2. IMP self-administration by the patients at their homes, between the site visits: via the AAS patient diary

Treatment compliance, with the meaning of receiving the IMP within the protocol-specified time window of +/- 3 days, was calculated separately for site administration versus self-administration.

6 of the 30 IMP site-administrations (all visits, all patients) were not performed according to the protocol. For details, please see table 14.5.6.-1 in section 14.5.6.

25 of the 95 IMP self-administrations (all occurrences/planned timepoints, all patients) were not performed according to the protocol. For details, please see table 14.5.6.-2 in section 14.5.6.

10.4 Efficacy Results

10.4.1 Analysis of efficacy

10.4.1.1: Primary Endpoint: Improvement of at least 75% in the Angioedema Activity Score AAS28 at weeks 45 -48 compared to the AAS28 at weeks -4 to -1 (baseline).

For 2 patients (ID 01 and ID 06) an improvement of more than 75% in the AAS28 at weeks 45 -48 compared to the AAS28 at weeks -4 to -1 (baseline) could be detected. For patient ID 01 the AAS28 score decreased from a value of 12 (observed) / 12 (imputed) at baseline to a value 0 (observed and imputed) at weeks 45 to 48. For patient ID 06 a reduction in the AAS28 score from a value of 49 (observed) / 91 (imputed) at baseline to a value 0 (observed and imputed) at weeks 45 to 48 was observed. For patient ID 02 an AAS28 score of 94 (observed) / 175 (imputed) was recorded for the baseline and an AAS28 score of 118 (observed) / 150 (imputed) for weeks 45 to 48. For patient ID 05 the AAS28 score increased from a value of 9 (observed) / 13 (imputed) at baseline to a value of 38 (observed) / 71 (imputed) at weeks 45 to 48. For patient ID 07 a AAS28 score of 24 (observed) / 24 (imputed) was recorded at baseline but a value at weeks 45 to 48 was not documented because the patient was removed from therapy due to AEs. Please see tables 10.4.1-1 and 10.4.1-2 below for AAS28 mean score (per subject 28-day windows) and the responder rate, respectively.

Table 10.4.1-1: AAS28 mean score (per subject 28-day windows)

Patient ID Number	Period	Observed days	Missing days	AAS28 observed	AAS28 imputed	Impute mean	Note
01	Week -5 to -2	28	0	12	12	0.43	
01	Week -4 to -1	28	0	12	12	0.43	
01	Week -3 to 1	28	0	12	12	0.43	
01	Week -2 to 2	28	0	0	0	0.00	
01	Week -1 to 3	28	0	9	9	0.32	
01	Week 1 to 4	28	0	9	9	0.32	
01	Week 2 to 5	28	0	9	9	0.32	
01	Week 3 to 6	28	0	9	9	0.32	
01	Week 4 to 7	28	0	0	0	0.00	
01	Week 5 to 8	28	0	7	7	0.25	
01	Week 6 to 9	28	0	7	7	0.25	
01	Week 7 to 10	28	0	7	7	0.25	
01	Week 8 to 11	28	0	7	7	0.25	
01	Week 9 to 12	28	0	3	3	0.11	
01	Week 10 to 13	28	0	3	3	0.11	
01	Week 11 to 14	28	0	3	3	0.11	
01	Week 12 to 15	28	0	3	3	0.11	

Patient ID Number	Period	Observed days	Missing days	AAS28 observed	AAS28 imputed	Impute mean	Note
01	Week 13 to 16	28	0	0	0	0.00	
01	Week 14 to 17	28	0	0	0	0.00	
01	Week 15 to 18	28	0	7	7	0.25	
01	Week 16 to 19	28	0	7	7	0.25	
01	Week 17 to 20	28	0	7	7	0.25	
01	Week 18 to 21	28	0	15	15	0.54	
01	Week 19 to 22	28	0	8	8	0.29	
01	Week 20 to 23	28	0	8	8	0.29	
01	Week 21 to 24	28	0	8	8	0.29	
01	Week 22 to 25	28	0	0	0	0.00	
01	Week 23 to 26	28	0	0	0	0.00	
01	Week 24 to 27	28	0	0	0	0.00	
01	Week 25 to 28	28	0	0	0	0.00	
01	Week 26 to 29	28	0	0	0	0.00	
01	Week 27 to 30	27	1	0	0	0.00	
01	Week 28 to 31	27	1	0	0	0.00	
01	Week 29 to 32	27	1	0	0	0.00	
01	Week 30 to 33	27	1	0	0	0.00	
01	Week 31 to 34	28	0	3	3	0.11	
01	Week 32 to 35	28	0	3	3	0.11	
01	Week 33 to 36	28	0	3	3	0.11	
01	Week 34 to 37	28	0	3	3	0.11	
01	Week 35 to 38	28	0	0	0	0.00	
01	Week 36 to 39	28	0	0	0	0.00	
01	Week 37 to 40	28	0	0	0	0.00	
01	Week 38 to 41	28	0	0	0	0.00	
01	Week 39 to 42	28	0	0	0	0.00	
01	Week 40 to 43	28	0	0	0	0.00	
01	Week 41 to 44	28	0	0	0	0.00	
01	Week 42 to 45	28	0	0	0	0.00	
01	Week 43 to 46	28	0	0	0	0.00	
01	Week 44 to 47	28	0	0	0	0.00	
01	Week 45 to 48	28	0	0	0	0.00	
01	Week 46 to 49	28	0	0	0	0.00	
01	Week 47 to 50	28	0	0	0	0.00	
01	Week 48 to 51	28	0	0	0	0.00	
01	Week 49 to 52	28	0	0	0	0.00	
01	Week 50 to 53	28	0	0	0	0.00	
01	Week 51 to 54	28	0	1	1	0.04	
01	Week 52 to 55	28	0	1	1	0.04	
01	Week 53 to 56	28	0	3	3	0.11	
01	Week 54 to 57	28	0	3	3	0.11	
01	Week 55 to 58	28	0	2	2	0.07	
01	Week 56 to 59	28	0	2	2	0.07	
01	Week 57 to 60	25	3	5	6	0.20	

Patient ID Number	Period	Observed days	Missing days	AAS28 observed	AAS28 imputed	Impute mean	Note
01	Week 58 to 61	18	10	5	8	0.28	
01	Week 59 to 62	11	17	5	9	0.33	<15 observed days; +4 zero(s) to 15
01	Week 60 to 63	4	24	5	9	0.33	<15 observed days; +11 zero(s) to 15
02	Week -5 to -2	12	16	83	155	5.53	<15 observed days; +3 zero(s) to 15
02	Week -4 to -1	13	15	94	175	6.27	<15 observed days; +2 zero(s) to 15
02	Week -3 to 1	15	13	98	183	6.53	
02	Week -2 to 2	17	11	72	119	4.24	
02	Week -1 to 3	21	7	97	129	4.62	
02	Week 1 to 4	25	3	90	101	3.60	
02	Week 2 to 5	24	4	91	106	3.79	
02	Week 3 to 6	24	4	123	144	5.12	
02	Week 4 to 7	22	6	83	106	3.77	
02	Week 5 to 8	22	6	100	127	4.55	
02	Week 6 to 9	23	5	97	118	4.22	
02	Week 7 to 10	21	7	88	117	4.19	
02	Week 8 to 11	21	7	111	148	5.29	
02	Week 9 to 12	21	7	112	149	5.33	
02	Week 10 to 13	20	8	99	139	4.95	
02	Week 11 to 14	21	7	100	133	4.76	
02	Week 12 to 15	20	8	115	161	5.75	
02	Week 13 to 16	18	10	93	145	5.17	
02	Week 14 to 17	19	9	104	153	5.47	
02	Week 15 to 18	18	10	123	191	6.83	
02	Week 16 to 19	20	8	131	183	6.55	
02	Week 17 to 20	22	6	176	224	8.00	
02	Week 18 to 21	23	5	187	228	8.13	
02	Week 19 to 22	23	5	167	203	7.26	
02	Week 20 to 23	22	6	157	200	7.14	
02	Week 21 to 24	23	5	171	208	7.43	
02	Week 22 to 25	22	6	159	202	7.23	
02	Week 23 to 26	23	5	171	208	7.43	
02	Week 24 to 27	24	4	155	181	6.46	
02	Week 25 to 28	25	3	121	136	4.84	
02	Week 26 to 29	25	3	139	156	5.56	
02	Week 27 to 30	26	2	127	137	4.88	
02	Week 28 to 31	26	2	179	193	6.88	
02	Week 29 to 32	25	3	163	183	6.52	
02	Week 30 to 33	26	2	117	126	4.50	
02	Week 31 to 34	25	3	130	146	5.20	
02	Week 32 to 35	22	6	82	104	3.73	
02	Week 33 to 36	21	7	99	132	4.71	

Patient ID Number	Period	Observed days	Missing days	AAS28 observed	AAS28 imputed	Impute mean	Note
02	Week 34 to 37	17	11	125	206	7.35	
02	Week 35 to 38	18	10	154	240	8.56	
02	Week 36 to 39	21	7	148	197	7.05	
02	Week 37 to 40	23	5	172	209	7.48	
02	Week 38 to 41	24	4	154	180	6.42	
02	Week 39 to 42	20	8	93	130	4.65	
02	Week 40 to 43	18	10	96	149	5.33	
02	Week 41 to 44	18	10	83	129	4.61	
02	Week 42 to 45	21	7	111	148	5.29	
02	Week 43 to 46	22	6	122	155	5.55	
02	Week 44 to 47	22	6	129	164	5.86	
02	Week 45 to 48	22	6	118	150	5.36	
02	Week 46 to 49	18	10	95	148	5.28	
02	Week 47 to 50	18	10	85	132	4.72	
02	Week 48 to 51	21	7	95	127	4.52	
02	Week 49 to 52	20	8	107	150	5.35	
02	Week 50 to 53	22	6	120	153	5.45	
02	Week 51 to 54	25	3	146	164	5.84	
02	Week 52 to 55	22	6	137	174	6.23	
02	Week 53 to 56	20	8	138	193	6.90	
02	Week 54 to 57	21	7	143	191	6.81	
02	Week 55 to 58	17	11	138	227	8.12	
02	Week 56 to 59	13	15	109	203	7.27	<15 observed days; +2 zero(s) to 15
02	Week 57 to 60	11	17	80	149	5.33	<15 observed days; +4 zero(s) to 15
02	Week 58 to 61	11	17	77	144	5.13	<15 observed days; +4 zero(s) to 15
02	Week 59 to 62	13	15	64	119	4.27	<15 observed days; +2 zero(s) to 15
02	Week 60 to 63	20	8	87	122	4.35	
02	Week 61 to 64	24	4	121	141	5.04	
02	Week 62 to 65	23	5	110	134	4.78	
02	Week 63 to 66	23	5	106	129	4.61	
02	Week 64 to 67	21	7	114	152	5.43	
02	Week 65 to 68	21	7	116	155	5.52	
02	Week 66 to 69	21	7	125	167	5.95	
02	Week 67 to 70	21	7	138	184	6.57	
02	Week 68 to 71	21	7	141	188	6.71	
02	Week 69 to 72	21	7	134	179	6.38	
02	Week 70 to 73	21	7	139	185	6.62	
02	Week 71 to 74	20	8	141	197	7.05	
02	Week 72 to 75	22	6	146	186	6.64	
02	Week 73 to 76	23	5	159	194	6.91	
02	Week 74 to 77	23	5	155	189	6.74	

Patient ID Number	Period	Observed days	Missing days	AAS28 observed	AAS28 imputed	Impute mean	Note
02	Week 75 to 78	22	6	152	193	6.91	
05	Week -5 to -2	19	9	19	28	1.00	
05	Week -4 to -1	19	9	9	13	0.47	
05	Week -3 to 1	19	9	17	25	0.89	
05	Week -2 to 2	20	8	8	11	0.40	
05	Week -1 to 3	21	7	8	11	0.38	
05	Week 1 to 4	21	7	15	20	0.71	
05	Week 2 to 5	22	6	7	9	0.32	
05	Week 3 to 6	23	5	7	9	0.30	
05	Week 4 to 7	22	6	7	9	0.32	
05	Week 5 to 8	21	7	0	0	0.00	
05	Week 6 to 9	22	6	0	0	0.00	
05	Week 7 to 10	22	6	9	11	0.41	
05	Week 8 to 11	23	5	25	30	1.09	
05	Week 9 to 12	24	4	25	29	1.04	
05	Week 10 to 13	25	3	32	36	1.28	
05	Week 11 to 14	24	4	23	27	0.96	
05	Week 12 to 15	24	4	7	8	0.29	
05	Week 13 to 16	25	3	7	8	0.28	
05	Week 14 to 17	23	5	0	0	0.00	
05	Week 15 to 18	21	7	5	7	0.24	
05	Week 16 to 19	21	7	5	7	0.24	
05	Week 17 to 20	19	9	5	7	0.26	
05	Week 18 to 21	19	9	28	41	1.47	
05	Week 19 to 22	20	8	23	32	1.15	
05	Week 20 to 23	19	9	23	34	1.21	
05	Week 21 to 24	19	9	23	34	1.21	
05	Week 22 to 25	20	8	0	0	0.00	
05	Week 23 to 26	21	7	0	0	0.00	
05	Week 24 to 27	21	7	0	0	0.00	
05	Week 25 to 28	23	5	0	0	0.00	
05	Week 26 to 29	21	7	0	0	0.00	
05	Week 27 to 30	22	6	0	0	0.00	
05	Week 28 to 31	22	6	0	0	0.00	
05	Week 29 to 32	20	8	0	0	0.00	
05	Week 30 to 33	23	5	0	0	0.00	
05	Week 31 to 34	19	9	0	0	0.00	
05	Week 32 to 35	20	8	0	0	0.00	
05	Week 33 to 36	23	5	0	0	0.00	
05	Week 34 to 37	22	6	0	0	0.00	
05	Week 35 to 38	24	4	0	0	0.00	
05	Week 36 to 39	24	4	0	0	0.00	
05	Week 37 to 40	23	5	0	0	0.00	
05	Week 38 to 41	23	5	0	0	0.00	
05	Week 39 to 42	21	7	0	0	0.00	

Patient ID Number	Period	Observed days	Missing days	AAS28 observed	AAS28 imputed	Impute mean	Note
05	Week 40 to 43	22	6	9	11	0.41	
05	Week 41 to 44	20	8	9	13	0.45	
05	Week 42 to 45	18	10	9	14	0.50	
05	Week 43 to 46	19	9	9	13	0.47	
05	Week 44 to 47	16	12	30	52	1.88	
05	Week 45 to 48	15	13	38	71	2.53	
05	Week 46 to 49	15	13	38	71	2.53	
05	Week 47 to 50	17	11	38	63	2.24	
05	Week 48 to 51	18	10	8	12	0.44	
05	Week 49 to 52	21	7	0	0	0.00	
05	Week 50 to 53	22	6	10	13	0.45	
05	Week 51 to 54	20	8	38	53	1.90	
05	Week 52 to 55	19	9	70	103	3.68	
05	Week 53 to 56	17	11	85	140	5.00	
05	Week 54 to 57	14	14	87	162	5.80	<15 observed days; +1 zero(s) to 15
05	Week 55 to 58	10	18	59	110	3.93	<15 observed days; +5 zero(s) to 15
05	Week 56 to 59	6	22	27	50	1.80	<15 observed days; +9 zero(s) to 15
05	Week 57 to 60	2	26	12	22	0.80	<15 observed days; +13 zero(s) to 15
06	Week -5 to -2	15	13	73	136	4.87	
06	Week -4 to -1	15	13	49	91	3.27	
06	Week -3 to 1	16	12	46	80	2.88	
06	Week -2 to 2	18	10	43	67	2.39	
06	Week -1 to 3	20	8	19	27	0.95	
06	Week 1 to 4	20	8	19	27	0.95	
06	Week 2 to 5	20	8	9	13	0.45	
06	Week 3 to 6	20	8	0	0	0.00	
06	Week 4 to 7	20	8	0	0	0.00	
06	Week 5 to 8	22	6	0	0	0.00	
06	Week 6 to 9	23	5	0	0	0.00	
06	Week 7 to 10	23	5	0	0	0.00	
06	Week 8 to 11	21	7	0	0	0.00	
06	Week 9 to 12	19	9	0	0	0.00	
06	Week 10 to 13	19	9	0	0	0.00	
06	Week 11 to 14	19	9	0	0	0.00	
06	Week 12 to 15	21	7	0	0	0.00	
06	Week 13 to 16	24	4	0	0	0.00	
06	Week 14 to 17	25	3	5	6	0.20	
06	Week 15 to 18	24	4	13	15	0.54	
06	Week 16 to 19	25	3	13	15	0.52	
06	Week 17 to 20	24	4	13	15	0.54	
06	Week 18 to 21	23	5	8	10	0.35	

Patient ID Number	Period	Observed days	Missing days	AAS28 observed	AAS28 imputed	Impute mean	Note
06	Week 19 to 22	23	5	0	0	0.00	
06	Week 20 to 23	23	5	0	0	0.00	
06	Week 21 to 24	24	4	0	0	0.00	
06	Week 22 to 25	21	7	0	0	0.00	
06	Week 23 to 26	21	7	0	0	0.00	
06	Week 24 to 27	21	7	0	0	0.00	
06	Week 25 to 28	21	7	0	0	0.00	
06	Week 26 to 29	22	6	0	0	0.00	
06	Week 27 to 30	23	5	0	0	0.00	
06	Week 28 to 31	21	7	0	0	0.00	
06	Week 29 to 32	20	8	0	0	0.00	
06	Week 30 to 33	20	8	0	0	0.00	
06	Week 31 to 34	19	9	0	0	0.00	
06	Week 32 to 35	20	8	0	0	0.00	
06	Week 33 to 36	19	9	0	0	0.00	
06	Week 34 to 37	18	10	0	0	0.00	
06	Week 35 to 38	18	10	0	0	0.00	
06	Week 36 to 39	18	10	0	0	0.00	
06	Week 37 to 40	20	8	0	0	0.00	
06	Week 38 to 41	22	6	0	0	0.00	
06	Week 39 to 42	22	6	0	0	0.00	
06	Week 40 to 43	23	5	0	0	0.00	
06	Week 41 to 44	22	6	0	0	0.00	
06	Week 42 to 45	24	4	0	0	0.00	
06	Week 43 to 46	26	2	0	0	0.00	
06	Week 44 to 47	21	7	0	0	0.00	
06	Week 45 to 48	23	5	0	0	0.00	
06	Week 46 to 49	22	6	0	0	0.00	
06	Week 47 to 50	20	8	0	0	0.00	
06	Week 48 to 51	24	4	12	14	0.50	
06	Week 49 to 52	23	5	23	28	1.00	
06	Week 50 to 53	23	5	32	39	1.39	
06	Week 51 to 54	21	7	32	43	1.52	
06	Week 52 to 55	22	6	32	41	1.45	
06	Week 53 to 56	19	9	21	31	1.11	
06	Week 54 to 57	13	15	12	22	0.80	<15 observed days; +2 zero(s) to 15
06	Week 55 to 58	10	18	12	22	0.80	<15 observed days; +5 zero(s) to 15
06	Week 56 to 59	3	25	0	0	0.00	<15 observed days; +12 zero(s) to 15
07	Week -5 to -2	22	6	11	14	0.50	
07	Week -4 to -1	28	0	24	24	0.86	
07	Week -3 to 1	28	0	13	13	0.46	
07	Week -2 to 2	28	0	13	13	0.46	

Patient ID Number	Period	Observed days	Missing days	AAS28 observed	AAS28 imputed	Impute mean	Note
07	Week -1 to 3	28	0	13	13	0.46	
07	Week 1 to 4	28	0	0	0	0.00	
07	Week 2 to 5	28	0	0	0	0.00	
07	Week 3 to 6	28	0	0	0	0.00	
07	Week 4 to 7	28	0	0	0	0.00	
07	Week 5 to 8	28	0	0	0	0.00	
07	Week 6 to 9	28	0	0	0	0.00	
07	Week 7 to 10	28	0	0	0	0.00	
07	Week 8 to 11	28	0	0	0	0.00	
07	Week 9 to 12	28	0	5	5	0.18	
07	Week 10 to 13	26	2	5	5	0.19	
07	Week 11 to 14	26	2	5	5	0.19	
07	Week 12 to 15	26	2	5	5	0.19	
07	Week 13 to 16	26	2	0	0	0.00	
07	Week 14 to 17	28	0	0	0	0.00	
07	Week 15 to 18	28	0	0	0	0.00	
07	Week 16 to 19	28	0	0	0	0.00	
07	Week 17 to 20	28	0	0	0	0.00	
07	Week 18 to 21	28	0	0	0	0.00	
07	Week 19 to 22	28	0	0	0	0.00	
07	Week 20 to 23	28	0	0	0	0.00	
07	Week 21 to 24	28	0	0	0	0.00	
07	Week 22 to 25	28	0	0	0	0.00	
07	Week 23 to 26	21	7	0	0	0.00	
07	Week 24 to 27	14	14	0	0	0.00	<15 observed days; +1 zero(s) to 15
07	Week 25 to 28	7	21	0	0	0.00	<15 observed days; +8 zero(s) to 15

Table 10.4.1-2: AAS28 ≥75% responders

Period	N evaluable	Responders (Yes)	Non-responders (No)	Proportion Yes	95% exact CI	Baseline mean (SD)	Period mean (SD)	Mean reduction (SD)	p (one-sided, exact binomial vs p0=0.30)	p Holm-adj
Weeks 9–12	4	3	1	3 (75.0%)	[24.9%, 100.0%]	35.18 (37.91)	9.29 (13.41)	25.89 (46.11)	0.0837	0.3348
Weeks 21–24	4	2	2	2 (50.0%)	[9.8%, 100.0%]	35.18 (37.91)	10.47 (16.06)	24.71 (48.10)	0.3483	0.6966
Weeks 33–36	3	3	0	3 (100.0%)	[36.8%, 100.0%]	38.91 (45.52)	1.00 (1.73)	37.91 (46.43)	0.0270	0.1350
Weeks 45–48	3	2	1	2 (66.7%)	[13.5%, 100.0%]	38.91 (45.52)	23.64 (40.95)	15.27 (74.62)	0.2160	0.6480

Period	N evaluable	Responders (Yes)	Non-responders (No)	Proportion Yes	95% exact CI	Baseline mean (SD)	Period mean (SD)	Mean reduction (SD)	p (one-sided, exact binomial vs p0=0.30)	p Holm-adj
Weeks 57–60	1	0	1	0 (0.0%)	[0.0%, 100.0%]	12.00 (NA)	5.60 (NA)	6.40 (NA)	1.0000	1.0000

10.4.1.2: Secondary Endpoints

10.4.1.2.1 Change in Angioedema Activity Score AAS28 at weeks 9 – 12, 21 - 24, 33 - 36 and 57 - 60 compared to -4 to -1 (baseline)

The AAS28 mean score declined from a mean value of 35.18 (SD = 37.91) at baseline (weeks -4 to -1) (n=4 patients), over a mean value of 9.29 (SD = 13.41) at weeks 9 to 12 (n=4 patients), to a mean value of 10.47 (SD = 16.06) at weeks 21 – 24 (n=4 patients). The AAS28 mean score at weeks 33 – 36 was 1.00 (SD = 1.73) (n=3 patients) and at weeks 57 – 60 the AAS28 mean score was shown to be 12.00 (SD = NA) (n=1 patient). Please see table 10.4.1-3 below for the mean AAS28 score compared to baseline.

This is a change of -25.89 units (SD = 46.11) from baseline to weeks 9 – 12, resp. a change of -24.71 (SD = 48.10) from baseline to weeks 21 – 24. From baseline to weeks 33 – 36 and 57 – 60 a change of –37.91 units (SD = 37.91) and -6.4 units (SD = NA) was estimated. Please see table 10.4.1-4 below for the mean AAS28 score compared to baseline.

Table 10.4.1-3: AAS28 — Mean score and Symptom-free days compared to baseline (week -4 to -1)

Period	N paired	AAS28 mean (SD)	SFD mean (SD)	SFD change (SD)	Mean change (SD)	p (Wilcoxon)	p (Sign exact)	p (Perm exact)	p (paired t)
Week -4 to -1	4	35.18 (37.91)	24.25 (2.87)			<na>	<na>	<na>	<na>
Week 1 to 4	4	13.90 (11.77)	26.00 (2.92)	3.00 (2.16)	-21.28 (31.76)	0.375	1.25	0.375	0.2727
Week 5 to 8	4	1.75 (3.50)	26.00 (3.46)	3.25 (3.40)	-33.43 (39.46)	0.125	0.25	0.125	0.1888
Week 9 to 12	4	9.29 (13.41)	25.40 (3.21)	2.50 (3.87)	-25.89 (46.11)	0.375	1.25	0.375	0.3432
Week 13 to 16	4	1.96 (3.92)	26.60 (2.61)	3.50 (3.11)	-33.22 (39.58)	0.125	0.25	0.125	0.1918
Week 17 to 20	4	7.38 (6.20)	24.80 (5.54)	3.00 (2.16)	-27.80 (33.50)	0.125	0.25	0.125	0.1956
Week 21 to 24	4	10.47 (16.06)	25.60 (3.78)	3.00 (3.56)	-24.71 (48.10)	0.375	1.25	0.375	0.3799
Week 25 to 28	3	0.00 (0.00)	25.25 (5.50)	4.00 (3.46)	-38.91 (45.52)	0.25	0.5	0.25	0.2769
Week 29 to 32	3	0.00 (0.00)	24.75 (5.85)	3.67 (3.79)	-38.91 (45.52)	0.25	0.5	0.25	0.2769
Week 33 to 36	3	1.00 (1.73)	25.75 (3.86)	3.67 (3.79)	-37.91 (46.43)	0.25	0.5	0.25	0.2929

Period	N paired	AAS28 mean (SD)	SFD mean (SD)	SFD change (SD)	Mean change (SD)	p (Wilcoxon)	p (Sign exact)	p (Perm exact)	p (paired t)
Week 37 to 40	3	0.00 (0.00)	24.25 (7.50)	4.00 (3.46)	-38.91 (45.52)	0.25	0.5	0.25	0.2769
Week 41 to 44	3	4.20 (7.27)	25.50 (4.36)	3.67 (3.79)	-34.71 (49.48)	0.25	0.5	0.25	0.3483
Week 45 to 48	3	23.64 (40.95)	24.25 (5.19)	2.67 (5.03)	-15.27 (74.62)	0.75	2	0.75	0.757
Week 49 to 52	3	9.33 (16.17)	25.25 (4.27)	3.33 (2.31)	-29.58 (29.36)	0.25	0.5	0.25	0.2231
Week 53 to 56	3	57.98 (72.39)	21.25 (5.50)	-1.00 (7.55)	19.07 (96.73)	1	2	1	0.7653
Week 57 to 60	1	5.60 (NA)	27.00 (NA)	1.00 (NA)	-6.40 (NA)	1	2	1	NA

10.4.1.2.2 Number of angioedema affected days (ASS opening question) at weeks 9 - 12; 21 - 24, 33 - 36 and 57 – 60

The number of angioedema-affected days was calculated as the difference between 28 days minus the number of symptom-free days (SFD). For the number of angioedema affected days a mean value of 2.6 at weeks -9 to 12 (n=4 patients), 2.4 at weeks 21 to 24 (n=4 patients) and 2.3 at weeks 33 – 36 (n=3 patients) was recorded. For only one patient there was data available at weeks 57 to 60. Here, the number of angioedema affected days was 4. Please see table 10.4.1-3 above for the SFD mean.

10.4.1.2.3 Change in disease control as assessed by Angioedema control test (AECT) (from Baseline to visit 7, and from visit 7 to visit 8.

The AECT total score increased from a mean value of 5.25 (SD = 5.56) at baseline (V2) (n=4 patients), to a mean value of 11.25 (SD = 5.50) at visit 7 (n=4 patients), and declined from a mean value of 9.67 (SD = 5.51) at visit 7 (n=3 patients) to a mean value of 6.33 (SD = 4.93) at visit 8 (n=3 patients).

This is a change of 6.00 units (SD = 6.78,) from baseline to visit 7, and a change of - 3.33 units (SD = 0.58) from visit 7 to visit 8. Please see also table 10.4.1-4 for the AECT mean values below.

Table 10.4.1-4: AECT — Change from Baseline to visit 7, and from visit 7 to visit 8

Parameter	Comparison	N evaluable	Baseline mean (SD)	Visit mean (SD)	Mean change (SD)	Primary test	p (primary)	p (Sign exact)	p (Perm exact)	p (paired t)
AECT total score	Baseline (V2) — raw	5	5.60 (4.88)							
AECT total score	Visit V7 vs Baseline (V2)	4	5.25 (5.56)	11.25 (5.50)	6.00 (6.78)	Wilcoxon signed-rank (exact)	0.125	0.25	0.125	0.175
AECT total score	FUP V8 vs Baseline (V2)	4	5.25 (5.56)	11.25 (5.50)	6.00 (6.78)	Wilcoxon signed-rank (exact)	0.125	0.25	0.125	0.175

Parameter	Comparison	N evaluable	Baseline mean (SD)	Visit mean (SD)	Mean change (SD)	Primary test	p (primary)	p (Sign exact)	p (Perm exact)	p (paired t)
AECT total score	Visit V7 vs FUP V8	3	9.67 (5.51)	6.33 (4.93)	-3.33 (0.58)	Wilcoxon signed-rank (exact)	0.1736	0.5	< 2.2e-16	0.0099

10.4.1.2.4 Change in quality of life as assessed by Angioedema-Quality of life questionnaire (AE-QoL) from baseline (Visit 2) to weeks 45 - 48, and from weeks 45 - 48 to weeks 57 - 60

The AE-QoL total score declined from a mean value of 51.10 (SD = 30.05) at baseline (V2) (n=4 patients) to a mean value of 37.13 (SD = 21.15) at visit 7 (n=4 patients), and then increased from a mean value of 32.35 (SD = 31.11) at visit 7 (n=3 patients) to a mean value of 48.04 (SD = 14.88) at visit 8 (n=3 patients).

This is a change of -13.97 units (SD = 15.95) from baseline to visit 7, and a change of 15.96 units (SD = 10.01) from visit 7 to visit 8. Please see also table 10.4.1-5 for the AE-QoL changes below.

The AE-QoL - Functioning score declined from a mean value of 57.81 (SD = 36.93) at baseline (V2) (n=4 patients) to a mean value of 45.31 (SD = 33.61) at visit 7 (n=4 patients), and then increased from a mean value of 43.75 (SD = 40.98) at visit 7 (n=3 patients) to a mean value of 79.17 (SD = 19.09) at visit 8 (n=3 patients). This is a change of -12.50 units (SD = 16.93) from baseline to visit 7, and a change of 35.42 units (SD = 23.66) from visit 7 to visit 8. Please see also table 10.4.1-5 for the AE-QoL changes below.

The AE-QoL – Fatigue / Mood score declined from a mean value of 48.75 (SD = 24.96) at baseline (V2) (n=4 patients) to a mean value of 30.00 (SD = 14.72) at visit 7 (n=4 patients), and then increased from a mean value of 26.67 (SD = 16.07.) at visit 7 (n=3 patients) to a mean value of 43.33 (SD = 11.55) at visit 8 (n=3 patients). This is a change of -18.75 units (SD = 19.74) from baseline to visit 7, and a change of 16.67 units (SD = 16.07) from visit 7 to visit 8. Please see also table 10.4.1-5 for the AE-QoL changes below.

The AE-QoL – Fears / Shame score declined from a mean value of 48.96 (SD = 38.40) at baseline (V2) (n=4 patients) to a mean value of 38.54 (SD = 29.14) at visit 7 (n=4 patients), and then increased from a mean value of 29.17 (SD = 27.32) at visit 7 (n=3 patients) to a mean value of 31.94 (SD = 30.71) at visit 8 (n=3 patients). This is a change of -10.42 units (SD = 16.14) from baseline to visit 7, and a change of 2.78 units (SD = 6.36) from visit 7 to visit 8. Please see also table 10.4.1-5 for the AE-QoL changes below.

The AE-QoL – Nutrition score declined from a mean value of 50.00 (SD = 57.74) at baseline (V2) (n=4 patients) to a mean value of 34.38 (SD = 47.19) at visit 7 (n=4 patients), and then increased from a mean value of 33.33 (SD = 57.74) at visit 7 (n=3 patients) to a mean value of 45.83 (SD = 50.52) at visit 8 (n=3 patients). This is a change of -15.62 units (SD = 31.25) from baseline to visit 7, and a change of 12.50 units (SD = 21.65) from visit 7 to visit 8. Please see also table 10.4.1-5 for the AE-QoL changes below.

Table 10.4.1-5: AE-QoL changes

Parameter	Comparison	N evaluable	Former period mean (SD)	Later period mean (SD)	Mean change (SD)	p (paired t)	p (Wilcoxon exact)	p (Sign exact)	p (Perm sign-flip exact)
AE-QoL total score	Baseline (V2) → V7	4	51.10 (30.05)	37.13 (21.15)	-13.97 (15.95)	0.1781	0.2500	0.6250	0.2500
	V7 → V8 FUP	3	32.35 (23.11)	48.04 (14.88)	15.69 (10.01)	0.1132	0.2500	0.2500	<0.0001

Parameter	Comparison	N evaluable	Former period mean (SD)	Later period mean (SD)	Mean change (SD)	p (paired t)	p (Wilcoxon exact)	p (Sign exact)	p (Perm sign-flip exact)
AE-QoL — Functioning	Baseline (V2) → V7	4	57.81 (36.93)	45.31 (33.61)	-12.50 (16.93)	0.2362	0.1736	0.2500	0.2500
	V7 → V8 FUP	3	43.75 (40.98)	79.17 (19.09)	35.42 (23.66)	0.1221	0.2500	0.2500	0.2500
AE-QoL — Fatigue/Mood	Baseline (V2) → V7	4	48.75 (24.96)	30.00 (14.72)	-18.75 (19.74)	0.1536	0.1975	0.6250	0.2500
	V7 → V8 FUP	3	26.67 (16.07)	43.33 (11.55)	16.67 (16.07)	0.2143	0.2500	0.2500	<0.0001
AE-QoL — Fears/Shame	Baseline (V2) → V7	4	48.96 (38.40)	38.54 (29.14)	-10.42 (16.14)	0.2872	0.2500	0.6250	0.2500
	V7 → V8 FUP	3	29.17 (27.32)	31.94 (30.71)	2.78 (6.36)	0.5286	0.5000	1.0000	0.2500
AE-QoL — Nutrition	Baseline (V2) → V7	4	50.00 (57.74)	34.38 (47.19)	-15.62 (31.25)	0.3910	1.0000	1.0000	1.0000
	V7 → V8 FUP	3	33.33 (57.74)	45.83 (50.52)	12.50 (21.65)	0.4226	1.0000	1.0000	1.0000

10.4.1.2.5 Change in number of symptom-free days as assessed by AAS28 (from weeks -4 - 1 (baseline) to weeks 45 - 48, and from weeks 45 - 48 to weeks 57 - 60)

The number of symptom free days (SFD) increased from a mean value of 23.67 (SD = 4.04) at baseline (weeks -4 to -1) (n=3 patients), to a mean value of 26.67 (SD = 2.31) at weeks 45 to 48 (n=3 patients), This is a change of 3.00 units (SD = 5.57) from baseline to weeks 45 to 48.

For one patient, the SFD from weeks 45 - 48 to weeks 57 – 60 could be calculated. Here the SFD declined from a mean value of 28.00 at weeks 45 to 48 to a mean value of 27.00 at weeks 57 – 60. This is a change of 1.00 unit from weeks 45 to 48 to weeks 57 - 60. Please see table 10.4.1-3 above for the SFD mean.

10.4.1.2.6 Change in number of intake of rescue medication (from weeks -4 to - 1 (baseline) to weeks 45 - 48, and from weeks 45 - 48 to weeks 57 - 60)

The number of intake of rescue medication declined from a mean value of 3.33 (SD = 2.31) (n=3 patients) at baseline (weeks -4 to -1) to a mean value of 0.67 (SD = 1.15) at weeks 45 to 48 (n=3 patients). This is a change of -2.67 units (SD = 3.06) from baseline to weeks 45 to 48.

For one patient, the change in the number of intakes of rescue medication from weeks 45 - 48 to weeks 57 – 60 could be calculated. Here, the number of intake of rescue medications increased from a mean value of 0.00 at baseline at weeks 45 to 48 to a mean value of 1.00 at weeks 57 – 60.

This is a change of 1.00 units (SD = NA) from weeks 45 to 48 to weeks 57 - 60. Please see also table 10.4.1-6 for the changes in the number of intakes of rescue medication below.

Table 10.4.1-6: Intake of rescue medication - changes

Comparison	N evaluable	Former period mean (SD)	Later period mean (SD)	Mean change (SD)	Primary test	p (primary)	p (Sign exact)	p (Perm exact)	p (paired t)
Baseline (–4…–1) → Weeks 45–48	3	3.33 (2.31)	0.67 (1.15)	-2.67 (3.06)	Wilcoxon signed-rank (exact)	0.3711	1	0.5	0.2697
Baseline (–4…–1) → Weeks 57–60	1	2.00 (NA)	1.00 (NA)	-1.00 (NA)	Wilcoxon signed-rank (exact)	1	2	1	NA
Weeks 45–48 → Weeks 57–60	1	0.00 (NA)	1.00 (NA)	1.00 (NA)	Wilcoxon signed-rank (exact)	1	2	1	NA

Secondary endpoint 8: Change in number of rescue medication intake from baseline (weeks –4 to –1) to weeks 45–48, and from weeks 45–48 to weeks 57–60.

10.4.1.2.9 Serum levels at baseline (Day 1) and changes from Day 1 to week 4, 24, 48 and 60 of serum levels of potential biomarkers in Lanadelumab-treated patients (e.g., FXII and prekallikrein levels).

For the serum level of prekallikrein the following mean values were recorded:

69.45 µg/ml (SD = 20.56) at baseline (Day 1, V2) (n=5 patients), 63.99 µg/ml (SD = 13.13) at week 4 (V3) (n=5 patients), 62.90 µg/ml (SD = 12.18) at week 24 (V5) (n=5 patients), 71.64 µg/ml (SD = 9.20) at week 48 (V7) (n=5 patients) and 66.18 µg/ml (SD = 15.26) at week 60 (n=1 patient) (FUP).

This is a change of – 5.46 µg/ml from V2 to V3, a change of - 1,09 µg/ml from V3 to V5, a change of 8,74 µg/ml from V5 to V7, and a change of -5.46 µg/ml from V7 to FUP. Please see table 10.4.1-7 below.

For the serum level of Factor XII no mean value could be determined at baseline (V2) because most of the values of the patient samples were above detection limit (> 120 %). The following mean values were recorded for the other visits: 84.50 % (value 1 and value 2, SD = 41.72) at week 4 (V3) (n=4 patients), 85.33 % (value 1, SD = 34.30) and 86.67 % (value 2, SD = 35.44) at week 24 (V5) (n=4 patients), 93.00 % (value 1, SD = 39.95) and 93.67 % (value 2, SD = 40.43) at week 48 (V7), 95.67 (value 1, SD = 24.01) and 96.67 % (value 1, SD = 25.01) at week 60 (FUP).

This is a change of approximately 1.5% from V3 to V5, a change of approximately 7 % from V5 to V7, and a change of about 3 % from V7 to FUP.

Table 10.4.1-7: Serum levels of biomarkers

Parameter	Units	Visit	Category/Statistics	Results
Biomarker Prekallikrein	µg/ml	Visit Baseline V2	Mean (SD)	69.45 (20.56)
			Median (IQR)	70.57 (5.15)
			Min, Max	40.46, 98.36
			Abnormal/Normal	0 / 0
		Visit V3	Mean (SD)	63.99 (13.13)
			Median (IQR)	67.74 (1.22)
			Min, Max	41.53, 76.18
			Abnormal/Normal	0 / 0
		Visit V5	Mean (SD)	62.89 (12.18)
			Median (IQR)	67.03 (2.19)

Parameter	Units	Visit	Category/Statistics	Results
			Min, Max	41.38, 71.35
			Abnormal/Normal	0 / 0
		Visit V7	Mean (SD)	71.64 (9.20)
			Median (IQR)	69.33 (8.09)
			Min, Max	63.32, 84.56
			Abnormal/Normal	0 / 0
		Visit Study completion	Mean (SD)	NA (NA)
			Median (IQR)	43.30 (0.00)
			Min, Max	43.30, 43.30
			Abnormal/Normal	0 / 0
		Visit FUP	Mean (SD)	66.18 (15.26)
			Median (IQR)	61.54 (14.72)
			Min, Max	53.77, 83.22
			Abnormal/Normal	0 / 0
Factor XII value 1	%	Visit Baseline V2	Mean (SD)	NA (NA)
			Median (IQR)	65.00 (0.00)
			Min, Max	65.00, 65.00
			Abnormal/Normal	0 / 0
		Visit V3	Mean (SD)	84.50 (41.72)
			Median (IQR)	84.50 (29.50)
			Min, Max	55.00, 114.00
			Abnormal/Normal	0 / 0
		Visit V5	Mean (SD)	85.33 (34.30)
			Median (IQR)	101.00 (31.50)
			Min, Max	46.00, 109.00
			Abnormal/Normal	0 / 0
		Visit V7	Mean (SD)	93.00 (39.95)
			Median (IQR)	113.00 (36.00)
			Min, Max	47.00, 119.00
			Abnormal/Normal	0 / 0
		Visit Study completion	Abnormal/Normal	1 / 0
		Visit FUP	Mean (SD)	95.67 (24.01)
			Median (IQR)	108.00 (21.50)
			Min, Max	68.00, 111.00
			Abnormal/Normal	0 / 0
Factor XII value 2		Visit Baseline V2	Mean (SD)	NA (NA)
			Median (IQR)	66.00 (0.00)
			Min, Max	66.00, 66.00
			Abnormal/Normal	0 / 0
		Visit V3	Mean (SD)	84.50 (41.72)
			Median (IQR)	84.50 (29.50)
			Min, Max	55.00, 114.00
			Abnormal/Normal	0 / 0
		Visit V5	Mean (SD)	86.67 (35.44)
			Median (IQR)	103.00 (32.50)

Parameter	Units	Visit	Category/Statistics	Results
			Min, Max	46.00, 111.00
			Abnormal/Normal	0 / 0
		Visit V7	Mean (SD)	93.67 (40.43)
			Median (IQR)	116.00 (35.50)
			Min, Max	47.00, 118.00
			Abnormal/Normal	0 / 0
		Visit Study completion	Abnormal/Normal	1 / 0
		Visit FUP	Mean (SD)	96.67 (25.01)
			Median (IQR)	108.00 (23.00)
			Min, Max	68.00, 114.00
			Abnormal/Normal	0 / 0

Note:Visit Study Completion corresponds to the last site-visit

10.4.2 Statistical issues

Details are described in section 8.8. No missing values replacement was applied otherwise.

10.4.3 Tabulation of individual response data

Not applicable

10.4.4 Drug dose, drug concentration, and relationships to response

All enrolled patients received Lanadelumab 300 mg subcutaneously every 2 weeks during the 48-week treatment phase.

10.4.5 Drug-drug and drug-disease interactions

Not applicable

10.4.6 By-patient displays

Not applicable

10.4.7 Efficacy conclusions

Limitations of the study are, on the one hand, the small sample size of n=5 and, on the other hand, that many diary entries for the determination of the AAS28 are missing. Overall results suggest a clinically relevant benefit in disease activity and disease control. The assessment of the primary endpoint revealed that 2 out of 5 patients showed an improvement of more than 75 % in their AAS28 score at week 45 – 48 compared to their AAS28 score at baseline. The assessment of secondary endpoints showed a decrease of AAS28 total score at weeks 9 – 12, 21 - 24, 33 - 36, and 57 - 60 compared to baseline (weeks -4 to -1). This was also mirrored by the increase in AECT total scores during Lanadelumab treatment compared to baseline. At baseline (V2), patients showed a mean

value of 5.25 (SD = 5.56), and at Visit 7 a mean value of 11.25 (SD = 5.50). This was a change of 6.00 units (SD = 6.78) from baseline to visit 7. Over the course of the study, this represents an increase in the AECT score of more than 3 points, which, according to the definition (see Section 8.5.1), indicates a clinically meaningful/relevant response. After stopping treatment with Lanadelumab, AECT total score decreased by 3.33 units (SD = 0.58) from visit 7 to visit 8. Moreover, the number of SFD slightly increased over time compared to baseline and the quality of life as assessed by AE-QoL was shown to improve in patients with HAE-nC1INH during Lanadelumab treatment. The AE-QoL total score as well as the scores of the subdomains functioning, fatique / mood and fears / shame declined during Lanadelumab treatment compared to baseline. During Lanadelumab treatment in patients with HAE-nC1INH, plasma prekallikrein and FXII serum levels were not noticeably affected.

11. Safety Evaluation

11.1 Extent of Exposure

All enrolled patients (N=5) received Lanadelumab 300 mg subcutaneously every 2 weeks during the 48-week treatment phase.

11.2 Adverse Events

11.2.1 Brief summary of adverse events

All 5 patients experienced adverse events. In total, 28 adverse events (AEs) were documented.

All 5 patients experienced treatment-emergent adverse events. In total, 22 AEs were classified as treatment-emergent.

3 AEs were classified as Serious Adverse Events (SAE).

3 of the AEs were assessed as "related," and 3 of the AEs were assessed as "possibly related" (see also section 11.2.3). All other AEs were "unlikely related" or "not related".

Details of the individual AEs are given in the following paragraph 11.2.2 "Display of adverse events".

11.2.2 Display of adverse events

Below you will find a tabular presentation of the adverse events (Table 11.2.2).

Table 11.2.2: Adverse events by SOC and PT (All AEs)

AE classification (SOC)	Dictionary-Derived Term (PT)	Results N (%) E	By severity (E)
Congenital, familial and genetic disorders	Hereditary Angioedema	1 (20.00%) 1	Mild 0; Moderate 1; Severe 0; Life-threatening 0; Death 0
Eye disorders	Dermatochalasis	1 (20.00%) 1	Mild 0; Moderate 1; Severe 0; Life-threatening 0; Death 0
Gastrointestinal disorders	Abdominal pain	1 (20.00%) 1	Mild 1; Moderate 0; Severe 0; Life-threatening 0; Death 0