

Analyses of secondary outcomes (exploratory analyses)

UAS-7 change

Table: The mean of UAS-7 over the study period between treatment groups

UAS-7 score	Rupatadine 10 mg On-demand (n=19)		Rupatadine 20 mg [#] Daily continuous (n=39)		Group difference (Daily continuous – On-demand) Mean (95%CI)	p-value*
	Mean	(95% CI)	Mean	(95% CI)		
Week 4 (Visit 3)	18.6	(14.2 to 23.0)	10.0	(7.5 to 12.5)	-8.2 (-12.9 to -3.5)	0.001
Week 10 (Visit 4)	15.2	(10.0 to 20.4)	9.9	(6.8 to 13.0)	-5.1 (-9.7 to -0.4)	0.035
Week 16 (Visit 5)	15.9	(11.8 to 20.1)	12.1	(9.3 to 14.9)	-3.5 (-7.9 to 0.9)**	0.122

- 1) * Post-hoc analysis based on GEE with adjusted for baseline UAS-7 and centre heterogeneity and based on multiple imputations
- 2) ** Regarding the adjustment for the baseline UAS-7, the effect of treatment between the absolute value at the different follow-up time or the changes from baseline should be the same result, therefore the treatment effect was taken from the UAS-7 changes from baseline analysis
- 3) [#] Rupatadine 10 mg (n=3) and 20 mg (n=36) in daily continuously group.

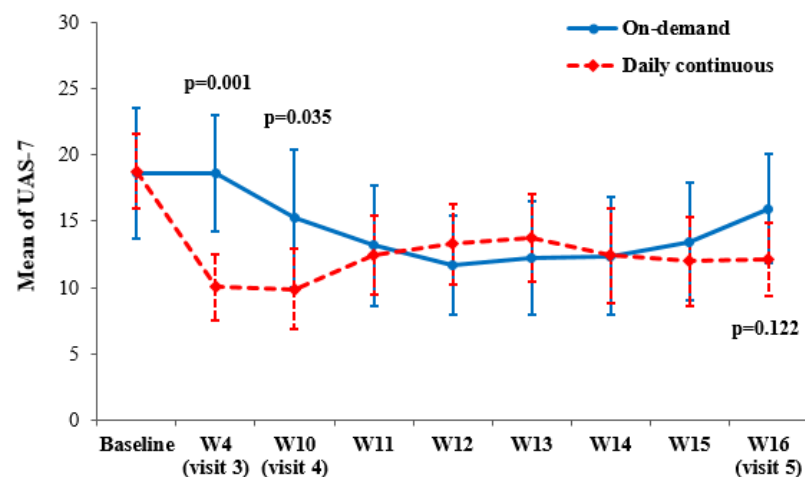


Figure: Mean and 95%CI error-bar of the UAS-7 changed over the study between treatment groups. Post-hoc analysis based on GEE with adjusted for baseline UAS-7 and centre heterogeneity and based on multiple imputations.

Rupatadine intake in follow up phase

Table: Number of Rupatadine 10 mg intake (per week) over the study periods

Number of rupatadine intake	Rupatadine 10 mg		Rupatadine 20 mg [#]	
	On-demand		Daily continuous	
	n	Median (IQR)	n	Median (IQR)
Week 4 (Visit 3)	19	2 (1, 4)	38	0 (0, 0)*
Week 10 (Visit 4)	19	2 (0, 4)	38	0 (0, 1)*
Week 11	17	4 (3, 5)	32	2 (1, 3)
Week 12	17	3 (2, 5)	32	3 (1, 4)
Week 13	17	3 (2, 6)	32	2 (1, 5)
Week 14	17	3 (1, 4)	31	2 (1, 4)
Week 15	17	3 (2, 5)	31	2 (1, 4)
Week 16 (Visit 5)	17	4 (2, 6)	31	2 (1, 4)

[#] Rupatadine 10 mg (n=3) and 20 mg (n=36) in daily continuously group

*Number of placebo intake in daily continuously group (maximum intake at week4=6 and week10=6)

Based on multilevel mixed-effects ordered logistic regression with 2 random intercepts for study centre and patient, there were no substantial differences of Rupatadine intake during the follow-up phase between treatment groups (p-value=0.084) and almost no differences during the follow-up time (p-value=0.796).

Comparison of UAS-7 change from baseline during the follow-up phase between response and non-response groups at the end of treatment phase

At the end of treatment phase (visit 4), 10 of 57 patients (17.5%) had a complete response to the treatment (UAS-7 score at visit 4=0) (2 patients from on-demand group and 8 patients from daily continuously group). Overall, patients with response to the treatment have more improvement then patients with non-response during the follow-up phase. After adjustment for baseline UAS-7 and the number of Rupatadine 10 mg intake (per week) during the follow-up phase, UAS-7 change from baseline was around 7 to 9 points in responders and 5 to 6 points in non-responders (Table 6).

Table 6 Comparison of the UAS-7 change from baseline during the follow-up phase between response and non-response at the end of treatment phase (visit 4)

UAS-7 change from baseline	Response [#] (n=10)		Non-response (n=47)		p-value*
	Mean	(95% CI)	Mean	(95% CI)	
Week 10	-15.6	(-20.5 to -10.7)	-5.1	(-8.7 to -1.4)	<0.001
Week 11	-9.0	(-12.6 to -5.4)	-5.5	(-8.6 to -2.4)	0.039
Week 12	-8.0	(-11.8 to -4.2)	-5.5	(-8.8 to -2.2)	0.117
Week 13	-9.5	(-13.9 to -5.1)	-4.8	(-7.9 to -1.6)	0.020
Week 14	-8.5	(-13.6 to -3.4)	-5.6	(-9.2 to -1.9)	0.155
Week 15	-7.8	(-12.6 to -3.0)	-5.5	(-8.9 to -2.1)	0.230
Week 16 (Visit 5)	-6.5	(-11.6 to -1.4)	-4.8	(-7.9 to -1.8)	0.289

[#] Response was defined as UAS-7=0 at visit 4 (week 10) – combine cases from on-demand group (n=2) and daily continuously group (n=8)

* Post-hoc analysis based on multilevel mixed linear regression with 2 random intercepts for study centre and patient with adjusted for baseline UAS-7 and number of Rupatadine 10 mg intake (per week) during the follow-up phase

Rupatadine intake in follow up phase in responders vs. non-responders

Table 7 shows the number of Rupatadine 10 mg intake (per week) during the follow-up phase between response and non-response groups. Based on multilevel mixed-effects ordered logistic regression with 2 random intercepts for study sites and patient, there was an interaction effect between treatment and the follow-up time (week) (p-value=0.022). The number of Rupatadine intake during the follow-up phase showed a slightly decrease over the follow-up time in response group, compared to almost no change over time in the non-response group.

Table 7 Number of Rupatadine 10 mg intake (per week) during the follow-up phase between response and non-response at the end of treatment phase (visit 4)

* One missing in response group and 8 missings in non-response group in the number of Rupatadine 10 mg intake (per week) during the follow-up phase.

Number of rupertadine intake – Median (IQR)	Response (n=9)*	Non-response (n=39)*
Week 11	2 (1, 5)	3 (1, 4)
Week 12	2 (1, 3)	3 (1, 4)
Week 13	2 (1, 4)	3 (1, 5)
Week 14	2 (0, 3)	3 (1, 4)
Week 15	2 (0, 3)	3 (1, 5)
Week 16 (Visit 5)	1 (0, 2)	2 (1, 5)

Comparison of the rates of therapy responders (based on UAS-7) between treatment groups

Table 8 shows four categories of therapy response by treatment groups. Based on multilevel mixed-effects ordered logistic regression with 2 random intercepts for study centre and patient with adjusted for baseline UAS-7, there was an interaction effect between treatment and follow up time (visit) (p-value=0.038). Post-hoc analysis showed that in daily continuously group more patients had at least 75% response than in the on-demand group at visit 3 (27.0% vs. 0.0%, p=0.008) and visit 4 (40.5% vs. 16.7%, p=0.049). However, there were only slightly differences of responder rates of at least 75% between treatment groups at visit 5 (20.0% vs. 11.8%, p=0.774).

Table 8 Comparison of the proportion of patients with response (based on the UAS-7)

Percentage of patients with UAS-7 response	Rupatadine 10 mg On-demand	Rupatadine 20 mg [#] Daily continuous	p-value*
Response at visit 3	n=18	n=37	0.008
Complete response	0 (0.0%)	2 (5.4%)	
75% - 99% response	0 (0.0%)	8 (21.6%)	
50% - 74% response	2 (11.1%)	7 (18.9%)	
<50% response	16 (88.9%)	20 (54.1%)	
Response at visit 4	n=18	n=37	0.049
Complete response	2 (11.1%)	8 (21.6%)	
75% - 99% response	1 (5.6%)	7 (18.9%)	
50% - 74% response	2 (11.1%)	4 (10.8%)	
<50% response	13 (72.2%)	18 (48.7%)	
Response at visit 5	n=17	n=30	0.774
Complete response	0 (0.0%)	1 (3.3%)	
75% - 99% response	2 (11.8%)	5 (16.7%)	
50% - 74% response	4 (23.5%)	5 (16.7%)	
<50% response	11 (64.7%)	19 (63.3%)	

[#] Rupatadine 10 mg (n=3) and 20 mg (n=36) in daily continuously group

*Post-hoc analysis based on multilevel mixed-effects ordered logistic regression with 2 random intercepts for study centre and patient with adjusted for baseline UAS-7

Table 9 presents rates of complete therapy response, partial response and non-partial response between treatment groups. Results were very similar to results from table 8. Based on multilevel mixed-effects ordered logistic regression with 2 random intercepts for study centre and patient with adjusted for baseline UAS-7, post-hoc analysis showed that daily continuously group had higher partial and complete response rate than on-demand group at visit 3 (43.2% vs. 1.1%, p=0.013) and visit 4 (54.0% vs. 33.3%, p=0.033). However, there were almost no differences between treatment groups at visit 5 (30.0% vs. 23.5%, p=0.486).

Table 9 Comparison of the proportion of patients with response (based on the UAS-7)

Percentage of patients with UAS-7 response	Rupatadine 10 mg On-demand	Rupatadine 20 mg [#] Daily continuous	p-value*
Response at visit 3	n=18	n=37	0.013
Complete response	0 (0.0%)	2 (5.4%)	
Partial response	2 (11.1%)	14 (37.8%)	
Non-Partial response	16 (88.9%)	21 (56.8%)	
Response at visit 4	n=18	n=37	0.033
Complete response	2 (11.1%)	8 (21.6%)	
Partial response	4 (22.2%)	12 (32.4%)	
Non-Partial response	12 (66.7%)	17 (46.0%)	
Response at visit 5	n=17	n=30	0.487
Complete response	0 (0.0%)	1 (3.3%)	
Partial response	4 (23.5%)	8 (26.7%)	
Non-Partial response	13 (76.5%)	21 (70.0%)	

[#] Rupatadine 10 mg (n=3) and 20 mg (n=36) in daily continuously group.

*Post-hoc analysis based on multilevel mixed-effects ordered logistic regression with 2 random intercepts for study centre and patient with adjusted for baseline UAS-7

Physician global assessment (PGA) disease activity

Table: Comparison of PGA between groups

	n	PGA – n (%)				p-value*
		None	Mild	Moderate	Severe	
Week 4 (Visit 3)						<0.001
On-demand	19	0 (0.0)	1 (5.3)	14 (73.7)	4 (21.1)	
Daily continuous	39	1 (2.6)	27 (69.2)	11 (28.2)	0 (0.0)	
Week 10 (Visit 4)						0.024
On-demand	19	2 (10.5)	7 (36.8)	8 (42.1)	2 (10.5)	
Daily continuous	37	11 (29.7)	17 (46.0)	3 (8.1)	6 (16.2)	
Week 16 (Visit 5)						0.319
On-demand	18	1 (5.6)	11 (61.1)	5 (27.8)	1 (5.6)	
Daily continuous	31	2 (6.5)	19 (61.3)	10 (32.3)	0 (0.0)	

*Adjusted for baseline PGA