Supplementary Table 1: Treatment-Emergent Serious Adverse Events in the Titration

Period (Safety Analysis Set)

	Number (%) of Subjects				
	NKTR-181 100 mg (N=135) n (%)	**NKTR-181 200 mg (N=199) n (%)**	**NKTR-181 300 mg (N=231) n (%)**	**NKTR-181 400 mg (N=624) n (%)**	**Total (N=1189) n (%)**
Total Number of TESAEs	5	1	2	3	11
Subjects Reporting at Least 1 TESAE	5 (3.7%)	1 (0.5%)	1 (0.4%)	2 (0.3%)	9 (0.8%)
Angioedema	0	1 (0.5%)	0	0	1 (<0.1%)
Atrial fibrillation	1 (0.7%)	0	0	0	1 (<0.1%)
Blindness transient	1 (0.7%)	0	0	0	1 (<0.1%)
Cellulitis	0	0	1 (0.4%)	0	1 (<0.1%)
Cerebrovascular accident	1 (0.7%)	0	0	0	1 (<0.1%)
Gastrointestinal infection	0	0	0	1 (0.2%)	1 (<0.1%)
Herpes virus infection	0	0	1 (0.4%)	0	1 (<0.1%)
Infective exacerbation of chronic obstructive airways disease	1 (0.7%)	0	0	0	1 (<0.1%)
Large intestine perforation	0	0	0	1 (0.2%)	1 (<0.1%)
Pneumonia	1 (0.7%)	0	0	0	1 (<0.1%)
Pulmonary embolism	0	0	0	1 (0.2%)	1 (<0.1%)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TESAE, treatment-emergent serious adverse event. Coding was based on MedDRA Version 17.1 The dose level was the highest dose that a subject was titrated to, except the 100 mg dose group. Subject was counted at most once within a preferred term.

Supplementary Table 2: Overview of Treatment-Emergent Adverse Events During the Randomized Treatment Period (All Randomized Subjects).

	Number (%) of Subjects					
	NKTR-181					
Randomized Treatment Period	100 mg (N=7)	200 mg (N=63)	300 mg (N=86)	400 mg (N=153)	Total (N=309)	Placebo (N=301)
Subjects Reporting at Least 1:						
TEAE	5 (71.4%)	32 (50.8%)	51 (59.3%)	80 (52.3%)	168 (54.4%)	150 (49.8%)
Drug-Related TEAE	1 (14.3%)	20 (31.7%)	31 (36.0%)	38 (24.8%)	90 (29.1%)	55 (18.3%)
Mild TEAE	1 (14.3%)	14 (22.2%)	22 (25.6%)	41 (26.8%)	78 (25.2%)	79 (26.2%)
Moderate TEAE	4 (57.1%)	16 (25.4%)	26 (30.2%)	36 (23.5%)	82 (26.5%)	66 (21.9%)
Severe TEAE	0	2 (3.2%)	3 (3.5%)	3 (2.0%)	8 (2.6%)	5 (1.7%)
TEAE Leading to Study Drug Withdrawal	0	5 (7.9%)	10 (11.6%)	7 (4.6%)	22 (7.1%)	8 (2.7%)
Serious TEAE	0	2 (3.2%)	0	3 (2.0%)	5 (1.6%)	6 (2.0%)