Table S1: Primary endpoint, components of the primary endpoint and secondary endpoints (per-protocol analysis set)

	Arm 1 (N=93)	Arm 2 (N=24)	Arm 3 (N=29)	Arm 4 (N=91)	Arm 5 (N=71)
Development of AKI using the KDIGO definition					
Incidence (%)	78.5	75.0	75.9	78.0	70.4
95% CI	68.8-86.3	53.3-90.2	56.5-89.7	68.1-86.0	58.4-80.7
Odds ratio*		0.89	0.91	1.01	0.68
95% CI		0.31-2.58	0.33-2.47	0.50-2.05	0.33-1.39
p-value†		0.83	0.85	0.98	0.29
Increase in serum creatinine ≥0.3 mg/dL within 48 h					
Incidence (%)	55.9	54.2	55.2	54.9	49.3
95% CI	45.2-66.2	32.8-74.4	35.7-73.6	44.2-65.4	37.2-61.4
Odds ratio		1.06	1.06	1.02	0.83
95% CI		0.41-2.73	0.44-2.56	0.55-1.87	0.43-1.58
Increase in serum creatinine ≥50% within 7 days					
Incidence (%)	19.4	29.2	20.7	19.8	19.7
95% CI	11.9-28.9	12.6-51.1	8.0-39.7	12.2-29.4	11.2-30.9
Odds ratio		1.73	1.09	1.03	1.04
95% CI		0.62-4.80	0.39-3.08	0.50-2.14	0.48-2.28
Urine output <0.5 ml/kg/h for ≥6 consecutive hours					
Incidence	59.1	54.2	58.6	50.5	57.7
95% CI	48.5-69.2	32.8-74.4	38.9-76.5	39.9-61.2	45.4-69.4

Odds ratio		0.81	0.97	0.70	0.97
95% CI		0.33-2.00	0.42-2.27	0.39-1.26	0.52-1.83
Development of AKI using the serum creatinine-based KDIGO definition					
Incidence (%)	57.0	54.2	58.6	56.0	49.3
95% CI	46.3-67.2	32.8-74.4	38.9-76.5	45.2-66.4	37.2-61.4
Odds ratio		1.00	1.17	1.01	0.79
95% CI		0.39=2.56	0.48-2.82	0.55-1.86	0.41-1.50
Composite of death, dialysis, or ≥30% decline in GFR at day 30					
Incidence	12.5	19.0	20.0	13.1	20.3
95% CI	6.4-21.3	5.441.9	6.8-40.7	6.7-22.2	11.0-32.8
Odds ratio		1.73	1.87	1.07	1.79
95% CI		0.49-6.15	0.58-6.05	0.44-2.63	0.73-4.38
Severity of AKI‡					
AKI stage 1 – no. (%)	47 (50.5)	10 (41.7)	12 (41.4)	48 (52.7)	29 (40.8)
AKI stage 2 – no. (%)	23 (24.7)	7 (29.2)	9 (31.0)	22 (24.2)	18 (25.4)
AKI stage 3 – no. (%)	3 (3.2)	1 (4.2)	1 (3.4)	1 (1.1)	3 (4.2)
Duration of AKI, within the first 7 days					
Median	3.0	2.0	2.0	2.0	2.0
Interquartile range	2-6	1-3	1-4	1-6	1-6

Arm 1 = placebo; Arm 2= 0.02 mg/kg pre-operative and post-operative doses, Arm 3= 0.12 mg/kg pre-operative and 0.02 mg/kg post-operative doses; Arm 4= 0.46 mg/kg pre-operative and 0.02 mg/kg post-operative doses; Arm 5= 0.46 mg/kg pre-operative and post-operative doses.

* compared to arm 1 (placebo)

† unadjusted p-value (2 sided) from logistic regression with baseline GFR as a covariate, comparing the active arm to arm 1 (placebo)

‡ using the KDIGO classification, and the full KDIGO definition of AKI

Table S2: Adverse events reported in at least 5% of the study population (safety analysis set)

Preferred term	Arm 1 (N=115)	Arm 2 (N=45)	Arm 3 (N=47)	Arm 4 (N=119)	Arm 5 (N=105)
Atrial fibrillation – no. (%)	43 (37.4)	15 (33.3)	23 (48.9)	39 (32.8)	39 (37.1)
Anemia – no. (%)	34 (29.6)	18 (40.0)	13 (27.7)	31 (26.1)	25 (23.8)
Pleural effusion – no. (%)	25 (21.7)	19 (42.2)	19 (40.4)	25 (21.0)	26 (24.8)
Procedural pain – no. (%)	22 (19.1)	9 (20.0)	9 (19.1)	34 (28.6)	27 (25.7)
Nausea – no. (%)	24 (20.9)	14 (31.1)	9 (19.1)	24 (20.2)	25 (23.8)
Fluid overload – no. (%)	16 (13.9)	12 (26.7)	13 (27.7)	30 (25.2)	18 (17.1)
Hypokalemia – no. (%)	24 (20.9)	7 (15.6)	7 (14.9)	35 (29.4)	14 (13.3)
Hypotension – no. (%)	25 (21.7)	8 (17.8)	14 (29.8)	21 (17.6)	19 (18.1)
Acute kidney injury – no. (%)	18 (15.7)	13 (28.9)	6 (12.8)	23 (19.3)	14 (13.3)
Hypocalcemia – no. (%)	16 (13.9)	9 (20.0)	10 (21.3)	27 (22.7)	12 (11.4)
Oedema peripheral – no. (%)	20 (17.4)	7 (15.6)	5 (10.6)	14 (11.8)	19 (18.1)
Thrombocytopenia – no. (%)	13 (11.3)	11 (24.4)	9 (19.1)	17 (14.3)	11 (10.5)
Constipation – no. (%)	19 (16.5)	10 (22.2)	4 (8.5)	14 (11.8)	11 (10.5)

Hyperglycemia – no. (%)	11 (9.6)	11 (24.4)	8 (17.0)	15 (12.6)	10 (9.5)
Hypoalbuminemia – no. (%)	12 (10.4)	6 (13.3)	5 (10.6)	17 (14.3)	10 (9.5)
Urinary tract infection – no. (%)	13 (11.3)	7 (15.6)	3 (6.4)	8 (6.7)	11 (10.5)
Atelectasis – no. (%)	9 (7.8)	6 (13.3)	7 (14.9)	10 (8.4)	7 (6.7)
Hyperkalemia – no. (%)	8 (7.0)	5 (11.1)	5 (10.6)	7 (5.9)	6 (5.7)
Hypertension – no. (%)	5 (4.3)	4 (8.9)	6 (12.8)	9 (7.6)	5 (4.8)
Low cardiac output syndrome – no. (%)	11 (9.6)	3 (6.7)	3 (6.4)	7 (5.9)	4 (3.8)
Hypomagnesemia – no. (%)	7 (6.1)	5 (11.1)	4 (8.5)	6 (5.0)	4 (3.8)
Wound complication – no. (%)	6 (5.2)	4 (8.9)	3 (6.4)	6 (5.0)	7 (6.7)
Anemia postoperative – no. (%)	5 (4.3)	6 (13.3)	1 (2.1)	8 (6.7)	5 (4.8)
Insomnia – no. (%)	4 (3.5)	5 (11.1)	1 (2.1)	3 (2.5)	12 (11.4)
Cardiac failure congestive – no. (%)	6 (5.2)	2 (4.4)	2 (4.30	7 (5.9)	7 (6.7)
Hemoglobin decreased – no. (%)	6 (5.2)	1 (2.2)	2 (4.3)	4 (3.4)	11 (10.5)
Leukocytosis – no. (%)	6 (5.2)	4 (8.9)	3 (6.4)	8 (6.7)	3 (2.9)
Post-operative wound infection – no. (%)	4 (3.5)	3 (6.7)	1 (2.1)	4 (3.4)	12 (11.4)
Vomiting – no. (%)	4 (3.5)	6 (13.3)	4 (8.5)	2 (1.7)	7 (6.7)
Delirium – no. (%)	9 (7.8)	1 (2.2)	1 (2.1)	4 (3.4)	7 (6.7)
Pneumonia – no. (%)	10 (8.7)	1 (2.2)	2 (4.3)	4 (3.4)	5 (4.8)

__ Arm 1 = placebo; Arm 2= 0.02 mg/kg pre-operative and post-operative doses, Arm 3= 0.12 mg/kg pre-operative and 0.02 mg/kg post-operative doses; Arm 4= 0.46 mg/kg pre-operative and 0.02 mg/kg post-operative doses; Arm 5= 0.46 mg/kg pre-operative and post-operative doses.

Table S3: Treatment-related adverse events reported in at least 2 subjects* (safety analysis set)

Preferred term	**Arm 1** (N=115)	**Arm 2** (N=45)	**Arm 3** (N=47)	**Arm 4** (N=119)	**Arm 5** (N=105)
AST increased – no. (%)	0	1 (2.2)	0	3 (2.5)	1 (1.0)
Blood bilirubin increased – no. (%)	0	1 (2.2)	1 (2.1)	0	0
Hepatic enzyme increased – no. (%)	0	0	1 (2.1)	1 (0.8)	0
Blood LDH increased – no. (%)	0	1 (2.2)	0	1 (0.8)	0
INR increased – no. (%)	0	0	0	1 (0.8)	1 (1.0)
Acute kidney injury – no. (%)	2 (1.7)	2 (4.4)	1 (2.1)	4 (3.4)	1 (1.0)
Hyperkalemia – no. (%)	0	1 (2.20	0	2 (1.7)	1 (1.0)
Coagulopathy – no. (%)	1 (0.9)	0	0	1 (0.8)	0
Thrombocytopenia – no. (%)	0	1 (2.2)	1 (2.1)	0	0

Nausea – no. (%)	2 (1.7)	0	0	0	2 (1.9)
Post-operative wound infection – no. (%)	0	0	0	0	3 (2.9)
Cardiac arrest – no. (%)	1 (0.9)	0	0	1 (0.8)	0
Hypotension – no. (%)	0	0	1 (2.10	1 (0.8)	0

Arm 1 = placebo; Arm 2= 0.02 mg/kg pre-operative and post-operative doses, Arm 3= 0.12 mg/kg pre-operative and 0.02 mg/kg post-operative doses; Arm 4= 0.46 mg/kg pre-operative and 0.02 mg/kg post-operative doses; Arm 5= 0.46 mg/kg pre-operative and post-operative doses.

*These adverse events were assessed by the investigator as possibly, probably or definitely related to the study drug

Table S4: Primary endpoint, components of the primary endpoint, and secondary endpoints (full analysis set, and per-protocol analysis set) for subjects with eGFR <60 mL/min/1.73m2

	Full analysis set		Per protocol analysis set	
	Arm 1	**Arm 5**	**Arm 1**	**Arm 5**
	(N=57)	(N=47)	(N=48)	(N=31)
Development of AKI using the full KDIGO definition				
Incidence (%)	86.0	80.9	85.4	74.2
95% CI	74.2-93.7	66.7-90.9	72.2-93.9	55.4-88.1
Odds ratio*		0.69		0.49
95% CI		0.24-1.95		0.16-1.53
Development of AKI using the serum creatinine-based KDIGO definition				
Incidence (%)	68.4	61.7	75.0	58.1
95% CI	54.8-80.1	46.4-75.5	60.4-86.4	39.1-75.5
Odds ratio		0.74		0.46
95% CI		0.33-1.67		0.18-1.21
Composite of death, dialysis, or ≥30% decline in GFR at day 30				
Incidence (%)	13.0	13.9	15.2	15.4
95% CI	5.4-24.9	4.7-29.5	6.3-28.9	4.4-34.9
Odds ratio		1.08		1.01
95% CI		0.32-3.72		0.27-3.85
Severity of AKI†				
AKI stage 1 – no. (%)	33 (57.9)	19 (40.4)	30 (62.5)	11 (35.5)
AKI stage 2 – no. (%)	13 (22.8)	17 (36.2)	8 (16.7)	10 (32.3)
AKI stage 3 – no. (%)	3 (5.3)	2 (4.3)	3 (6.3)	2 (6.5)

Duration of AKI, within the first 7 days

Median	4.0	5.0	4.0	4.5
Interquartile range	2-7	2-7	2-7	2-7

Arm 1 = placebo; Arm 5= 0.46 mg/kg pre-operative and post-operative doses.

* compared to arm 1 (placebo)

† using the KDIGO classification, and the full KDIGO definition of AKI

Figure S1: Plasma concentration of THR 184 at the end of the pre-surgery infusion, according to the dose (mean ± SD). Patients from arms 4 & 5 were combined in the 460 µg/kg/dose.