

BRIEF COMMUNICATION

Rupatadine improves quality of life in mastocytosis: a randomized, double-blind, placebo-controlled trial

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Keywords

antihistamine; mastocytosis; platelet-activating factor; rupatadine; urticaria pigmentosa.

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Abstract

Background: Mastocytosis is frequently associated with mast cell-mediated symptoms which require relieving medication. While second generation antihistamines (sgAHs) are the first line therapeutic strategy to treat mast cell mediator-related symptoms, controlled clinical trials on how they improve quality of life have not been performed.

Methods: This randomized, double-blind, placebo-controlled, cross-over trial assessed rupatadine 20 mg daily in the treatment of mastocytosis symptoms in 30 adult patients. Symptoms were assessed by a visual analogue scale (VAS) and symptom specific quality of life questionnaire (ItchyQoL).

Results: The mean ItchyQoL total score and VAS symptom score were significantly improved in the rupatadine treatment phase compared with placebo. There were also significant reductions from placebo in the severity of itch, wheal and flare, flushing, tachycardia and headache but not gastrointestinal symptoms.

Conclusions: In this first comprehensive trial of a sgAH in mastocytosis, rupatadine 20 mg daily for 4 weeks significantly controlled symptoms and improved patients' quality of life.

Mastocytosis is a heterogenic disease characterized by a pathological increase of mast cells in different organs, particularly in the skin and bone marrow. The disease categories range from benign cutaneous mastocytosis (CM) to progressive forms with organ dysfunction (1). Most adult patients show indolent systemic mastocytosis (ISM) associated with maculopapular skin lesions. Symptoms due to mast cell mediator release include not only whealing, erythema, and pruritus after mechanical irritation of skin lesions, but also flushing, headaches, bone pain, and gastrointestinal symptoms, up to severe and life-threatening allergic shock (2). Therefore, many patients experience a markedly impaired quality of life. Second-generation antihistamines (sgAHs) are the first-line therapeutic strategy and routinely used for the treatment of mastocytosis although data on the safety and efficacy of nsAHs in mastocytosis obtained from controlled clinical

trials are largely missing. The present study investigated the effects of 20-mg rupatadine daily in patients with mastocytosis with skin involvement by assessing changes in quality of life and disease severity.

Methods

Study design and clinical outcome

The study was designed as a double-blind, placebo-controlled, cross-over trial, approved by the Ethics Committee of Berlin and conducted according to the regulatory authorities and the Declaration of Helsinki (ClinicalTrials.gov identifier: NCT01481909). Patients were recruited by the university mastocytosis outpatient clinics at the Department of Dermatology and Allergy of Charité - Universitätsmedizin Berlin.

A total of 30 patients with positive skin provocation testing (3) were enrolled, provided that they met all inclusion criteria and none of the exclusion criteria (Table S1) and that they gave informed consent. Patients received treatment for 28 days (minimal 25, maximal 30 days) and were not allowed to use concomitant medication, which might influence the study outcome, except for loratadine 10-mg tablets as rescue medication. Patients were randomized in a 1 : 1 ratio to receive 20 mg rupatadine or placebo, identical in appearance, in one of two possible sequences in a cross-over design (Figure S1). All patients evaluated their quality of life retrospectively over a 4-week period at baseline and at the end of each treatment period using a German version of the symptom-specific questionnaire ItchyQoL (4), which has been translated according to international guidelines, and pruritus severity by 10-cm visual analog scale (VAS) upon standardized skin provocation testing at each study visit (3). Additionally, severity of skin reactions, flushing, tachycardia, gastrointestinal symptoms, and headache were evaluated by five-point Likert scales (none, mild, moderate, severe, and very severe).

Statistical analyses

Results from the ItchyQoL questionnaire and 10-cm VAS were normally distributed. Statistical significances between observation periods were calculated using Student's *t*-test for paired samples and correlations using the Pearson correlation test. Results from the five-point Likert scales were compared using the paired Wilcoxon test for nonparametric data.

A probability value of $P < 0.05$ was accepted as a statistically significant difference.

Results

Study population

Of the 39 patients screened, 33 were enrolled in the study. Two patients discontinued the study due to adverse events; one stopped administering placebo due to severe bone pain, a typical symptom of ISM, while another patient withdrew from the study due to fatigue during the rupatadine treatment phase. A further patient was excluded because of non-compliance (Figure S2). The remaining 30 patients (20 female, 10 male, mean age 49.4 years, range 20–70 years) completed the study according to the protocol. Among the 30 patients, 23 were diagnosed ISM, 7 CM, mean serum tryptase level 50.3 (6.27–272) $\mu\text{g/l}$. Twenty-eight patients reported a total of 40 treatment-emergent adverse events (TEAEs), 20 under rupatadine treatment and 20 during placebo phase. None of the TEAEs was considered to be severe.

Efficacy of treatment

The individual changes in ItchyQoL total scores at the end of the placebo and rupatadine treatment periods and the corresponding responder analysis are shown in Fig. 1. There is one obvious outlier, indicated by a broken line (Fig. 1A)

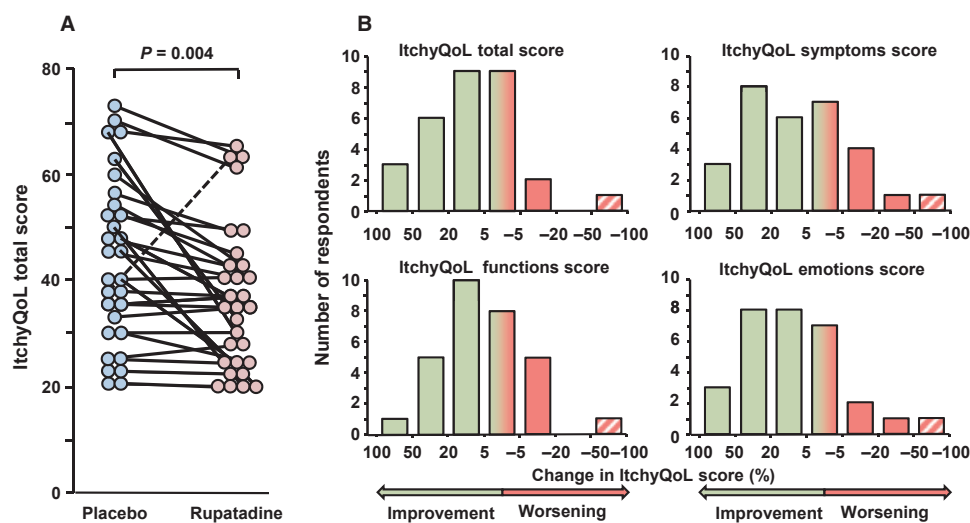


Figure 1 Treatment outcome on quality of life. A. ItchyQoL total scores are shown for the 30 individual patients on placebo and rupatadine, 20 mg daily. The significance of difference was calculated by Student's *t*-test for paired data. One outlier (shown as a broken line) became 68% worse during the treatment period. If this was drug related could not be determined. B. The response of individuals taking rupatadine 20 mg daily was calculated as a percentage improvement from placebo. The patients were stratified into the following categories:

50–100% very good improvement; 20–50% marked improvement; 5–20% some improvement; $0 \pm 5\%$ no effect; -5 to -20% slight worsening; -20 to -50% marked worsening; -50 to -100% much worse. Responder analyses showed that three, six, and nine patients showed $>50\%$, 20–50%, and 5–20% improvement over placebo, respectively, in their ItchyQoL total scores, whereas one patient exhibited 20–50% and one 5–20% improvement during placebo treatment. Suspected outlier indicated by the hatched bar.

and hatched columns (Fig. 1B). The data from this patient, who had a marked exacerbation of symptoms during the rupatadine treatment period, were not included in the statistical analyses.

The mean ItchyQoL total score was significantly improved in the rupatadine treatment phase compared with placebo (16.1% reduction $P = 0.004$). Of the domains within ItchyQoL, the 17.4%, 10.6%, and 18.5% reductions in the scores for symptoms, functions, and emotions were also statistically significantly different from placebo (Table S2). There was a significant correlation ($r = 0.490$, $P = 0.007$) between patients' improvement in ItchyQoL total score during the rupatadine treatment phase and their ItchyQoL total score in the placebo phase. This suggests that those patients with a higher ItchyQoL total score, that is, poorer quality of life, receive more benefit from rupatadine. There were also statistically significant correlations between percentage improvement during the rupatadine treatment phase and placebo ItchyQoL scores for symptoms ($r = 0.564$, $P = 0.001$) and emotions ($r = 0.394$, $P = 0.031$) but not for the functions domain ($r = 0.150$, $P = 0.427$).

Visual analog scale was significantly improved in the rupatadine treatment phase compared with placebo (30.3% reduction, $P = 0.041$). The VAS and ItchyQoL total scores were significantly correlated both in the placebo ($r = 0.536$, $P = 0.003$) and the rupatadine treatment ($r = 0.579$, $P = 0.001$) phases. Although the reduction in VAS was numerically greater than that of the ItchyQoL total score, its greater variability and consequential lower level of statistical significance ($P = 0.041$ vs $P < 0.005$) suggested that it is less sensitive to therapy-induced changes.

Additionally, there were statistically significant reductions in the severity of skin reactions, flushing, tachycardia, and headache, but not gastrointestinal symptoms, during the

rupatadine treatment period compared with placebo (Fig. 2A).

Eight patients (27%) required rescue medication during the placebo phase, whereas only three patients (10%) during rupatadine treatment. The mean number of required tablets per patient was significantly higher during the placebo phase (Fig. 2B).

Discussion

This study shows a highly significant beneficial effect of the second-generation H_1 -antihistamine, rupatadine (20 mg daily), on the quality of life of patients with cutaneous mastocytosis or indolent systemic mastocytosis. In addition, there were significant improvements in the patients' assessment of severity of their symptoms. To our knowledge, this is the first comprehensive clinical trial of a second-generation H_1 -antihistamine assessing quality of life and symptom reduction in patients with mastocytosis. While older studies have assessed sedating first-generation antihistamines (5–8), our knowledge of the efficacy of second-generation antihistamines has been limited to case reports. In addition to histamine, platelet-activating factor (PAF) has been shown to be generated in mastocytosis and has been suggested to play roles in episodic hypotension and cutaneous flushing (9). The H_1 -antihistamine used in this study, rupatadine, also has the ability to reduce the effects of PAF (10). It is possible therefore that the significant reductions in flushing and tachycardia seen in this study may be, at least in part, due to the anti-PAF effects of rupatadine although this was not the focus of this study. Further studies will evaluate the potential benefit of up-dosing regimens on mastocytosis symptoms, as earlier experienced in the treatment of chronic urticaria (11–14), and evaluate the potential benefits of PAF antagonism.

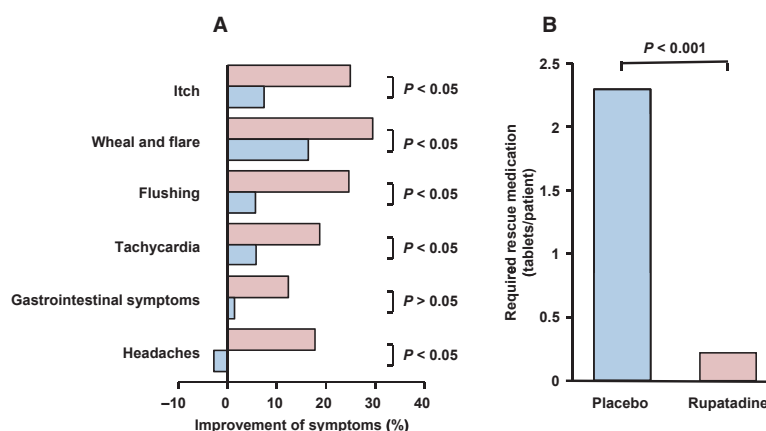


Figure 2 Treatment outcome on mediator-related symptoms. A. Patients scored the intensity of related symptoms on a five-point Likert scale while taking placebo (lower blue bars) or rupatadine (upper purple bars) 20 mg daily. P values were calculated by the Wilcoxon signed rank

test. B. Patients were allowed to take rescue medication during the entire study course according to the protocol and documented the number of tablets taken in the patient diary. The statistical difference between treatments was calculated using Student's t -test for paired data.

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Author contributions

Principal investigator of study, statistics and preparation of manuscript: Frank Siebenhaar; Conduction of study data analyses and preparation of manuscript: Andrea Förtsch; Statistics and preparation of the manuscript: Martin Church; Conduction of study, intellectual input to manuscript: Karolin Krause, Karsten Weller, Martin Metz, Markus Magerl; Data analyses and statistics: Peter Martus; Study coordinator, intellectual input to manuscript: Marcus Maurer.

Conflicts of interest

Frank Siebenhaar and Karsten Weller have been speakers for Uriach. Marcus Maurer and Martin K Church have been speakers or consultants for Uriach. Karoline Krause has received honoraria from Dr. Pfleger GmbH, Martin Metz from Dr. Pfleger GmbH and Uriach.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Study design.

Figure S2. Study flow chart.

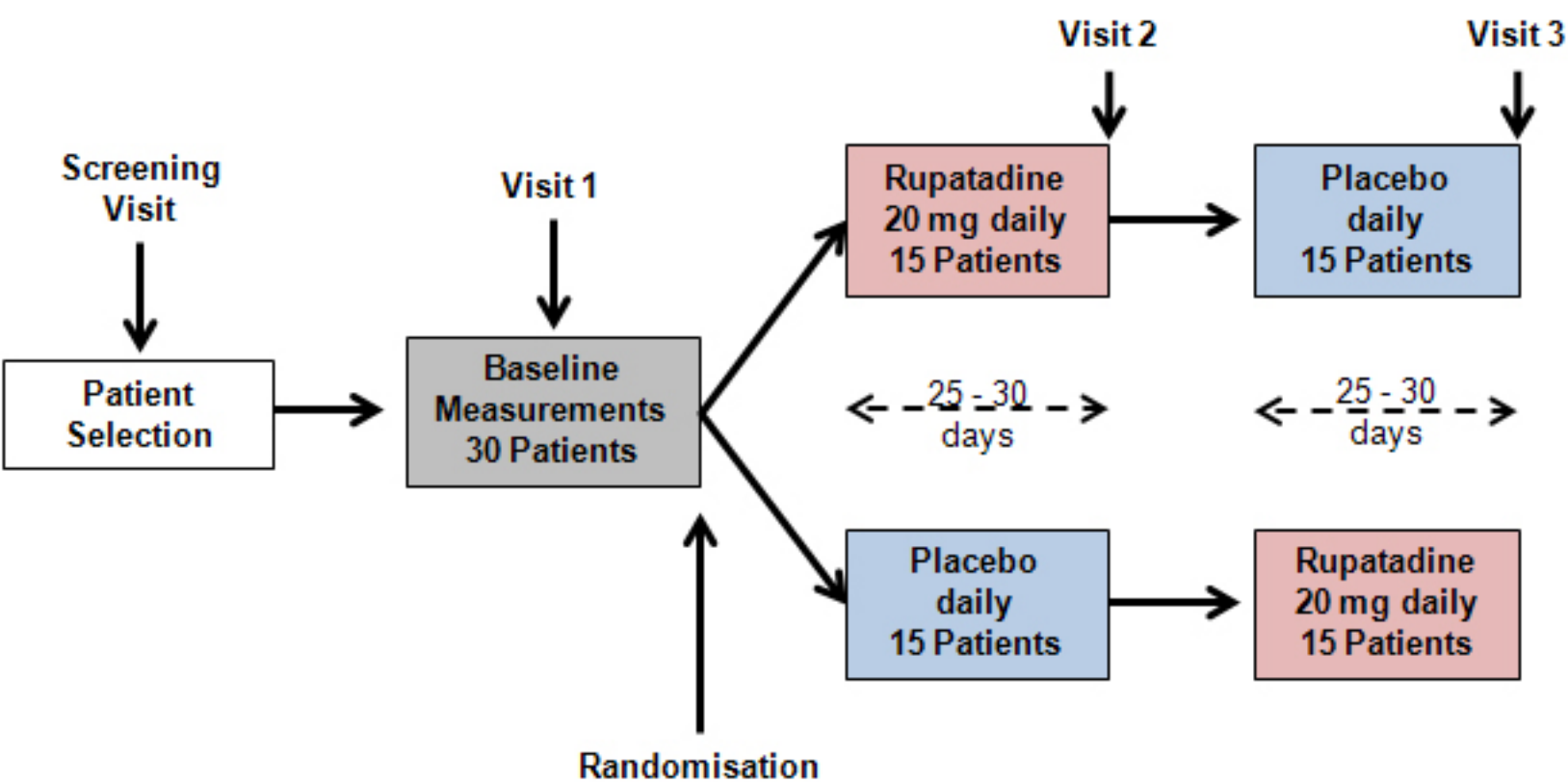
Table S1. Inclusion and exclusion criteria.

Table S2. Detailed information on VAS and ItchyQoL outcome.

Table S3. Information on the frequency of mast cell mediator related symptoms.

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39 patients screened

6 patients not eligible

- 1 had elevated liver enzymes
- 1 had history of myocardial infarction
- 2 had increased QTc intervals
- 1 had withdrawn consent
- 1 had pathological blood count

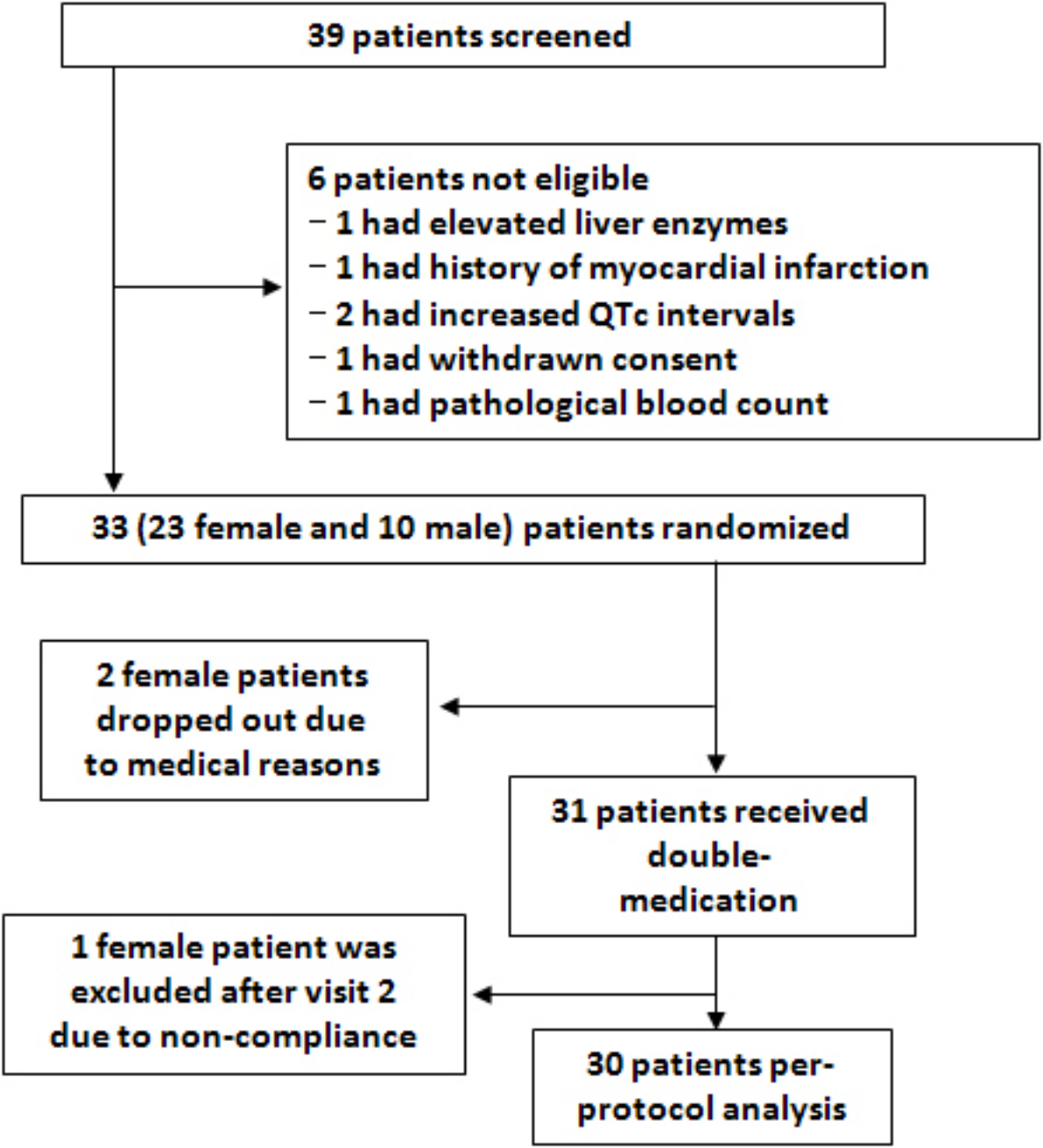
33 (23 female and 10 male) patients randomized

**2 female patients
dropped out due
to medical reasons**

**1 female patient was
excluded after visit 2
due to non-compliance**

**31 patients received
double-
medication**

**30 patients per-
protocol analysis**



Supplementary figure legends

Figure S1: Study design. The study was designed as a double-blind, placebo-controlled, cross-over trial. Patients received treatment for 28 days (minimal 25, maximal 30 days) and were randomized in a 1:1 ratio to receive 20 mg rupatadine or placebo, identical in appearance, in one of two possible sequences.

Figure S2: Study flow chart. 39 patients were screened, 33 were enrolled in the study. Two patients discontinued the study due to adverse events; one stopped administering placebo due to severe bone pain, a typical symptom of ISM, while another patient withdrew from the study due to fatigue during the rupatadine treatment phase. A further patient was excluded because of non-compliance.

Table S1: Inclusion and exclusion criteria. A total of 30 patients with positive skin provocation testing were enrolled, provided that they met all inclusion criteria and none of the exclusion criteria and that they gave informed consent.

Table S2: Detailed information on VAS and ItchyQoL outcome. The table shows results, expressed as mean $\pm$ SEM for 30 patients, taken at the baseline assessment and after patients had taken placebo or rupatadine 20 mg daily for 28 days. The symptom score was assessed on a 10 cm visual analogue scale (VAS) at the baseline assessment. Scores for ItchyQoL represent the total score (21 questions with answers from 1=none to 5=severe, lowest score 21, highest score 105) and sub-scores to assess symptoms (6 questions, lowest score 6, highest score 30), functional limitations (7 questions, lowest score 7, highest score 35) and emotions (8 questions, lowest score 8, highest score 40). The significances of differences were calculated by Student's t test for paired data.

Table S3: Information on the frequency of mast cell mediator related symptoms. The table shows results, expressed as mean $\pm$ SEM for 30 patients, taken at the baseline assessment and after each treatment period (placebo resp. rupatadine 20 mg daily). The symptom scores were assessed on a 5-point Likert scale. The significances of differences were calculated by Student's t test for paired data.

Inclusion Criteria The subjects had to fulfil the following criteria:	1. Chronic stable symptomatic maculopapulous cutaneous mastocytosis or indolent systemic mastocytosis with skin involvement and a positive Darier's Sign 2. Age between 18 and 70 years. 3. Female patients must be using a highly effective method of birth control (such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence, vasectomised partner), or they must be postmenopausal, surgically sterilised, or hysterectomised. 4. Voluntarily signed written informed consent.
Exclusion Criteria Any of the following excluded the subject from the study:	1. The presence of permanent severe diseases, especially those affecting the immune system, except for mastocytosis 2. History or presence of epilepsy, significant neurological disorders, cerebrovascular attacks or ischemia 3. History or presence of myocardial infarction or cardiac arrhythmia which requires drug therapy, hyper-/hypokalemia, bradycardia < 50bpm, QTc interval > 440ms 4. Evidence of severe renal dysfunction (creatinine > 1,5 x upper reference value) 5. Evidence of significant hepatic disease (liver enzymes > 2 x upper reference value) 6. History of adverse reactions to RUP, or other ingredients of the IMP 7. Presence of active cancer which requires chemotherapy or radiation therapy 8. Aggressive systemic mastocytosis 9. History or presence of alcohol abuse or drug addiction 10. Participation in any clinical trial within 4 weeks prior to enrolment 11. Commitment to an institution in terms of § 40 Abs. 1 S. 3 Nr. 4 AMG 12. Intake of antihistamines or leukotriene antagonists within 7 days prior to the beginning of the study 13. Intake of oral corticosteroids within 14 days prior to the beginning of the study 14. Use of depot corticosteroids or chronic systemic corticosteroids within 21 days before beginning of the study 15. Pregnancy or breast-feeding

	Baseline (B)	Placebo (P)	Rupatadine (R)	Significance B vs P	Significance B vs R	Significance P vs R
Symptoms (cm VAS)	4.50 ± 0.55	3.71 ± 0.49	2.72 ± 0.42	<i>P</i> = 0.112	<i>P</i> = 0.003	<i>P</i> = 0.073
IchyQoL						
-Total	45.7 ± 2.7	43.9 ± 2.9	36.8 ± 2.5	<i>P</i> = 0.643	<i>P</i> = 0.025	<i>P</i> = 0.004
-Symptoms	13.8 ± 0.8	12.5 ± 0.8	10.3 ± 0.6	<i>P</i> = 0.245	<i>P</i> = 0.002	<i>P</i> = 0.007
-Functions	15.5 ± 1.1	14.2 ± 1.0	12.7 ± 1.0	<i>P</i> = 0.364	<i>P</i> = 0.063	<i>P</i> = 0.022
-Emotions	16.4 ± 1.2	16.9 ± 1.4	13.8 ± 1.2	<i>P</i> = 0.765	<i>P</i> = 0.125	<i>P</i> = 0.006

	Baseline (B)	Placebo (P)	Rupatadine (R)	Significance B vs P	Significance B vs R	Significance P vs R	Percent of pts. improved
Itch	2.77 ± 0.92	2.57 ± 0.98	2.07 ± 0.45	<i>P</i> = 0.136	<i>P</i> = 0.001	<i>P</i> = 0.007	47
Wheal and flare	2.80 ± 0.95	2.33 ± 0.69	1.97 ± 0.39	<i>P</i> = 0.024	<i>P</i> = 0.001	<i>P</i> = 0.039	43
Flushing	1.93 ± 0.77	1.70 ± 0.76	1.40 ± 0.53	<i>P</i> = 0.083	<i>P</i> = 0.021	<i>P</i> = 0.022	26
Tachycardia	1.77 ± 0.66	1.67 ± 0.67	1.43 ± 0.58	<i>P</i> = 0.375	<i>P</i> = 0.001	<i>P</i> = 0.017	23
GI symptoms	2.43 ± 1.00	2.40 ± 1.03	2.13 ± 0.85	<i>P</i> = 0.873	<i>P</i> = 0.037	<i>P</i> = 0.211	30
Headaches	2.40 ± 0.99	2.47 ± 1.19	1.97 ± 0.71	<i>P</i> = 0.778	<i>P</i> = 0.005	<i>P</i> = 0.037	33