Phase 1 Trial of Intrapleural LTI-01; Single Chain Urokinase in Complicated Parapneumonic Effusions or Empyema

Supplement

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Group	LTI-01 50,000 IU n=3	LTI-01 100,000 IU n=3	LTI-01 200,000 n=3	LTI-01 400,000 IU n=3	LTI-01 800,000 IU n=2
Color/ Purulence	Cloudy	Brown, Purulent	Cloudy	Turbid	No comment
	Blood Stained	Yellow	Purulent	Blood Stained	Turbid
	Turbid	Straw colored	Pus	Blood Stained	-
pH	7.35*	-	6.84	6.91	7.00
	7.2	7.16	6.68	6.76	7.07
	7.2	7.2	-	6.5	-
Culture	N.G.	*Strep. constellatus*	N.G.	*E.coli, Klebsiella pneumoniae*	N.G.
	N.G.	N.G.	*Strep intermedius*	*Provitella melaninogenicus, Strep. Oralis, Moraxella catatthalis, Eikenella coorodens*	N.G.
	N.G.	N.G.	- (Clotted)	N.G.	-
Antibiotic Coverage (Start Day, End Day)	Azithromycin (-7, 1) Amoxicillin (-7, 2) Ceftriaxone (2, 5) Clindamycin (5, 12)	Amoxicillin (-2, 5) Benzylpenicillin (5, 22) Amoxycillin (22, 51)	Azithromycin (-4, 1) Amoxicillin (-4, 2) Piperacillin/tazobactam (2, 16)	Cefuroxime (-8, -5) Metronidazole (-8, -5) Gentamicin (-7, -6) Meropenem (-5, -1) Ciprofloxacin -1, 37) Meropenem (2, 2) Ceftriaxone (2, 12) Metronidazole (8, 37)	Amoxycillin / Clavulanate (-6, -4) Ceftriaxone (-4, 7) Ciprofloxacin (7, 22)
	Ceftriaxone (-14, -6) Metronidazole (-12, -8) Amoxycillin / Clavulanate (-5, -2) Piperacillin/tazobactam (-1, 7) Clindamycin (7, 17)	Amoxycillin / Clavulanate (-3, -3) Amoxycillin (-3, -1) Roxithromycin (-3, -1) Amoxycillin / Clavulanate (-1, 6) Amoxycillin (6, 35) Amoxycillin / clavulanate (6, 35)	Amoxycillin / Clavulanate (-2, -2) Azithromycin (-2, 2) Amoxycillin (-2, 13) Azithromycin (4, 4) Amoxycillin / Clavulanate (14, 42)	Ceftriaxone (-23, 69) Metronidazole 7, 39)	Amoxycillin / clavulanate (-2, 4) Amoxycillin / clavulanate (4, ongoing)
	Doxycycline (-4, -2) Piperacillin/tazobactam (-2,5) Clindamycin (5, 25)	Azithromycin (-5, -2) Piperacillin/tazobactam (-5, -2) Clindamycin (-1, 6) Piperacillin/tazobactam (6, 10)	Doxycycline (-11, -3) Ceftrixone (-10, -6) Ceftazidine (-4, -2) Clindamycin (-4, 49)	Ceftriaxone (-10, -8) Doxycycline (-10, -7)	

Table 1. Pleural Fluid Characteristics, Cultures and Antibiotic Use.

Group	LTI-01 50,000 IU n=3	LTI-01 100,000 IU n=3	LTI-01 200,000 n=3	LTI-01 400,000 IU n=3	LTI-01 800,000 IU n=2
Color/ Purulence	Cloudy	Brown, Purulent	Cloudy	Turbid	No comment
	Blood Stained	Yellow	Purulent	Blood Stained	Turbid
	Turbid	Straw colored	Pus	Blood Stained	-
pH	7.35*	-	6.84	6.91	7.00
	7.2	7.16	6.68	6.76	7.07
	7.2	7.2	-	6.5	-
Culture	N.G.	*Strep. constellatus*	N.G.	*E.coli, Klebsiella pneumoniae*	N.G.
	N.G.	N.G.	*Strep intermedius*	*Provitella melaninogenicus, Strep. Oralis, Moraxella catatthalis, Eikenella coorodens*	N.G.
	N.G.	N.G.	- (Clotted)	N.G.	-
Antibiotic Coverage (Start Day, End Day)	Azithromycin (-7, 1) Amoxicillin (-7, 2) Ceftriaxone (2, 5) Clindamycin (5, 12)	Amoxicillin (-2, 5) Benzylpenicillin (5, 22) Amoxycillin (22, 51)	Azithromycin (-4, 1) Amoxicillin (-4, 2) Piperacillin/tazobactam (2, 16)	Cefuroxime (-8, -5) Metronidazole (-8, -5) Gentamicin (-7, -6) Meropenem (-5, -1) Ciprofloxacin -1, 37) Meropenem (2, 2) Ceftriaxone (2, 12) Metronidazole (8, 37)	Amoxycillin / Clavulanate (-6, -4) Ceftriaxone (-4, 7) Ciprofloxacin (7, 22)
	Ceftriaxone (-14, -6) Metronidazole (-12, -8) Amoxycillin / Clavulanate (-5, -2) Piperacillin/tazobactam (-1, 7) Clindamycin (7, 17)	Amoxycillin / Clavulanate (-3, -3) Amoxycillin (-3, -1) Roxithromycin (-3, -1) Amoxycillin / Clavulanate (-1, 6) Amoxycillin (6, 35) Amoxycillin / clavulanate (6, 35)	Amoxycillin / Clavulanate (-2, -2) Azithromycin (-2, 2) Amoxycillin (-2, 13) Azithromycin (4, 4) Amoxycillin / Clavulanate (14, 42)	Ceftriaxone (-23, 69) Metronidazole 7, 39)	Amoxycillin / clavulanate (-2, 4) Amoxycillin / clavulanate (4, ongoing)
	Doxycycline (-4, -2) Piperacillin/tazobactam (-2,5) Clindamycin (5, 25)	Azithromycin (-5, -2) Piperacillin/tazobactam (-5, -2) Clindamycin (-1, 6) Piperacillin/tazobactam (6, 10)	Doxycycline (-11, -3) Ceftrixone (-10, -6) Ceftazidine (-4, -2) Clindamycin (-4, 49)	Ceftriaxone (-10, -8) Doxycycline (-10, -7)	

		Clindamycin (10, 35)		Amoxycillin / Clavulanate (-7, -6) Pipercillin/ Tazobactam (-7, 4) Clindamycin (4, 37)	

Legend: Start day and end day for antibiotic use refer to Study Day (first day of LTI-01 administration was Study Day 1). Minus signs indicate antibiotic use prior to day 1. Brackets indicate initiation and final day of administration of the indicated antibiotic agent. If an antibiotic is listed twice for the same subject the dose or route of administration was changed. N.G.: No growth on aerobic or anaerobic PF cultures. * The subject had a PF pH of exactly 7.2 at screening. The subject was enrolled into the study as all other entry criteria were met and no additional safety risk of enrollment was foreseen. The patient entered the study under a protocol exception waiver.

Table 2: Study Schedule

STUDY DAY►	SCREEN Day -1	Day 1-2			Day 2-3			Day 3-4			Days 4-7	Days 7-28 or Hospital Discharge
		Within 3 h pre-dose	Hours post-dose		Within 3 h pre-dose	Hours post-dose		Within 3 h pre-dose	Hours post-dose			
EVENT▼			3	23		3	23		3	23		
Informed Consent	X											
Medical/medication History	X											
Inclusion/Exclusion Criteria	X											
Confirmation of Eligibility	X	X[2]										
Demographics (incl. height and weight)	X											
Physical Examination	X									X		
Vital Signs (pre-dose and 3, 6, 12, 18 hours post-dose)	X	X	X	X[6]		X	X[6]		X	X	X*	
Serum Pregnancy Test (WOCBP)	X											
Chest X-ray	X									X		
Chest CT (preferably high resolution)	X									X		
Chest Ultrasonography	X			X			X			X		
Tube thoracostomy under CT guidance and initiation of antibiotics	X											
Review of Blood and PF Screening	X[5]	X										
Dosing		X			X[3]			X[3]				
Clamp Chest Tube[i]		X			X			X				
Blood sample for hematology (local) [1]	X	X	X	X[6]		X	X[6]		X	X	X*	
Blood sample for central lab[1]		X	X	X[6]		X	X[6]		X	X		
Blood sample for ADA[11]		X										X
Blood chemistries	X	X		X[6]			X[6]			X	X*	
CRP (blood)		X		X[6]			X[6]			X	X*	X*
PF collected[4] (half of sample for central lab)		X	X	X		X	X		X	X		
Assessment of PF drainage	X	X[3]		X[3]			X[3]			X		
Adverse Events (post-enrollment)		X	X	X	X	X	X	X	X	X	X[8]	
SAE (post-enrollment)	X	X	X	X	X	X	X	X	X	X	X	X[9]
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X[10]	X[10]

Legend: Study Design and Schedule of Assessments

*As available in medical record.
[1] Complete blood count with differential and platelets, coagulation tests (i.e. PT/PTT, fibrinogen) done locally; half of sample processed for PK/PD at UTHSCT on days when required
[2] Reassessment of PT/PTT, fibrinogen and platelets
[3] PF drainage volume recorded daily once the subject was enrolled. PF volume from the chest tube also recorded during the period of time in between enrollment and the first dose. The total amount of pleural drainage from study entry to completion was totaled from these assessments. Second and third LTI-01 doses were not given if there was complete resolution of pleural process after the prior dose.
[4] PF cell count, hematocrit and protein performed at local lab; half of sample processed for PK/PD at UTHSCT
[5] PF assessment of purulency, Gram stain, culture, pH and volume; blood culture results
[6] 23 hours post-dose sample served as pre-dose sample for next dose and was performed within 3 hours pre-dose
[8] Grade 3 and 4 AEs, and fever
[9] Through Day 28 or hospital discharge, whichever occurred first.
[10] Total days of antibiotics
[11] Blood sample for ADA screening at Day 28 or hospital discharge, whichever occurred first.

Table 3: Overall Summary of Adverse Events

Adverse Event Summary	**LTI-01 50,000 IU (N=3)**	**LTI-01 100,000 IU (N=3)**	**LTI-01 200,000 IU (N=3)**	**LTI-01 400,000 IU (N=3)**	**LTI-01 800,000 IU (N=2)**	**All LTI-01 (N=14)**
Number of subjects (%) Number of TEAEs						
All TEAEs	2 (66.7%) 10	2 (66.7%) 6	2 (66.7%) 5	1 (33.3%) 1	0	7 (50.0%) 22
Severe TEAEs	1 (33.3%) 2	0	0	1 (33.3%) 1	0	2 (14.3%) 3
Treatment-related TEAEs	0	0	0	0	0	0
SAEs	1 (33.3%) 1	0	0	1 (33.3%) 1	0	2 (14.3%) 2
TEAEs leading to study drug withdrawal	0	2 (66.7%) 2	1 (33.3%) 1	0	0	3 (21.4%) 3
TEAEs leading to discontinuation from study	0	0	0	0	0	0
Life threatening TEAEs	0	0	0	0	0	0
TEAEs leading to death	1 (33.3%) 1	0	0	0	0	1 (7.1%) 1

Section 1. Protocol Deviations. A total of 116 protocol deviations in all 14 subjects occurred during the study. No deviation led to exclusion of subject data from an analysis population. Two described below required a protocol waiver as did dosing of two patients at one time, waiver date March 21, 2018.

Subject 202-1001 (50,000 IU) did not meet Inclusion Criterion #3 at the time of Screening (listed as *PF with a pH ≤7.2*, but with a protocol inconsistency elsewhere requiring subjects to have a PF pH of <7.2). The subject had a PF pH of exactly 7.2 at Screening. The subject was enrolled into the study as all other entry criteria were met and no additional safety risk of enrolment was foreseen. A protocol exception waiver request form for Subject 202-1001 was obtained. Following the inclusion of the subject, a protocol clarification memo was issued to confirm the intended inclusion criterion of PF pH ≤7.2. The Inclusion criterion failure for Subject 202-1001 is not included in, owing to the protocol clarification.

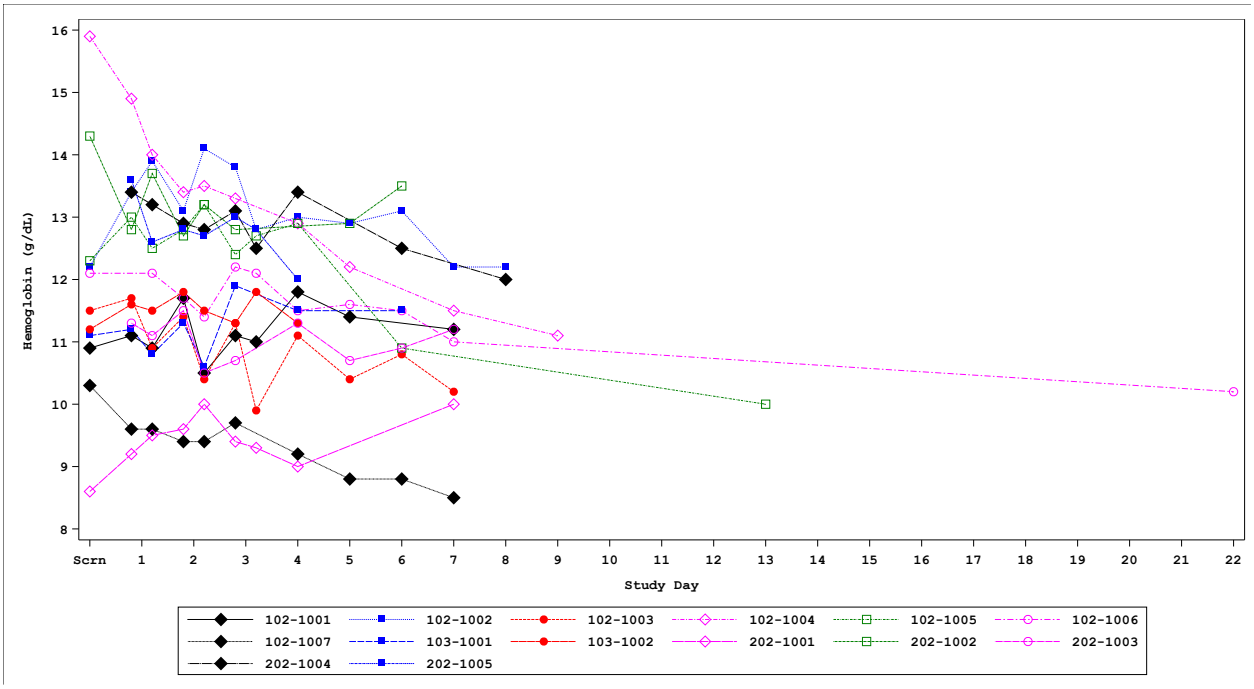
One (1) subject met Exclusion Criterion #12 (*Estimated creatinine clearance [CL_{CR}] <30 mL/minute or eGFR <30 mL/minute*) at Screening and Day 1. Creatinine and GFR measurement readings for Subject 102-1007 (800,000 IU) at Screening and Day 1 (pre-dose) were 21 and 23 ml/min. Screening and Day 1 creatinine and GFR values preceded study drug administration, were considered to be clinically significant and related to the subject's underlying medical condition.

Section 2. Individual Patient Biochemical Findings and Outcomes. We further examined the findings in the two patients who died remote to their LTI-01 IPFT. Both had relatively elevated PF levels of PAI-1 during the LTI-01 treatment period (Supplement). One; 102-1006, who received 3 doses of 400,000 IU LTI-01 IPFT, developed a right lower lobe cavity associated with ipsilateral pneumonia and CPE. This patient also had right hilar and subcarinal adenopathy causing narrowing of the bronchus intermedius and died at d86, 5 days after completion of treatment and had persistently increased PF PAI-1 in the 4 μg/ml range in post-dose PFs at days 2 and 3 despite a relative reduction of pleural density of 31 % at d4. The patient with empyema and concomitant metastatic head and neck cancer; 202-1001, received 3 doses of 50,000 IU LTI-01 IPFT and had a two order of magnitude increment of PF uPA to about 15 μg/ml 3h post-treatment on day 1, but PAI-1 levels increased to almost 4 μg/ml in PF by day 2 pre-dose concurrent with a loculated effusion failed to resolve by CXR at d4.

Of the four patients treated with follow-up tPA or tPA/DNase after LTI-01 IPFT, subject 202-1003 did not receive the third dose of 100,000 IU LTI-01 IPFT because an elevated PT. This patient developed increased white cell counts; (+12.6 x 109/L) and neutrophil counts (+13.5 x 109/L) at day 6, and was the treated with tPA/DNase between days 5 and 8. CRP levels fell between days 2 and 5 during LTI-01 IPFT and at the beginning of tPA/DNase and were unavailable at days 5-8. Interestingly, this patient's PF uPA increased with decreased PF PAI-1 during the LTI-01 treatment phase (Figure 7 A and B). Subject 202-1002 had 2 doses of 50,000 IU of LTI-01 IPFT and had after which chest ultrasound showing no additional fluid to drain so that the third dose was not administered. The CRP was falling but remained elevated at 230 mg/DL at d3, so that tPA, then tPA/DNase IPFT was given at days 4 and 5 via a newly placed chest tube into a pleural collection that was identified at that time. In this patient, uPA antigen post-dosing of LTI-01 IPFT at day 2 did not increase versus predose levels (Fig 7A) and levels of PF PAI-1 remained elevated, suggesting that delivery of the second dose of LTI-01 could have been inadequate or incomplete. In two other patients; 202-1004 and 202-1005, treated with tPA/DNase after receiving 3 doses of either 200,000 or 400,000 IU respectively, levels of PF uPA were among the highest noted 3h post LTI-01 dosing at which point PAI-1 levels were markedly decreased. In the patient receiving 200,000 IU, CRP levels were lower than in any other patient, falling during LTI-01 IPFT and white/PMN counts were falling. The treating physician chose to add tPA/DNase because of residual empyema. In the patient receiving 400,000 IU LTI-01, CRP initially fell during LTI-01 IPFT versus baseline, but rose at day 4 despite normal white and neutrophil counts and the patient received tPA/DNase to provide additional assurance that this patient would be ready to travel shortly after hospitalization.

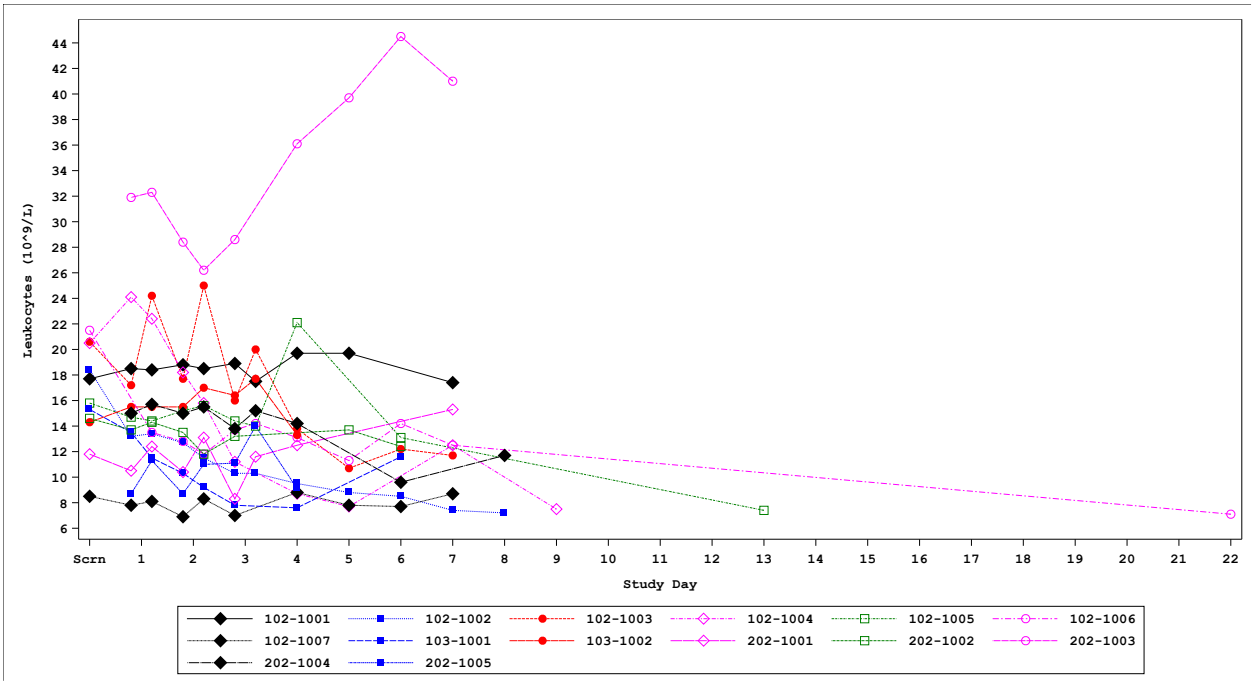
Of the four remaining subjects, two were in the 100,000 IU group, two in the 200,000 IU group. These patients all had relative reductions in pleural density of 15, 83, 71 and 37 percent, respectively with no switch to alternative IPFT or surgical intervention. Both patients in the 100,000 IU group had clear increments of PF uPA post-dosing (Figure 7A) and relatively low; <2 μg/ml; subject 102-1001 or relatively high initial; about 4 mg/ml, levels of PF PAI-1, that fell to about 2 μg/ml after LTI-01 IPFT (subject 103-1001, Figure 7B). Subject 103-1001 received only two doses of LTI-01 as the chest tube migrated and recovered without further intervention beyond customary care. In the remaining two subjects treated with 200,000 IU/ml, post-treatment (3h) PF uPA was about 100 mg/ml and PF PAI-1 fell from about 3.75 μg/ml; subject 102-1003 to about 2 μg/ml or remained within a range of about 2 μg/ml throughout the treatment period (subject 102-1004, Figure 7B). Subject 102-1004 required only two treatments of LTI-01 IPFT as the patient had a chest wall hematoma felt to be due to chest tube insertion. This patient was clinically improving. The PF was felt to be adequately drained and the patient recovered.

Figure S1: Individual Changes In Hemoglobin Over Time (All Subjects)



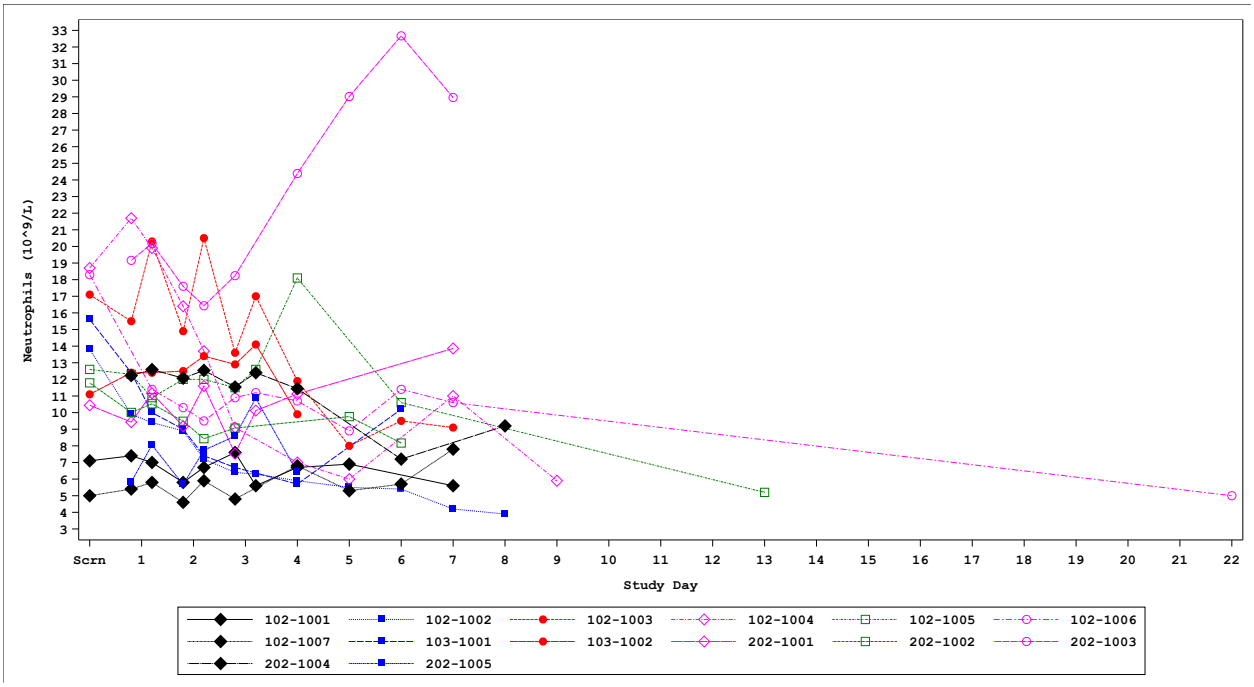
Legend. Hemoglobin determinations were all measured at the clinical laboratories of the participating sites.

Figure S2. Individual Changes in Total White Blood Cell Counts (All Patients).Legend.



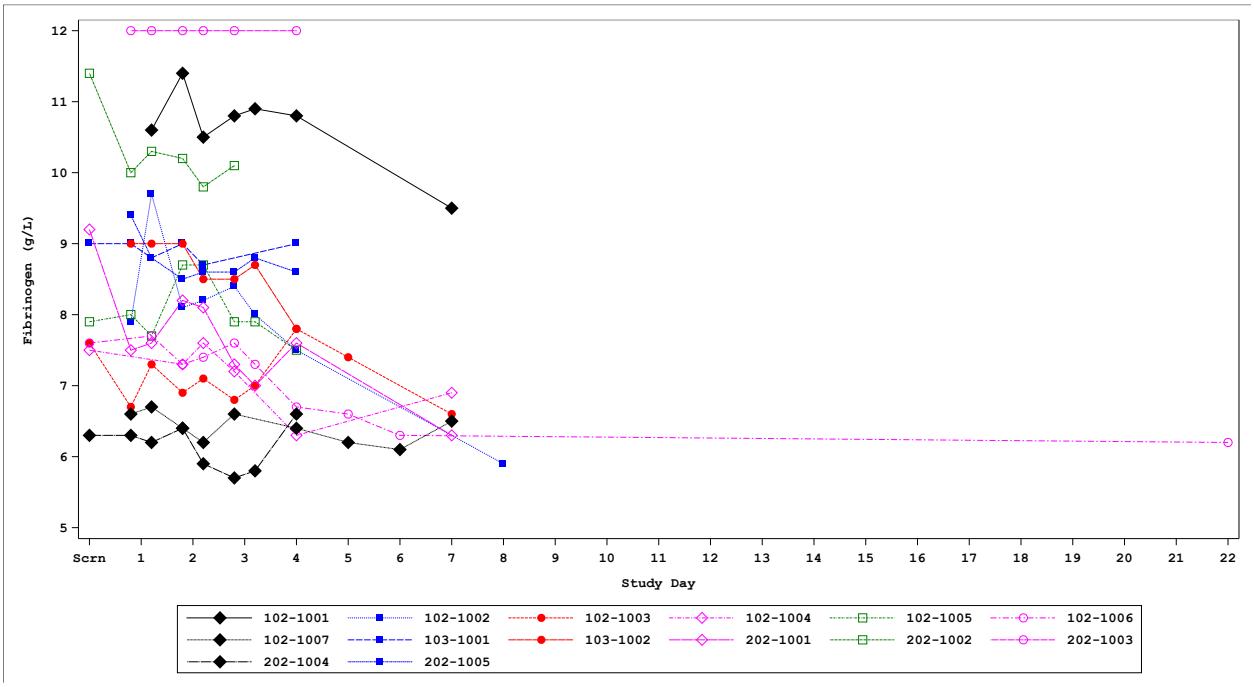
Legend. Total leuocytes were measured as partt of the complete blood cell determinations (CBCs) mesured by the paticipating clinical laboratories.

Figure S3. Individual Changes in Blood Neutrophil (All Patients).



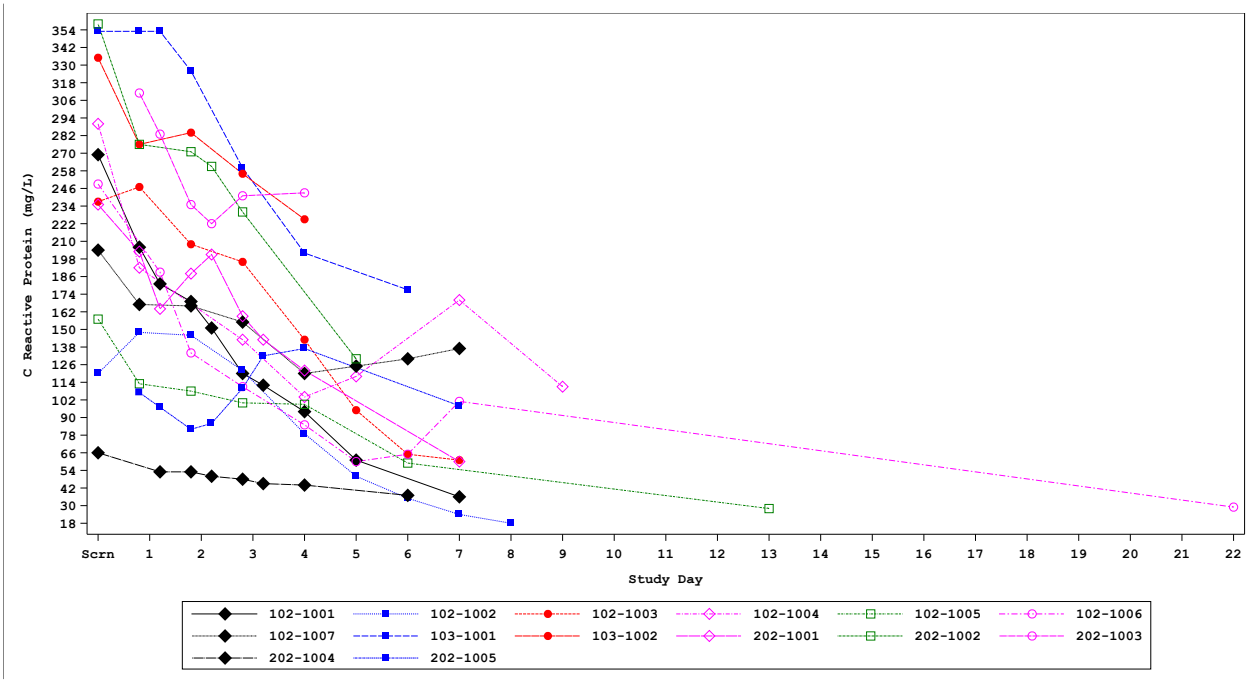
Legend. The blood neutrophil counts were determined by the clinical laboratories of the participating institutions as part of the CBC determinations at each interval.

Figure S4. Individual Changes in Plasma Fibrinogen (All Patients).



Legend. Plasma fibrinogen levels were determined by the clinical laboratories of the participating institutions.

Figure S5. Individual Changes In Plasma C-Reactive Protein (CRP, All Patients).



Legend. Plasma CRP levels were determined by the clinical laboratories of the participating institutions.

Table 4. Pharmacokinetic (PK) and Pharmacodynamic (PD in PFs) Information (All Available Samples, All Patients).

PK Listing 1 (Plasma PK)

Analyte	Matrix	Subject group	Treatment Description (units)	Subject	Day	Hour	Concentration pg/mL	Comment
Urokinase	Plasma	A	50,000	102-1001	Day1	pre	515	
Urokinase	Plasma	A	50,000	102-1001	Day1	post (3h)	452	
Urokinase	Plasma	A	50,000	102-1001	Day 2	pre	594	
Urokinase	Plasma	A	50,000	102-1001	Day 2	post (3h)	547	
Urokinase	Plasma	A	50,000	102-1001	Day 3	pre	535	
Urokinase	Plasma	A	50,000	102-1001	Day 3	post (3h)	594	
Urokinase	Plasma	A	50,000	102-1001	Day4		922	
Urokinase	Plasma	B	100,000	102-1002	Day1	pre	599	
Urokinase	Plasma	B	100,000	102-1002	Day1	post (3h)	671	
Urokinase	Plasma	B	100,000	102-1002	Day 2	pre	618	
Urokinase	Plasma	B	100,000	102-1002	Day 2	post (3h)	602	
Urokinase	Plasma	B	100,000	102-1002	Day 3	pre	674	
Urokinase	Plasma	B	100,000	102-1002	Day 3	post (3h)	579	
Urokinase	Plasma	B	100,000	102-1002	Day4		955	

Urokinase	Plasma	C	200,000	102-1003	Day1	pre	493	
Urokinase	Plasma	C	200,000	102-1003	Day1	post (3h)	517	
Urokinase	Plasma	C	200,000	102-1003	Day 2	pre	386	
Urokinase	Plasma	C	200,000	102-1003	Day 2	post (3h)	612	
Urokinase	Plasma	C	200,000	102-1003	Day 3	pre	399	
Urokinase	Plasma	C	200,000	102-1003	Day 3	post (3h)	465	
Urokinase	Plasma	C	200,000	102-1003	Day4		518	
Urokinase	Plasma	C	200,000	102-1004	Day1	pre	422	
Urokinase	Plasma	C	200,000	102-1004	Day1	post (3h)	321	
Urokinase	Plasma	C	200,000	102-1004	Day 2	pre	366	
Urokinase	Plasma	C	200,000	102-1004	Day 2	post (3h)	376	
Urokinase	Plasma	C	200,000	102-1004	Day 3	pre	434	
Urokinase	Plasma	C	200,000	102-1004	Day 3	post (3h)		No Sample
Urokinase	Plasma	C	200,000	102-1004	Day4		666	
Urokinase	Plasma	D	400,000	102-1005	Day1	pre	475	
Urokinase	Plasma	D	400,000	102-1005	Day1	post (3h)	391	
Urokinase	Plasma	D	400,000	102-1005	Day 2	pre	450	
Urokinase	Plasma	D	400,000	102-1005	Day 2	post (3h)	544	

Urokinase	Plasma	D	400,000	102-1005	Day 3	pre	467	
Urokinase	Plasma	D	400,000	102-1005	Day 3	post (3h)	577	
Urokinase	Plasma	D	400,000	102-1005	Day4		834	
Urokinase	Plasma	D	400,000	102-1006	Day1	pre	730	
Urokinase	Plasma	D	400,000	102-1006	Day1	post (3h)	782	
Urokinase	Plasma	D	400,000	102-1006	Day 2	pre	754	
Urokinase	Plasma	D	400,000	102-1006	Day 2	post (3h)	829	
Urokinase	Plasma	D	400,000	102-1006	Day 3	pre	762	
Urokinase	Plasma	D	400,000	102-1006	Day 3	post (3h)	909	
Urokinase	Plasma	D	400,000	102-1006	Day4		1152	
Urokinase	Plasma	E	800,000	102-1007	Day1	pre	743	
Urokinase	Plasma	E	800,000	102-1007	Day1	post (3h)	1446	
Urokinase	Plasma	E	800,000	102-1007	Day 2	pre	785	
Urokinase	Plasma	E	800,000	102-1007	Day 2	post (3h)	1085	
Urokinase	Plasma	E	800,000	102-1007	Day 3	pre	788	
Urokinase	Plasma	E	800,000	102-1007	Day 3	post (3h)		No Sample
Urokinase	Plasma	E	800,000	102-1007	Day4		1069	
Urokinase	Plasma	A	50,000	202-1001	Day1	pre	732	

Urokinase	Plasma	A	50,000	202-1001	Day1	post (3h)	561	
Urokinase	Plasma	A	50,000	202-1001	Day 2	pre	563	
Urokinase	Plasma	A	50,000	202-1001	Day 2	post (3h)	677	
Urokinase	Plasma	A	50,000	202-1001	Day 3	pre	741	Repeated
Urokinase	Plasma	A	50,000	202-1001	Day 3	post (3h)	770	
Urokinase	Plasma	A	50,000	202-1001	Day4		632	
Urokinase	Plasma	A	50,000	202-1002	Day1	pre	457	Repeated
Urokinase	Plasma	A	50,000	202-1002	Day1	post (3h)	517	Repeated
Urokinase	Plasma	A	50,000	202-1002	Day 2	pre	432	Repeated
Urokinase	Plasma	A	50,000	202-1002	Day 2	post (3h)	513	Repeated
Urokinase	Plasma	A	50,000	202-1002	Day 3	pre	539	Repeated
Urokinase	Plasma	A	50,000	202-1002	Day 3	post (3h)		No Sample
Urokinase	Plasma	A	50,000	202-1002	Day4			No Sample
Urokinase	Plasma	B	100,000	202-1003	Day1	pre	1822	
Urokinase	Plasma	B	100,000	202-1003	Day1	post (3h)	2141	
Urokinase	Plasma	B	100,000	202-1003	Day 2	pre	1786	
Urokinase	Plasma	B	100,000	202-1003	Day 2	post (3h)	1998	
Urokinase	Plasma	B	100,000	202-1003	Day 3	pre	2199	

Urokinase	Plasma	B	100,000	202-1003	Day 3	post (3h)		No Sample
Urokinase	Plasma	B	100,000	202-1003	Day 4			No Sample
Urokinase	Plasma	C	200,000	202-1004	Day1	Pre	621	Repeated
Urokinase	Plasma	C	200,000	202-1004	Day1	Post (3h)	640	Repeated
Urokinase	Plasma	C	200,000	202-1004	Day2	Pre	657	Repeated
Urokinase	Plasma	C	200,000	202-1004	Day2	Post (3h)	664	Repeated
Urokinase	Plasma	C	200,000	202-1004	Day3	Pre	592	Repeated
Urokinase	Plasma	C	200,000	202-1004	Day3	Post (3h)	631	
Urokinase	Plasma	C	200,000	202-1004	Day4		580	Repeated
Urokinase	Plasma	D	400,000	202-1005	Day1	pre	562	Repeated
Urokinase	Plasma	D	400,000	202-1005	Day1	post (3h)	572	
Urokinase	Plasma	D	400,000	202-1005	Day 2	pre	504	
Urokinase	Plasma	D	400,000	202-1005	Day 2	post (3h)	604	Repeated
Urokinase	Plasma	D	400,000	202-1005	Day 3	pre	796	Repeated
Urokinase	Plasma	D	400,000	202-1005	Day 3	post (3h)	686	
Urokinase	Plasma	D	400,000	202-1005	Day 4		559	Repeated
Urokinase	Plasma	B	100,000	103-1001	Day1	pre	434	Repeated
Urokinase	Plasma	B	100,000	103-1001	Day1	post (3h)	390	Repeated

Urokinase	Plasma	B	100,000	103-1001	Day 2	pre	414	Repeated
Urokinase	Plasma	B	100,000	103-1001	Day 2	post (3h)	404	Repeated
Urokinase	Plasma	B	100,000	103-1001	Day 3	pre	532	Repeated
Urokinase	Plasma	B	100,000	103-1001	Day 3	post (3h)		No Sample
Urokinase	Plasma	B	100,000	103-1001	Day4		493	Repeated
Urokinase	Plasma	E	800,000	103-1002	Day1	pre	554	
Urokinase	Plasma	E	800,000	103-1002	Day1	post (3h)	554	
Urokinase	Plasma	E	800,000	103-1002	Day 2	pre	240	
Urokinase	Plasma	E	800,000	103-1002	Day 2	post (3h)	599	
Urokinase	Plasma	E	800,000	103-1002	Day 3	pre	605	
Urokinase	Plasma	E	800,000	103-1002	Day 3	post (3h)	637	
Urokinase	Plasma	E	800,000	103-1002	Day4		507	

PK Listing (PF PK)

Analyte	Matrix	Subject Group	LTI-03 Dose	Subject ID	Day	Hour	Concentration (pg/ml)	Comment
Urokinase	Pleural Fluid	A	50,000	102-1001	Day1	pre	1015	
Urokinase	Pleural Fluid	A	50,000	102-1001	Day1	post (3h)	744741	
Urokinase	Pleural Fluid	A	50,000	102-1001	Day 2	pre	1002	

Urokinase	Pleural Fluid	A	50,000	102-1001	Day 2	post (3h)	191217	
Urokinase	Pleural Fluid	A	50,000	102-1001	Day 3	pre		No sample
Urokinase	Pleural Fluid	A	50,000	102-1001	Day 3	post (3h)	154610	
Urokinase	Pleural Fluid	A	50,000	102-1001	Day4		2156	
Urokinase	Pleural Fluid	B	100,000	102-1002	Day1	pre	21168	
Urokinase	Pleural Fluid	B	100,000	102-1002	Day1	post (3h)	1150617	
Urokinase	Pleural Fluid	B	100,000	102-1002	Day 2	pre	27144	
Urokinase	Pleural Fluid	B	100,000	102-1002	Day 2	post (3h)	417340	
Urokinase	Pleural Fluid	B	100,000	102-1002	Day 3	pre		No sample
Urokinase	Pleural Fluid	B	100,000	102-1002	Day 3	post (3h)	823621	
Urokinase	Pleural Fluid	B	100,000	102-1002	Day4			No sample
Urokinase	Pleural Fluid	C	200,000	102-1003	Day1	pre	2157	
Urokinase	Pleural Fluid	C	200,000	102-1003	Day1	post (3h)	2014684	
Urokinase	Pleural Fluid	C	200,000	102-1003	Day 2	pre		No sample
Urokinase	Pleural Fluid	C	200,000	102-1003	Day 2	post (3h)	1305630	
Urokinase	Pleural Fluid	C	200,000	102-1003	Day 4			No sample
Urokinase	Pleural Fluid	C	200,000	102-1004	Day1	pre	20159	
Urokinase	Pleural Fluid	C	200,000	102-1004	Day1	post (3h)	1606368	

Urokinase	Pleural Fluid	C	200,000	102-1004	Day 2	pre	84862	
Urokinase	Pleural Fluid	C	200,000	102-1004	Day 2	post (3h)	2302378	
Urokinase	Pleural Fluid	C	200,000	102-1004	Day 3	pre	36156	
Urokinase	Pleural Fluid	C	200,000	102-1004	Day 3	post (3h)		No sample
Urokinase	Pleural Fluid	C	200,000	102-1004	Day4		10748	
Urokinase	Pleural Fluid	D	400,000	102-1005	Day1	pre	17860	
Urokinase	Pleural Fluid	D	400,000	102-1005	Day1	post (3h)	2308244	
Urokinase	Pleural Fluid	D	400,000	102-1005	Day 2	pre		No sample
Urokinase	Pleural Fluid	D	400,000	102-1005	Day 2	post (3h)	4356460	
Urokinase	Pleural Fluid	D	400,000	102-1005	Day 3	pre		No sample
Urokinase	Pleural Fluid	D	400,000	102-1005	Day 3	post (3h)	6136156	
Urokinase	Pleural Fluid	D	400,000	102-1005	Day4			No sample
Urokinase	Pleural Fluid	D	400,000	102-1006	Day1	pre		No sample
Urokinase	Pleural Fluid	D	400,000	102-1006	Day1	post (3h)	234980	
Urokinase	Pleural Fluid	D	400,000	102-1006	Day 2	pre		No sample
Urokinase	Pleural Fluid	D	400,000	102-1006	Day 2	post (3h)	1972144	
Urokinase	Pleural Fluid	D	400,000	102-1006	Day 3	pre		No sample
Urokinase	Pleural Fluid	D	400,000	102-1006	Day 3	post (3h)	3274536	

Urokinase	Pleural Fluid	D	400,000	102-1006	Day4			No sample
Urokinase	Pleural Fluid	E	800,000	102-1007	Day1	pre		No sample
Urokinase	Pleural Fluid	E	800,000	102-1007	Day1	post (3h)	1447792	
Urokinase	Pleural Fluid	E	800,000	102-1007	Day 2	pre		No sample
Urokinase	Pleural Fluid	E	800,000	102-1007	Day 2	post (3h)	1461872	
Urokinase	Pleural Fluid	E	800,000	102-1007	Day 3	pre		No sample
Urokinase	Pleural Fluid	E	800,000	102-1007	Day 3	post (3h)		No sample
Urokinase	Pleural Fluid	E	800,000	102-1007	Day4			No sample
Urokinase	Pleural Fluid	A	50,000	202-1001	Day1	pre	5704	
Urokinase	Pleural Fluid	A	50,000	202-1001	Day1	post (3h)	283226	
Urokinase	Pleural Fluid	A	50,000	202-1001	Day 2	pre	58597	
Urokinase	Pleural Fluid	A	50,000	202-1001	Day 2	post (3h)		No sample
Urokinase	Pleural Fluid	A	50,000	202-1001	Day 3	pre		No sample
Urokinase	Pleural Fluid	A	50,000	202-1001	Day 3	post (3h)		No sample
Urokinase	Pleural Fluid	A	50,000	202-1001	Day4			No sample
Urokinase	Pleural Fluid	A	50,000	202-1002	Day1	pre	4337	
Urokinase	Pleural Fluid	A	50,000	202-1002	Day1	post (3h)	102523	
Urokinase	Pleural Fluid	A	50,000	202-1002	Day 2	pre	16131	

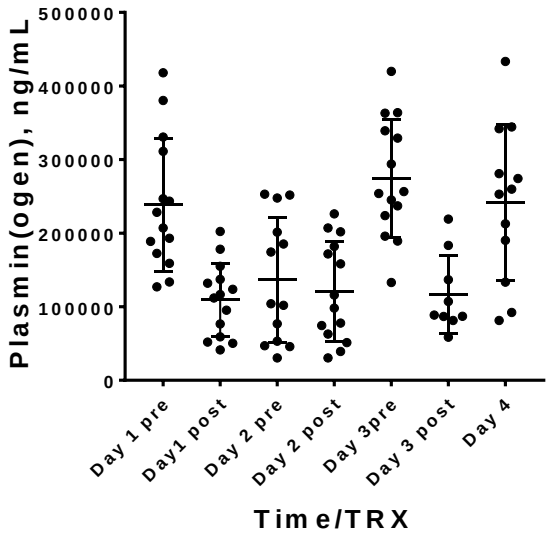
Urokinase	Pleural Fluid	A	50,000	202-1002	Day 2	post (3h)	14562	
Urokinase	Pleural Fluid	A	50,000	202-1002	Day 3	pre		No sample
Urokinase	Pleural Fluid	A	50,000	202-1002	Day 3	post (3h)		No sample
Urokinase	Pleural Fluid	A	50,000	202-1002	Day4			No sample
Urokinase	Pleural Fluid	B	100,000	202-1003	Day1	pre	1388	
Urokinase	Pleural Fluid	B	100,000	202-1003	Day1	post (3h)	588251	
Urokinase	Pleural Fluid	B	100,000	202-1003	Day 2	pre		No sample
Urokinase	Pleural Fluid	B	100,000	202-1003	Day 2	post (3h)	120641	
Urokinase	Pleural Fluid	B	100,000	202-1003	Day 3	pre		No sample
Urokinase	Pleural Fluid	B	100,000	202-1003	Day 3	post (3h)		No sample
Urokinase	Pleural Fluid	B	100,000	202-1003	Day4			No sample
Urokinase	Pleural Fluid	C	200,000	202-1004	Day1	pre	14445.36	
Urokinase	Pleural Fluid	C	200,000	202-1004	Day1	post (3h)	1047424	
Urokinase	Pleural Fluid	C	200,000	202-1004	Day 2	pre	69434	
Urokinase	Pleural Fluid	C	200,000	202-1004	Day 2	post (3h)	3245870	
Urokinase	Pleural Fluid	C	200,000	202-1004	Day 3	pre	9479	
Urokinase	Pleural Fluid	C	200,000	202-1004	Day 3	post (3h)	3616920	
Urokinase	Pleural Fluid	C	200,000	202-1004	Day 4		8438	

Urokinase	Pleural Fluid	D	400,000	202-1005	Day 1	pre	5467	
Urokinase	Pleural Fluid	D	400,000	202-1005	Day1	post (3h)	811888	
Urokinase	Pleural Fluid	D	400,000	202-1005	Day 2	pre	27335	
Urokinase	Pleural Fluid	D	400,000	202-1005	Day 2	post (3h)	2266940	
Urokinase	Pleural Fluid	D	400,000	202-1005	Day 3	pre		No sample
Urokinase	Pleural Fluid	D	400,000	202-1005	Day 3	Post (3h)	4663664	
Urokinase	Pleural Fluid	D	400,000	202-1005	Day 4		53887	
Urokinase	Pleural Fluid	B	100,000	103-1001	Day1	pre	1235.21	
Urokinase	Pleural Fluid	B	100,000	103-1001	Day1	post (3h)	475563	
Urokinase	Pleural Fluid	B	100,000	103-1001	Day 2	pre	9689	
Urokinase	Pleural Fluid	B	100,000	103-1001	Day 2	post (3h)	201680	
Urokinase	Pleural Fluid	B	100,000	103-1001	Day 3	pre		No sample
Urokinase	Pleural Fluid	B	100,000	103-1001	Day 3	post (3h)		No sample
Urokinase	Pleural Fluid	B	100,000	103-1001	Day4			No sample
Urokinase	Pleural Fluid	E	800,000	103-1002	Day1	pre	3690	
Urokinase	Pleural Fluid	E	800,000	103-1002	Day1	post (3h)	2811760	
Urokinase	Pleural Fluid	E	800,000	103-1002	Day 2	pre	13795	
Urokinase	Pleural Fluid	E	800,000	103-1002	Day 2	post (3h)	8720920	

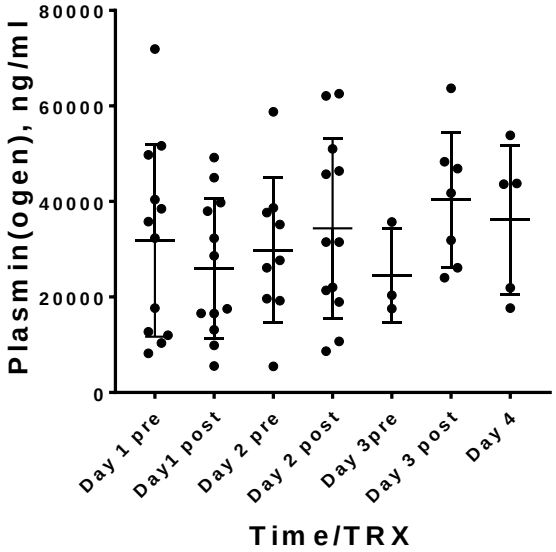
Urokinase	Pleural Fluid	E	800,000	103-1002	Day 3	pre		No sample
Urokinase	Pleural Fluid	E	800,000	103-1002	Day 3	post (3h)		No sample
Urokinase	Pleural Fluid	E	800,000	103-1002	Day4			No sample

Figure S6.

A.



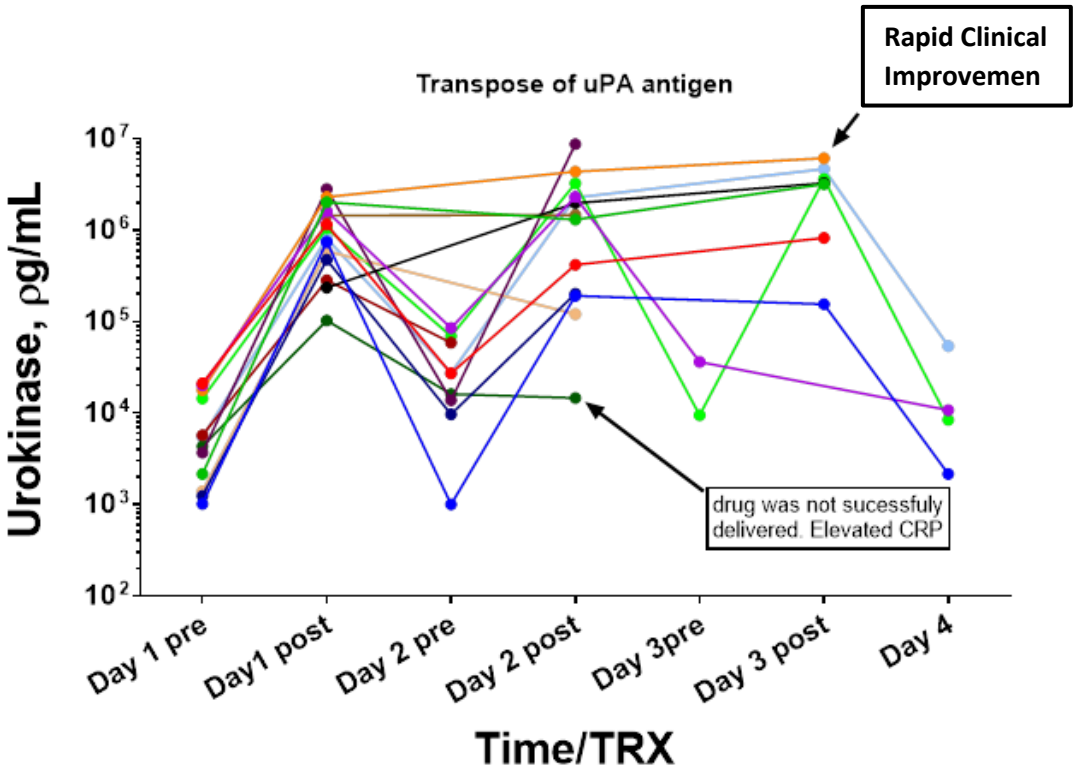
B.



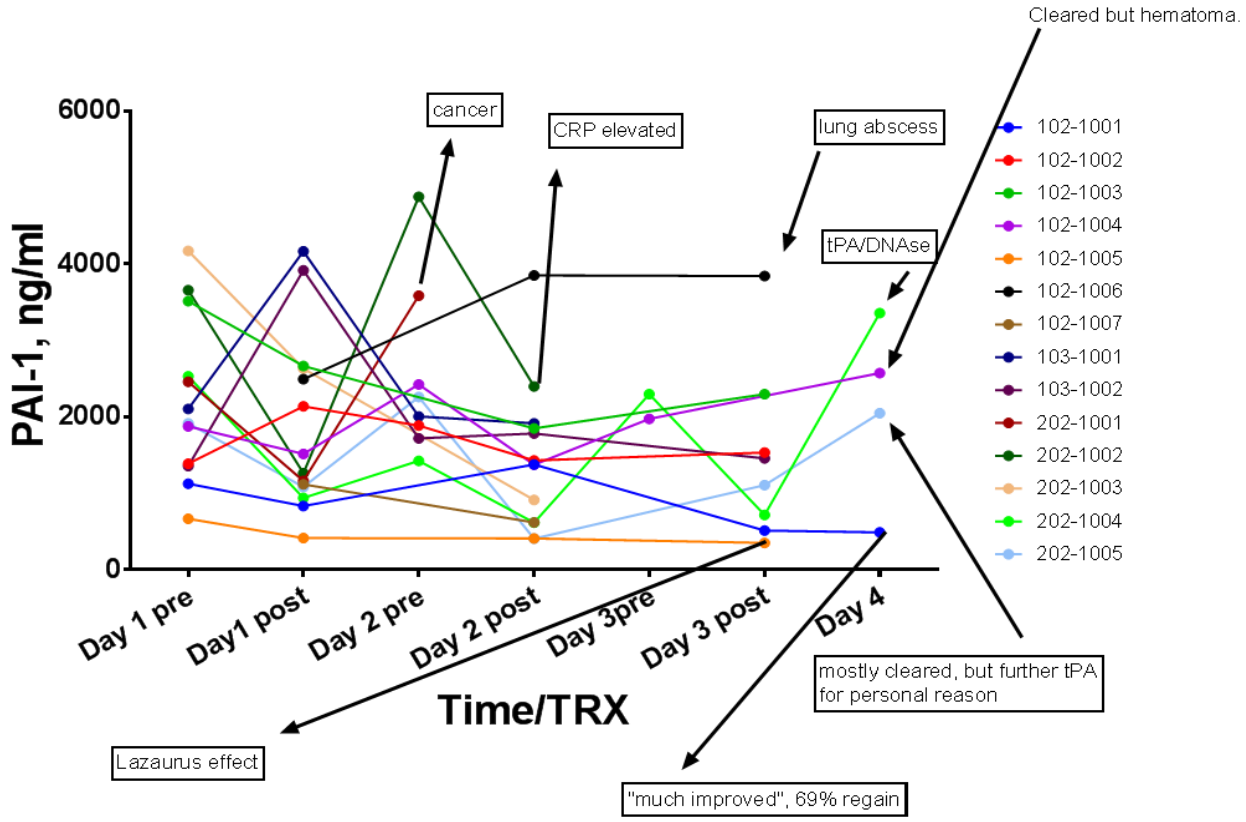
Legend. Plasma (A) and PF total plasminogen levels were measured by ELISA (R&D Systems, MN). Data are presented as dot plots with horizontal lines indicating the medians and whiskers representing interquartile range. While levels of PF plasminogen were at least there were no significant differences in the plasminogen levels in either plasma or PF at any of the tested intervals.

Figure S7. Trended PF uPA and PAI-1 values and Clinical Outcomes in Selected Patients.

A.



B.



Legend. A. PF uPA antigen concentrations plotted as line plots for all subjects (n=14). Pre-: within 3h pre-dosing of LTI-01 IPFT. Pos-t: within 3h of administration of the dose of LTI-01 IPFT. **B.** PAI-1 antigen concentrations in PF at the same intervals pre- and post-dosing of LTI-01 IPFT. Clinical Outcomes are indicated for selected patients and as described text.