via subcutaneous injection at the site. Study participants who were not present at the injection study visits, missing the IMP doses as scheduled in the protocol, were excluded from the per-protocol analysis.

Data obtained within +/- 4 days outside of the scheduled assessment time were analyzed as the visit closest to the collection. Administration of study drug had to be recorded in the source documents and the corresponding CRF for each administration in order to reconstruct an accurate dosing history for each patient. The summary statistics were produced total and by treatment group.

4.1.7 Analysis of the primary endpoint

The main aim of this exploratory efficacy analysis was to determine superiority of Dupilumab compared to placebo for patients with CSU over 16 weeks of treatment.

The primary analysis of the primary endpoint (change of the UAS7 from baseline to week 16, with lower values indicating an improvement) was performed on the ITT-population comparing treatments (Dupilumab vs. placebo) in an analysis of covariance (ANCOVA) model with the fixed factors treatment and study sites (sites with 10 or less patients were pooled together for this analysis), and with baseline UAS7 score (visit 1) as a covariate. The adjusted (least square, LS) group means for each treatment group was presented with their respective 95% confidence interval and an exploratory p-value for the group difference.

The primary endpoint was tested for treatment differences using the non-parametric Wilcoxon Rank Sum Test and with an (unadjusted) analysis of variance (ANOVA) model as sensitivity analyses. In addition, the primary analysis was repeated for the per-protocol-population and for the full analysis set (FAS).

4.1.8 Analysis of secondary endpoints

Continuous secondary efficacy endpoints were analysed analogous to the primary endpoint (ANCOVA adjusting for site and respective baseline value), as yielding adjusted treatment means and mean difference with 95% confidence intervals. The angioedema burdened days and AE-QoL will be assessed analogously, but only in the population of patients with angioedema at baseline.

Binary secondary efficacy endpoints, responder rates, were analyzed with logistic regression (adjusted for site and baseline value if available). Time to event endpoints (e.g. time to response) were analyzed with Cox proportional hazards models (adjusted for center and baseline value if available). Study participants were censored at the end of treatment (v9) or at the time of drop out. Time to non-response was analysed also using the Cox proportional hazard models (adjusted for centre and baseline value) but included only study responders (responders at visit 9) and was assessed using only the follow-up data, collected after IMP discontinuation (visits 9-12).

Other secondary endpoints (rescue medication use, angioedema free days) were summarized descriptively by treatment group. Since this was an exploratory phase II study, all results (including p-values) were considered explorative.

Analyses of secondary endpoints were performed in the FAS. Missing data for secondary endpoints were not imputed and subjects with missing data were excluded from the respective analysis.

4.1.9 Exploratory Efficacy Analyses

The exploratory endpoints, including rescue medication use and angioedema free days, were summarized descriptively by treatment group for the FAS. The change from baseline to all assessment time points was evaluated. The planned analyses of serological and histological markers have not been performed yet.

4.1.10 Safety

Safety analysis was conducted in the safety population. The adverse events were summarized by the number and percentage of patients in each primary system class and by preferred term.

Adverse events (AE) were recorded from Visit 1. Between screening and visit 1 only screening-related AEs were documented. AEs were coded by primary system organ class and preferred term (PT) according to MedDRA version 21.1_EN. An AE related to study drug was defined as one considered by the investigator or sponsor representative to have a suspected relationship with the study drug and was document adequately in the eCRF.

Multiple occurrences of the same AE or SAE in a given patient was counted only once, using the worst severity and drug relationship. In the data listings of adverse events, the severity of an AE, whether or not an AE was study drug related, and whether or not it was a serious AE, was indicated.

4.1.11 Laboratory data

Laboratory was summarized by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges). The results can be presented upon request.

The individual laboratory data including vital parameters were evaluated at every visit and, if abnormal and considered clinical significant, listed as an adverse event. List of adverse events can be found in section 6.1.

4.2 Changes in the conduct of the study or planned analyses

4.2.1 Protocol amendments

The study protocol was amended three times. The original and amended protocol versions are provided in the annex 02_CSR. Previous sections of this report describe the study conduct as amended. The amendment primarily aimed to introduce measures to better define exclusion criteria to allow more study sites to take part in the trial and to enroll patients. To this end, it was clarified in the exclusion that only other active skin diseases are an exclusion and that highly effective, instead of “effective” contraception is to be used.

Further, changes related to the COVID-19 pandemic have been introduced in the last amendment. This included the possibility for self-application of IMP at home in combination with telephone based visits and an adjustment of assessments and rules for rescreening.

4.2.2 Changes in planned analysis

There are no differences between the methods described in this statistical analysis plan and methods described in the protocol.

However, in the current version of the trial protocol, the Hives Severity Score (HSS) was accidentally not included in the tabled listings of the secondary endpoint. HSS was always planned as a secondary endpoint (as stated in the synopsis of the trial protocol) and is included as secondary endpoint.

5 Results

5.1 Demographic and other baseline characteristics

5.1.1 Study subject disposition and demographics

The CONSORT flow diagram can be found in the annex 03_CSR. Overall, 92 patients were screened and 73 were randomized (full analysis set, FAS). One patient was randomized by mistake and is therefore a randomization failure. Three of the randomized patients did not receive study drug, therefore 70 patients comprised the intention-to-treat (ITT) population. Overall, six centers participated in the trial and have randomized patients, the study initiation (first patient first visit) was on 12-NOV-2018, study completion (last patient last visit) on 07-JUL-2021.

The mean (SD) age of the subjects at baseline was 41.8 (15.3) years, and the majority of subjects (60.3%) were female (Table 5-1a).

Table 5-1a. Demographic characteristics (full analysis set, FAS)

Variable	Value	Total	Dupilumab	Placebo
		(n=73)	**(n=48)**	**(n=25)**
Sex	Male	29 (39.7%)	20 (41.7%)	9 (36.0%)
n (%)	Female	44 (60.3%)	28 (58.3%)	16 (64.0%)
Age	Mean (SD)	41.8±15.3	40.0 (14.5)	45.3 (6.3)
	Median (Range)	38 (18-74)	37 (18-68)	45 (21-74)
Skin type (Fitzpatrick)	I	2 (2.7%)	1 (2.1%)	1 (4.0%)
n (%)	II	53 (72.6%)	36 (75.0%)	17 (68.0%)
	III	15 (20.5%)	10 (20.8%)	5 (20.0%)
	IV	3 (4.1%)	1 (2.1%)	2 (8.0%)
Weight (kg)	Mean (SD)	79.0±19.0	78.0 (18.3)	81.0 (20.5)
	Median (Range)	75 (46-127)	75 (46-127)	77 (49-127)
Height (cm)	Mean (SD)	172.2±8.7	172.3±8.7	172.1±8.8
	Median (Range)	173 (148-187)	174 (150-187)	171 (148-185)
BMI	Mean (SD)	26.6 (6.3)	26.4 (6.6)	27.2 (5.6)
	Median (Range)	25 (16-52)	25 (16-52)	25 (20-41)

Table 5-1b. Demographic characteristics (Intention-to-treat population, ITT)

Variable	Value	Total	Dupilumab	Placebo
		(n=70)	**(n=46)**	**(n=24)**
Sex	Male	29 (41.4%)	20 (43.5%)	9 (37.5%)
n (%)	Female	44 (60.3%)	28 (58.3%)	16 (64.0%)
Age	Mean (SD)	41.8±15.5	39.8±14.7	45.7±16.6
	Median (Range)	39 (18-74)	35 (18-68)	45 (21-74)
Skin type (Fitzpatrick)	I	2 (2.9%)	1 (2.2%)	1 (4.2%)
n (%)	II	52 (74.3%)	35 (76.1%)	17 (70.8%)

	III	15 (21.4%)	10 (21.7%)	5 (20.8%)
	IV	1 (1.4%)	0	1 (4.2%)
Weight (kg)	Mean (SD)	80.0±18.8	78.8±18.3	82.4±19.8
	Median (Range)	77 (46-127)	76 (46-127)	78 (53-127)
Height (cm)	Mean (SD)	172.9±8.1	172.8±8.5	173.1±7.3
	Median (Range)	174 (150-187)	174 (150-187)	172 (160-185)
BMI	Mean (SD)	26.8±6.3	26.5±6.7	27.4±5.7
	Median (Range)	26 (16-52)	26 (16-52)	26 (20-41)

5.1.2 Baseline disease characteristics

The mean UAS7 and UCT scores were 26.2 and 5.1, respectively. Half of all subjects had elevated total IgE and 51.4% of patients had a CSU duration of 2-10 years (Table 5-2a).

Table 5-2a. Baseline disease characteristics (full analysis set, FAS)

Variable	Value	Total	Dupilumab	Placebo
		(n=70)	**(n=46)**	**(n=24)**
Total IgE	Mean (SD)	163.0±193.4	199.2±223.8	90.6±70.6
	Median (Range)	104 (2-846)	122 (2-846)	71 (3-226)
Total IgE subgroups	<100 kU/l	35 (50.0%)	20 (43.5%)	15 (62.5%)
(n, %)	≥100 kU/l	35 (50.0%)	26 (56.5%)	9 (37.5%)
	<40 kU/l	21 (30.0%)	13 (28.3%)	8 (33.3%)
	≥40 kU/l	49 (70.0%)	33 (71.7%)	16 (66.7%)
UAS7 score	Mean (SD)	26.2±7.9	25.9±7.5	26.8±8.9
	Median (Range)	26 (1-42)	25 (11-42)	29 (1-42)
UAS7 subgroup	UAS7 < 28	36 (51.4%)	26 (56.5%)	10 (41.7%)
(n, %)	UAS7 ≥ 28	34 (48.6%)	20 (43.5%)	14 (58.3%)
HSS7 score	Mean (SD)	12.8±5.1	12.6±5.1	13.3±5.1
	Median (Range)	14 (0-21)	13 (0-21)	14 (0-21)
ISS7 score	Mean (SD)	13.4±4.4	13.4±4.2	13.5±4.7
	Median (Range)	14 (1-21)	14 (5-21)	14 (1-21)
UCT score	Mean (SD)	5.1±3.0	5.3±2.9	4.9±3.2
	Median (Range)	5 (0-11)	5 (0-11)	5 (0-11)
DLQI score	Mean (SD)	11.8±6.8	11.4±6.5	12.4±7.6
	Median (Range)	11 (1-29)	11 (1-28)	11 (1-29)
CU-Q2oL	Mean (SD)	44.4±17.1	44.1±17.7	45.1±16.5
	Median (Range)	43 (9-83)	42 (11-83)	45 (9-78)
Patients with angioedema (n, %)	yes at baseline	36 (72.0%)	26 (78.8%)	10 (58.8%)
AAS7	Mean (SD)	33.2±21.0	33.5±22.1	32.3±19.0
	Median (Range)	32 (3-82)	32 (4-82)	32 (3-58)
CSU duration	>10 years	25 (35.7%)	15 (32.6%)	10 (41.7%)
	2-10 years	36 (51.4%)	27 (58.7%)	9 (37.5%)
	<2 years	9 (12.9%)	4 (8.7%)	5 (20.8%)

Table 5-2b. Baseline disease characteristics (Intention-to-treat population, ITT)

Variable	Value	Total	Dupilumab	Placebo
		(n=73)	**(n=48)**	**(n=25)**
Total IgE	Mean (SD)	168.8 (198.5)	205.5 (229.8)	95.2(72.6)
	Median (Range)	105 (2-846)	122 (2-846)	74 (3-226)
Total IgE subgroups	<100 kU/l	36 (49.3%)	21 (43.8%)	15 (60.0%)
(n, %)	≥100 kU/l	37 (50.7%)	27 (56.3%)	10 (40.0%)
UAS7 score	Mean (SD)	26.2 (8.0)	25.8 (7.7)	27.0 (8.7)
	Median (Range)	26 (1-42)	25 (11-42)	29 (1-42)
UAS7 subgroup	UAS7 < 28	37 (50.7%)	27 (56.3%)	10 (40.0%)
(n, %)	UAS7 ≥ 28	36 (49.3%)	21 (43.8%)	15 (60.0%)
HSS7 score	Mean (SD)	12.7±5.1	12.4±5.2	13.4±5.0
	Median (Range)	14 (0-21)	13 (0-21)	14 (0-21)
ISS7 score	Mean (SD)	13.5±4.4	13.4±4.3	13.6±4.6
	Median (Range)	14 (1-21)	14 (5-21)	14 (1-21)
UCT score	Mean (SD)	5.2 (2.9)	5.3 (2.9)	4.9 (3.1)
	Median (Range)	5 (0-11)	5 (0-11)	5 (0-11)
DLQI score	Mean (SD)	11.9±7.1	11.3±6.4	13.0±8.2
	Median (Range)	11 (1-29)	11 (1-28)	11 (1-29)
CU-Q2oL	Mean (SD)	44.4±17.1	44.1±17.7	45.1±16.5
	Median (Range)	43 (9-83)	42 (11-83)	45 (9-78)
Patients with angioedema (n, %)	yes at baseline	37 (72.5%)	27 (79.44%)	10 (58.8%)
AAS7	Mean (SD)	32.4±21.3	32.4±22.4	32.3±19.0
	Median (Range)	30 (3-82)	30 (4-82)	32 (3-58)
CSU duration	>10 years	26 (35.6%)	16 (33.3%)	10 (40.0%)
	2-10 years	36 (49.3%)	27 (56.3%)	9 (36.0%)
	<2 years	11 (15.1%)	5 (10.4%)	6 (24.0%)

5.1.3 Prior and concomitant therapies

The most common prior CSU medications by type of therapy included non-sedating antihistamines, systemic corticosteroids, and omalizumab (Table 5-3).

Table 5-3. Prior medications for CSU

CSU medication	Total	Dupilumab	Placebo
	(n=73)	(n=48)	(n=25)
Antihistamines	**142**	**81**	**61**
Fexofenadine	28	12	16
Cetirizine	26	18	8
Ebastine	23	12	11
Rupatadine	20	10	10
Desloratadine	18	12	6
Loratadine	14	9	5
Levocetirizine	6	6	0
Bitosen	4	2	2
Dimetinden	2	0	2
Clemastine	1	0	1
Systemic corticosteroids	**33**	**29**	**4**
Methylprednisolone	24	22	2
Prednisolone	6	5	1
Betamethasone	3	2	1
Omalizumab	**10**	**4**	**6**
Dapsone	**5**	**0**	**5**
Cyclosporine	**1**	**1**	**0**

As per protocol, all subjects were expected to remain on the same antihistamine background medication they were taking before randomization. The most common antihistamines used were fexofenadine, cetirizine, ebastine, and desloratadine (Table 5-4).

Table 5-4. Concomitant antihistamines used within the study as baseline CSU medication

Antihistamine (n, %)	Total	Dupilumab	Placebo
	(n=73)	(n=48)	(n=25)
Fexofenadine	17 (23.3%)	9 (18.8%)	8 (32.0%)
Cetirizine	12 (16.4%)	10 (20.8%)	2 (8.0%)
Ebastine	12 (16.4%)	7 (14.6%)	5 (20.0%)
Loratadine	11 (15.1%)	8 (16.7%)	3 (12.0%)
Desloratadine	9 (12.3%)	5 (10.4%)	4 (16.0%)
Rupatadine	6 (8.2%)	4 (8.3%)	2 (8.0%)
Levocetirizine	4 (5.5%)	4 (8.3%)	0

Concomitant non-CSU medication: Concomitant non-CSU medications are provided in annex04_CSR, in Table 04_01 and 04_02 CSR.

5.2 Primary efficacy results

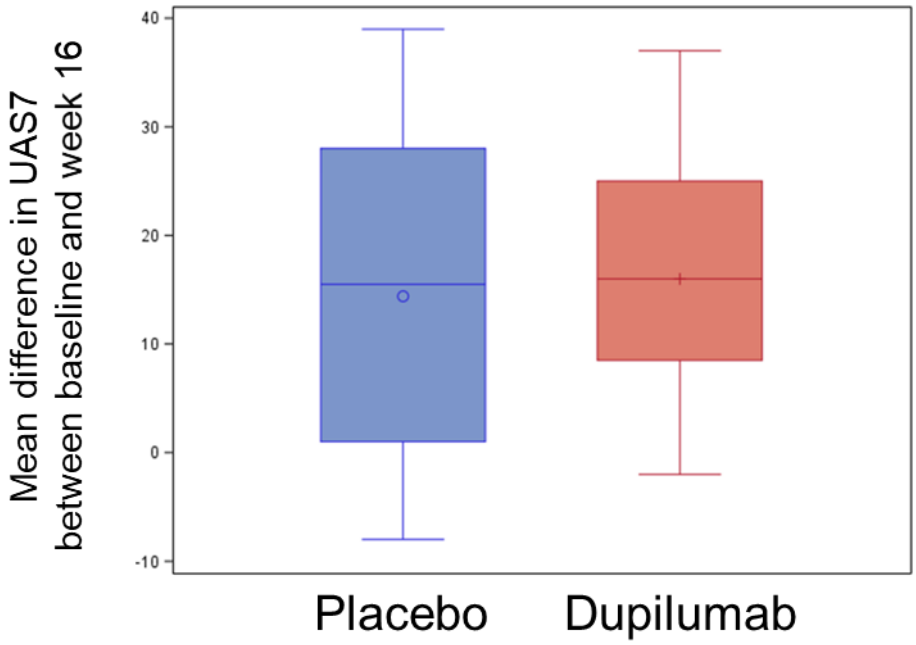
The primary outcome was defined as the difference in the change in urticaria activity score 7 (UAS7) from baseline to week 16 (with negative values indicating an improvement). Treatment with Dupilumab did not show a relevant difference compared to placebo. A superiority of Dupilumab to placebo could thus not be identified (Table 5-5 and Figure 5-1).

5.2.1 Primary endpoint

Table 5-5. Primary endpoint analysis (ITT)

Treatment	N	Change in UAS7 from baseline to week 16	95% Confidence Limits		Mean difference (95% CI)	P-value
		Adjusted mean				
Dupilumab	36	-15.6	-11.5	-19.8	-3.1 (-9.2; 3.0)	0.307
Placebo	22	-12.5	-7.3	-17.7		

Figure 5-1. Boxplot for the mean difference in UAS7 from baseline to week 16 (descriptive, unadjusted)



5.2.2 Secondary analysis of the primary endpoint

The secondary analysis of the primary outcome was performed for treatment differences using the non-parametric Wilcoxon Rank Sum Test (Table 5-6) and with an (unadjusted) analysis of variance (ANOVA) model (Table 5-7) as sensitivity analyses. In addition, the primary analysis was repeated for the per-protocol-population (Table 5-8) and for the full analysis set (FAS) (Table 5-9). Neither of the secondary analysis of the primary endpoint showed a relevant difference compared to placebo. Here: Negative values indicate an improvement in disease severity.

Table 5-6 Secondary analysis of the primary endpoint: Wilcoxon mRank Sum test (ITT, unadjusted)

Treatment	N	Median	Inter-quartile range	Sum of scores	Expected under H_0	Standard dev. Under H_0	p-value
Dupilumab	36	16.0	8.5 – 25.0	1091.0	1062.0	62.4	0.642
Placebo	22	15.0	1.0 – 28.0	620.0	649.0	62.4	

Table 5-7. Secondary analysis of the primary endpoint: ITT, unadjusted)

Treatment	N	Change in UAS7 from baseline to week 16	95% Confidence Limits		Mean difference (95% CI)	P-value
		Adjusted mean				
Dupilumab	36	-15.9	-11.9	-20.1	-1.6 (-8.3; 5.1)	0.635
Placebo	22	-14.4	-9.1	-19.7		

Table 5-8.Secondary analysis of the primary endpoint: Per-protocol population

Treatment	N	Change in UAS7 from baseline to week 16	95% Confidence Limits		Mean difference (95% CI)	P-value
		Adjusted mean				
Dupilumab	27	-15.6	-10.8	-20.4	-3.2 (-10.4; 3.9)	0.371
Placebo	16	-12.4	-6.0	-18.7		

Table 5-9. Secondary analysis of the primary endpoint: FAS

Treatment	N	Change in UAS7 from baseline to week 16	95% Confidence Limits		Mean difference (95% CI)	P-value
		Adjusted mean				
Dupilumab	36	-15.6	-11.5	-19.8	-3.1 (-9.2; 3.0)	0.307
Placebo	22	-12.5	-7.3	-17.7		

5.2.3 Primary endpoint analyses by pre-defined subgroups

Pre-defined and post hoc subgroup analyses have been carried out for the following baseline variables: severity (UAS ≥28 or <28), total IgE levels (≥100 kU/l or <100 kU/l; and ≥40 kU/l or <40 kU/l), presence of angioedema, duration of disease (<2 years, 2-10 years, ≥10 years), and previous omalizumab treatment (Tables 5-10 to 5-15). Results indicating that the treatment effect is different within the subgroups, was only observed for a better response to Dupilumab treatment in patients with very low total IgE (<40kU/l). All subgroups analyses have been performed using ANCOVA (by treatment group with fixed center and baseline UAS7 scores as covariates and with subgroup interaction) in the ITT population. Here: higher values indicate higher disease severity.

Table 5-10. Change in UAS7 from baseline to week 16, depending on total IgE level (cut-off 40kU/l)

			Change in UAS7		
Treatment	**Total IgE group**	**N**	**Adj. Mean**	**CI95%**	**P-value**
Dupilumab	<40 kU/l	8	18.56	11.03; 26.10	0.023
Dupilumab	≥40 kU/l	28	15.12	10.65; 19.58	
Placebo	<40 kU/l	8	5.41	-2.35; 13.17	
Placebo	≥40 kU/l	14	17.00	10.76; 23.25	

Table 5-11. Change in UAS7 from baseline to week 16, depending on total IgE level (cut-off 100kU/l)

			Change in UAS7		
Treatment	**Total IgE group**	**N**	**Adj. Mean**	**CI95%**	**p-value**
Dupilumab	<100	14	18.16	11.78; 24.55	0.436
Dupilumab	≥100	22	14.05	8.89; 19.21	
Placebo	<100	15	12.23	5.95; 18.51	
Placebo	≥100	7	13.18	4.17; 22.20	

Table 5-12. Change in UAS7 from baseline to week 16, depending on UAS7 severity

			Change in UAS7		
Treatment	**UAS7 score**	**N**	**Adj. Mean**	**CI95%**	**P-value**
Dupilumab	<28	19	12.39	5.00; 19.79	0.411
Dupilumab	≥28	17	18.98	11.59; 26.38	
Placebo	<28	9	12.13	2.60; 21.66	
Placebo	≥28	13	13.46	5.29; 21.63	

Table 5-13. Change in UAS7 from baseline to week 16, depending on presence of angioedema

			Change in UAS7		
Treatment	**Angioedema**	**N**	**Adj. Mean**	**CI95%**	**P-value**
Dupilumab	Yes	17	14.74	8.31; 21.17	0.153
Dupilumab	No	7	19.08	9.57; 28.60	
Placebo	Yes	9	15.97	7.76; 24.18	
Placebo	No	6	8.60	-1.42; 18.60	

Table 5-14. Change in UAS7 from baseline to week 16, depending on duration of CSU

			Change in UAS7		
Treatment	**CSU Duration**	**N**	**Adj. Mean**	**CI95%**	**p-value**
Dupilumab	<2 years	12	19.51	13.32; 25.71	0.102
Dupilumab	2-10 years	22	15.17	10.42; 19.91	
Dupilumab	≥10 years	2	13.94	-1.29; 29.17	
Placebo	<2 years	9	15.38	7.94; 22.83	
Placebo	2-10 years	9	18.82	11.23; 26.41	
Placebo	≥10 years	4	-3.56	-14.21; 7.08	

Table 5-15. Change in UAS7 from baseline to week 16, depending on previous omalizumab use*

			Change in UAS7		
Treatment	**Previous omalizumab**	**N**	**Adj. Mean**	**CI95%**	**p-value**
Dupilumab	Yes	11	14.71	7.81; 21.22	0.131

Dupilumab	No	8	20.71	12.78; 28.65
Placebo	Yes	5	19.91	9.86; 20.87
Placebo	No	8	12.87	4.86; 20.87

*Data available form only 1 out of 6 study centers

5.3 Secondary efficacy results

5.3.1 Efficacy over time

The mean change of UAS7, AAS7, UCT, HSS7, ISS7, IGA, PGA, and the use of rescue medication (per week) over time (ANCOVA Repeated measures model adjusted for baseline and study center) is shown in Figure 5-2 and Table 5-16 to 5-24. Here, comparable rates of improvement and similar use of rescue medication between Dupilumab and placebo can be observed in all analyses.

Figure 5-2. Change in UAS7 from baseline over time shows comparable rates of improvement in both treatment groups [negative values indicate an improvement in disease severity; adjusted]

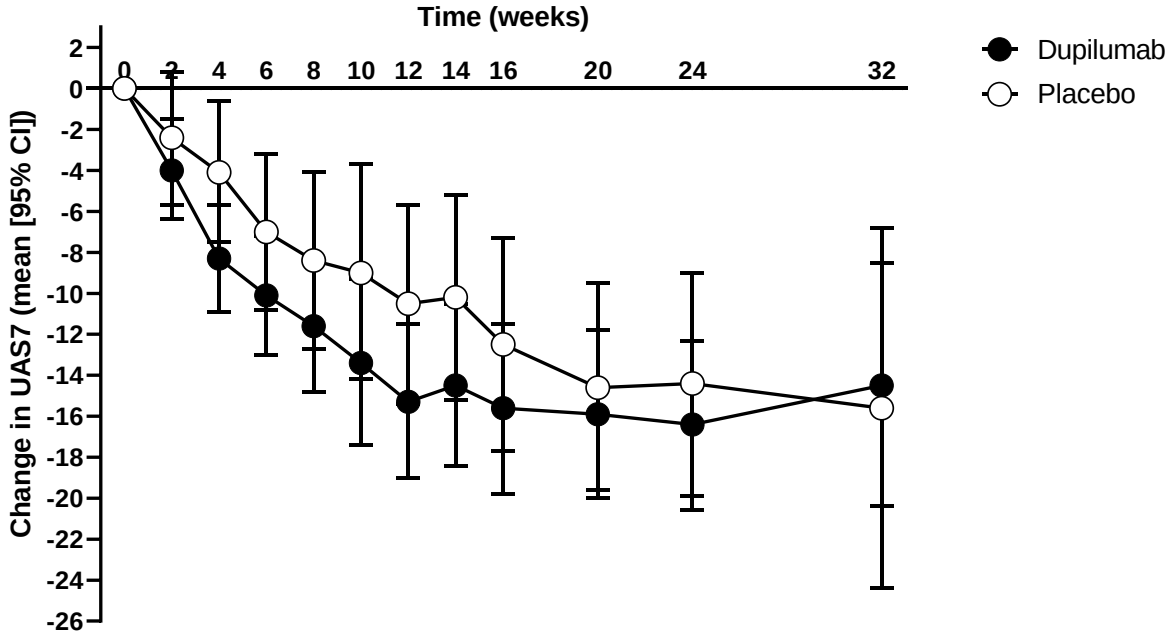


Table 5-16. Change versus baseline over time for UAS7 [FAS population]. Change calculated as change from baseline (Week 0) to a given time point (Week 0 minus week X); Here: in the treatment groups higher values indicate an improvement of disease severity as compared to baseline.

Week	N	Dupilumab Adj. Mean [95% CI]	Placebo Adj. Mean [95% CI]	Difference Adj. Mean [95% CI]	p-Value
2	71	4.0 [1.5;6.4]	2.4 [-0.8;5.7]	1.5 [-2.2;5.3]	0.412
4	69	8.3 [5.7;10.9]	4.1 [0.6;7.5]	4.2 [0.2;8.2]	0.039
6	69	10.1 [7.2;13.0]	7.0 [3.2;10.8]	3.1 [-1.3;7.5]	0.167
8	67	11.6 [8.5;14.8]	8.4 [4.1;12.7]	3.2 [-1.7;8.1]	0.193
10	62	13.4 [9.3;17.4]	9.0 [3.7;14.2]	4.4 [-1.7;10.4]	0.153
12	60	15.3 [11.5;19.0]	10.5 [5.7;15.4]	4.7 [-0.9;10.4]	0.100
14	59	14.5 [10.5;18.4]	10.2 [5.2;15.2]	4.3 [-1.5;10.1]	0.146

Week	N	Dupilumab Adj. Mean [95% CI]	Placebo Adj. Mean [95% CI]	Difference Adj. Mean [95% CI]	p-Value
16	58	15.6 [11.5;19.8]	12.5 [7.3;17.7]	3.1 [-3.0;9.2]	0.307
20	57	15.9 [11.8;20.0]	14.6 [9.5;19.6]	1.3 [-4.6;7.2]	0.659
24	54	16.4 [12.3;20.6]	14.4 [9.0;19.9]	2.0 [-4.3;8.3]	0.530
32	33	14.5 [8.5;20.4]	15.6 [6.8;24.4]	-1.1 [-9.9;7.6]	0.790

Table 5-17. Change versus baseline over time for AAS7 [FAS population]. Change calculated as change from baseline (Week 0) to a given time point (Week 0 minus Week X); in the treatment groups higher values indicate an improvement of disease severity as compared to baseline.

Week	N	Treatment Adj. Mean [95% CI]	Placebo Adj. Mean [95% CI]	Difference Adj. Mean [95% CI]	p-Value
2	48	7.2 [0.3;14.0]	3.8 [-4.6;12.2]	3.3 [-6.3;13.0]	0.489
4	48	11.9 [4.0;19.9]	1.8 [-7.9;11.5]	10.2 [-1.0;21.3]	0.073
6	48	11.1 [3.9;18.4]	5.8 [-3.1;14.8]	5.3 [-5.0;15.6]	0.306
8	47	11.6 [3.8;19.4]	3.4 [-6.7;13.5]	8.2 [-3.2;19.6]	0.152
10	41	13.0 [5.2;20.9]	7.0 [-2.3;16.2]	6.1 [-4.6;16.7]	0.255
12	40	14.1 [6.2;22.0]	0.6 [-9.0;10.2]	13.5 [2.4;24.6]	0.019
14	40	16.7 [9.7;23.8]	6.2 [-2.2;14.6]	10.6 [0.8;20.3]	0.035
16	39	12.9 [5.2;20.5]	7.1 [-2.0;16.2]	5.8 [-4.8;16.4]	0.277
20	39	14.0 [6.1;21.8]	9.4 [0.0;18.7]	4.6 [-6.3;15.5]	0.397
24	36	13.6 [8.3;18.9]	14.7 [8.0;21.4]	-1.1 [-8.8;6.6]	0.773
32	28	17.8 [10.7;25.0]	16.8 [7.0;26.6]	1.1 [-7.9;10.1]	0.809

Table 5-18. Change versus baseline over time for UCT [FAS population]. Change calculated as change from baseline (Week 0) to a given time point (Week 0 minus week X); in the treatment groups the negative values indicate an improvement as compared to baseline

Week	N	Dupilumab Adj. Mean [95% CI]	Placebo Adj. Mean [95% CI]	Difference Adj. Mean [95% CI]	p-Value
2	70	-2.0 [-2.8; -1.2]	-1.7 [-2.8; -0.6]	-0.3 [-1.5;1.0]	0.653
4	68	-2.8 [-3.8; -1.8]	-2.5 [-3.9; -1.1]	-0.3 [-1.9;1.2]	0.670
6	66	-3.7 [-4.7; -2.8]	-2.4 [-3.7; -1.1]	-1.4 [-2.9;0.1]	0.076
8	61	-4.3 [-5.4; -3.1]	-4.3 [-5.9; -2.7]	0.0 [-1.8;1.9]	0.962
10	57	-4.4 [-5.6; -3.2]	-3.9 [-5.6; -2.2]	-0.5 [-2.4;1.4]	0.605
12	56	-4.8 [-6.2; -3.4]	-3.9 [-5.8; -2.0]	-0.9 [-3.0;1.2]	0.401
14	56	-5.3 [-6.8; -3.8]	-4.5 [-6.5; -2.5]	-0.8 [-3.1;1.5]	0.485
16	60	-5.4 [-7.0; -3.9]	-4.5 [-6.5; -2.5]	-1.0 [-3.3;1.3]	0.400
20	57	-4.7 [-6.3; -3.1]	-5.5 [-7.5; -3.5]	0.9 [-1.5;3.2]	0.466
24	50	-5.9 [-7.7; -4.0]	-5.1 [-7.4; -2.8]	-0.8 [-3.6;2.0]	0.564
32	62	-4.9 [-6.6; -3.1]	-5.0 [-7.2; -2.8]	0.2 [-2.3;2.7]	0.895

Table 5-19. Change versus baseline over time for PGA [FAS population]. Change calculated as change from baseline (Week 0) to a given time point (Week 0 minus week X); in the treatment groups higher values indicate an improvement of PGA as compared to baseline.

Week	N	Dupilumab Adj. Mean [95% CI]	Placebo Adj. Mean [95% CI]	Difference Adj. Mean [95% CI]	p-Value
2	70	12.7 [5.0;20.3]	10.9 [0.7;21.1]	1.8 [-10.0;13.5]	0.766
4	68	17.4 [9.8;25.0]	14.9 [4.4;25.3]	2.6 [-9.3;14.4]	0.666
6	66	25.9 [18.3;33.4]	17.2 [6.9;27.5]	8.7 [-3.2;20.5]	0.150
8	61	26.9 [17.4;36.4]	28.3 [15.3;41.2]	-1.4 [-16.0;13.2]	0.849
10	57	32.4 [22.2;42.5]	24.0 [10.2;37.8]	8.4 [-7.4;24.2]	0.291
12	56	35.6 [26.1;45.1]	31.2 [18.8;43.7]	4.3 [-10.0;18.7]	0.546
14	56	37.7 [28.5;46.8]	37.4 [25.3;49.5]	0.3 [-13.7;14.2]	0.969
16	60	34.3 [23.2;45.3]	35.7 [21.9;49.5]	-1.4 [-17.5;14.6]	0.858
20	57	33.4 [23.1;43.7]	40.4 [27.5;53.3]	-7.0 [-22.3;8.3]	0.363
24	50	40.8 [29.9;51.8]	37.8 [24.4;51.2]	3.1 [-13.4;19.6]	0.709
32	62	35.3 [24.3;46.4]	37.7 [24.1;51.3]	-2.4 [-18.1;13.3]	0.763v

Table 5-20. Change versus baseline over time for IGA [FAS population]. Change calculated as change from baseline (Week 0) to a given time point (Week 0 minus week X); in the treatment groups higher values indicate an improvement of IGA as compared to baseline.

Week	N	Dupilumab Adj. Mean [95% CI]	Placebo Adj. Mean [95% CI]	Difference Adj. Mean [95% CI]	p-Value
2	70	13.0 [5.2;20.8]	15.8 [5.4;26.1]	-2.7 [-14.5;9.1]	0.646
4	68	20.0 [12.3;27.8]	20.6 [9.9;31.3]	-0.6 [-12.5;11.4]	0.922
6	66	23.3 [15.1;31.5]	20.0 [8.9;31.1]	3.3 [-9.3;16.0]	0.598
8	61	28.9 [20.8;37.0]	34.1 [23.0;45.1]	-5.2 [-17.5;7.1]	0.402
10	57	35.2 [25.5;44.9]	30.6 [17.4;43.8]	4.5 [-10.3;19.4]	0.543
12	56	37.5 [27.9;47.1]	32.9 [20.3;45.6]	4.5 [-9.8;18.8]	0.528
14	56	40.1 [30.0;50.2]	38.3 [24.9;51.6]	1.8 [-13.3;16.9]	0.811
16	62	34.1 [22.4;45.7]	32.0 [17.6;46.4]	2.1 [-14.5;18.6]	0.803
20	59	30.6 [20.2;41.1]	37.5 [24.5;50.4]	-6.8 [-21.9;8.3]	0.368
24	49	36.7 [25.4;48.0]	32.1 [19.1;45.1]	4.6 [-11.6;20.7]	0.570
32	62	35.0 [22.4;47.5]	37.8 [22.7;52.8]	-2.8 [-20.1;14.4]	0.743

Table 5-21. Change versus baseline over time for HSS7 [FAS population]. Change calculated as change from baseline (Week 0) to a given time point (Week 0 minus week X); in the treatment groups higher values indicate an improvement of HSS7 as compared to baseline.

Week	N	Treatment Adj. Mean [95% CI]	Placebo Adj. Mean [95% CI]	Difference Adj. Mean [95% CI]	p-Value
2	71	1.8 [0.5;3.1]	0.9 [-0.8;2.7]	0.9 [-1.1;2.9]	0.379
4	69	3.9 [2.5;5.2]	1.4 [-0.4;3.2]	2.4 [0.4;4.5]	0.022
6	69	4.4 [2.9;5.8]	2.9 [0.9;4.8]	1.5 [-0.8;3.7]	0.191
8	67	5.7 [4.1;7.3]	3.8 [1.6;6.0]	1.9 [-0.6;4.4]	0.127
10	62	6.9 [4.8;9.0]	3.7 [1.0;6.5]	3.2 [0.0;6.4]	0.048
12	60	8.0 [6.0;9.9]	4.9 [2.3;7.4]	3.1 [0.2;6.0]	0.039
14	59	7.2 [5.1;9.3]	4.7 [2.1;7.4]	2.5 [-0.6;5.6]	0.115
16	58	7.6 [5.4;9.7]	5.8 [3.1;8.5]	1.8 [-1.4;5.0]	0.269
20	57	8.3 [6.1;10.5]	7.2 [4.5;9.9]	1.1 [-2.1;4.2]	0.498
24	54	8.7 [6.5;10.9]	6.9 [4.1;9.8]	1.8 [-1.6;5.1]	0.289
32	33	8.0 [4.9;11.1]	7.5 [2.9;12.2]	0.5 [-4.1;5.1]	0.830

Table 5-22. Change versus baseline over time for IGA [FAS population]. Change calculated as change from baseline (Week 0) to a given time point (Week 0 minus week X); in the treatment groups higher values indicate an improvement of ISS7 as compared to baseline.

Week	N	Treatment Adj. Mean [95% CI]	Placebo Adj. Mean [95% CI]	Difference Adj. Mean [95% CI]	p-Value
2	71	2.2 [0.8;3.6]	1.5 [-0.3;3.4]	0.7 [-1.5;2.8]	0.533
4	68	4.2 [2.9;5.6]	1.9 [-0.0;3.8]	2.4 [0.2;4.5]	0.032
6	68	5.4 [4.0;6.9]	3.3 [1.3;5.4]	2.1 [-0.2;4.5]	0.075
8	67	5.8 [4.1;7.5]	4.5 [2.2;6.9]	1.3 [-1.4;4.0]	0.343
10	62	6.3 [4.2;8.5]	5.2 [2.5;8.0]	1.1 [-2.1;4.3]	0.492
12	60	7.3 [5.3;9.2]	5.6 [3.0;8.1]	1.7 [-1.3;4.7]	0.256
14	59	7.2 [5.2;9.2]	5.4 [2.9;8.0]	1.7 [-1.2;4.7]	0.243
16	57	7.9 [5.8;9.9]	6.1 [3.4;8.8]	1.8 [-1.3;4.9]	0.259
20	57	7.6 [5.5;9.6]	7.3 [4.8;9.9]	0.2 [-2.7;3.2]	0.880
24	54	7.6 [5.5;9.8]	7.6 [4.7;10.4]	0.1 [-3.2;3.4]	0.964
32	33	6.4 [3.4;9.5]	8.2 [3.7;12.7]	-1.8 [-6.3;2.7]	0.423

Table 5-23. Change versus baseline over time for Angioedema burden days (descriptive analysis [mean±SD]) [FAS population]. Change calculated as change from baseline (Week 0) to a given time point (Week 0 minus week X); higher values indicate a decrease in burden days as compared to baseline.

Week	N	Total (mean±SD)	Treatment (mean±SD)	Placebo (mean±SD)
2	35	0.3±1.7	0.5±1.8	0.0±1.6
4	34	1.1±2.2	1.2±2.4	0.7±1.7
6	34	1.1±2.3	1.0±2.5	1.3±1.7
8	34	0.9±2.6	1.0±2.6	0.7±2.6
10	28	1.4±2.7	1.4±2.6	1.5±3.1
12	27	1.6±2.8	1.7±2.7	1.4±3.2
14	27	2.0±2.2	2.0±1.9	2.1±3.0
16	26	2.1±2.5	1.9±1.9	2.4±3.4
20	26	2.2±2.5	2.1±2.4	2.2±2.8
24	23	2.3±2.6	2.1±2.3	2.5±3.2
32	17	3.0±2.4	2.5±2.2	3.8±2.6

Table 5-24. Use of rescue medication (antihistamines) per week (descriptive analysis [mean±SD]) [FAS population] Change calculated as change from baseline (Week 0) to a given time point (Week 0 minus week X); higher values indicate a decrease in taken rescue medications H1AH as compared to baseline.

Week	N	Total (mean±SD)	Treatment (mean±SD)	Placebo (mean±SD)
2	71	1.4±4.3	1.3±4.1	1.4±4.7
4	68	1.8±5.2	2.0±4.9	1.5±6.0
6	69	1.8±5.9	1.8±5.3	1.7±6.9
8	66	1.0±5.1	1.0±4.7	0.9±5.9
10	61	1.3±5.9	1.6±6.5	0.8±4.6
12	60	1.9±6.1	2.7±5.8	0.5±6.5
14	57	1.3±6.3	2.2±6.0	-0.3±6.5
16	58	1.2±6.5	2.1±6.2	-0.1±6.8
20	56	1.5±6.0	2.6±6.0	-0.2±5.7
24	54	2.6±5.9	3.0±6.6	1.9±4.6
32	35	1.7±6.0	1.2±7.3	2.3±3.8

5.3.2 Effects on quality of life

Organ- and disease-specific quality of life was assessed using the dermatology life quality index (DLQI), the chronic urticaria questionnaire for the quality of life (CU-Q2oL), and angioedema quality of life questionnaire (AE-QoL). ANCOVA analyses adjusted for baseline values and study center showed comparable rates of improvement in quality of life between Dupilumab and placebo can be observed in all analyses (Tables 5-25 to 5-27).

Table 5-25. Change versus baseline over time for DLQI [FAS population]. Change calculated as change from baseline (Week 0) to a given time point (Week 0 minus week X); Overall, higher values indicate worse QoL; here: positive values indicate an improvement of QoL as compared to baseline.

Week	N	Treatment Adj. Mean [95% CI]	Placebo Adj. Mean [95% CI]	Difference Adj. Mean [95% CI]	p-Value
2	70	3.0 [1.6;4.5]	1.1 [-0.9;3.1]	1.9 [-0.3;4.2]	0.094
4	68	3.3 [1.8;4.8]	2.2 [0.2;4.3]	1.0 [-1.3;3.4]	0.379
6	66	5.5 [4.0;7.1]	3.6 [1.5;5.7]	2.0 [-0.5;4.4]	0.111
8	61	5.3 [3.7;6.8]	5.2 [3.1;7.4]	0.0 [-2.4;2.5]	0.970
10	57	5.5 [3.4;7.5]	3.2 [0.4;6.0]	2.3 [-0.9;5.4]	0.162
12	56	6.2 [4.4;8.1]	3.7 [1.3;6.2]	2.5 [-0.3;5.3]	0.077
14	56	6.4 [4.5;8.2]	5.1 [2.7;7.5]	1.2 [-1.5;4.0]	0.372
16	60	6.4 [4.6;8.2]	6.1 [3.9;8.4]	0.2 [-2.4;2.9]	0.868
20	56	6.6 [4.6;8.6]	5.6 [3.2;8.1]	1.0 [-2.0;3.9]	0.514
24	50	6.8 [4.5;9.0]	5.4 [2.6;8.1]	1.4 [-2.0;4.8]	0.405
32	62	5.8 [3.7;7.8]	6.1 [3.6;8.6]	-0.3 [-3.3;2.6]	0.828

Table 5-26. Change versus baseline over time for CU-Q2oL [FAS population]. Change calculated as change from baseline (Week 0) to a given time point (Week 0 minus week X); Overall, lower values indicate better QoL; here: positive values indicate an improvement of QoL as compared to baseline.

Week	N	Treatment Adj. Mean [95% CI]	Placebo Adj. Mean [95% CI]	Difference Adj. Mean [95% CI]	p-Value
2	71	16.8 [12.0;21.6]	16.5 [9.9;23.2]	0.3 [-7.2;7.8]	0.944
4	68	20.2 [14.5;25.8]	13.8 [6.0;21.5]	6.4 [-2.4;15.2]	0.151
6	68	20.2 [14.6;25.8]	13.8 [6.3;21.3]	6.4 [-2.2;15.0]	0.142
8	67	22.9 [17.0;28.8]	17.0 [9.2;24.9]	5.9 [-3.1;14.9]	0.194
10	62	21.6 [15.3;28.0]	18.1 [10.2;26.1]	3.5 [-5.8;12.8]	0.451
12	60	21.8 [15.5;28.1]	19.7 [11.8;27.7]	2.1 [-7.2;11.4]	0.653
14	59	21.6 [14.2;29.0]	19.2 [10.1;28.4]	2.4 [-8.8;13.5]	0.672
16	57	18.6 [11.8;25.5]	19.7 [11.2;28.2]	-1.1 [-10.9;8.7]	0.821
20	57	16.8 [12.0;21.6]	16.5 [9.9;23.2]	0.3 [-7.2;7.8]	0.944
24	54	20.2 [14.5;25.8]	13.8 [6.0;21.5]	6.4 [-2.4;15.2]	0.151
32	33	20.2 [14.6;25.8]	13.8 [6.3;21.3]	6.4 [-2.2;15.0]	0.142

Table 5-27. Change versus baseline over time for AE-Q2oL [FAS population]. Change calculated as change from baseline (Week 0) to a given time point (Week 0 minus week X); Overall, higher values indicate better QoL; here: positive values indicate an improvement of QoL as compared to baseline.

Week	N	Treatment Adj. Mean [95% CI]	Placebo Adj. Mean [95% CI]	Difference Adj. Mean [95% CI]	p-Value
2	52	4.3 [-1.6;10.1]	9.2 [2.1;16.3]	-4.9 [-13.1;3.2]	0.230
4	51	7.0 [0.8;13.2]	11.1 [3.2;19.1]	-4.1 [-13.1;4.9]	0.362
6	49	15.7 [8.6;22.8]	15.6 [6.5;24.7]	0.0 [-10.4;10.5]	0.992
8	44	12.5 [5.7;19.2]	13.2 [4.5;21.8]	-0.7 [-10.5;9.1]	0.885

Week	N	Treatment Adj. Mean [95% CI]	Placebo Adj. Mean [95% CI]	Difference Adj. Mean [95% CI]	p-Value
10	42	18.6 [11.0;26.1]	17.9 [8.1;27.6]	0.7 [-10.5;11.9]	0.899
12	41	20.2 [11.6;28.8]	13.7 [2.9;24.5]	6.5 [-6.0;19.0]	0.299
14	41	20.9 [11.5;30.4]	14.9 [3.1;26.8]	6.0 [-7.8;19.7]	0.384
16	43	18.3 [9.0;27.6]	18.4 [7.5;29.3]	-0.1 [-13.0;12.8]	0.988
20	41	18.8 [8.8;28.7]	16.8 [4.9;28.7]	1.9 [-12.3;16.2]	0.784
24	37	18.8 [9.2;28.5]	15.9 [4.8;27.1]	2.9 [-11.0;16.7]	0.675
32	45	16.3 [6.4;26.2]	17.4 [5.8;29.0]	-1.1 [-14.7;12.5]	0.871

5.3.3 Responder analyses

5.3.3.1 Clinical response based on minimal important difference (MID)

Responder analyses have been performed regarding a clinical response in UAS7 (reduction of 10 points [MID]), UCT (reduction of 10 points [MID]) and CU-Q2oL (reduction of 15 points [MID]) compared to baseline (Tables 5-28 to 5-35). Overall, no relevant differences have been observed between the treatment groups.

Table 5-28. UAS7 - Clinical responders - descriptive analysis, unadjusted (n,%) [FAS population]

UAS response	N	Missing	Outcome	Total (n=73)	Dupilumab (n=48)	Placebo (n=25)
Week 2	71	2	responder	16 (22.5%)	13 (27.7%)	3 (12.5%)
Week 4	69	4	responder	26 (37.7%)	18 (40.0%)	8 (33.3%)
Week 6	69	4	responder	33 (47.8%)	21 (46.7%)	12 (50.0%)
Week 8	67	6	responder	36 (53.7%)	24 (54.5%)	12 (52.2%)
Week 10	62	11	responder	35 (56.5%)	23 (59.0%)	12 (52.2%)
Week 12	60	13	responder	39 (65.0%)	25 (65.8%)	14 (63.6%)
Week 14	59	14	responder	39 (66.1%)	26 (70.3%)	13 (59.1%)
Week 16	58	15	responder	41 (70.7%)	27 (75.0%)	14 (63.6%)

Table 5-29. UAS7 - proportion of clinical responders – logistic regression adjusted for baseline and study center [FAS population]

Week	N	Odds ratio (Dupilumab vs placebo)	95% Confidence interval		p-value
2	71	2.82	0.71	11.21	0.142
4	69	1.46	0.50	4.28	0.488
6	69	0.98	0.34	2.85	0.967
8	67	1.32	0.43	4.04	0.632
10	62	1.49	0.48	4.60	0.490
12	60	1.33	0.41	4.37	0.637
14	59	2.17	0.63	7.43	0.218
16	58	2.17	0.61	7.72	0.230

Table 5-30. ISS7 - Clinical responders - descriptive analysis, unadjusted (n,%) [FAS population]

ISS response	N	Missing	Outcome	Total (n=73)	Dupilumab (n=48)	Placebo (n=25)
Week 2	71	2	responder	21 (29.6%)	16 (34.0%)	5 (20.8%)
Week 4	68	5	responder	30 (44.1%)	21 (46.7%)	9 (39.1%)

ISS response	N	Missing	Outcome	Total (n=73)	Dupilumab (n=48)	Placebo (n=25)
Week 6	68	5	responder	38 (55.9%)	26 (57.8%)	12 (52.2%)
Week 8	67	6	responder	34 (50.7%)	22 (50.0%)	12 (52.2%)
Week 10	62	11	responder	38 (61.3%)	25 (64.1%)	13 (56.5%)
Week 12	60	13	responder	38 (63.3%)	25 (65.8%)	13 (59.1%)
Week 14	59	14	responder	40 (67.8%)	27 (73.0%)	13 (59.1%)
Week 16	57	16	responder	41 (71.9%)	27 (75.0%)	14 (66.7%)

Table 5-31. ISS7 - proportion of clinical responders – logistic regression adjusted for baseline and study center [FAS population]

Week	N	Odds ratio (Dupilumab vs placebo)	95% Confidence interval		p-value
2	71	2.11	0.64	6.90	0.218
4	68	1.57	0.53	4.68	0.420
6	68	1.67	0.53	5.25	0.382
8	67	1.11	0.37	3.36	0.853
10	62	1.97	0.60	6.51	0.267
12	60	2.11	0.57	7.78	0.261
14	59	2.56	0.74	8.92	0.140
16	57	2.192	0.57	8.51	0.257

Table 5-32. UCT - Clinical responders - descriptive analysis, unadjusted (n,%) [FAS population]

UCT responder	N	Missing	Value	Total (n=73)	Dupilumab (n=48)	Placebo (n=25)
Week 2	70	3	responder	14 (20.0%)	9 (19.6%)	5 (20.8%)
Week 4	68	5	responder	23 (33.8%)	15 (33.3%)	8 (34.8%)
Week 6	66	7	responder	36 (54.5%)	24 (55.8%)	12 (52.2%)
Week 8	61	12	responder	35 (57.4%)	20 (51.3%)	15 (68.2%)
Week 10	57	16	responder	38 (66.7%)	24 (64.9%)	14 (70.0%)
Week 12	56	17	responder	35 (62.5%)	24 (66.7%)	11 (55.0%)
Week 14	56	17	responder	37 (66.1%)	22 (61.1%)	15 (75.0%)
Week 16	60	13	responder	37 (61.7%)	23 (62.2%)	14 (60.9%)

Table 5-33. UCT - proportion of clinical responders – logistic regression adjusted for baseline and study center [FAS population]

Week	N	Odds ratio (Dupilumab vs placebo)	95% Confidence Interval		p-value
2	70	1.20	0.29	5.01	0.805
4	68	1.29	0.36	4.19	0.743
6	66	1.75	0.53	5.84	0.361
8	61	0.43	0.12	1.52	0.189
10	57	0.76	0.21	2.70	0.666
12	56	1.78	0.48	6.60	0.388
14	56	0.57	0.15	2.08	0.382
16	60	1.17	0.38	3.57	0.784

Table 5-34. CU-Q2oL - Clinical responders - descriptive analysis, unadjusted (n,%) [FAS population]

CU-Q2oL responder	N	Missing	Value	Total (n=73)	Dupilumab (n=48)	Placebo (n=25)
Week 2	70	3	responder	15 (21.4%)	11 (23.9%)	4 (16.7%)
Week 4	67	6	responder	26 (38.8%)	16 (36.4%)	10 (43.5%)
Week 6	65	8	responder	31 (47.7%)	21 (50.0%)	10 (43.5%)
Week 8	60	13	responder	31 (51.7%)	21 (55.3%)	10 (45.5%)
Week 10	57	16	responder	32 (56.1%)	22 (59.5%)	10 (50.0%)
Week 12	56	17	responder	35 (62.5%)	25 (69.4%)	10 (50.0%)
Week 14	56	17	responder	37 (66.1%)	26 (72.2%)	11 (55.0%)
Week 16	59	14	responder	36 (61.0%)	24 (66.7%)	12 (52.2%)

Table 5-35. CU-Q2oL - proportion of clinical responders – logistic regression adjusted for baseline and study center [FAS population]

Week	N	Odds ratio (Dupilumab vs placebo)	95% Confidence Interval		p-value
2	70	1.64	0.44	6.03	0.456
4	67	0.78	0.26	2.27	0.642
6	65	1.71	0.54	5.46	0.362
8	60	1.68	0.53	5.37	0.378
10	57	1.78	0.58	6.10	0.361
12	56	3.16	0.87	11.56	0.082
14	56	3.71	0.84	16.38	0.083
16	59	2.47	0.76	8.31	0.144

5.3.3.2 Complete response

Responder analyses have been performed regarding a complete response in UAS7 (≤ 6 or reduction of ≥90% compared to baseline), UCT (UCT of ≥12) and AAS7 (ASS of 0 or a reduction of ≥90%) compared to baseline (Tables 5-36 to 5-45). Overall, no relevant differences have been observed between the treatment groups.

Table 5-36. UAS7 - Complete responders - descriptive analysis, unadjusted (n,%) [FAS population]

UAS7 Complete responder	N	Missing	Value	Total (n=73)	Dupilumab (n=48)	Placebo (n=25)
Week 2	71	2	responder	5 (7.0%)	5 (10.6%)	0
Week 4	69	4	responder	5 (7.2%)	5 (11.1%)	0
Week 6	69	4	responder	12 (17.4%)	8 (17.8%)	4 (16.7%)
Week 8	67	6	responder	11 (16.4%)	9 (20.5%)	2 (8.7%)
Week 10	62	11	responder	18 (29.0%)	13 (33.3%)	5 (21.7%)
Week 12	60	13	responder	22 (36.7%)	14 (36.8%)	8 (36.4%)
Week 14	59	14	responder	23 (39.0%)	14 (37.8%)	9 (40.9%)
Week 16	58	15	responder	26 (44.8%)	16 (44.4%)	10 (45.5%)

Table 5-37. UAS7 - proportion of complete responders – logistic regression adjusted for baseline and study center [FAS population]

Week	N	Odds ratio (Dupilumab vs placebo)	95% Confidence Interval		p-value
2	71	>999.99	<0.01	>999.99	0.879
4	69	>999.99	<0.01	>999.99	0.943
6	69	0.99	0.22	4.37	0.984
8	67	2.67	0.51	13.92	0.245
10	62	1.81	0.54	6.10	0.338
12	60	0.96	0.31	2.99	0.939
14	59	0.77	0.25	2.40	0.661
16	58	1.03	0.34	3.11	0.953

Table 5-38. ISS7 - Complete responders - descriptive analysis, unadjusted (n,%) [FAS population]

ISS7 Complete responder	N	Missing	Value	Total (n=73)	Dupilumab (n=48)	Placebo (n=25)
Week 2	71	2	responder	1 (1.4%)	1 (2.1%)	
Week 4	68	5	responder	1 (1.5%)	1 (2.2%)	
Week 6	68	5	responder	5 (7.4%)	4 (8.9%)	1 (4.3%)
Week 8	67	6	responder	8 (11.9%)	6 (13.6%)	2 (8.7%)
Week 10	62	11	responder	12 (19.4%)	9 (23.1%)	3 (13.0%)
Week 12	60	13	responder	14 (23.3%)	9 (23.7%)	5 (22.7%)
Week 14	59	14	responder	14 (23.7%)	10 (27.0%)	4 (18.2%)
Week 16	57	16	responder	18 (31.6%)	12 (33.3%)	6 (28.6%)

Table 5-39. ISS7 - proportion of complete responders – logistic regression adjusted for baseline and study center [FAS population]

Week	N	Odds ratio (Dupilumab vs placebo)	95% Confidence Interval		p-value
2	71	177.58	<0.01	>999.99	0.964
4	68	>999.99	<0.01	>999.99	0.940
6	68	2.52	0.24	26.01	0.439
8	67	1.55	0.27	8.98	0.626
10	62	2.32	0.54	10.08	0.260
12	60	1.03	0.29	3.66	0.968
14	59	1.40	0.35	5.55	0.631
16	57	1.51	0.44	5.13	0.510

Table 5-40. HSS7 - Complete responders - descriptive analysis, unadjusted (n,%) [FAS population]

HSS7 Complete responder	N	Missing	Value	Total (n=73)	Dupilumab (n=48)	Placebo (n=25)
Week 2	71	2	responder	3 (4.2%)	3 (6.4%)	
Week 4	69	4	responder	2 (2.9%)	2 (4.4%)	
Week 6	69	4	responder	9 (13.0%)	7 (15.6%)	2 (8.3%)
Week 8	67	6	responder	7 (10.4%)	6 (13.6%)	1 (4.3%)
Week 10	62	11	responder	13 (21.0%)	9 (23.1%)	4 (17.4%)
Week 12	60	13	responder	14 (23.3%)	9 (23.7%)	5 (22.7%)

HSS7 Complete responder	N	Missing	Value	Total (n=73)	Dupilumab (n=48)	Placebo (n=25)
Week 14	59	14	responder	14 (23.7%)	9 (24.3%)	5 (22.7%)
Week 16	58	15	responder	16 (27.6%)	9 (25.0%)	7 (31.8%)

Table 5-41. HSS7 - proportion of complete responders – logistic regression adjusted for baseline and study center [FAS population]

Week	N	Odds ratio (Dupilumab vs placebo)	95% Confidence Interval		p-value
2	71	>999.99	<0.01	>999.99	0.934
4	69	>999.99	<0.01	>999.99	0.935
6	69	2.11	0.33	13.28	0.428
8	67	3.72	0.39	36.73	0.255
10	62	1.61	0.42	6.17	0.489
12	60	1.09	0.31	3.91	0.891
14	59	1.13	0.32	4.04	0.850
16	58	0.74	0.22	2.43	0.617

Table 5-42. UCT - Complete responders - descriptive analysis, unadjusted (n,%) [FAS population]

UCT complete responder	N	Missing	Value	Total (n=73)	Dupilumab (n=48)	Placebo (n=25)
Week 2	70	3	responder	0	0	0
Week 4	68	5	responder	1 (1.5%)	1 (2.2%)	0
Week 6	66	7	responder	1 (1.5%)	1 (2.3%)	0
Week 8	61	12	responder	2 (3.3%)	2 (5.1%)	0
Week 10	57	16	responder	1 (1.8%)	1 (2.7%)	0
Week 12	56	17	responder	2 (3.6%)	2 (5.6%)	0
Week 14	56	17	responder	5 (8.9%)	4 (11.1%)	1 (5.0%)
Week 16	60	13	responder	6 (10.0%)	4 (10.8%)	2 (8.7%)

Table 5-43. UCT - proportion of complete responders – logistic regression adjusted for baseline and study center [FAS population]

Week	N	Odds ratio (Dupilumab vs placebo)	95% Confidence Interval		p-value
2	69	0.00	-	-	-
4	68	115.43	<0.01	>999.99	0.960
6	66	128.56	<0.01	>999.99	0.959
8	61	>999.99	<0.01	>999.99	0.927
10	57	>999.99	<0.01	>999.99	0.934
12	56	>999.99	<0.01	>999.99	0.937
14	56	3.70	0.28	47.75	0.319
16	60	3.29	0.32	33.60	0.314

Table 5-44. AAS7 - Complete responders - descriptive analysis, unadjusted (n,%) [FAS population]

AAS7 complete responder	N	Missing	Value	Total (n=73)	Dupilumab (n=48)	Placebo (n=25)
Week 2	37	43	responder	8 (27.6%)	6 (22.2%)	2 (20.0%)

AAS7 complete responder	N	Missing	Value	Total (n=73)	Dupilumab (n=48)	Placebo (n=25)
Week 4	37	43	responder	11 (29.7%)	10 (37.0%)	1 (10.0%)
Week 6	37	43	responder	15 (40.5%)	11 (40.7%)	4 (40.0%)
Week 8	37	43	responder	13 (35.1%)	11 (40.3%)	2 (20.0%)
Week 10	37	43	responder	20 (54.1%)	17 (63.0%)	3 (30.0%)
Week 12	37	43	responder	22 (59.5%)	18 (66.7%)	4 (40.0%)
Week 14	37	43	responder	24 (64.9%)	19 (78.3%)	5 (50.0%)
Week 16	37	43	responder	26 (70.3%)	19 (78.3%)	7 (70.0%)

Table 5-45. AAS7 - proportion of clinical responders – logistic regression adjusted for baseline and study center [FAS population]

Week	N	Odds ratio (Dupilumab vs placebo)	95% Confidence Interval		p-value
2	37	0.94	0.12	7.32	0.950
4	37	5.60	0.60	53.06	0.134
6	37	1.08	0.22	5.28	0.924
8	37	3.30	0.53	20.60	0.202
10	37	5.54	0.89	34.52	0.067
12	37	3.07	0.68	13.89	0.146
14	37	2.88	0.56	14.73	0.205
16	37	1.06	0.19	6.01	0.948

5.3.4 Time to response

Time to clinical response and to complete response was assessed for UAS7, UCT, CU-Q2oL, and AAS7 (Figures 5-28 to 5-45). Hazard ratios (CI 95%) for clinical and complete responders were assessed for all 9 pre-defined responders' categories (Table 5-46). No relevant difference was observed between the treatment groups.

Table 5-46. The hazard ratio for dupilumab vs placebo responders [FAS]

Clinical Responder				
Responder	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**		**p-value**
UAS7 Clinical Responder	1.34	0.76	2.37	0.3074
ISS7 Clinical Responder	1.31	0.75	2.29	0.342
UCT Clinical Responder	1.08	0.61	1.93	0.784
CuQ2ol Clinical Responder	1.46	0.80	2.66	0.217
Complete Responders				
Responder	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**		**p-value**
UAS7 Complete Responder	1.10	0.55	2.15	0.808

Clinical Responder				
Responder	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**		**p-value**
ISS7 Complete Responder	1.21	0.56	2.64	0.627
HSS7 Complete Responder	1.18	0.55	2.56	0.672
UCT Complete Responder	2.64	0.45	15.51	0.282
AAS7 Complete Responder*	1.51	0.62	3.66	0.361
*Analyzed only for participants with angioedema at baseline				

Figure 5-3. Time to clinical response UAS7 (Failure probability=probability of becoming a responder)

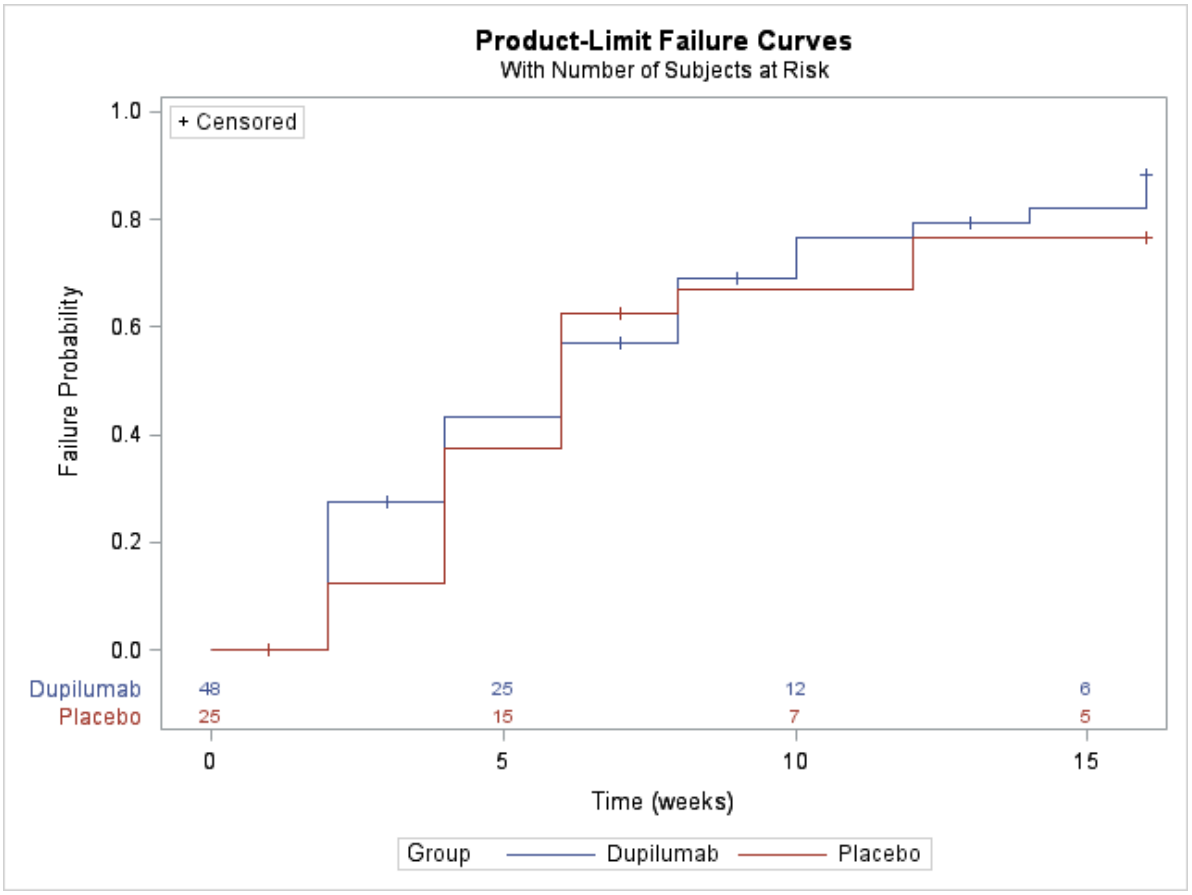


Figure 5-4. Time to complete response UAS7 (Failure probability= probability of becoming a responder)

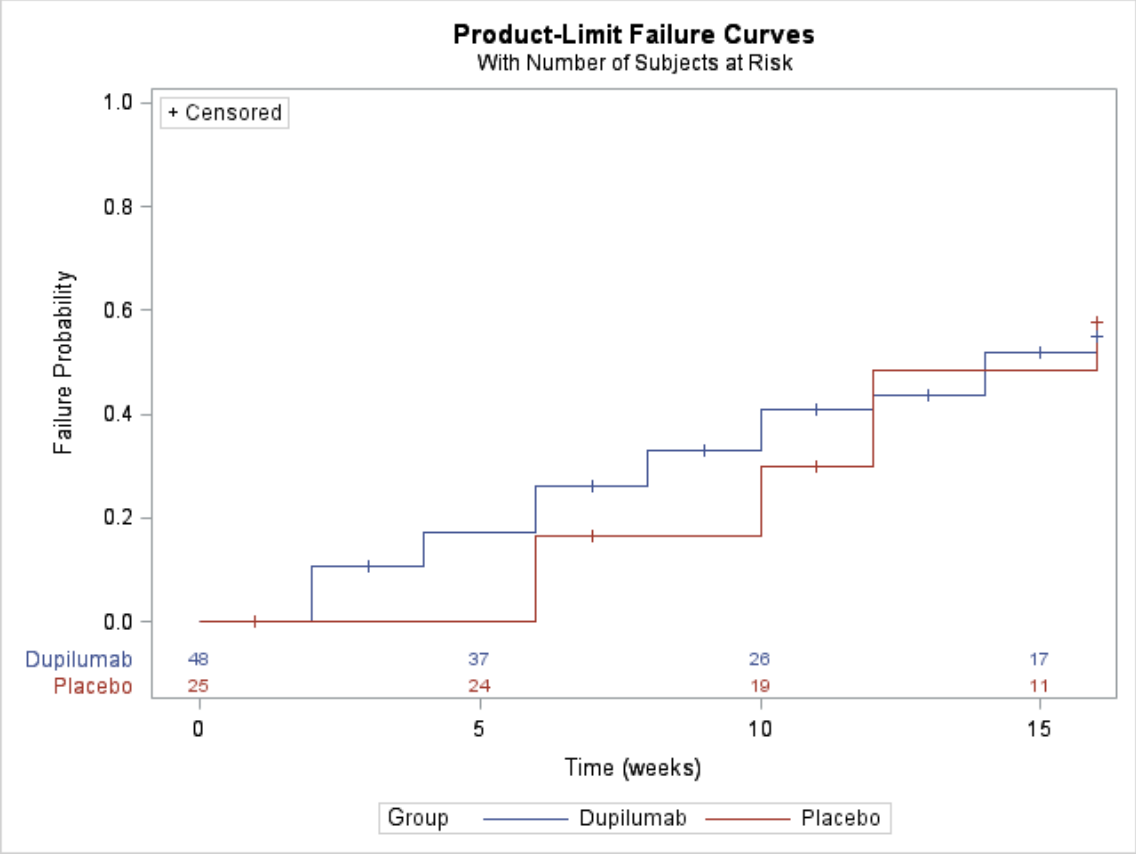


Figure 5-5. Time to clinical response UCT (Failure probability= probability of becoming a responder)

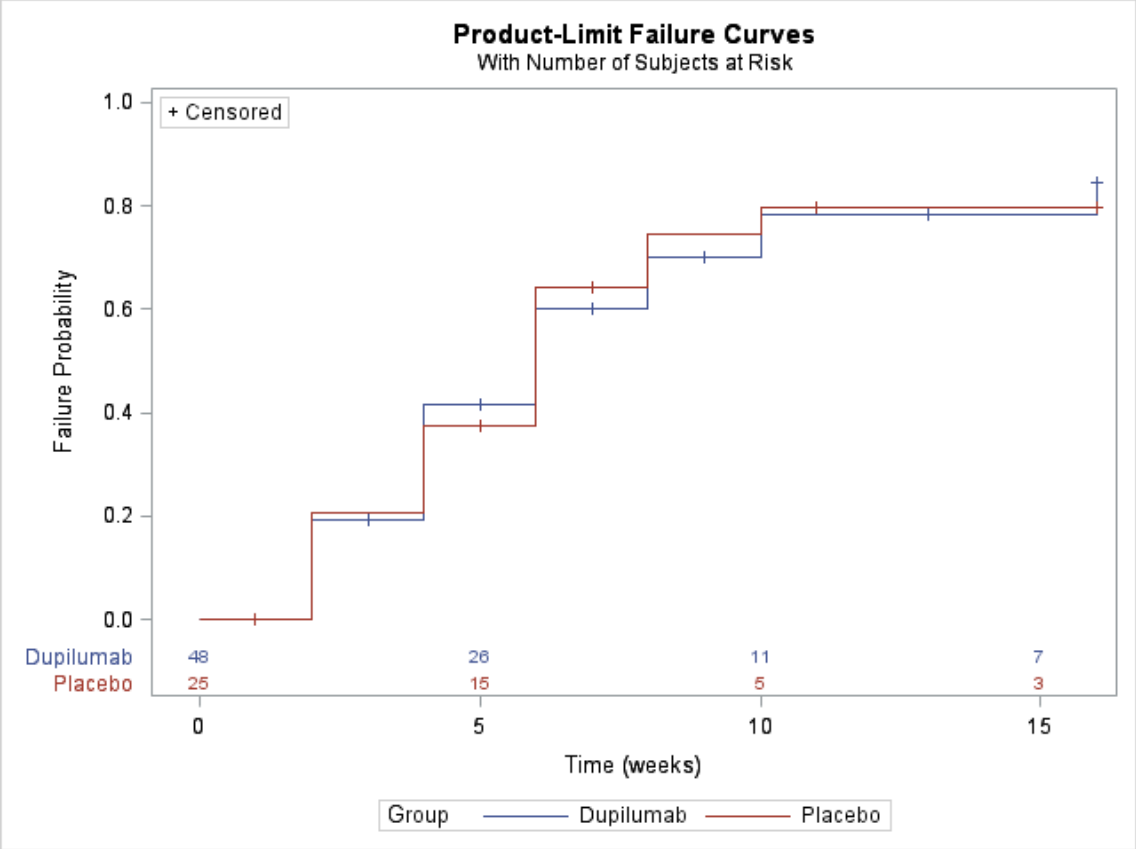


Figure 5-6. Time to complete response UCT (Failure probability= probability of becoming a responder)

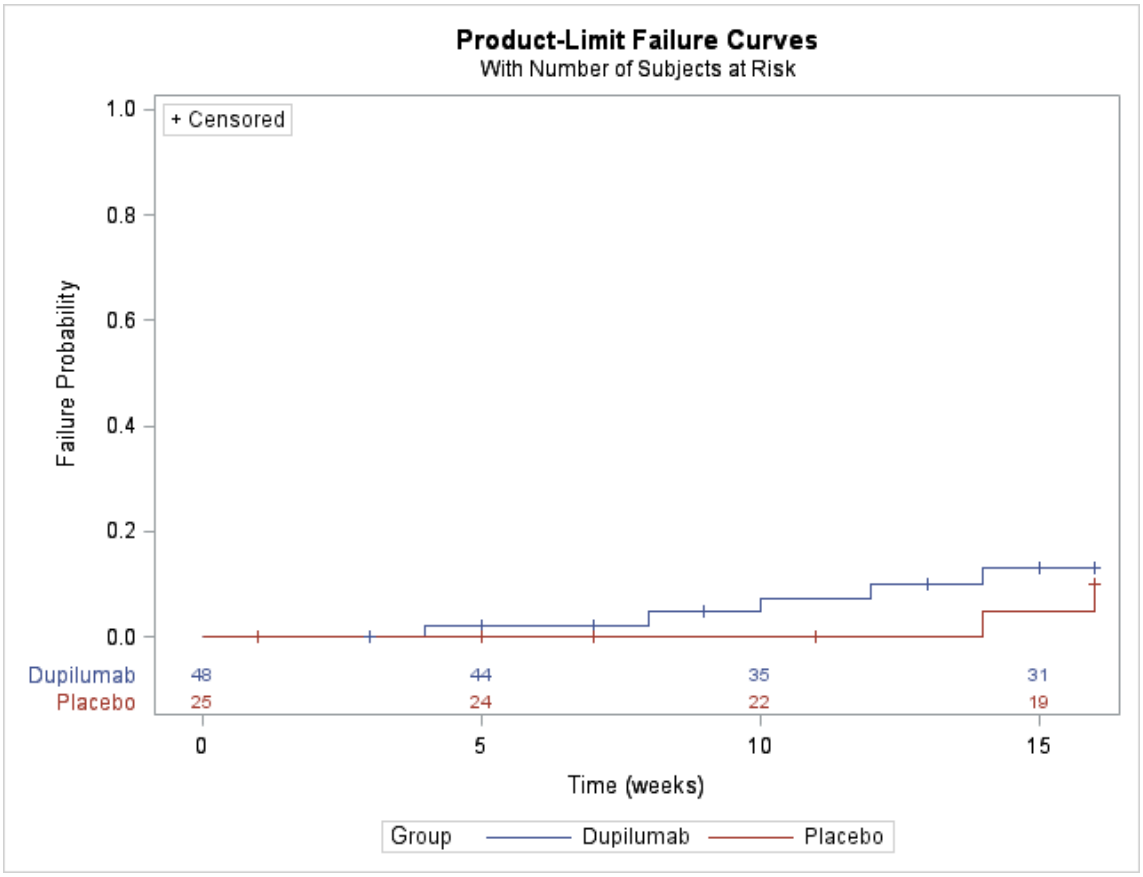


Figure 5-7. Time to clinical response CU-Q2oL (Failure probability= probability of becoming a responder)