(s):

Evaluate the safety items of different subtype acute rejection, renal transplantation/patient survival, delayed graft function(DGF), renal function.

Methodology:

Number of Patients (Planned, Enrolled and Analyzed):

Planned: 280;

Enrolled: 280;

Analyzed: 280.

This is a multicenter, randomized, open and parallel group study comparing two ATG-F induction therapies. Totally, 280 patients underwent kidney allograft transplantation had been randomized to one of the following treatments as 1:1, 140 patients each group:

- Arm A: ATG-F, 7-9 mg/kg, single dose;
- Arm B: ATG-F, 2 mg/kg, once daily, five doses.

For each patient the study duration will be 12 months, 10 visits are scheduled.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

Patients will be enrolled in this study only if they meet all of the following criteria

① primary kidney transplant.

② 18 to 65 years old, male or female.

③ ABO compatible kidney transplantation.

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④. PRA <50%.

⑤. Women of childbearing age need to meet negative pregnancy test 48 hours before randomizing, and throughout the study period and 6 weeks after the end of the study, a medically approved method should be applied for contraception.

⑥. the patient can understand the purpose and risks of the study, and are willing to participate in the study and give written informed consent.

Exclusion criteria:

Patients will be excluded from this study if they meet any of the following criteria

①. Subject has previously received or is receiving an organ transplant other than kidney.

②. received kidney transplantation before.

③. cold ischemic time more than 24 hours.

④. patients receiving HLA identical living-donor kidney transplants.

⑤. patients with contraindications of ATG-F:

- known rabbit protein allergy;
- patients with severe platelet reduction;
- bacterial, viral or fungal infections, and have not yet been treated and controlled.

⑥. Known contraindication to administration of ATG-F or rabbit proteins (hypersensitivity)/ADV. Subject has known hypersensitivity to tacrolimus, macrolide antibiotics, mycophenolate mofetil, or any of the product excipients.

⑦. judged by investigators, patients are less likely to comply with study visit arrangements or patients have a poor compliance history.

⑧. pregnant and lactating women, and women of childbearing age do not want to accept contraception.

⑨. patients with evidence of active liver disease (liver function tests ≥ 2 ULN) or chronic active hepatitis B or hepatitis C.

⑩. serum HIV-positive renal transplant recipients or donors.

⑪ active systemic infection treated with antibiotics.

⑫ patients without established central venous access or a peripheral pathway with larger aperture for the purposes of study drug administration.

⑬ unstable cardiovascular disease or myocardial infarction within six months of enrollment.

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⑭ patients with malignant tumors or a history of malignant tumors in the past five years, except of successful treated non-metastatic basal cell carcinoma or squamous cell carcinoma, or cervical carcinoma in situ.

⑮ patients with a medical or mental illness, which will affect compliance by investigator's judgment.

Test Product, Dose and Mode of Administration, Batch Numbers:

Patients will be randomized to one of the following treatment arms:

①. Treatment Arm A:

Day 0: ATG-F, 7-9 mg/kg was administered as a single IV infusion via central venous catheter or large peripheral venous catheter before reperfusion of the allograft.

②. Treatment Arm B:

Day 0--4: ATG-F, 2 mg/kg was administered as IV infusion via central venous catheter or large peripheral venous catheter, once daily.

Batch Numbers:

Duration of Treatment (or Duration of Study, if applicable):

- Arm A (investigational): ATG-F, 7-9 mg/kg, single dose (day 0);
- Arm B (control): ATG-F, 2 mg/kg, once daily, five days (day 0-4).

10 visits were scheduled. The endpoints of the study were assessed at 12 months after transplantation.

Reference Product, Dose and Mode of Administration, Batch Numbers: N/A.

Criteria for Evaluation:

1) Primary observation indicators were treatment failure rate 12 months after transplantation. Treatment failure was defined as any one of the following events occurred:

- patients died
- graft loss
- acute rejection

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- lost to follow-up

The event first occurred should be used in the classification of patients.

2) Secondary Endpoint:

- Incidence of acute rejection determined by signs and symptoms.
- Acute rejection incidence confirmed by biopsy.
- Steroid-resistant acute rejection incidence.
- Incidence of delayed graft renal function recovery.
- Survival rate of patients.
- Graft survival rate.
- Graft renal function determined by serum creatinine levels.

3) Safety Assessment:

- Incidence and severity of adverse events
- Incidence of infection and malignant tumors
- Incidence of cytokine release syndrome and allergic reactions
- Laboratory findings
- Vital signs.

Statistical Methods:

1. Analysis Set

- ***Full Analysis Set (FAS)***

The FAS included all the patients who were randomized into the study.

- ***Per Protocol Set (PPS)***

PPS included all of the randomized subjects that have used the study drug compliantly to the treatment according to the protocol, and without meeting any of the following criteria:

- Subjects who had any inclusion/exclusion violations;
- Subjects who used a prohibited concomitant medication that affects the assessment of the study endpoints;
- Subjects who was not compliant to the treatment as protocol;

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- Subjects who had major protocol deviations that impacted the evaluation of endpoints.

A comprehensive list of the subjects to be excluded from the PPS population was confirmed by the principal investigator and documented before the database is locked.

- ***Safety Analysis Set (SAF)***

SAF included all patients who have used the study drugs and received at least one efficacy assessment after baseline.

2. Statistical Methods

1) Demographic and Baseline characteristics of the subjects

Demographic and baseline characteristics were listed and summarized by treatment group and overall for FAS and SAF.

2) Primary Efficacy Evaluation

Primary Efficacy Evaluation was the rate of efficacy failure at 12 months after transplantation. Efficacy failure was defined as any of the following events:

- Patient's death,
- Graft loss,
- Acute rejection,
- lost to follow-up.

π_A and π_B represented the treatment failure rate of single high dose ATG-F (7-9 mg/kg) group and five dose ATG-F (2mg /kg each dose) respectively. Non inferiority boundary value δ is 15%, the hypothesis test for the primary efficacy evaluation:

$H_0: \pi_A - \pi_B \leq -\delta$

$H_A: \pi_A - \pi_B > -\delta$

Because of the treatment failure rate is low optimal index, the hypothesis test for the primary efficacy evaluation was adjusted to:

$H_0: \pi_B - \pi_A \leq -\delta$

$H_A: \pi_B - \pi_A > -\delta$

Calculated the asymptotic confidence interval with 97.5% of unilateral confidence of $\pi_B - \pi_A$. If the lower limit of the left side of the confidence interval was greater than-δ, H_0 would be rejected, and non-inferiority would be concluded. The exact confidence interval of binomial distribution was calculated for two treatment groups.

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Primary analysis was based on PPS.

3) Secondary Efficacy Evaluation:

For variables associated with the incidence, the binomial exact confidence intervals of two treatment groups were calculated respectively. Two-sided 95% confidence intervals of the incidence difference between two treatment groups was calculated. Two treatment groups were compared by Fisher's test.
Patient survival and graft survival were compared using Kaplan-Meier estimates and log-rank test.
Descriptive statistics were used to summarize continuous variables. ANCOVA analysis were used to compare differences between the two treatment groups.

4) Safety Evaluation:

Adverse events were encoded using MedDRA (v. 18.1) dictionary. The analysis of adverse events was based on treatment-emergent adverse events (TEAE). TEAE was defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments. The incidence of TEAE was described according to the system organ class (SOC) and the term (PT). Serious adverse events (SAEs) and adverse events leading to study termination were summarized and listed. The incidence of infections and malignancies and incidence of cytokine release syndrome and allergies also were summarized in a similar way.

Summary of Results/Conclusions:

The results showed that the efficacy of single dose administration of ATG-F in the de novo kidney transplant recipients was not inferior to that of the multiple dose administration. There was no statistical difference on the secondary objectives and safety index between Arm A and Arm B. Each one of the two schemes can be used as the choice of the induction treatment for de novo kidney transplant recipients.

Efficacy/Pharmacokinetic/Pharmacodynamic Results:

1) The rate of efficacy failure at 12 months after transplantation:

In the total 233 subjects of PPS within 12-month post-transplant, the failure rates of the single high dose group (Arm A) and the multiple dose group (Arm B) were 17.24% (95%CI:10.86~25.36) vs. 23.08% (95%CI:15.79~31.77) respectively. In PPS, the 95% CI of one side π_B - π_A is -4.44%, greater than -15%, and P value of the non-inferiority test was P<.0001, non-inferiority would be concluded (Table 3). The single high dose group was non-inferiority to the five low dose group on the efficacy failure at 12 months after transplantation, by the non-inferiority test.

2) The incidence of acute rejection determined by signs and symptoms:

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14 patients (12.07%) in Arm A and 18 patients (15.38%) in Arm B had occurred acute rejection determined by signs and symptoms in PPS, and the incidence of acute rejection by signs and symptoms showed no statistical significant difference between Arm A and Arm B (*P*=0.4622).

3) Acute rejection incidence confirmed by biopsy:

3 patients (2.59%) in Arm A and 6 patients (5.31%) in Arm B had occurred biopsy proven acute rejection in PPS, and the acute rejection incidence confirmed by biopsy showed no statistical difference between Arm A and Arm B *(P*=0.5049).

4) Steroid-resistant acute rejection incidence:

0 patients (0.00%) in Arm A and 4 patients (3.42%) in Arm B had occurred steroid resistant acute rejection in PPS, and the incidence of steroid resistant acute rejection showed no statistical difference between Arm A and Arm B *(P*=0.1325).

5) The incidence of DGF:

14 patients (12.07%) in Arm A and 8 patients (6.84%) in Arm B had occurred DGF in PPS, and the incidence of DGF showed no statistical difference between Arm A and Arm B *(P*=0.1721).

6) The survival rate of recipients:

There were 112 patients (96.55%) in Arm A and 115 patients (98.29%) in Arm B survival within 12 months after transplantation in PPS, and the survival rate showed no statistical difference between Arm A and Arm B (*P*=0.6714).

7) The survival rate of graft:

There were 6 patients (5.17%) in Arm A and 2 patients (1.71%) in Arm B lost the graft within 12 months after transplantation in PPS, and the survival rate of graft showed no statistical difference between Arm A (94.83%) and Arm B (98.29) (*P*=0.2754).

8) The renal graft function determined by serum creatinine level:

At each visit, the range of serum creatinine compared to the baseline showed no statistical difference between Arm A and Arm B (*P*> 0.05) within 12 months after transplantation.

Safety Results:

In total, there were 111 and 123 patients who experienced adverse events in Arm A and B respectively, the incidence rate was 82.22% vs. 87.23% (Arm A vs. Arm B), *P*= 0.2466. There was no significant difference on total adverse events incidence between Arm A and Arm B. The summary of AE and SAE of each system is shown in Table 4 and 5 respectively.

CONCLUSIONS:

The results indicated that, the single high dose administration of ATG-F in the de novo kidney transplant recipients was non-inferiority to the five low dose administration on the efficacy failure at 12 months after transplantation. There was no significant difference on incidence of acute rejection (including acute rejection determined by signs and symptoms, acute rejection confirmed by biopsy and steroid-resistant acute rejection), survival rate of patients and graft, incidence of DGF, renal graft function and incidence of adverse events

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between Arm A and Arm B within 12 months after transplantation in de novo kidney transplantation. Each of the two therapeutic regimens can be used as the choice of the induction treatment for de novo kidney transplant recipients because of the comparative clinical outcome.

Date of Report:

16th Nov 2016

Figure 1 Disposition of Subjects

CONSORT Flow Diagrams

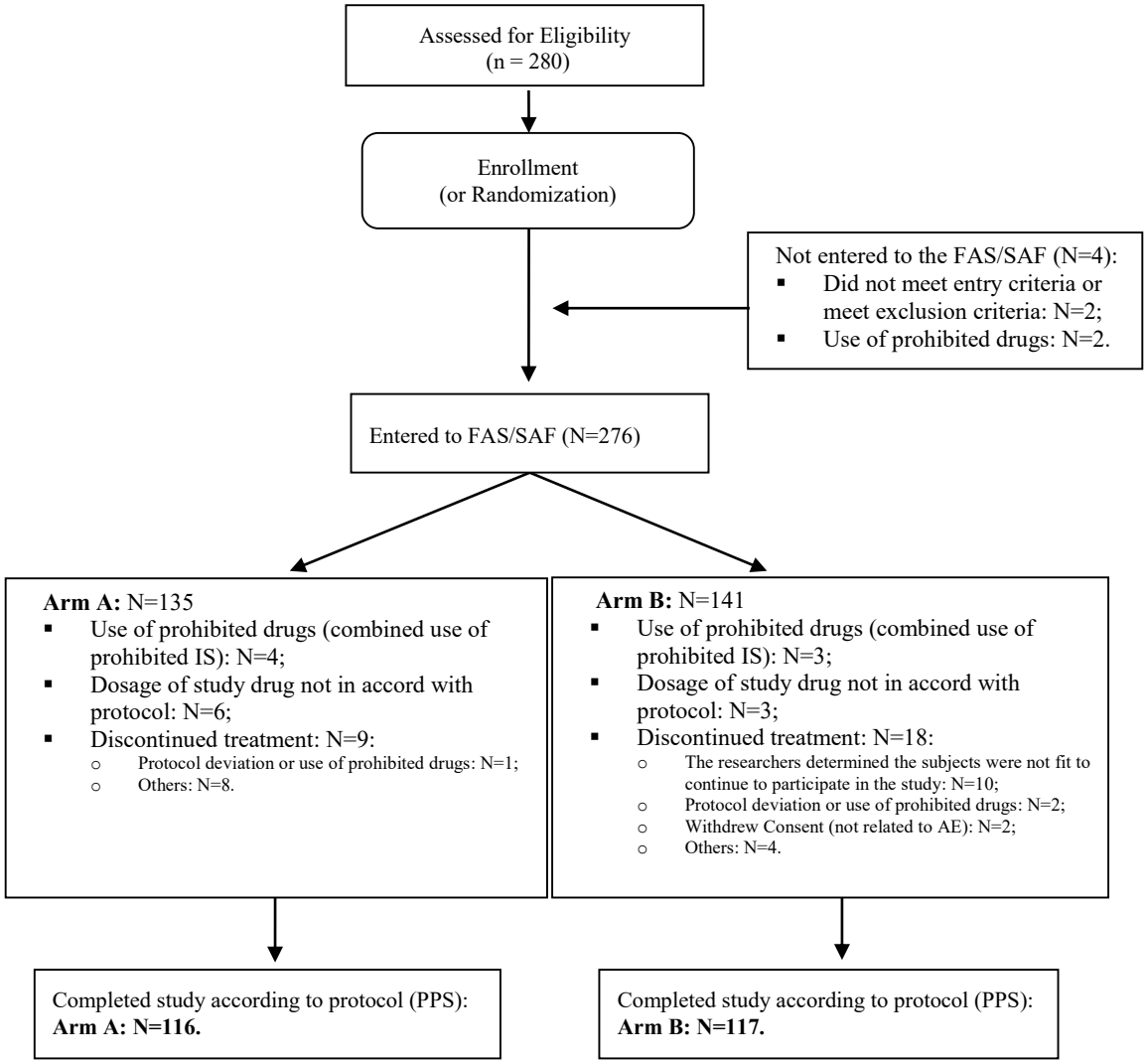

Table 1 Patient Disposition

Enrolled	**280**	
	Arm A	**Arm B**
Randomized	138	142
Use of banned drugs	2	0
Violation of inclusion criteria or Meet the exclusion criteria	1	1
Completed Treatment?		
Yes	118	117
No	20	25
Reasons for Discontinuation		
Protocol deviation	3	2
Withdrew Consent (not related to AE)	0	2
The researchers determined the subjects were not fit to continue to participate in the study	[3]	13
Others	14	8
Adverse Event Resulted in Death	4	2
No	107	121

Table 2 Demographic Characteristics

Characteristic	Arm A	Arm B
Sex		
Male	97	104
Female	38	37
Ethnicity		
ethnic Han	131	133
ethnic non-Han	4	8
Age (years)		
Mean ± Standard Deviation	36.96±9.49	35.63±10.23
Median	35.96	32.82
Minimum-Maximum	19.36~60.33	18.38~63.36
Height (cm)		
Mean ± Standard Deviation	1.68±0.08	1.67±0.07
Median	1.70	1.69
Minimum-Maximum	1.48~1.83	1.50~1.81
Weight (kg)		
Mean ± Standard Deviation	60.30±10.81	59.85±11.48
Median	60.00	58.00
Minimum-Maximum	36.50~90.00	39.00~90.00

Patient/Subject Base: FAS

Table 3 The Non-inferiority of the Two Regimens with Regard to Failure Rate

	Groups	
	Arm A	**Arm B**
Failure of treatment		
N(missing)	116(0)	117(0)
No	96(82.76)	90(76.92)
Yes	20(17.24)	27(23.08)
Death	4(3.45)	2(1.71)
Graft loss	2(1.72)	0(0.00)
Acute rejection	14(12.07)	25(21.37)
95% CI of failure rate	10.86~25.36	15.79~31.77
95% CI of one side π_B - π_A (δ=15%)		-4.44~∞
Non-inferiority test statistic		3.98
Non-inferiority P-value(single-side α=0.025)		<.0001

Analysis set: PPS

Table 4 Summary of Treatment-Emergent Adverse Events Occurring in at Least 5% of Patients in Either Treatment Arm (Preferred Term)

MedDRA (v. 18.1)	Number of Patients (%)	
System Organ Class (Preferred Term)	Arm A (n=135)	Arm B (n=141)
All Systems, Any AE	111(82.22)	123(87.23)
Investigations	64(47.41)	63(44.68)
Blood glucose increased	24(17.78)	33(23.40)
White blood cell count increased	19(14.07)	13(9.22)
Platelet count decreased	19(14.07)	11(7.80)
Haemoglobin decreased	13(9.63)	7(4.96)
Lymphocyte count decreased	11(8.15)	8(5.67)
Red blood cell count decreased	10(7.41)	6(4.26)
Granulocyte count increased	10(7.41)	7(4.96)
Haematocrit decreased	8(5.93)	4(2.84)
Blood creatinine increased	7(5.19)	9(6.38)
White blood cell count decreased	6(4.44)	12(8.51)
Blood triglycerides increased	4(2.96)	8(5.67)
Infections and infestations	52(38.52)	50(35.46)
Lung infection	25(18.52)	25(17.73)
Upper respiratory tract infection	10(7.41)	9(6.38)
Urinary tract infection	8(5.93)	9(6.38)
Hepatobiliary disorders	27(20.00)	19(13.48)
Hepatic function abnormal	27(20.00)	17(12.06)
Gastrointestinal disorders	27(20.00)	23(16.31)
Diarrhoea	13(9.63)	12(8.51)
Renal and urinary disorders	25(18.52)	21(14.89)
Urinary tract inflammation	7(5.19)	4(2.84)
Metabolism and nutrition disorders	23(17.04)	23(16.31)
Hyperlipidaemia	3(2.22)	8(5.67)
Blood and lymphatic system disorders	23(17.04)	26(18.44)
Anaemia	23(17.04)	25(17.73)
Immune system disorders	18(13.33)	22(15.60)
Kidney transplant rejection	14(10.37)	22(15.60)
General disorders and administration site conditions	18(13.33)	11(7.8)
Pyrexia	15(11.11)	9(6.38)

Analysis set: SAF.

Table 5 Summary of Serious Treatment-Emergent Adverse Events

MedDRA (v. 18.1) Primary System Organ Class (Preferred Term)	Number of Patients (%)	
	Arm A (n=135)	Arm B (n=141)
All Systems, Any SAE	45(33.33)	50(35.46)
Infections and Infestations	27(20)	27(19.15)
Lung infection	18(13.33)	17(12.06)
Upper respiratory tract infection	3(2.22)	1(0.71)
Pyelonephritis acute	2(1.48)	1(0.71)
Urinary tract infection	2(1.48)	1(0.71)
Gastroenteritis	2(1.48)	0(0)
Encephalitis	1(0.74)	0(0)
Human polyomavirus infection	1(0.74)	1(0.71)
Tuberculosis	0(0)	1(0.71)
Cytomegalovirus infection	0(0)	1(0.71)
Pneumonia cytomegaloviral	0(0)	2(1.42)
Septic shock	0(0)	1(0.71)
Wound infection	0(0)	1(0.71)
perinephric abscess	0(0)	1(0.71)
Renal and urinary disorders	13(9.63)	10(7.09)
Urinary tract inflammation	4(2.96)	0(0)
Renal failure	2(1.48)	3(2.13)
Renal injury	2(1.48)	0(0)
IgA nephropathy	1(0.74)	0(0)
Renal vein thrombosis	1(0.74)	0(0)
Renal tubular necrosis	1(0.74)	3(2.13)
Renal tubular disorder	1(0.74)	0(0)
Hydronephrosis	1(0.74)	0(0)
Ureteric stenosis	1(0.74)	2(1.42)
Acute kidney injury	0(0)	1(0.71)
Renal artery stenosis	0(0)	1(0.71)
Renal artery thrombosis	0(0)	1(0.71)
Kidney fibrosis	0(0)	1(0.71)
Mesangioproliferative glomerulonephritis	0(0)	1(0.71)
Hepatobiliary disorders	5(3.7)	0(0)
Hepatic function abnormal	4(2.96)	0(0)
Drug-induced liver injury	1(0.74)	0(0)
Metabolism and nutrition disorders	3(2.22)	1(0.71)
Diabetes mellitus	2(1.48)	1(0.71)
Gout	1(0.74)	0(0)
Respiratory, thoracic and mediastinal disorders	3(2.22)	2(1.42)
Respiratory failure	2(1.48)	0(0)
Acute respiratory distress syndrome	1(0.74)	0(0)
Pulmonary bulla	0(0)	1(0.71)
Interstitial lung disease	0(0)	1(0.71)
Immune system disorders	3(2.22)	9(6.38)
Acute allograft nephropathy	2(1.48)	0(0)
Kidney transplant rejection	1(0.74)	9(6.38)

Gastrointestinal disorders	3(2.22)	2(1.42)
Enteritis	1(0.74)	0(0)
Diarrhoea	1(0.74)	0(0)
Gastrointestinal haemorrhage	1(0.74)	0(0)
Abdominal pain upper	0(0)	1(0.71)
Duodenal ulcer	0(0)	1(0.71)
Injury, poisoning and procedural complications	2(1.48)	4(2.84)
Post procedural haemorrhage	1(0.74)	1(0.71)
Procedural hypotension	1(0.74)	0(0)
Delayed graft function	1(0.74)	2(1.42)
Wound complication	0(0)	1(0.71)
Vascular disorders	2(1.48)	0(0)
Arteriovenous fistula	1(0.74)	0(0)
Pulmonary embolism	1(0.74)	0(0)
Investigations	1(0.74)	1(0.71)
Blood creatinine increased	1(0.74)	1(0.71)
General disorders and administration site conditions	1(0.74)	1(0.71)
Multi-organ failure	1(0.74)	0(0)
Pyrexia	0(0)	1(0.71)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0(0)	1(0.71)
Sarcoma uterus	0(0)	1(0.71)
Cardiac disorders	0(0)	2(1.42)
Cardiac failure	0(0)	2(1.42)

Analysis set: SAF.

Patients/subjects may have experienced more than 1 type of adverse event within a system organ class.

AE: adverse event