Study Design

We performed the study as an open-label, phase 1 clinical trial approved by the Danish Medicines Agency (EudraCT no. 2015-005583-42) and the Ethical Committee of the Capital Region of Denmark (protocol H-18015477). Patients signed written informed consent prior to inclusion. The study was conducted in accordance with the requirements for Good Clinical Practice including independent monitoring by the Good Clinical Practice unit of Copenhagen University Hospital and the trial was registered at ClinicalTrials.gov (NCT03790423). Eligible patients were ≥ 18 years, diagnosed with breast, lung, pancreatic, cervical, or ovarian cancer, and capable of understanding the patient information in Danish and giving full informed consent. Exclusion criteria were pregnancy/breast-feeding, weight above 140 kg or history of allergic reaction attributable to compounds of similar chemical or biologic composition to ^{18}F-ASIS.

From January to November 2019, after giving informed consent, 10 patients with pancreatic cancer (n=4), breast cancer (n=3), lung cancer (n=2), and cervical cancer (n=1) were included in the study and referred to a ^{18}F-ASIS PET/CT imaging series. The mean and standard deviation of the administered mass of ^{18}F-ASIS was 0.67 ± 0.12 mg (range, 0.41–0.84 mg). The mean administered activity was 157 ± 35 MBq (range, 93–198 MBq) yielding a mean specific activity of 245 ± 84 MBq/mg (range, 126-412 MBq/mg) at the time of injection. Sequential whole-body PET/CT imaging was performed 1 hour (h), 2h, and 4h after injection of ^{18}F-ASIS.

Blood samples were collected prior to administration of ^{18}F-ASIS for plasma tissue factor (TF) measurements in all patients. In a subset of eight patients (patients 1-8), blood samples were collected for pharmacokinetic analysis, including radiotracer metabolism and plasma half-life, approximately 1h, 2h, and 4h after injection. In the same eight patients, urine collection was performed throughout the study period and sampled immediately prior to the 1h and 2h PET/CT and following the 4h

PET/CT scans (at approximately 1h, 2h, and 5h after injection) for determination of urinary metabolism, excretion, and dosimetry calculations.

Safety measures included observation of the patients by a medical doctor up to 5h after injection of ^{18}F-ASIS and monitoring of heart rate, blood pressure, and pulse oximetry with regular intervals before, during, and after the last PET/CT scan (pre-injection, 10 min, and approximately 1h, 2h, and 4h after injection). Electrocardiograms were performed pre-injection, and approximately 1h, and 4h after injection. Hematologic (hemoglobin, white blood cells, platelets), liver (alanine amino transferase, aspartate transaminase, alkaline phosphatase), and renal function (creatinine, glomerular filtration rate, sodium, potassium), and c-reactive protein (CRP) were measured before radiotracer administration, 4h after injection, and as follow-up on the patient's routine return to the hospital 3–21 days after the study day. Adverse events were registered up to 48 hours after administration of ^{18}F-ASIS and coded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

When available, tumor biopsies or surgically excised primary tumor tissue and local lymph nodes were collected for target validation by analysis of expression of TF with immunohistochemistry (IHC) and enzyme-linked immunosorbent assay (ELISA).

PET/CT Image Acquisition and PET Image Reconstruction

Image acquisition was performed on a Siemens Biograph 128 mCT PET/CT with an axial-field-of-view (FOV) of 221 mm (Siemens Healthineers, Erlangen, Germany) and PET acquisition commenced 1h, 2h and 4h after injection of ^{18}F-ASIS. Patients were preferably placed with their arms above the head. Prior to the 1h and 2h PET, whole body (from fingertips to toes) low-dose CT (2 mm slice thickness, 40 mAs exposure, 120 kV kilovoltage peak) were performed. Following the 4h PET, a diagnostic whole-body 2 mm slice thickness CT was performed: Quality reference mAs = 225, kV = 120. Dose and kV modulation

were activated meaning that the output from the X-ray tube was modulated according to patient size using the build-in CARE software (Siemens Healthineers, Erlangen, Germany). Unless otherwise contraindicated, patients were injected with intravenous iodine-based contrast (Optiray 300 mg I/ml, 70-100 ml, injection rate 1.5-2.5 ml/s) using an automated injection system. The PET acquisitions covered the whole body (from fingertips to toes). To allow for sufficient count statistics, while keeping the acquisition times at an acceptable level, differential acquisition times were employed. For the 1h and 2h PET, the acquisition time was 3 minutes per bed from head to midthighs and 1 minute per bed from midthighs and downwards. For the 4h PET, the corresponding acquisitions times were 4 and 2 minutes per bed, respectively. PET data were reconstructed iteratively using 3-dimensional ordinary Poisson ordered subsets expectation maximization (3D-OP-OSEM) with point-spread-function using the vendor supplied TrueX algorithm (Siemens Healthineers, Erlangen, Germany). 2 iterations and 21 subsets were used including time-of-flight information (540 ps) and smoothed by a Gaussian filter (2 mm full-width-half-maximum) with a slice thickness of 2 mm. For the 1h and 2h PETs, the corresponding low-dose CTs were used for localization and attenuation correction. For the 4h PET, the diagnostic CT was used.

Dosimetry and Biodistribution

Dosimetry was based on the non-decay corrected PET image sets from the 3 time-points (n=10) supplemented with sampled urine-data (n=8). The following organs were considered: adrenal, bone, brain, blood pool, heart wall, kidney, liver, lung, red marrow (L3–L5 vertebrae), ascending and descending colon, small intestine, spleen, stomach contents, and thyroid. For each patient, organ, and time-point, tissue activity concentration (kBq/mL) was calculated as the average of the mean values from 3 volumes of interest (VOIs) drawn on the PET images using MIRADA DBx version 1.2.0 (Mirada Medical, Denver CO, USA). For presentation of the organ-specific radiotracer distribution, the average decay-corrected tissue activity concentration was calculated as body-weight adjusted mean standardized uptake values

(SUV_{mean}). For the dosimetry calculations, total activity (per patient, organ, and time) was estimated by multiplying these average values by organ masses of the OLINDA male adult phantom (*1,2*). Activity values were normalized to 1 MBq by dividing with injected activity and scaled with the ratio of actual patient weight to the weight of the standard male model (73 kg). Time integrated activity coefficients (TIAC; unit *h*) for each patient and organ were determined by numerical integration up to the third (last) data point and analytical extrapolation to infinity assuming only physical decay. Piecewise linearity was assumed from time zero up to the second data point and a mono-exponential was used between the second and third data points. The resulting organ TIACs were averaged over patients. All data were entered into OLINDA/EXM 2.0 software (Vanderbilt University, Nashville, TN, USA and HERMES Medical Solutions, Stockholm, Sweden). The cumulated decay corrected activity (in MBq) of the excreted urine, normalized to 1 MBq of injection, was plotted over time for all 8 subjects and data fitted to a one phase exponential association (exponential growing towards a limit) using the Excel Solver. The resulting limit and half-life were used as input to the bladder voiding model of OLINDA, yielding the TIAC for bladder contents. A bladder voiding interval of 2 hours was selected for the calculation. The value for "remainder tissue" was determined as the total area (in h) for 1 MBq minus the sum (except bladder) of the organ-specific values minus the value passed to urine (based on the fitted model parameters). The output from OLINDA consists of absorbed doses for organs and effective dose with tissue weighting factors according to International Commission on Radiological Protection (ICRP) 103 (*3*).

Ex vivo Tumor Tissue Samples

Tissue preparation

Tumor tissue samples were obtained from resected surgical specimens or from tumor biopsies performed in relation to routine clinical investigation. Samples intended for quantification of TF by ELISA were immediately frozen in liquid nitrogen and subsequently stored at -80^{o}C until use. Samples intended for histological preparation were fixated in 4% paraformaldehyde for 48h followed by storage in 96% alcohol until embedding into paraffin.

Measurement of Tissue Factor Expression in *Ex Vivo* Tumor Tissue Samples and Plasma

Tissue homogenization

Following thawing, tumor samples were weighed and 1 ml of RIPA buffer (89900, Thermo Fischer Scientific, Waltham, MA, USA) per g of tissue were added in a CKmix tissue homogenizing tube (Bertin Instruments, Rockville, MD, USA). Samples were homogenized on a Precellys Evolution Homogenizer (Bertin Instruments, Rockville, MD, USA) with the following program settings: 2 cycles of 35 sec, 9500 RPM, 4°C.

ELISA measurements

The TF protein concentration in tumor samples and plasma were measured with ELISA using the manufacturer's protocol (Human Coagulation Factor III/Tissue Factor Quantikine ELISA, DCF300, R&D systems, Minneapolis, MN, USA). Standards were applied in duplicates in the range 7.8–500 pg/mL, and a standard curve was fitted to a 3-parameter dose–response curve (Microsoft Excel 2016, Microsoft, Redmond, WN, USA). Samples were diluted to 1:3 (plasma) and 1:300 (tumor samples)

and measured in duplicates, and the TF concentration interpolated from the standard curve. Finally, the TF concentration in the tumor samples was normalized to total protein concentration measured with the Micro BCA™ Protein Assay Kit (23235, Thermo Scientific, Pierce Biotechnology, IL, USA) according to the manufacturer's protocol.

Immunohistochemistry of Tissue Factor in *Ex Vivo* Tumor Tissue

Biopsies where fixated in buffered 4% paraformaldehyde (pH 7.2) followed by preparation in Shandon Excelsior AS Tissue Processor O/N (Thermo Fisher Scientific, Waltham, MA, USA) and embedded in paraffin. Biopsies were cut in sections of 4 µm and dewaxed through xylene to tap water. For antigen retrieval, the sections were heat treated for 15 min in citrate buffer (pH 6). This was followed by a blocking step with Peroxidase-Blocking Solution (S2023, Agilent, Santa Clara, CA, USA) and pre-incubation in 2 % bovine serum albumin for 10 min. Sections were incubated with primary anti-tissue factor antibody (ADG4508, ImmBioMed, Pfugstadt, Germany) in a 1:500 dilution in 2% bovine serum albumin 1 hour at RT. For visualization, the sections were incubated with Envision+ system Anti-Mouse (K4001, Agilent, Santa Clara, CA, USA) for 45 min followed by incubation with DAB+ system (K3468, Agilent, Santa Clara, CA, USA) for 10 min. Counterstaining was performed with Mayer's Hematoxylin. Imaging was performed on Carl Zeiss Axio Lab.A1 (Carl Zeiss Microscopy GmbH, Jena, Germany) and analyzed with ZEN 3.2 Blue Edition (Carl Zeiss Microscopy GmbH, Jena, Germany). Immunohistochemistry TF expression was stratified as low, intermediate and high based on visual assessment.

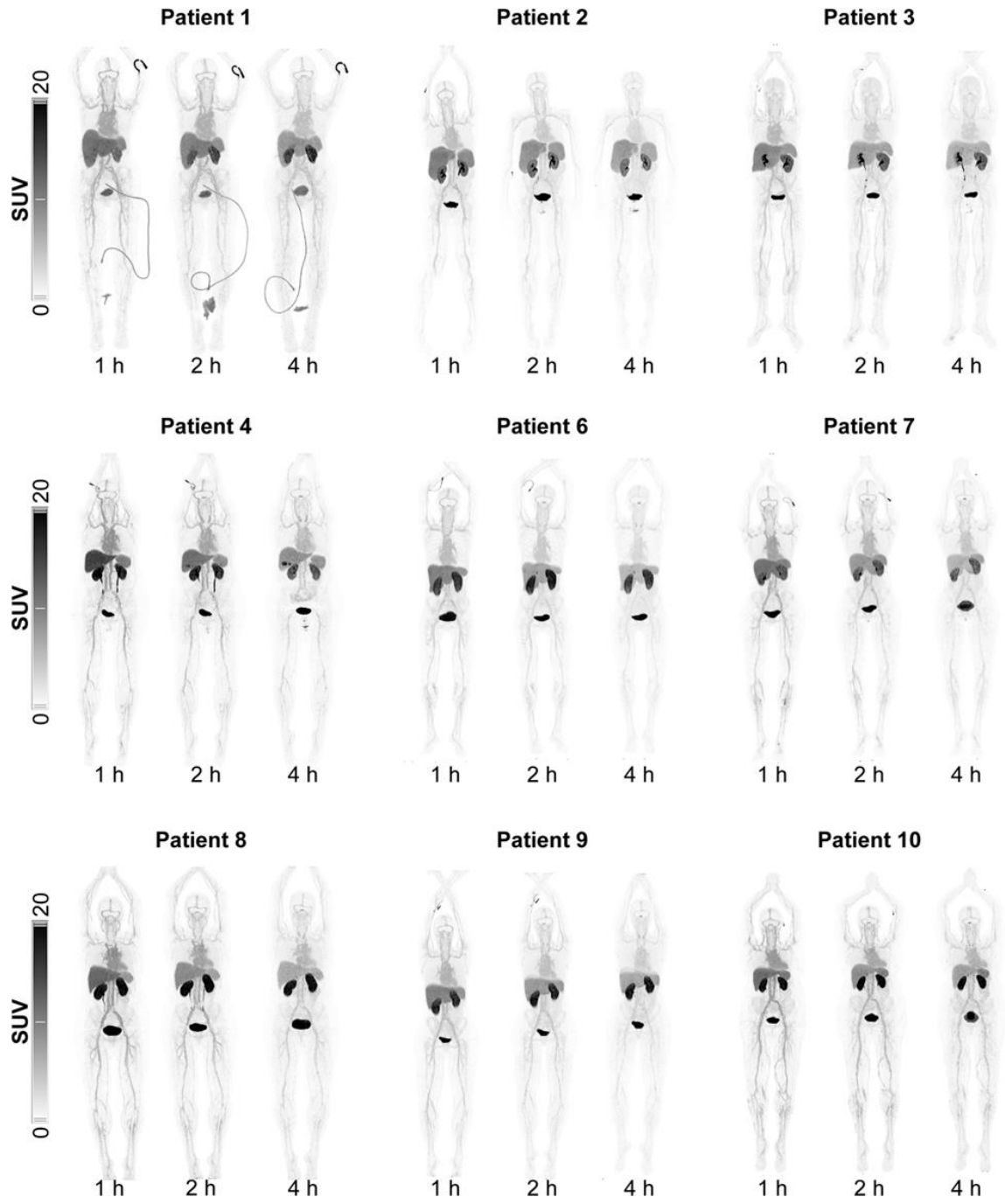
SUPPLEMENTAL REFERENCES

1. Stabin MG, Siegel JA. Physical models and dose factors for use in internal dose assessment. Health Phys. 2003;85:294-310.

2. ICRP. Basic anatomical and physiological data for use in radiological protection: reference values. ICRP Publication 89. Ann ICRP. 2002;32:5-265.

3. ICRP. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103. Ann ICRP. 2007;37:1-332.

SUPPLEMENTAL FIGURES AND TABLES



SUPPLEMENTAL FIGURE 1 Maximum intensity projections (MIPs) showing the distribution of ^{18}F-ASIS for patients 1-4 and patients 6-10. h: hours.

SUPPLEMENTAL TABLE 1 Quality control parameters for ^{18}F-ASIS

Test	Method	Specification	Results (n=10)
Physical Tests			
Radioactivity	Dose Calibrator	200 MBq – 330 MBq at end of synthesis	220.5 ± 58.1 MBq
Physical appearance	Visual inspection	Clear and colorless solution, free from visible particulates or cloudiness	Complies for all batches
pH	Calibrated pH meter	6.0-8.0	7.2 ± 0.1
Radioactivity and chemical Tests			
^{18}F-Fluoride	HPLC	≤ 2%	0.0 ± 0.0 %
Unspecified ^{18}F-impurities	HPLC	≤ 2%	0.2 ± 0.2 %
Overall radio-chemical purity	HPLC	≥ 95%	99.9 ± 0.2 %
Identification of ^{18}F-ASIS	HPLC	The labeled product corresponds in retention time to an authentic reference standard of ASIS	Complies for all batches
ASIS content	HPLC	0.05 mg/ml - 0.15 mg/ml	0.08 ± 0.01 mg/ml
Acetonitrile	GC	≤ 410 ppm	30.9 ± 82.5 ppm
Tetrabutylammonium ions	Color-spot test	< 0.1 mg/ml	< 0.1 mg/ml for all batches
HEPES	Color-spot test	< 20 µg/ml	< 20 µg/ml for all batches
Protein and cell assays			
Immunoreactive fraction*	Lindmo assay	≥ 75 %	≥ 75 % for all batches

Microbiology tests			
Sterility*	Ph. Eur. test for sterility	Must comply	Complies for all batches
Endotoxins test	Ph. Eur. test for endotoxins	≤ 1EU/ml	≤ 1EU/ml for all batches

Data is presented as mean ± standard deviation unless otherwise indicated. *Not release test. Performed retrospectively following release of every batch. EU: Endotoxin units. HEPES: N-2-Hydroxyethylpiperazine-N'-2-Ethanesulfonic Acid. HPLC: high-pressure liquid chromatograph, GC: gas chromatography.

SUPPLEMENTAL TABLE 2 Vital signs for patients pre-injection, 10 min, 1 hour, 2 hours, 4 hours following injection of ^{18}F-ASIS

	Before injection				10 min post injection				1 hour post injection				2 hours post injection				4 hours post injection			
Pt	Sys	Dia	HR	PO_2	Sys	Dia	HR	PO_2	Sys	Dia	HR	PO_2	Sys	Dia	HR	PO_2	Sys	Dia	HR	PO_2
1	122	60	52	99	132	62	51	98	146	71	52	99	133	61	54	96	136	60	54	100
2	128	80	89	97	131	69	87	98	144	84	91	99	127	77	88	98	136	80	85	100
3	145	92	72	93	153	89	68	100	144	79	81	97	142	73	79	93	154	92	71	100
4	153	76	69	96	161	71	71	96	162	76	81	97	166	78	83	97	170	69	81	95
5	125	75	72	98	119	74	67	98	123	71	63	97	115	80	80	98	128	79	81	96
6	100	59	67	99	100	57	68	99	109	52	52	99	112	62	59	98	98	55	73	99
7	150	94	79	99	146	93	75	100	139	82	77	99	139	82	77	99	143	79	78	98
8	121	78	70	95	116	71	63	93	129	78	63	97	141	85	52	96	134	74	79	93
9	127	66	44	97	112	66	47	100	133	72	44	100	125	73	47	100	131	70	59	99
10	150	72	68	99	136	80	74	98	162	84	66	98	174	83	67	100	146	102	76	98

Sys: Systolic blood pressure, Dia: Diastolic blood pressure HR: Heart rate, PO_2: pulse oximetry.

SUPPLEMENTAL TABLE 3 Safety blood parameters measured before and after injection of ^{18}F-ASIS

Pt	Parameter (normal range)	Pre-injection	4 hours p.i.	Follow-up (*21* days p.i.)
1	Hemoglobin (7.3-9.5 mM)	7.3	6.2*,a	5.5*,b
	Leucocytes (3.5-8.8 10^7/l)	11.2*,b	12.6*,b	14.4*,b
	Platelets (145-390 10^7/l)	429*,b	356	497*,b
	CRP (<10 mg/l)	27*,b	28*,b	14*,b
	eGFR (> 60 ml/min/1.73 m^2)	21*,c	22*,c	34*,c
	Creatinine (50-90 μM)	186*,c	175*,c	123*,c
	Sodium (137-144 mM)	134*,b	132*,b	138
	Potassium (3.5-4.4 mM)	4.1	3.8	4.8*,a
	ALAT (10-45 U/l)	67*,b	62*,b	97*,b
	ASAT (15-35 U/l)	85*,b	80*,b	NA
	ALP (35-105 U/l)	407*,b	353*,b	868*,b
	Comments *Outside normal ranges. [a]Not considered clinically significant. [b]Related to patient's cancer disease (pancreatic cancer). [c]Related to patient's chronic kidney disease. NA: Not available.			
Pt	**Parameter (normal range)**	**Pre-injection**	**4 h. p.i.**	**Value (*18* days p.i.)**
2	Hemoglobin (7.3-9.5 mM)	7.8	6.8*[a]	7.2*[a,c]
	Leucocytes (3.5-8.8 10^7/l)	8.0	7.7	12.8*[a,c]
	Platelets (145-390 10^7/l)	371	NA	958*[a,c]
	CRP (<10 mg/l)	2	2	2
	eGFR (> 60 ml/min/1.73 m^2)	>90	>90	>90
	Creatinine (50-90 μM)	48*[a]	47*[a]	48*[a]
	Sodium (137-144 mM)	136*,a	138	136*,a
	Potassium (3.5-4.4 mM)	3.9	NA	4.0
	ALAT (10-45 U/l)	105*,b	80*,b	37
	ASAT (15-35 U/l)	124*,b	65*,b	69*,b
	ALP (35-105 U/l)	343*,b	287*,b	83
	Comments *Outside normal ranges. [a]Not considered clinically significant. [b]Related to patient's cancer disease (pancreatic cancer). [c]Related to sequelae from post-surgical infection. NA: Not available.			
Pt	**Parameter (normal range)**	**Pre-injection**	**4 hours p.i.**	**Follow-up (*4* days p.i.)**
3	Hemoglobin (7.3-9.5 mM)	6.0*,b	5.7*,b	6.8*,b
	Leucocytes (3.5-8.8 10^7/l)	7.4	6.2	6.7
	Platelets (145-390 10^7/l)	377	343	308
	CRP (<10 mg/l)	1	1	1
	eGFR (> 60 ml/min/1.73 m^2)	90	90	90

	Creatinine (50-90 μM)	55	55	53
	Sodium (137-144 mM)	143	142	143
	Potassium (3.5-4.4 mM)	3.8	4.2	4.1
	ALAT (10-45 U/l)	28	28	31
	ASAT (15-35 U/l)	37[*,a]	47[*,a]	37[*,a]
	ALP (35-105 U/l)	92	89	100
	Comments [*]Outside normal ranges. [a]Not considered clinically significant. [b]Patient has anemia.			
Pt	**Parameter (normal range)**	**Pre-injection**	**4 h. p.i.**	**Value (5 days p.i.)**
4	Hemoglobin (7.3-9.5 mM)	7.6	7.6	7.3
	Leucocytes (3.5-8.8 10^7/l)	11.0[*,a]	11.8[*,a]	12.3[*,a]
	Platelets (145-390 10^7/l)	374	343	309
	CRP (<10 mg/l)	7	6	66[*,a]
	eGFR (> 60 ml/min/1.73 m^2)	83	83	86
	Creatinine (50-90 μM)	61	60	55
	Sodium (137-144 mM)	137	138	135[*,a]
	Potassium (3.5-4.4 mM)	4.7[*,a]	4.4	4.1
	ALAT (10-45 U/l)	24	24	20
	ASAT (15-35 U/l)	23	24	20
	ALP (35-105 U/l)	59	59	64
	Comments [*]Outside normal ranges. [a]Not considered clinically significant.			
Pt	**Parameter (normal range)**	**Pre-injection**	**4 hours p.i.**	**Follow-up (15 days p.i.)**
5	Hemoglobin (8.3-10.5 mM)[#]	7.3[*,a]	7.4[*,a]	8.0[*,a]
	Leucocytes (3.5-8.8 10^7/l)[#]	8.9[*,a]	7.6	9.8[*,a]
	Platelets (145-390 10^7/l)	327	332	370
	CRP (<10 mg/l)	13[*,a]	15[*,a]	36[*,a]
	eGFR (> 60 ml/min/1.73 m^2)	67	69	79
	Creatinine (60-105 μM)[#]	101	99	88
	Sodium (137-144 mM)	140	140	139
	Potassium (3.5-4.4 mM)	4.2	4.4	4.3
	ALAT (10-70 U/l)[#]	25	25	20
	ASAT (15-45 U/l)[#]	28	28	NA
	ALP (35-105 U/l)	123[*,a]	126[*,a]	150[*,a]
	Comments [*]Outside normal ranges. [a]Not considered clinically significant. [#]Different normal ranges due to male gender. NA: Not available.			
Pt	**Parameter (normal range)**	**Pre-injection**	**4 hours p.i.**	**Follow-up (6 days p.i.)**
6	Hemoglobin (7.3-9.5 mM)	6.7[*,a]	7.3	7.4
	Leucocytes (3.5-8.8 10^7/l)	1.9[*,a]	2.0[*,a]	4.3
	Platelets (145-390 10^7/l)	220	222	267
	CRP (<10 mg/l)	1	2	3

	eGFR (> 60 ml/min/1.73 m^2)	74	87	>90
	Creatinine (50-90 μM)	77	67	54
	Sodium (137-144 mM)	135[*,a]	140	138
	Potassium (3.5-4.4 mM)	4.6[*,a]	4.2	4.4
	ALAT (10-45 U/l)	16	18	26
	ASAT (15-35 U/l)	25	26	32
	ALP (35-105 U/l)	54	59	60
	Comments [*]Outside normal ranges. [a]Not considered clinically significant.			
Pt	**Parameter (normal range)**	**Pre-injection**	**4 hours p.i.**	**Follow-up (11 days p.i.)**
7	Hemoglobin (7.3-9.5 mM)	8.5	8.2	8.1
	Leucocytes (3.5-8.8 10^7/l)	7.6	6.3	6.5
	Platelets (145-390 10^7/l)	354	303	311
	CRP (<10 mg/l)	2	2	3
	eGFR (> 60 ml/min/1.73 m^2)	70	87	71
	Creatinine (50-90 μM)	82	74	81
	Sodium (137-144 mM)	136[*,a]	134[*,a]	131[*,a]
	Potassium (3.5-4.4 mM)	4.0	3.7	3.9
	ALAT (10-45 U/l)	22	18	22
	ASAT (15-35 U/l)	32	29	33
	ALP (35-105 U/l)	51	49	47
	Comments [*]Outside normal ranges. [a]Not considered clinically significant.			
Pt	**Parameter (normal range)**	**Pre-injection**	**4 hours p.i.**	**Follow-up (4 days p.i.)**
8	Hemoglobin (7.3-9.5 mM)	8.1	8.2	8.2
	Leucocytes (3.5-8.8 10^7/l)	4.8	5.7	5.7
	Platelets (145-390 10^7/l)	190	189	200
	CRP (<10 mg/l)	1	1	1
	eGFR (> 60 ml/min/1.73 m^2)	87	87	82
	Creatinine (50-90 μM)	67	67	70
	Sodium (137-144 mM)	137	140	142
	Potassium (3.5-4.4 mM)	3.5	3.7	4.1
	ALAT (10-45 U/l)	26	26	23
	ASAT (15-35 U/l)	25	21	23
	ALP (35-105 U/l)	71	62	68
Pt	**Parameter (normal range)**	**Pre-injection**	**4 hours p.i.**	**Follow-up (13 days p.i.)**
9	Hemoglobin (7.3-9.5 mM)	6.0[*,a]	6.2[*,a]	7.3
	Leucocytes (3.5-8.8 10^7/l)	4.5	5.5	5.1
	Platelets (145-390 10^7/l)	174	195	259
	CRP (<10 mg/l)	1	1	NA

	eGFR (> 60 ml/min/1.73 m^2)	72	75	77
	Creatinine (50-90 μM)	86	83	81
	Sodium (137-144 mM)	141	143	136[*,a]
	Potassium (3.5-4.4 mM)	3.8	3.4[*,a]	4.1
	ALAT (10-45 U/l)	13	15	NA
	ASAT (15-35 U/l)	19	18	NA
	ALP (35-105 U/l)	39	42	NA
	Comments [*]Outside normal ranges. [a]Not considered clinically significant. NA: Not available.			
Pt	**Parameter (normal range)**	**Pre-injection**	**4 hours p.i.**	**Follow-up (4 days p.i.)**
10	Hemoglobin (7.3-9.5 mM)	9.0	9.0	9.3
	Leucocytes (3.5-8.8 10^7/l)	7.6	7.3	6.3
	Platelets (145-390 10^7/l)	246	251	239
	CRP (<10 mg/l)	1	1	1
	eGFR (> 60 ml/min/1.73 m^2)	57[*,a]	49[*,a]	58[*,a]
	Creatinine (50-90 μM)	87	98[*,a]	86
	Sodium (137-144 mM)	140	144	141
	Potassium (3.5-4.4 mM)	4.3	3.9	4.2
	ALAT (10-45 U/l)	22	21	24
	ASAT (15-35 U/l)	24	21	23
	ALP (35-105 U/l)	49	49	48
	Comments [*]Outside normal ranges. [a]Not considered clinically significant.			

Safety blood samples measuring hematologic parameters (hemoglobin, leucocytes, platelets), liver parameters (ALAT: alanine amino transferase, ASAT: aspartate transaminase, ALP: alkaline phosphatase), and renal function (creatinine, GFR: glomerular filtration rate, sodium, potassium), and c-reactive protein (CRP) prior to injection, 1 hour after injection and 3-21 days post injection (p.i.)