






## ORIGINAL ARTICLE

Atopic Dermatitis, Urticaria and Skin Disease

# Efficacy and safety of on-demand versus daily rupatadine in chronic spontaneous urticaria: A randomized trial

Karsten Weller<sup>1,2</sup>  | Ana Maria Gimenez-Arnau<sup>3</sup>  | Jens Baron<sup>4</sup> | Randolf Brehler<sup>5</sup> |  
 Marta Ferrer<sup>6,7</sup>  | Adriane Groffik<sup>8</sup> | Sonja Grundmann<sup>9</sup> | Thilo Jakob<sup>10</sup> |  
 Moisés Labrador-Horrillo<sup>11</sup> | Sabine Müller<sup>12</sup> | Petra Staubach<sup>13</sup> | Gerda Wurpts<sup>14</sup> |  
 Martin Metz<sup>1,2</sup>  | Marcus Maurer<sup>1,2</sup> 

<sup>1</sup>Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany<sup>2</sup>Institute of Allergology, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany<sup>3</sup>Department of Dermatology, Hospital del Mar, IMIM, Universitat Pompeu Fabra, Barcelona, Spain<sup>4</sup>Department of Dermatology and Allergy, University Hospital, RWTH Aachen, Aachen, Germany<sup>5</sup>Department of Dermatology, University Hospital Muenster, Muenster, Germany<sup>6</sup>Department of Allergy, Clinica Universidad de Navarra, Pamplona, Spain<sup>7</sup>RICORS Red De Enfermedades Inflamatorias (REI)-RD21/0002/0028, Madrid, Spain<sup>8</sup>Department of Dermatology, University Medical Center Mainz, Mainz, Germany<sup>9</sup>Hospital of Dermatology, Bad Rothenfelde, Germany<sup>10</sup>Department of Dermatology and Allergy, University Medical Center, Justus Liebig University Gießen, Giessen, Germany<sup>11</sup>Allergy Department, Hospital Universitario Vall d'Hebron, VHIR, Universitat Autònoma de Barcelona, Barcelona, Spain<sup>12</sup>Department of Dermatology, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany<sup>13</sup>Department of Dermatology and Allergy, University Medical Center, Mainz, Germany<sup>14</sup>Clinic for Dermatology and Allergology, Aachen Comprehensive Allergy Center (ACAC), Uniklinik RWTH Aachen, Aachen, Germany**Correspondence**

Marcus Maurer, Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany.  
 Email: [marcus.maurer@charite.de](mailto:marcus.maurer@charite.de)

**Funding information**

Charité - Universitätsmedizin Berlin;  
 Uriach

**Abstract**

**Background:** Non-sedating H<sub>1</sub>-antihistamines (nsAH) are the most commonly used treatment for chronic spontaneous urticaria (CSU). Many patients use them as on-demand (OD) therapy rather than a maintenance treatment. Here, we compared OD versus daily maintenance treatment with the nsAH rupatadine, assessed the efficacy of rupatadine up dosing, and investigated potential long-term disease-modifying effects. **Methods:** This multicenter, randomized study consisted of 2 weeks of screening, 8 weeks of double-blind treatment, and 6 weeks of treatment-free follow-up (OD allowed). Adult patients were randomized to 10 mg rupatadine OD or 10 mg rupatadine daily. At Week 4, if patients did not have a complete response, they switched from 10 to 20 mg rupatadine daily or underwent sham up dosing (patients on 10 mg rupatadine OD). The primary aim was to compare CSU disease activity at the end of follow-up

**Abbreviations:** AE, adverse event; CFB, change from baseline; CI, confidence interval; CSU, chronic spontaneous urticaria; CU-Q2oL, chronic urticaria quality of life questionnaire; DLQI, dermatology life quality index; GEE, generalized estimating equation; nsAH, non-sedating antihistamine; OD, on-demand; PAF, platelet-activating factor; PGA, physician global assessment; QoL, quality of life; SD, standard deviation; UAS7, weekly Urticaria Activity Score; UCT, urticaria control test.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2023 The Authors. *Allergy* published by European Academy of Allergy and Clinical Immunology and John Wiley & Sons Ltd.

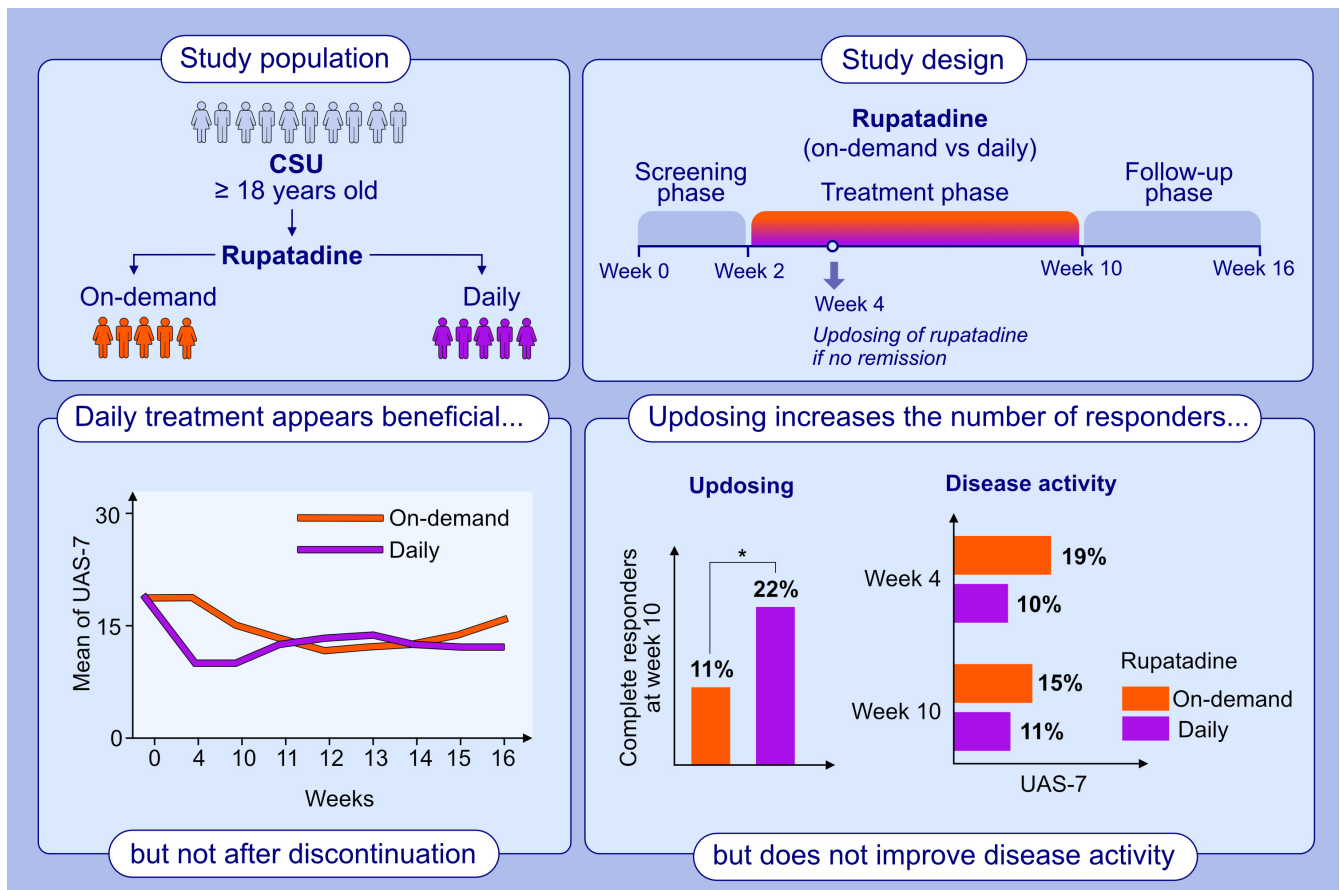
between daily versus OD. Additionally, we assessed the efficacy of rupatadine updosing. Major outcomes were disease activity, CSU-related quality of life (QoL), and disease control.

**Results:** At Week 4, disease activity and QoL significantly improved in daily versus OD-treated patients. Updosing of rupatadine did not improve the mean disease activity, but the number of complete responders increased during up dosing from 5% to 22%. At the end of follow-up, the disease activity of patients treated OD versus daily was not significantly different.

**Conclusions:** Daily rupatadine treatment significantly improved CSU disease activity and QoL during treatment versus OD treatment but not after discontinuation of rupatadine, indicating the benefits of a daily maintenance nsAH schedule.

#### KEYWORDS

chronic spontaneous urticaria, disease activity, on-demand, rupatadine, up dosing



#### GRAPHICAL ABSTRACT

This study assessed the longer term potential disease-modifying effects of rupatadine, evaluated the effects of up dosing, and compared daily versus OD treatment in patients with CSU. Daily rupatadine treatment significantly improved CSU disease activity and QoL during treatment versus OD treatment but not after discontinuation of rupatadine. Up dosing rupatadine from 10 to 20 mg increased the number of complete responders but did not improve the overall disease activity.

Abbreviations: CSU, chronic spontaneous urticaria; OD, on-demand; QoL, quality of life; vs., versus

## 1 | INTRODUCTION

Chronic spontaneous urticaria (CSU) is a common, distressing, itchy skin condition of long duration.<sup>1,2</sup> Due to severe pruritus and the

highly fluctuating, unpredictable nature, CSU can drastically affect patients' quality of life (QoL).<sup>3,4</sup> Urticaria is a predominantly mast-cell driven disease,<sup>5</sup> with the release of histamine, lipid mediators including platelet-activating factor (PAF), and inflammatory cytokines, which

cause sensory nerve activation, vasodilation, extravasation, and the recruitment of eosinophils, basophils and other inflammatory cells.<sup>1</sup>

The daily use of a second-generation, non-sedating H<sub>1</sub>-antihistamine (nsAH) is the recommended first-line treatment in CSU.<sup>1</sup> However, many patients use antihistamines as needed, that is, on-demand (OD), rather than taking them as daily, preventive control medication. Studies in allergic rhinitis have indicated that nsAHs control symptoms better and with higher efficacy if taken daily rather than OD for symptomatic relief.<sup>6-8</sup> However, only a few studies exist in CSU comparing these two treatment approaches. A small study demonstrated that daily treatment with the nsAH desloratadine significantly improved QoL at 4 and 8 weeks post-randomization compared to OD treatment in CSU.<sup>9</sup> Together, these data indicate that the treatment schedule can strongly influence outcomes, but the superiority of daily versus OD nsAH treatment in CSU is yet to be confirmed.

Achieving sufficient control over urticaria symptoms often requires up dosing to a higher than licensed nsAH dose.<sup>10-13</sup> Patients can increase the standard dose fourfold, which is more effective in certain types of chronic urticaria<sup>10,11,13</sup>; however, in many cases, up-dosing neither controls nor suppresses symptoms.<sup>14</sup>

The mode of action of nsAHs suggests a purely symptomatic therapeutic effect, but there are hints of potential disease-modifying effects resulting from long-term treatment. One study demonstrated that 3-month continuous maintenance nsAH therapy in patients with CSU resulted in a lower recurrence rate after discontinuation than the same treatment for only 1 month.<sup>15</sup>

Rupatadine is an oral nsAH indicated for the relief of urticaria in adults and children  $\geq 2$  years old.<sup>16,17</sup> It suppresses histamine H<sub>1</sub> and PAF,<sup>18-20</sup> thought to contribute to the major signs and symptoms of CSU.<sup>21</sup> Furthermore, rupatadine inhibits early- and late-phase inflammation,<sup>20,22</sup> thus producing fast and long-lasting symptomatic relief with once-daily dosing.<sup>23</sup> It is effective and well tolerated in the treatment of urticaria up to 1 year at 10 mg,<sup>24,25</sup> and has a notable improvement in disease activity when the dose is increased up to 20 mg.<sup>26</sup>

Here, we sought to assess the longer term potential disease-modifying effects, assess the effects of up dosing, and compare OD versus daily treatment to evaluate the efficacy of rupatadine in patients with CSU.

## 2 | METHODS

### 2.1 | Trial design

This multicenter, randomized, double-blind, dose-escalating study on the efficacy, safety, and long-term outcomes of OD versus daily treatment of CSU with rupatadine was conducted at urticaria centers across Germany and Spain.

Figure 1 shows the study design, which consists of a screening phase (2 weeks), treatment phase (8 weeks), and a follow-up phase (6 weeks). Patients were randomized 1:2 into one of two blinded treatment arms

at the end of the screening phase: Group A1 received 10 mg rupatadine OD (one placebo tablet daily/one OD rupatadine 10 mg tablet if required); Group B1 received 10 mg rupatadine daily (one 10 mg rupatadine tablet daily/one OD placebo tablet if required). At Week 4 (after 2 weeks of treatment), the investigator assessed the patient's response to treatment: if patients had a complete response (UAS7=0), they remained in Groups A1 or B1. If there was no remission, patients from Group A1 switched to Group A2, which was only a sham (false) change (they remained on 10 mg rupatadine OD [two placebo tablets daily plus one 10 mg rupatadine tablet if required]) and patients from Group B1 (10 mg rupatadine daily) switched to Group B2 (20 mg rupatadine daily [two 10 mg rupatadine tablets daily plus one OD placebo tablet if required]). After the end of the treatment phase at Week 10, all patients entered the open label follow-up phase, in which the patients had no daily treatment but only OD therapy, that is, they were allowed to take a maximum of one 10 mg rupatadine tablet per day if required.

### 2.2 | Patients

Patients were eligible for this trial if they were  $\geq 18$  years old, had a documented history of CSU with or without associated angioedema for at least 3 days per week over the last 6 weeks prior to screening (urticaria symptoms must comprise of wheals and itch), had a weekly Urticaria Activity Score (UAS7)  $\geq 6$  during the screening phase, had a duration of CSU for at least 3 months, and provided written informed consent. Women of child-bearing age had to use effective contraception.

Patients were excluded from the trial if their CSU was known to be resistant to nsAH at four times the licensed doses, had CSU with a known resistance to rupatadine, had dominant inducible urticaria, had a history of adverse events (AEs) or hypersensitivity to rupatadine or its ingredients, had been taking oral or intravenous corticosteroids within a 28-day period prior to screening, had been using depot corticosteroids within 3 months of screening, or had been using systemic immunosuppressants within 28 prior to screening. The full list of inclusion and exclusion criteria is displayed in Table S1. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines.

### 2.3 | Study objectives

The primary aim of this study was to compare CSU disease activity measured by UAS7 at the end of the follow-up phase (Week 16) between patients who had been treated with rupatadine OD versus those patients who had received daily treatment during the treatment phase.

Other key secondary objectives presented here include the comparison of (1) the efficacy of rupatadine 10 mg during the treatment phase between patients treated OD versus daily; (2) disease activity during treatment with rupatadine 10 mg and in patients who received up dosing to 20 mg (Group B2; paired analysis); (3) UAS7 during the follow-up period between patients with a complete response (UAS7=0) versus those without at the end of the treatment phase;

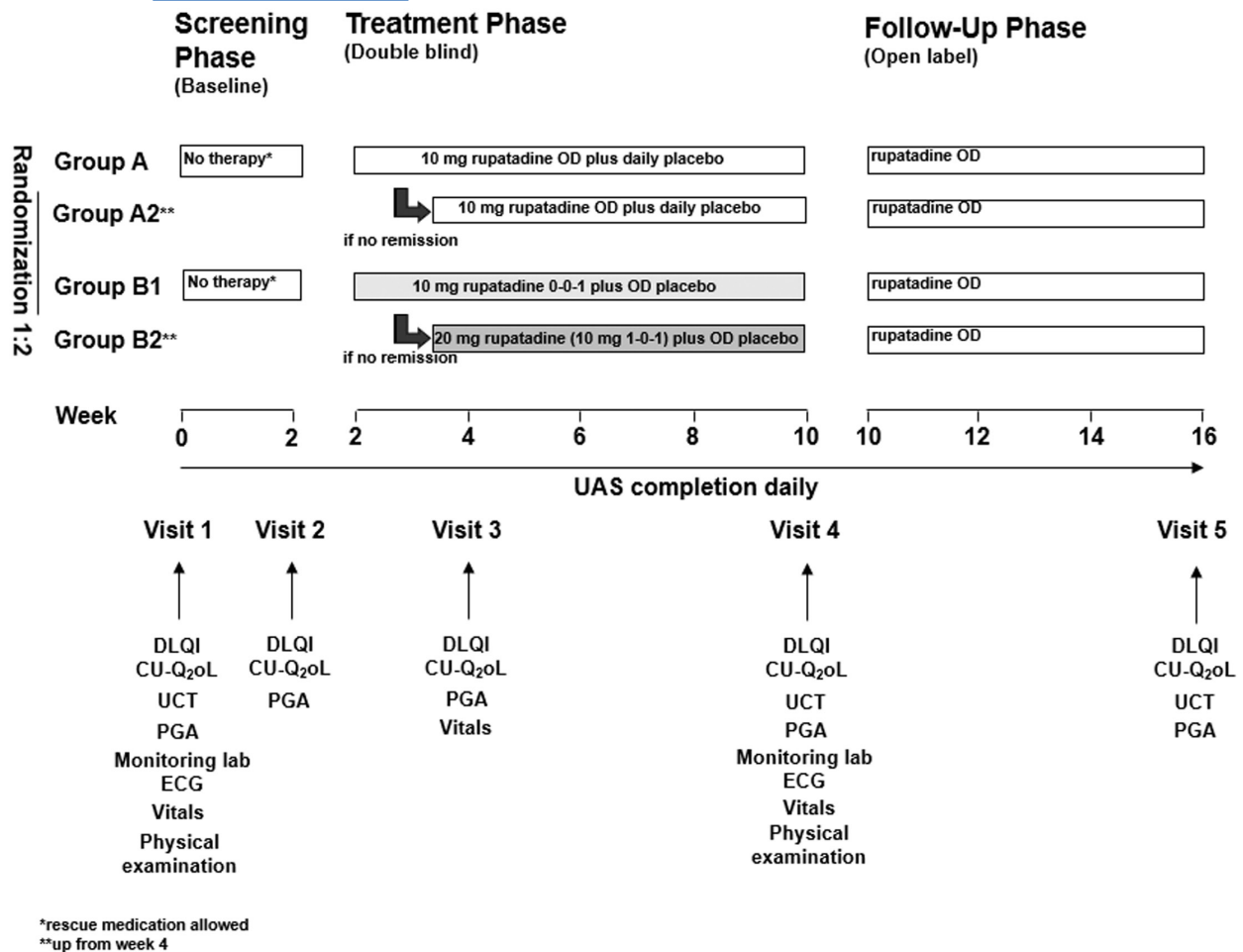


FIGURE 1 Study design.

and (4) disease activity during the follow-up phase between patients who had been treated OD versus daily in the treatment phase. The safety and tolerability of rupatadine 10mg and 20mg were also assessed.

## 2.4 | Study endpoints

UAS7 (range of 0–42), which assesses wheals and pruritus, was used to measure disease activity at specified timepoints.<sup>27</sup> Achieving a UAS7 of 0, measured at Week 4 and 10, was considered as a complete response to treatment. Additionally, disease activity was assessed by the physician global assessment (PGA) with Likert scale options: none, mild, moderate, and severe.

The urticaria control test (UCT, range of 0–16) was used to measure disease control with scores of  $\geq 12$  indicating well-controlled disease, and scores of  $< 11$  indicating poorly controlled disease.<sup>28</sup>

Patients' CSU-related QoL was measured using the Dermatology Life Quality Index (DLQI, scale 0–30)<sup>29</sup> and the Chronic Urticaria Quality of Life Questionnaire (CU-Q<sub>2</sub>oL, scale 0–100 with higher scores indicating more impairment).<sup>30</sup> Safety assessments were based on physical examinations, vital signs, and

AE reporting. Assessments were conducted at baseline and Weeks 2, 4, 10, and 16.

## 2.5 | Statistical analysis

The sample size calculation for the primary endpoint of this study was highly hypothetical because there was no available evidence to base this on. It assumed that the difference between the study arms in the follow-up phase is five UAS7 points with a standard deviation (SD) of 10 points, a drop-out rate of 20%, and the UAS7 values show a normal distribution. For this assumption, the number of patients needed per treatment arm was calculated to be 64 ( $n = 192$  patients in total). Descriptive statistics for continuous variables are presented as mean and SD for sufficiently normally distributed variables, or median for continuous not sufficiently normally distributed variables. For nominal data, absolute and relative frequencies are displayed for each category. In case of incomplete data, multiple imputation by chained equations with 10 imputed data sets was applied for imputing missing values separated by treatment groups. The variables that contributed to the imputation model were age, gender, study sites, UAS7, rupatadine intake, UCT, PGA, DLQI, and CU-Q<sub>2</sub>oL.

The primary outcome was analyzed using generalized estimating equations (GEEs) with Gaussian family, identity link function and exchangeable correlation structure to account for center heterogeneity and adjusted for baseline UAS7. The primary objective was tested at a two-sided significance level of  $\alpha=0.05$ . All secondary analyses were done in an exploratory framework. No adjustment was made for multiple comparisons.

Multilevel mixed linear regression was performed for comparing the UAS7 change from baseline (CFB) during the follow-up phase between responders and non-responders at Week 10, for comparing the UAS7 and QoL change over study periods between treatment groups. Multilevel mixed-effects logistic regression was applied to compare of disease control ( $UCT \leq 11$ ) and multilevel mixed-effects ordered logistic regression was performed for comparing rates of therapy responders and number of rupatadine intake between treatment groups.

PGA was compared between treatment arms using random effects ordered logistic models to account for center heterogeneity and baseline PGA was adjusted in the model.

The number of AEs and comparison of the incidence rates of AEs between treatment groups was carried out using the safety set by using Poisson regression. All analyses and summaries were performed with Stata version 15/IC (StataCorp, 2017).

### 3 | RESULTS

#### 3.1 | Baseline characteristics were balanced between the treatment arms

Overall, 77 patients with CSU were assessed for eligibility, and 63 patients were randomized to the treatment arms (21 patients in arm A1 and 42 patients in arm B1). Finally, 18 patients in the OD arm and 31 patients in the daily arm completed the study and were analyzed as the per-protocol set (Figure S1).

Females comprised 69.8% (44/63) of patients and the mean age was 43 years (SD=15 years). The baseline characteristics, including study outcomes (UAS7, DLQI score, CU-Q<sub>2</sub>oL total score, and UCT score), were similar across both study arms. The median rescue medication intake during the screening phase was higher in the OD arm (rescue medication intake on 4 days) compared to the daily treatment arm (rescue medication intake on 1 day). In contrast, from the physician's perspective, more patients in the daily treatment arm had severe disease activity versus the OD arm in the screening phase (PGA, 26.2% vs. 9.5%; Table 1).

#### 3.2 | At Week 16, no difference was observed in disease activity between patients receiving daily treatment versus OD treatment

At the end of the follow-up phase (Week 16), the primary endpoint was not met; patients who had been treated OD versus daily until

TABLE 1 Comparison of baseline demographics and characteristics between the OD and daily treatment arms.

Baseline characteristics	Rupatadine 10 mg OD (n = 21)	Rupatadine 10 mg daily (n = 42)	Total (n = 63)
Gender, n (%)			
Male	9 (42.9%)	10 (23.8%)	19 (30.2%)
Female	12 (57.1%)	32 (76.2%)	44 (69.8%)
Age (years)			
Mean (SD)	42 (16)	43 (15)	43 (15)
Minimum, maximum	21, 72	19, 69	19, 72
Weight (kg)			
Mean (SD)	78.8 (13.6)	74.5 (15.2)	75.9 (14.7)
BMI (kg/m <sup>2</sup> )			
Mean (SD)	27.1 (4.9)	26.4 (5.4)	26.6 (5.2)
Urticaria history			
Duration of CSU (months)			
Median (IQR)	22 (8–36)	24 (7–60)	24 (7–52)
Comorbid Sympt. Derm., n (%)	4 (19.1%)	4 (9.52%)	8 (12.70%)
Comorbid Chol. urticaria, n (%)	1 (4.8%)	3 (7.14%)	4 (6.35%)
Comorbid Cold urticaria, n (%)	-	1(2.38%)	1 (1.59%)
Comorbid Pressure urticaria, n (%)	-	3 (7.14%)	3 (4.76%)
Urticaria activity score (UAS7), n	20	40	60
Mean (SD)	19 (10)	18 (9)	19 (9)
Number of days with rescue medicine intake (during screening phase), n	21	41	62
Median (IQR)	4 (0–5)	1 (0–3)	2 (0–4)
Dermatology Life Quality Index (DLQI)			
Median (IQR)	8 (3–11)	9 (7–13)	9 (5–12)
Chronic Urticaria Quality of Life Questionnaire (CU-Q <sub>2</sub> oL)			
Mean (SD)	37 (23)	35 (16)	36 (18)
Median (IQR)	38 (16–49)	34 (24–48)	35 (21–49)
Urticaria control test (UCT)			
Mean (SD)	7 (2)	7 (3)	7 (3)
UCT $\leq 11$	21 (100.0%)	41 (97.6%)	62 (98.4%)
Physician global assessment (PGA) of disease activity, n (%)			
Mild	4 (19.1%)	8 (19.0%)	12 (19.1%)
Moderate	15 (71.4%)	23 (54.8%)	38 (60.3%)
Severe	2 (9.5%)	11 (26.2%)	13 (20.6%)

Week 10 had only minor differences in UAS7 disease activity (15.9 vs. 12.1,  $p = .122$ ; Figure 2). Additionally, at Week 16, no difference was observed in UAS7 between patients who had achieved a complete response (UAS7=0) versus those with no response (all other patients) at the end of the treatment phase at Week 10.

The UAS7 of the previously treated OD patients slightly decreased, along with an increase in their rupatadine intake, while the UAS7 of the previously treated daily arm increased, alongside a decrease in their rupatadine intake (Figure 2). This was mirrored in the CSU-related QoL, which improved slightly further in patients previously treated with OD with an increase in their rupatadine intake and subsequently slightly worsened in patients previously treated daily, alongside a decrease in their rupatadine intake. No difference in disease activity was observed with PGA, UCT, or QoL (Table 2).

### 3.3 | Updosing rupatadine until Week 10 did not improve UAS7 but increased the number of complete responders

All the OD-treated patients changed to sham up dosing (A2) at the end of Week 4, meaning they remained on the same schedule of 10mg rupatadine OD. In the daily treatment arm, 36 patients (34 of whom were included in the analysis) changed to the real up dosing arm (B2; one patient who did not reach complete remission at Week 4 falsely stayed in the 10mg treatment arm with two complete responders). The up dosing of rupatadine did not significantly improve the UAS7 between Week 4 and Week 10; this was also true for the sham up dosing (Table 3).

However, at Week 10, the up dosing of rupatadine from 10 to 20mg led to an increase in the number of complete responders by

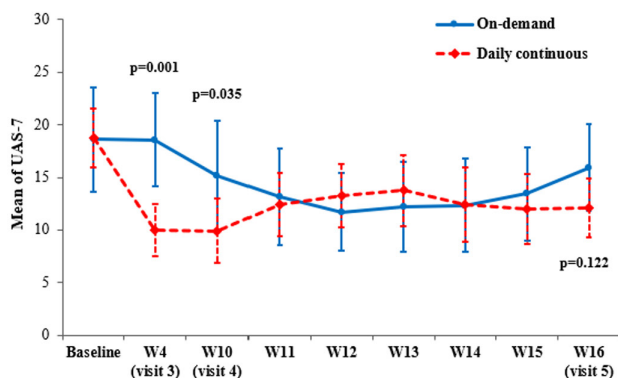
six patients to a total of eight (22%; Table 4), and a mean UAS7 CFB of  $-15.6$  in responders versus  $-5.1$  in non-responders (Table S2). Additionally, there was a UAS7 reduction of  $\geq 75\%$  by five patients to 15 (41%). This is supported by the proportion of patients (42%) with a UCT score of  $\geq 12$  (indicating well-controlled disease) in the daily treatment arm at Week 10 (Table S3).

### 3.4 | Treatment with daily rupatadine resulted in significantly improved disease activity versus OD treatment at Week 4

At baseline, patients had comparable UAS7 in the OD and daily treatment arms (19 and 18, respectively); at Week 4, the mean UAS7 had significantly improved in the daily treatment arm versus the OD arm (10.0 vs. 18.6;  $p = .001$ ; Table 3). As with the UAS7 results, the CSU-related QoL significantly improved with daily versus OD treatment at Week 4: DLQI 4.8 versus 7.6 ( $p = .047$ ) and CU-Q<sub>2</sub>oL was 21.2 versus 32.6 ( $p = .015$ ), respectively (Table 2).

### 3.5 | The safety profile was similar between the daily and OD treatment arms

There were no significant differences between the OD versus daily treatment arms in the overall frequency of AEs (Table S4). Overall, 81 AEs were reported in the study, with no AEs reported in the 10mg rupatadine daily arm. In the 20mg rupatadine daily treatment arm and the 10mg rupatadine OD arm, the most common AEs were tiredness and headache, respectively. Fatigue did not increase with a



UAS7 score	Rupatadine 10 mg OD (n=19)		Rupatadine 20 mg <sup>#</sup> Daily (n=39)		Group difference (Daily-OD) Mean (95%CI)	p-value <sup>#</sup>
	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

Weekly intake of rupatadine 10 mg tablets over the study period				
Number of rupatadine intake	Rupatadine 10 mg OD		Rupatadine 20 mg <sup>#</sup> Daily	
	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)

**FIGURE 2** Disease activity and weekly intake of rupatadine in patients treated OD versus daily throughout the study. Until Week 10 (visit 4) double blind design, up from Week 10 open label treatment of both patient arms OD. Mean and 95% CI error bar of the UAS7 changed over the study between treatment arms. Posthoc analysis based on GEE with adjusted for baseline UAS7 and center heterogeneity and based on multiple imputations. # rupatadine 10mg ( $n = 3$ ) and 20mg ( $n = 36$ ) in daily arm. \*Post-hoc analysis based on GEE with adjusted for baseline UAS7 and center heterogeneity and based on multiple imputations. \*Regarding the adjustment for the baseline UAS7, 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 UAS7 changes from baseline analysis. #Rupatadine 10mg ( $n = 3$ ) and 20mg ( $n = 36$ ) in daily arm. \*\*Number of placebo intake in daily continuously group (maximum intake at Week 4=6 and Week 10=6). Based on multilevel mixed-effects ordered logistic regression with 2 random intercepts for study center and patient, there were no substantial differences of rupatadine intake during the follow-up phase between treatment groups ( $p$ -value=.084) and almost no differences during the follow-up time ( $p$ -value=.796).

TABLE 2 Comparison of health-related quality of life impairment and PGA.

	Rupatadine 10mg OD (n = 19)	Rupatadine 20mg Daily (n = 39)	Mean difference between groups (Daily-OD)	
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	p-Value*
<b>DLQI</b>				
Baseline	9.5 (6.0–13.1)	9.1 (7.7–10.4)	-	-
Week 4 (Visit 3)	7.6 (4.8–10.4)	4.8 (3.3–6.3)	-2.4 (-4.7 to -0.03)	.047
Week 10 (Visit 4)	6.9 (3.9–10.0)	4.0 (2.5–5.5)	-2.6 (-5.0 to -0.2)	.033
Week 16 (Visit 5)	5.7 (2.8–8.6)	5.1 (3.3–6.9)	-0.2 (-2.7 to 2.2)	.852
<b>CU-Q<sub>2</sub>oL</b>				
Baseline	38.6 (27.7–49.6)	35.2 (30.3–40.1)	-	-
Week 4 (Visit 3)	32.6 (23.9–41.2)	21.2 (16.1–26.3)	-8.9 (-16.1 to -1.8)	.015
Week 10 (Visit 4)	29.7 (19.8–39.6)	19.9 (14.6–25.1)	-7.4 (-14.5 to -0.2)	.044
Week 16 (Visit 5)	25.9 (16.4–35.4)	24.2 (17.9–30.5)	0.7 (-6.7 to 8.2)	.844
<b>PGA, n (%)</b>				
None				
Week 4	0 (0.0)	1 (2.6)		<.001
Week 10	2 (10.5)	11 (29.7)		.024
Week 16	1 (5.6)	2 (6.5)		.319
Mild				
Week 4	1 (5.3)	27 (69.2)		
Week 10	11 (29.7)	17 (46.0)		
Week 16	1 (5.6)	2 (6.5)		
Moderate				
Week 4	14 (73.7)	11 (73.7)		
Week 10	8 (42.1)	2 (8.1)		
Week 16	5 (27.8)	10 (32.3)		
Severe				
Week 4	4 (21.1)	0 (0.0)		
Week 10	2 (10.5)	6 (16.2)		
Week 16	1 (5.6)	0 (0.0)		

\*Post-hoc analysis based on multilevel mixed-effects linear regression with 2 random intercepts for study center and patient with adjusted for baseline PGA, DLQI or CU-Q<sub>2</sub>oL, and based on multiple imputations.

TABLE 3 Comparison of the mean UAS7 in the 34 and 19 patients who underwent up dosing to rupatadine 20 mg and sham-up dosing (rupatadine 10 mg OD).

UAS7	Rupatadine 10mg OD	Rupatadine 20mg Daily	Group difference (Daily-OD)	
	Mean (SD)	Mean (SD)	Mean (95% CI)	p-Value
Complete case analysis	n = 19	n = 34*		
Week 4 (Visit 3)	18.6 (9.7)	10.4 (7.6)		
Week 10 (Visit 4)	15.2 (11.4)	10.7 (9.8)		
UAS7 change from Week 4 (Week 10-Week 4)	-3.4 (6.6)	0.3 (7.8)	3.7 (-0.4 to 7.9)	.078**
p-Value within group	.038	.861		

\*36 cases but two patients were missing UAS7 scores; \*\*Adjusted for baseline UAS7.

more frequent intake, or an increased dose of rupatadine and headache appeared more commonly in female patients during rupatadine up dosing.

The incidence rate of AEs in the 20mg rupatadine daily arm and the 10mg rupatadine OD arms were 11.83 per 100 person-weeks (95% confidence interval [CI]: 8.91–15.40 per 100 person-weeks)

**TABLE 4** Comparison of the proportion of patients with response (based on the UAS7).

Percentage of patients with UAS7 response	Rupatadine 10mg OD	Rupatadine 20mg <sup>a</sup> Daily	p-value <sup>*</sup>
Response at visit 3 (Week 4)	n=18	n=37	.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 (Week 10)	n=18	n=37	.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 (week 16)	n=17	n=30	.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%)	

<sup>a</sup>Rupatadine 10mg (n=3) and 20mg (n=36) in daily continuously group.

<sup>\*</sup>Post-hoc analysis based on multilevel mixed-effects ordered logistic regression with two random intercepts for study center and patient with adjusted for baseline UAS7.

and 9.96 per 100 person-weeks (95% CI: 6.51–14.60 per 100 person-weeks). There was only one event with a Grading according to CTCAE of 3. This patient had epigastric pain that was unlikely related to the study medication.

## 4 | DISCUSSION

The present study aimed to address three main questions regarding the use of rupatadine for the treatment of CSU: (1) the potential disease-modifying effects; (2) the effects of normal dosing versus updosing of rupatadine, and updosing in patients who do not reach complete remission under normal dosing, and (3) the comparison of OD versus daily treatment. We will discuss each outcome below.

The treatment arms were well balanced at baseline except for the intake of rescue medication during the screening phase, which was higher in the OD arm versus the daily treatment arm (four doses vs. one dose and the physicians' scored more patients in the daily treatment arm with severe disease activity compared to the OD arm (PGA rated as 26.2% vs. 9.5%), so this imbalance should be accounted for when interpreting the results. Additionally, the limited sample size should be considered when interpreting the results. For the statistical assumptions in the methods to be fully valid, a total sample size of 192 patients was required; however, only 63 patients overall were

included in the analysis. This was partly due to the expiration of the study medication before the intended sample size was reached.

According to the current treatment guidelines for chronic urticaria,<sup>1</sup> the first-line treatment is a standard-dose second-generation H<sub>1</sub>-antihistamine, which is increased up to 4× the dose if needed. Second-generation H<sub>1</sub>-antihistamines, such as desloratadine and fexofenadine, have over 40 years' worth of evidence in clinical use. Their safety has been extensively studied in randomized, controlled trials,<sup>31,32</sup> mainly in allergic rhinitis, and good tolerance of rupatadine has been demonstrated at higher doses.<sup>33</sup> At the end of the follow-up period, there was no difference in disease activity between those treated OD and daily. Daily dosing appears to provide significant benefits while a patient is undergoing treatment but does not provide a longer term advantage after treatment ceases. There was no longer term advantage in patients who reached remission under treatment versus those who did not. This was also true for disease activity measured by the PGA, UCT, and QoL. Together, these results suggest that there is no long-term disease-modifying effect of rupatadine regardless of the treatment schedule, and rupatadine, therefore, appears to be effective against CSU during active treatment only. It is, however, possible that for significant differences in the attenuation of symptoms to become evident, a longer treatment period is required, especially as some patients' inflammatory symptoms do not respond immediately to nsAHs.

Updosing of rupatadine did not lead to further significant reductions in CSU activity by the end of the treatment phase. The same was true for sham updosing. However, rupatadine updosing led to a 22% increase in the number of complete responders and an increase in patients achieving ≥75% UAS7 reduction. The inconsistency of the UAS7 results and the responder rates/UCT results is likely explained by six patients in the daily treatment arm having severe disease activity at Week 10 but not at Week 4, as rated by the physicians (PGA).

Two weeks of treatment with daily rupatadine resulted in significantly improved disease activity compared with OD treatment. These results indicate that during treatment, patients achieved better control over their CSU activity when treated with a daily maintenance rupatadine schedule. One study has shown that the beneficial effects of nsAH given OD appear to be low, and thus, a preventive treatment strategy should be considered in CSU.<sup>12</sup> Our aim to test the hypothesis of OD versus daily treatment arose from literature showing that a preventive nsAH treatment schedule was more effective and had longer term benefits than OD therapy in allergic rhinitis.<sup>6–8</sup> However, contradictory results have also been reported in allergic rhinitis.<sup>34</sup> The data presented in our study reinforce the Grob et al. results<sup>9</sup>; we demonstrate significantly reduced disease activity of CSU and better QoL in patients treated with daily rupatadine versus OD. This could be because antihistamines work better if they are already bound to the receptor when the histamine is released in urticaria patients. If the medication is taken only when the histamine has already been released and has activated its receptors, antihistamine could be less effective.<sup>35</sup> Additionally, it follows that UAS7 is



higher in patients in the OD treatment group since symptoms must be present to trigger the intake, while this is not the case in the daily treatment group. The results are supported by the observation that the UAS7 of the previously daily-treated patients worsened when their rupatadine intake decreased (during the follow-up phase). In previously OD-treated patients, UAS7 improved slightly when patients increased their rupatadine intake, showing a correlation between dose and effect.

The CSU-related QoL followed the same pattern of UAS7 in both arms by improving significantly in patients treated daily compared to those treated OD at Week 4. Subsequently, QoL slightly worsened in the previously daily treated patients on decreasing their rupatadine intake and improved slightly more in the previously OD-treated patients on increasing their rupatadine intake. These results show that CSU symptoms are a major driver of QoL impairment.

There were no significant differences between OD and daily treatment arms regarding the overall frequency of AEs. Tiredness did not increase with a more frequent intake of rupatadine or an increased dose. In contrast, headaches seemed to be more common in female patients during rupatadine up dosing.

This study shows convincing evidence that a daily treatment regimen with rupatadine is more effective than an OD schedule. In addition, the results show a tendency towards a higher rate of complete responders to rupatadine up dosing versus normal dosing. However, the study does have certain limitations; we test only one nsAH, and since other antihistamines possess different pharmacokinetic and pharmacodynamic properties, it cannot be assumed that using another nsAH would produce the same results. When interpreting the results, the limited sample size should be considered, which was partly due to the expiration of the study medication before the intended sample size was reached. Additionally, the treatment period lasted only 8 weeks. The potential for any disease-modifying effects may take longer to exert its influence and become apparent. Further, the manufacturers of rupatadine only allowed us to use up to double the standard dose, whereas the urticaria guidelines recommend using up to a fourfold dose to gain full benefits. We were not able to test this in our study. It is possible that improved effects of up dosing or disease-modifying effects were missed compared to the real-world use of rupatadine.

In conclusion, patients treated with daily rupatadine had significantly improved disease activity compared with OD treatment, which continued to improve until treatment was stopped. Up dosing rupatadine did not improve its effectiveness but slightly increased the number of complete responders. However, after treatment had ceased, rupatadine did not produce any long-term disease-modifying effects in CSU. We, therefore, recommend treating patients with CSU daily rather than OD rupatadine.

#### AUTHOR CONTRIBUTIONS

Karsten Weller and Marcus Maurer made substantial contributions to the conception and design of the work, to the acquisition, analysis, and interpretation of the data, drafting of the manuscript,

and final approval of the manuscript version to be published. Ana Maria Gimenez-Arnau made substantial contributions to the conception and design of the work, to the acquisition and interpretation of the data, to reviewing the manuscript critically for important intellectual content, and to the final approval of the manuscript version to be published. Jens Baron, Randolph Brehler, Marta Ferrer, Adriane Groffik, Sonja Grundmann, Thilo Jakob, Moises Labrador-Horillo, Sabine Müller, Petra Staubach-Renz, Gerda Wurpts and Martin Metz made substantial contributions to the acquisition and interpretation of the data, reviewing the manuscript critically for important intellectual content, and final approval of the manuscript version to be published.

#### ACKNOWLEDGMENTS

Gillian Brodie, MSc, of Orbit Medical Communications Ltd., provided writing support for this manuscript, funded by Charité. Open Access funding enabled and organized by Projekt DEAL.

#### FUNDING INFORMATION

This study was funded in part by URIACH, and the analysis was funded by Charité—Universitätsmedizin Berlin as part of the “CULATER” study. Other features of the study were supported by intramural funding. In addition, this study benefited from the network of Urticaria Centers of Reference and Excellence (UCAREs; <https://ga2len-ucare.com>) of GA<sup>2</sup>LEN, the Global Allergy and Asthma European Network.

#### CONFLICT OF INTEREST STATEMENT

Karsten Weller has received honoraria for educational lectures from Biocryst, Biomarin, CSL Behring, MOXIE, Novartis, and Shire/Takeda. He has also received honoraria for advisory activities from Biocryst, Biomarin, MOXIE, Novartis, and Shire/Takeda. Ana Maria Gimenez-Arnau has been a speaker and/or advisor for and/or has received research funding from Almirall, Amgen, AstraZeneca, Avene, Celldex, Escient Pharmaceuticals, Genentech, GSK, Instituto Carlos III- FEDER, Leo Pharma, Menarini, Novartis, Sanofi-Regeneron, Thermo Fisher Scientific, Uriach Pharma/Neucor. Jens Baron has been a speaker for and/or has received research funding from Abbvie, Bayer Vital, Galderma, Janssen-Cilag GmbH, Leo Pharma, Lilly Pharma, Mt Derm, Novartis, Orthogen, and Skinceuticals. Randolph Brehler has participated in lectures for ALK, Allergopharma, Almirall, Astra Zeneca, Behring, Bencard, Gesellschaft zur Förderung der Dermatologischen Forschung und Fortbildung e.V., Gesellschaft für Information und Organisation mbH, GSK, HAL, Leti, Lofarma, MedUpdate, Merck, Novartis, Omnicuris, Sanofi, Stallergenes, Takeda, Thermo-Fischer. In addition, he has been an advisor for Allergopharma, Astra Zeneca, GSK, HAL, Leti, Lofarma, and Novartis and has been involved in clinical trials for ALK, Allergopharma, Bencard, Biotech Tools, Circassia, Genentech, Novartis. Marta Ferrer has received honoraria (advisory board, speaker) from Novartis, Menarini, Uriach, FAES, and Pfizer. Adriane Groffik has no conflicts of interest to disclose. Sonja Grundmann has no conflicts of interest to disclose.


Thilo Jakob has been a speaker and advisor for and/or has received research funding from ALK-Abello, Allergy Therapeutics/Bencard, Novartis and Thermo-Fisher Scientific. Moisés Labrador-Horrillo has been a speaker and/or advisor for Astrazeneca, GSK, Novartis, Sanofi-Regeneron and Thermo Fisher Scientific. Sabine Müller has received lecture fees and has taken part in advisory boards for Novartis. Petra Staubach-Renz has no conflicts of interest to disclose. Gerda Wurpts has no conflicts of interest to disclose. Martin Metz has received honoraria as a speaker and/or consultant for Amgen, AstraZeneca, argenx, Celldex, Escient, Jasper Therapeutics, Novartis, Pharvaris, Sanofi-Aventis, and ThirdHarmonicBio. Marcus Maurer has been a speaker and/or advisor for and/or has received research funding from Allakos, Alvotech, Amgen, Aquestive, Aralez, AstraZeneca, Bayer, Celldex, Celltrion, Evommune, GSK, Ipsen, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Mitsubishi Tanabe Pharma, Moxie, Noucor, Novartis, Orion Biotechnology, Resonance Medicine, Sanofi/Regeneron, Septerna, Trial Form Support International AB, Third HarmonicBio, ValenzaBio, Yuhan Corporation, and Zurabio.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

#### ORCID

Karsten Weller  <https://orcid.org/0000-0003-4437-0313>

Ana Maria Gimenez-Arnau  <https://orcid.org/0000-0001-5434-7753>

Marta Ferrer  <https://orcid.org/0000-0001-8495-1302>

Martin Metz  <https://orcid.org/0000-0002-4070-9976>

Marcus Maurer  <https://orcid.org/0000-0002-4121-481X>

#### REFERENCES

- Zuberbier T, Abdul Latif AH, Abuzakouk M, et al. The international EAACI/GA<sup>2</sup>LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*. 2022;77(3):734-766. (In English). doi:10.1111/all.15090
- Kolkhir P, Giménez-Arnau AM, Kulthanan K, Peter J, Metz M, Maurer M. Urticaria. *Nat Rev Dis Primers*. 2022;8(1):61. (In English). doi:10.1038/s41572-022-00389-z
- Maurer M, Weller K, Bindslev-Jensen C, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA<sup>2</sup>LEN task force report. *Allergy*. 2011;66(3):317-330. (In English). doi:10.1111/j.1398-9995.2010.02496.x
- Gonçalo M, Giménez-Arnau A, Al-Ahmad M, et al. The global burden of chronic urticaria for the patient and society. *Br J Dermatol*. 2021;184(2):226-236. (In English). doi:10.1111/bjd.19561
- Radonjic-Hoesli S, Hofmeier KS, Micalletto S, Schmid-Grendelmeier P, Bircher A, Simon D. Urticaria and angioedema: an update on classification and pathogenesis. *Clin Rev Allergy Immunol*. 2018;54(1):88-101. (In English). doi:10.1007/s12016-017-8628-1
- Canonica GW, Fumagalli F, Guerra L, et al. Levocetirizine in persistent allergic rhinitis: continuous or on-demand use? A pilot study. *Curr Med Res Opin*. 2008;24(10):2829-2839. (In English). doi:10.1185/03007990802395927
- Ciprandi G, Passalacqua G, Mincarini M, Ricca V, Canonica GW. Continuous versus on demand treatment with cetirizine for allergic rhinitis. *Ann Allergy Asthma Immunol*. 1997;79(6):507-511. (In English). doi:10.1016/s1081-1206(10)63057-8
- Ciprandi G, Tosca M, Passalacqua G, Canonica GW. Long-term cetirizine treatment reduces allergic symptoms and drug prescriptions in children with mite allergy. *Ann Allergy Asthma Immunol*. 2001;87(3):222-226. (In English). doi:10.1016/s1081-1206(10)62230-2
- Grob JJ, Auquier P, Dreyfus I, Ortonne JP. How to prescribe antihistamines for chronic idiopathic urticaria: desloratadine daily vs PRN and quality of life. *Allergy*. 2009;64(4):605-612. (In English). doi:10.1111/j.1398-9995.2008.01913.x
- Siebenhaar F, Degener F, Zuberbier T, Martus P, Maurer M. High-dose desloratadine decreases wheal volume and improves cold provocation thresholds compared with standard-dose treatment in patients with acquired cold urticaria: a randomized, placebo-controlled, crossover study. *J Allergy Clin Immunol*. 2009;123(3):672-679. (In English). doi:10.1016/j.jaci.2008.12.008
- Staevska M, Popov TA, Kralimarkova T, et al. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. *J Allergy Clin Immunol*. 2010;125(3):676-682. (In English). doi:10.1016/j.jaci.2009.11.047
- Weller K, Viehmann K, Bräutigam M, et al. Management of chronic spontaneous urticaria in real life—in accordance with the guidelines? A cross-sectional physician-based survey study. *J Eur Acad Dermatol Venereol*. 2013;27(1):43-50. (In English). doi:10.1111/j.1468-3083.2011.04370.x
- Weller K, Ziege C, Staubach P, et al. H1-antihistamine up-dosing in chronic spontaneous urticaria: patients' perspective of effectiveness and side effects—a retrospective survey study. *PLoS ONE*. 2011;6(9):e23931. (In English). doi:10.1371/journal.pone.0023931
- Türk M, Yılmaz İ, Şahiner ÜM, et al. Experience-based advice on stepping up and stepping down the therapeutic management of chronic spontaneous urticaria: where is the guidance? *Allergy*. 2022;77(5):1626-1630. (In English). doi:10.1111/all.15227
- Takeshi Kono MK. Evaluation of the prognosis of chronic urticaria with antihistamine therapy (EPOCH). *EADV*. 2010.
- AP Ltd. *Rupatadine 1mg/ml Oral Solution*. EMC; 2022.
- AP Ltd. *Rupatadine 10mg Tablets*. EMC; 2022.
- Pağan K, Bartuzi Z. Platelet activating factor in allergies. *Int J Immunopathol Pharmacol*. 2015;28(4):584-589. (In English). doi:10.1177/0394632015600598
- Munoz-Cano R, Ainsua-Enrich E, Torres-Atencio I, et al. Effects of rupatadine on platelet-activating factor-induced human mast cell degranulation compared with desloratadine and levocetirizine (the MASPAF study). *J Invest Allergol Clin Immunol*. 2017;27(3):161-168. (In English). doi:10.18176/jiaci.0117
- Mullol J, Bousquet J, Bachert C, et al. Update on rupatadine in the management of allergic disorders. *Allergy*. 2015;70(Suppl 100):1-24. (In English). doi:10.1111/all.12531
- Krause K, Giménez-Arnau A, Martínez-Escala E, et al. Platelet-activating factor (PAF) induces wheal and flare skin reactions independent of mast cell degranulation. *Allergy*. 2013;68(2):256-258. (In English). doi:10.1111/all.12083
- Vasiadi M, Kalogeromitros D, Kempuraj D, et al. Rupatadine inhibits proinflammatory mediator secretion from human mast cells triggered by different stimuli. *Int Arch Allergy Immunol*. 2010;151(1):38-45. (In English). doi:10.1159/000232569
- Peña J, Carbo ML, Solans A, Nadal T, Izquierdo I, Merlos M. Antihistaminic effects of rupatadine and PKPD modelling. *Eur J Drug Metab Pharmacokinet*. 2008;33(2):107-116. (In English). doi:10.1007/bf03191027
- Valero A, de la Torre F, Castillo JA, et al. Safety of rupatadine administered over a period of 1 year in the treatment of persistent allergic rhinitis: a multicentre, open-label study in

- Spain. *Drug Saf.* 2009;32(1):33-42. (In English). doi:[10.2165/00002018-200932010-00003](https://doi.org/10.2165/00002018-200932010-00003)
25. Metz M, Scholz E, Ferrán M, Izquierdo I, Giménez-Arnau A, Maurer M. Rupatadine and its effects on symptom control, stimulation time, and temperature thresholds in patients with acquired cold urticaria. *Ann Allergy Asthma Immunol.* 2010;104(1):86-92. (In English). doi:[10.1016/j.anai.2009.11.013](https://doi.org/10.1016/j.anai.2009.11.013)
  26. Giménez-Arnau A, Izquierdo I, Maurer M. The use of a responder analysis to identify clinically meaningful differences in chronic urticaria patients following placebo-controlled treatment with rupatadine 10 and 20 mg. *J Eur Acad Dermatol Venereol.* 2009;23(9):1088-1091. (In English). doi:[10.1111/j.1468-3083.2009.03289.x](https://doi.org/10.1111/j.1468-3083.2009.03289.x)
  27. Hawro T, Ohanyan T, Schoepke N, et al. The urticaria activity score-validity, reliability, and responsiveness. *J Allergy Clin Immunol Pract.* 2018;6(4):1185-1190.e1. (In English). doi:[10.1016/j.jaip.2017.10.001](https://doi.org/10.1016/j.jaip.2017.10.001)
  28. Weller K, Groffik A, Church MK, et al. Development and validation of the urticaria control test: a patient-reported outcome instrument for assessing urticaria control. *J Allergy Clin Immunol.* 2014;133(5):1365-1372.e6. (In English). doi:[10.1016/j.jaci.2013.12.1076](https://doi.org/10.1016/j.jaci.2013.12.1076)
  29. Finlay AY, Khan GK. Dermatology life quality index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol.* 1994;19(3):210-216. (In English). doi:[10.1111/j.1365-2230.1994.tb01167.x](https://doi.org/10.1111/j.1365-2230.1994.tb01167.x)
  30. Baiardini I, Pasquali M, Braidò F, et al. A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-QoL). *Allergy.* 2005;60(8):1073-1078. (In English). doi:[10.1111/j.1398-9995.2005.00833.x](https://doi.org/10.1111/j.1398-9995.2005.00833.x)
  31. Salmun LM, Lorber R. 24-hour efficacy of once-daily desloratadine therapy in patients with seasonal allergic rhinitis [ISRCTN32042139]. *BMC Fam Pract.* 2002;3:14. (In English). doi:[10.1186/1471-2296-3-14](https://doi.org/10.1186/1471-2296-3-14)
  32. Sussman GL, Mason J, Compton D, Stewart J, Ricard N. The efficacy and safety of fexofenadine HCl and pseudoephedrine, alone and in combination, in seasonal allergic rhinitis. *J Allergy Clin Immunol.* 1999;104(1):100-106. (In English). doi:[10.1016/s0091-6749\(99\)70120-x](https://doi.org/10.1016/s0091-6749(99)70120-x)
  33. Donado E, Izquierdo I, Pérez I, et al. No cardiac effects of therapeutic and supratherapeutic doses of rupatadine: results from a 'thorough QT/QTc study' performed according to ICH guidelines. *Br J Clin Pharmacol.* 2010;69(4):401-410. (In English). doi:[10.1111/j.1365-2125.2009.03599.x](https://doi.org/10.1111/j.1365-2125.2009.03599.x)
  34. Dizdar EA, Sekerel BE, Keskin O, et al. The effect of regular versus on-demand desloratadine treatment in children with allergic rhinitis. *Int J Pediatr Otorhinolaryngol.* 2007;71(6):843-849. (In English). doi:[10.1016/j.ijporl.2007.02.003](https://doi.org/10.1016/j.ijporl.2007.02.003)
  35. Thangam EB, Jemima EA, Singh H, et al. The role of histamine and histamine receptors in mast cell-mediated allergy and inflammation: the hunt for new therapeutic targets. *Front Immunol.* 2018;9:1873. (In English). doi:[10.3389/fimmu.2018.01873](https://doi.org/10.3389/fimmu.2018.01873)

### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Weller K, Gimenez-Arnau AM, Baron J, et al. Efficacy and safety of on-demand versus daily rupatadine in chronic spontaneous urticaria: A randomized trial. *Allergy.* 2024;79:93-103. doi:[10.1111/all.15854](https://doi.org/10.1111/all.15854)