Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Scully M, Cataland SR, Peyvandi F, et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. N Engl J Med 2019;380:335-46. DOI: 10.1056/NEJMoa1806311

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Supplementary Figures

Figure S1: HERCULES study design

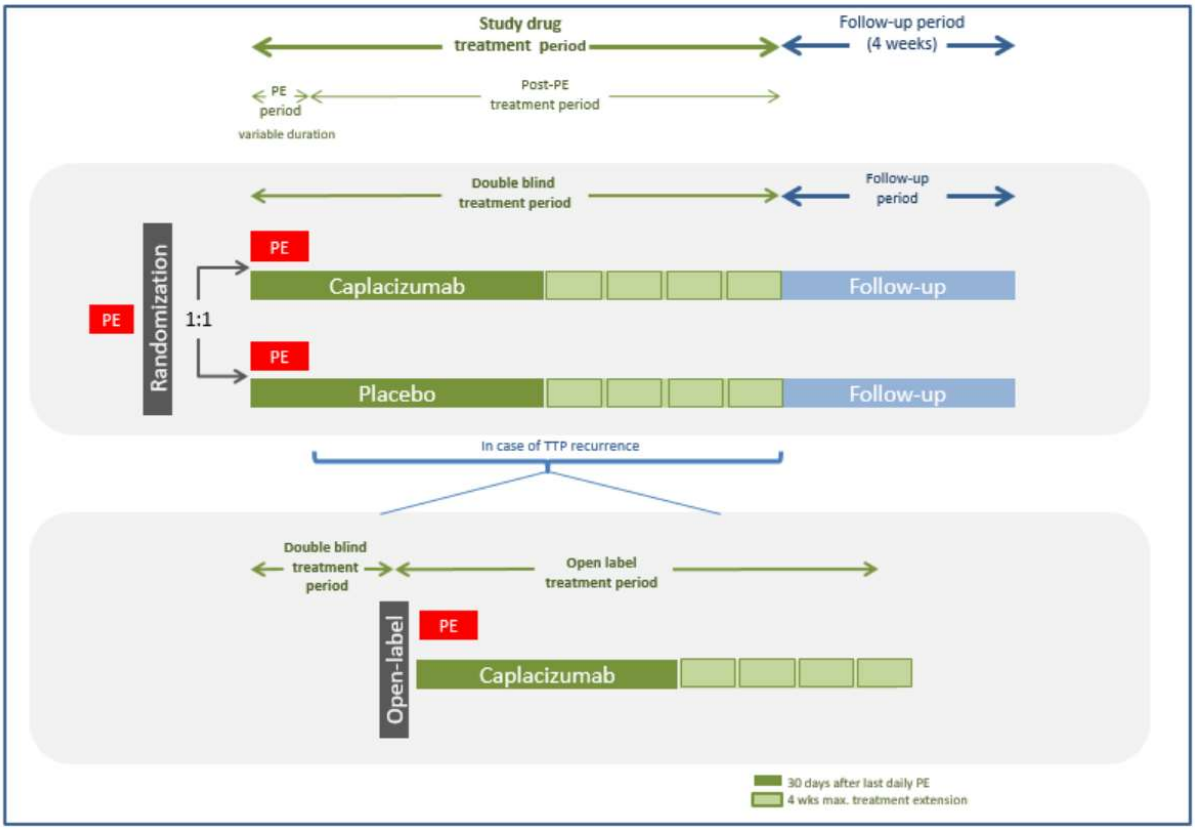
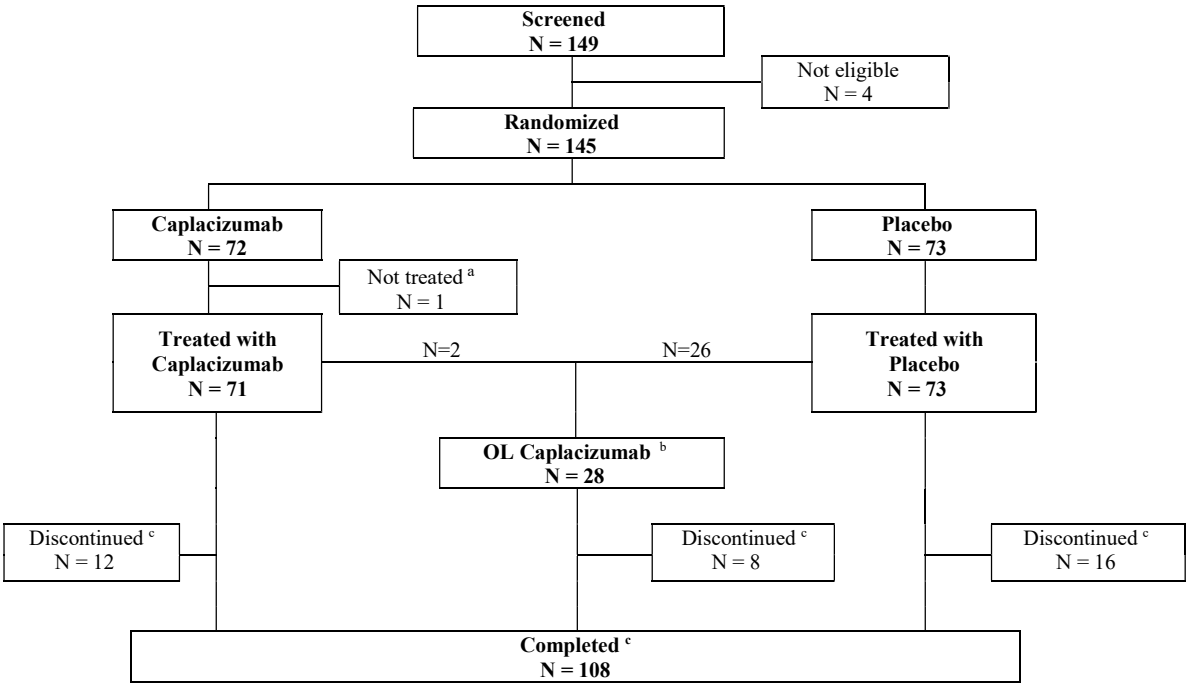


Figure S2: Patient disposition



[a]: One subject randomized to caplacizumab withdrew consent prior to first dosing.

[b] : OL = Open-Label

[c] : Of note, according to the protocol, subjects who discontinued study drug intake but were not withdrawing consent for post treatment FU, had to return for an early termination visit and the first and final FU visits. The Day 7 FU visit was attended by 121 subjects and the Day 28 FU visit by 124 subjects.

Figure S3: Graphical representation of time to platelet count normalization – 25th, 50th, 75th percentile, 95% Confidence Interval

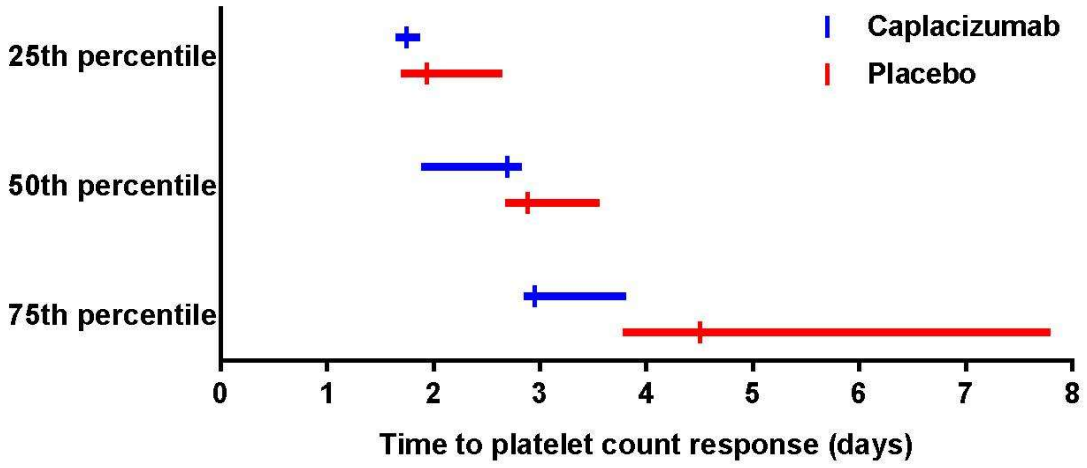
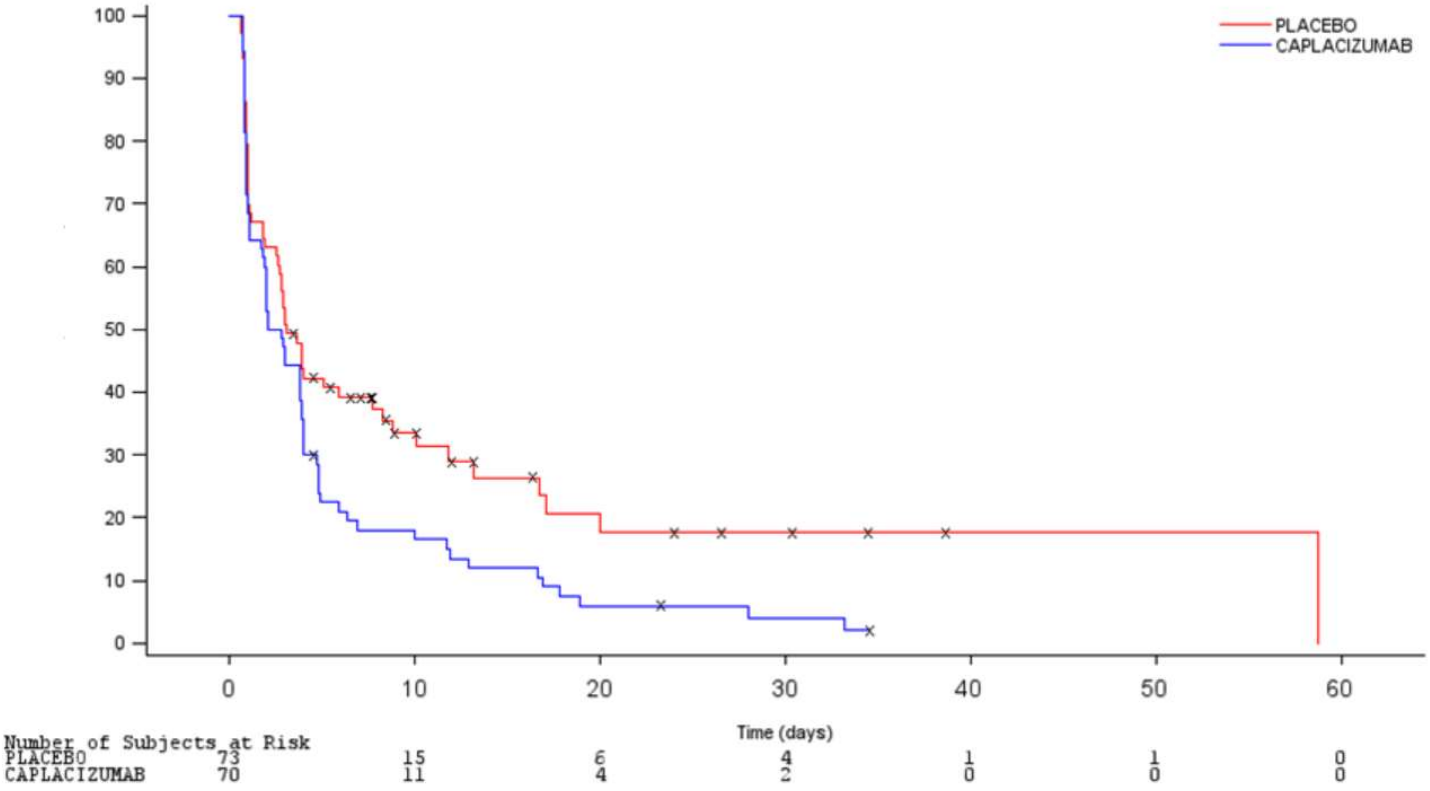
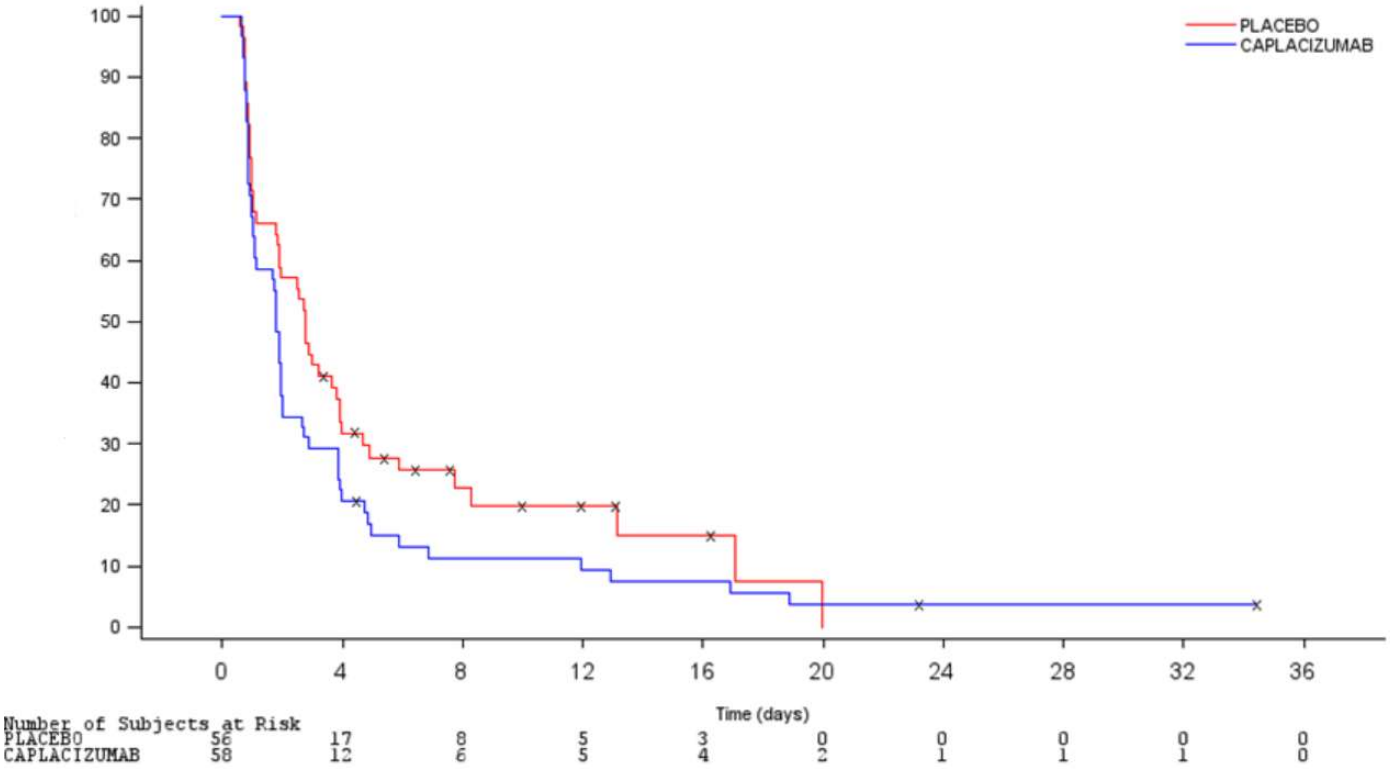


Figure S4: Time to normalization of organ damage markers LDH, cardiac Troponin I, creatinine (A), LDH (B), cardiac Troponin I (C), and creatinine (D)

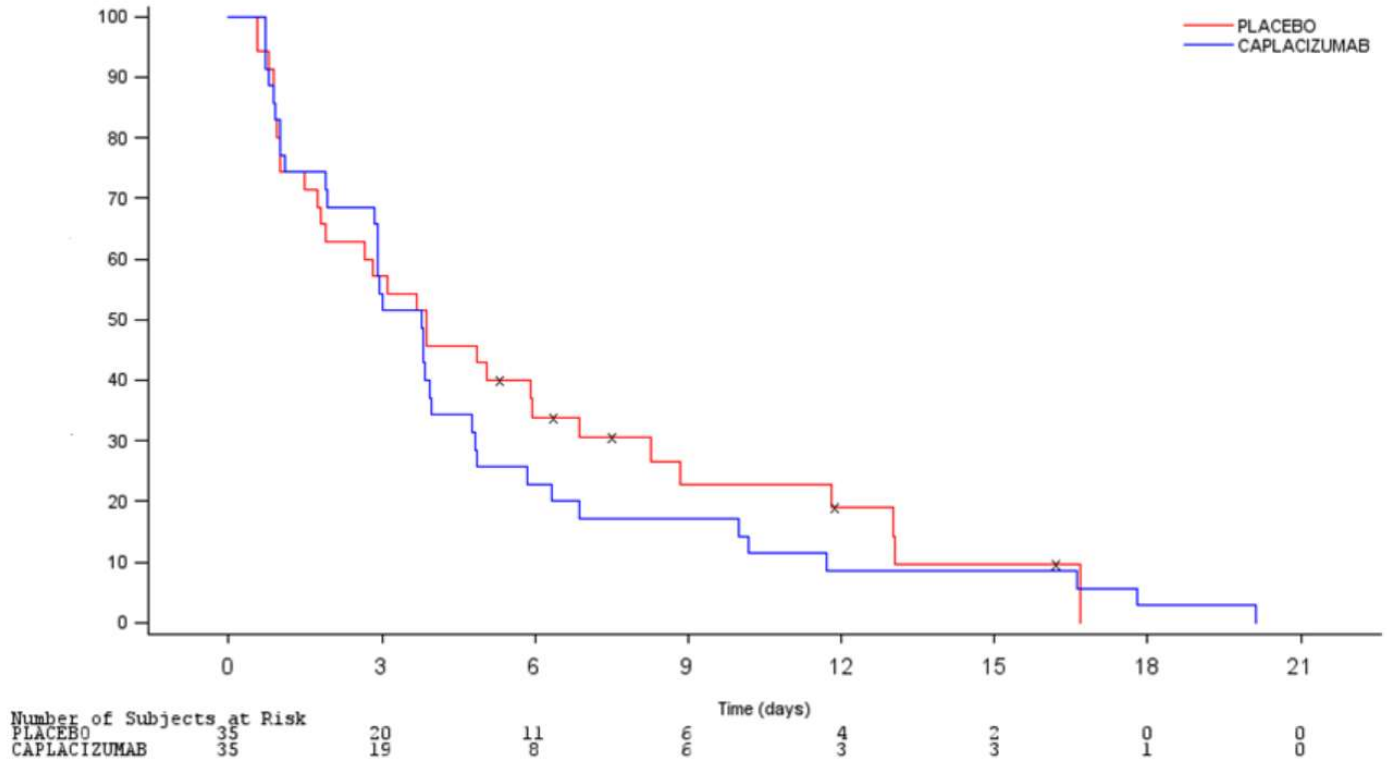
Panel A: Time to normalization of LDH, cardiac Troponin I, creatinine



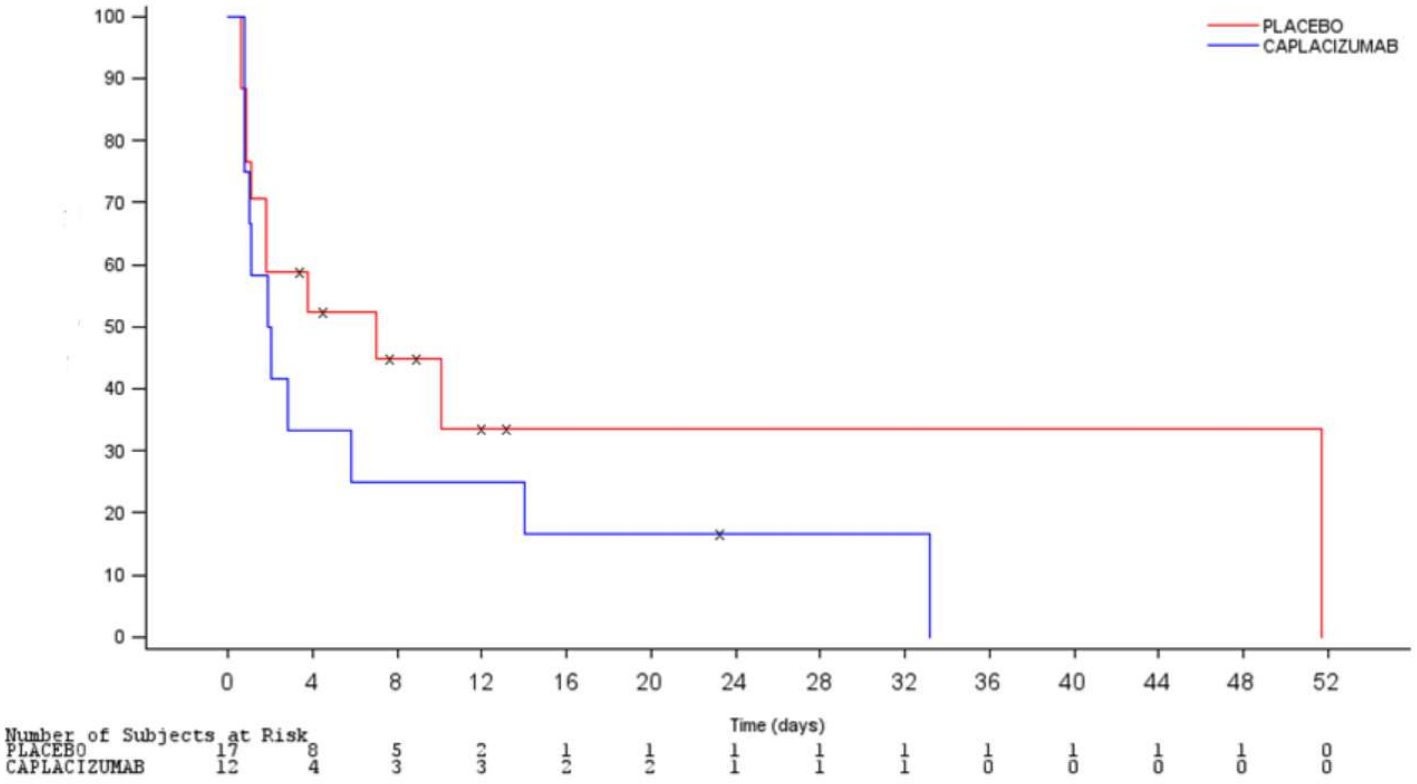
Panel B: Time to first LDH normalization



Panel C: Time to first cTnI normalization



Panel D: Time to first creatinine normalization



Supplementary Tables

Table S1: TEAEs (excluding TEAE's of TTP) reported in at least 5% of subjects in either treatment group, per treatment group during the Overall Study Period for the double-blind groups (Safety Population)

System Organ Class Preferred Term; n (%)	Double-Blind Caplacizumab (N = 71)	Double-Blind Placebo (N = 73)
At least one TEAE	**68 (95.8)**	**66 (90.3)**
General Disorders and Administration Site Conditions	**37 (52.1)**	**36 (49.3)**
Catheter site hemorrhage	5 (7.0)	5 (6.8)
Fatigue	10 (14.1)	6 (8.2)
Pyrexia	10 (14.1)	6 (8.2)
Edema peripheral	4 (5.6)	7 (9.6)
Asthenia	3 (4.2)	4 (5.5)
Chest pain	1 (1.4)	5 (6.8)
Catheter site pain	1 (1.4)	5 (6.8)
Injection site pain	1 (1.4)	4 (5.5)
Pain	4 (5.6)	1 (1.4)
Gastrointestinal Disorders	**36 (50.7)**	**27 (37.0)**
Nausea	10 (14.1)	7 (9.6)
Gingival bleeding	13 (18.3)	1 (1.4)
Constipation	7 (9.9)	5 (6.8)
Diarrhea	7 (9.9)	5 (6.8)
Abdominal pain	5 (7.0)	4 (5.5)
Vomiting	3 (4.2)	4 (5.5)
Nervous System Disorders	**32 (45.1)**	**27 (37.0)**
Headache	16 (22.5)	6 (8.2)
Dizziness	7 (9.9)	8 (11.0)
Paresthesia	8 (11.3)	6 (8.2)
Skin and Subcutaneous Tissue Disorders	**23 (32.4)**	**28 (38.4)**
Urticaria	12 (16.9)	5 (6.8)
Rash	5 (7.0)	9 (12.3)
Pruritus	5 (7.0)	6 (8.2)
Petechiae	4 (5.6)	5 (6.8)
Ecchymosis	2 (2.8)	4 (5.5)
Respiratory, Thoracic and Mediastinal Disorders	**32 (45.1)**	**14 (19.2)**
Epistaxis	23 (32.4)	2 (2.7)
Dyspnea	7 (9.9)	2 (2.7)
Blood and Lymphatic System Disorders	**6 (8.5)**	**8 (11.0)**
Anemia	4 (5.6)	6 (8.2)
Infections and infestations	**25 (35.2)**	**16 (21.9)**
Urinary tract infection	4 (5.6)	4 (5.5)
Viral upper respiratory tract infection	4 (5.6)	0
Musculoskeletal and Connective Tissue Disorders	**20 (28.2)**	**20 (27.4)**
Pain in extremity	4 (5.6)	6 (8.2)
Arthralgia	4 (5.6)	3 (4.1)
Back pain	5 (7.0)	3 (4.1)
Muscular weakness	4 (5.6)	2 (2.7)
Metabolism and Nutrition Disorders	**15 (21.1)**	**26 (35.6)**
Hypokalemia	6 (8.5)	14 (19.2)
Hyperglycemia	4 (5.6)	4 (5.5)
Hypocalcemia	1 (1.4)	5 (6.8)
Psychiatric Disorders	**16 (22.5)**	**22 (30.1)**
Insomnia	6 (8.5)	8 (11.0)
Anxiety	4 (5.6)	6 (8.2)
Agitation	5 (7.0)	4 (5.5)
Injury, Poisoning and Procedural Complications	**11 (15.5)**	**18 (24.7)**
Contusion	5 (7.0)	10 (13.7)
Vascular Disorders	**15 (21.1)**	**14 (19.2)**
Hypertension	4 (5.6)	8 (11.0)
Hypotension	4 (5.6)	2 (2.7)
Cardiac Disorders	**16 (22.5)**	**14 (19.2)**
Sinus tachycardia	4 (5.6)	3 (4.1)
Tachycardia	2 (2.8)	4 (5.5)
Investigations	**10 (14.1)**	**12 (16.4)**
Renal and Urinary Disorders	**8 (11.3)**	**11 (15.1)**
Hematuria	5 (7.0)	2 (2.7)
Reproductive System and Breast Disorders	**12 (16.9)**	**4 (5.5)**
Vaginal Hemorrhage	4 (5.6)	2 (2.7)

System Organ Class Preferred Term; n (%)	Double-Blind Caplacizumab (N = 71)	Double-Blind Placebo (N = 73)
Eye Disorders	**8 (11.3)**	**7 (9.6)**
Vision blurred	5 (6.8)	5 (7.0)

Abbreviations: N = total number of subjects in treatment group; n = number of subjects with events; TEAE = treatment-emergent adverse event
Note: Percentage was calculated using the number of subjects in the Safety Population as the denominator.

Table S2: Treatment-emergent SAEs (excluding SAEs of TTP) per treatment group during the Overall Study Period (Safety Population)

System Organ Class Preferred Term; n (%)	Double-Blind Caplacizumab (N = 71)	Double-Blind Placebo (N = 73)
At least one SAE	**23 (32.4)**	**12 (16.4)**
Blood and Lymphatic System Disorders	**0**	**1 (1.4)**
Thrombotic microangiopathy	0	1 (1.4)
Gastrointestinal Disorders	**5 (7.0)**	**1 (1.4)**
Gingival bleeding	1 (1.4)	0
Upper gastrointestinal hemorrhage	1 (1.4)	0
Colitis	1 (1.4)	0
Gastric ulcer hemorrhage	1 (1.4)	0
Gastrointestinal necrosis	0	1 (1.4)
Hematemesis	1 (1.4)	0
Intestinal ischemia	0	1 (1.4)
Intestinal perforation	0	1 (1.4)
Small intestinal obstruction	0	1 (1.4)
Respiratory, Thoracic and Mediastinal Disorders	**5 (7.0)**	**2 (2.7)**
Epistaxis	4 (5.6)	0
Hypoxia	0	1 (1.4)
Respiratory failure	0	1 (1.4)
Pulmonary embolism	1 (1.4)	0
Cardiac Disorders	**4 (5.6)**	**1 (1.4)**
Myocardial infarction	1 (1.4)	1 (1.4)
Arteriospasm coronary	1 (1.4)	0
Cardiac tamponade	1 (1.4)	0
Cardiogenic shock	1 (1.4)	0
Ventricular fibrillation	1 (1.4)	0
Nervous System Disorders	**4 (5.6)**	**2 (2.7)**
Headache	2 (2.8)	0
Cerebral ischaemia	1 (1.4)	0
Encephalopathy	1 (1.4)	0
Hemorrhagic transformation stroke	0	1 (1.4)
Hemiparesis	0	1 (1.4)
Infections and infestations	**3 (4.2)**	**2 (2.7)**
Septic shock	0	2 (2.7)
Bacteremia	1 (1.4)	0
Device related sepsis	1 (1.4)	0
Diverticulitis	1 (1.4)	0
Musculoskeletal and Connective Tissue Disorders	**2 (2.8)**	**0**
Pain in extremity	1 (1.4)	0
Arthropathy	1 (1.4)	0
Reproductive System and Breast Disorders	**2 (2.8)**	**0**
Menorrhagia	1 (1.4)	0
Hemorrhagic ovarian cyst	1 (1.4)	0
Injury, Poisoning and Procedural Complications	**1 (1.4)**	**3 (4.1)**
Anaphylactic transfusion reaction	0	3 (4.1)
Subarachnoid hemorrhage	1 (1.4)	0
Investigations	**1 (1.4)**	**1 (1.4)**
Gamma-glutamyltransferase increase	0	1 (1.4)
Platelet count decreased	1 (1.4)	0
General Disorders and Administration Site Conditions	**1 (1.4)**	**1 (1.4)**
Asthenia	1 (1.4)	0
Systemic inflammatory response syndrome	0	1 (1.4)
Hepatobiliary Disorders	**1 (1.4)**	**1 (1.4)**
Bile duct stone	1 (1.4)	0
Cholecystitis	0	1 (1.4)
Gallbladder necrosis	0	1 (1.4)
Immune System Disorders	**1 (1.4)**	**0**
Serum sickness	1 (1.4)	0
Vascular Disorders	**0**	**2 (2.8)**
Deep vein thrombosis	0	1 (1.4)
Jugular vein thrombosis	0	1 (1.4)

Abbreviations: N = total number of subjects in treatment group; n = number of subjects with events; SAE = serious adverse event
Note: Percentage was calculated using the number of subjects in the Safety Population as the denominator.

Table S3: Bleeding TEAEs (SMQ, excluding the preferred terms 'TTP' and 'TMA') during the Overall Study Period for the double-blind groups (Safety Population)

System Organ Class Preferred Term; n (%)	Double-Blind Caplacizumab (N = 71)	Double-Blind Placebo (N = 73)
Any bleeding TEAE (SMQ)	**46 (64.8)**	**35 (47.9)**
General disorders and administration site conditions	**12 (16.9)**	**14 (19.2)**
Catheter site hemorrhage	5 (7.0)	5 (6.8)
Injection site bruising	3 (4.2)	3 (4.1)
Injection site hematoma	1 (1.4)	3 (4.1)
Injection site hemorrhage	3 (4.2)	0
Vessel puncture site bruise	0	2 (2.7)
Vessel puncture site hemorrhage	1 (1.4)	1 (1.4)
Gastrointestinal disorders	**20 (28.2)**	**2 (2.7)**
Gingival bleeding	13 (18.3)	1 (1.4)
Hematochezia	2 (2.8)	0
Rectal hemorrhage	3 (4.2)	0
Mouth hemorrhage	0	1 (1.4)
Upper gastrointestinal hemorrhage	1 (1.4)	0
Abdominal wall hematoma	1 (1.4)	0
Gastric ulcer hemorrhage	1 (1.4)	0
Hematemesis	1 (1.4)	0
Melena	1 (1.4)	0
Nervous system disorders	**1 (1.4)**	**1 (1.4)**
Hemorrhagic cerebral infarction	1 (1.4)	0
Hemorrhagic transformation stroke	0	1 (1.4)
Skin and subcutaneous tissue disorders	**6 (8.5)**	**8 (11.0)**
Petechiae	4 (5.6)	5 (6.8)
Ecchymosis	2 (2.8)	4 (5.5)
Respiratory, thoracic and mediastinal disorders	**25 (35.2)**	**2 (2.7)**
Epistaxis	23 (32.4)	2 (2.7)
Haemoptysis	2 (2.8)	0
Injury, poisoning and procedural complications	**6 (8.5)**	**11 (15.1)**
Contusion	5 (7.0)	10 (13.7)
Post procedural hematoma	0	1 (1.4)
Subarachnoid hemorrhage	1 (1.4)	0
Vascular disorders	**3 (4.2)**	**2 (2.7)**
Hematoma	3 (4.2)	2 (2.7)
Renal and urinary disorders	**5 (7.0)**	**2 (2.7)**
Hematuria	5 (7.0)	2 (2.7)
Reproductive system and breast disorders	**7 (9.9)**	**3 (4.1)**
Vaginal hemorrhage	4 (5.6)	2 (2.7)
Menorrhagia	3 (4.2)	1 (1.4)
Hemorrhagic ovarian cyst	1 (1.4)	0
Eye disorders	**1 (1.4)**	**0**
Eye hemorrhage	1 (1.4)	0
Surgical and medical procedures	**1 (1.4)**	**0**
Astringent therapy	1 (1.4)	0

Abbreviations: N = total number of subjects in treatment group; n = number of subjects with events; SMQ = Standardized MedDRA Query; TEAE = treatment-emergent adverse event.
Note: Percentage was calculated using the number of subjects in the Safety Population as the denominator