*Appendix S1.*

## MATERIALS AND METHODS

The study was a 2-centre, randomized, double-blind, 3-way crossover, placebo-controlled study in which patients with a confirmed diagnosis of ColdU of at least 6 months' duration were recruited from the Departments of Dermatology Charité-Universitätsmedizin, Berlin and Hospital del Mar, Barcelona. The study was approved by the ethics committee and regular authorities of Berlin and Barcelona (EudraCTnumber: 2011-004094-93) and was conducted according to the Declaration of Helsinki and applicable local and European laws and regulations. The clinicaltrials.gov number is NCT01605487. All participants signed informed consent at the beginning of the study.

### *Patients*

Patient recruitment began in June 2012 and the study was completed in September 2013. A total number of 24 patients (6 males and 18 females, mean age 45 years, age range 19–68 years) participated in the study. The group size was estimated based on the significance level of 0.05 and a power of 80% and a medium effect of 1.2 standard deviations (SD). All women of childbearing potential were required to use effective contraception for the duration of the study. Exclusion criteria included a history of significant gastroenterological, neurological, cardiac, oncological, psychiatric, renal, or liver diseases that could have interfered with patient safety or the conduct of the study. Patients with a history of hypersensitivity or an allergic reaction to rupatadine or other $H_1$-antihistamines were also excluded. Before the start of the study, the participants followed washout periods of 7 days for $H_1$-antihistamines or anti-leukotrienes, 28 days for oral or 3 months for depot corticosteroids and 28 days for immunosuppressants/immunomodulators, such as cyclosporine A, dapsone, methotrexate, mycophenolate, and chloroquine. The administration of ketoconazole, erythromycin or potential inhibitors of the isoenzyme CYP3A4 of the cytochrome P450 was also forbidden.

### *Study design*

Patients with ColdU were randomized according to a balanced experimental design. Each of the 6 possible sequences of placebo, rupatadine 20 mg, or rupatadine 40 mg was applied to an equal number of patients once daily (morning intake) for one week with a 2-week washout period before crossing over to the next treatment group (Fig. 1). The study medication was provided by J. Uriach & Co.: S.A. The tablets of placebo and rupatadine were enclosed in identical blisters. During the treatment phase 4 tablets of placebo, or 2 tablets of rupatadine each of 10 mg and 2 tablets of placebo, or 4 tablets of rupatadine each of 10 mg daily were given. Tablets were taken each morning on a daily basis during the treatment period.

### *Study outcome*

The main study outcomes were the determination of critical temperature (CTT) and critical stimulation time (CsTT) thresholds after provocation with TempTest® 3.0, defined respectively as the highest temperature and shortest time of wheal appearance (14). CTT was determined using a TempTest® 3.0 (7, 15). The temperature head of this device, which was placed directly on the volar surface of the forearm, consists of 12 elements, each 10 mm in diameter, arranged in 2 parallel rows. The device was set to deliver temperatures of 26, 24, 22, 20, 18, 16, 14, 12, 10, 8, 6 and 4°C (each $\pm$ 0.1°C) to the skin for a constant period of 5 min. A positive response is the development of a wheal assessed 10 min after removing the TempTest® 3.0 from the skin, the appearence of wheals is measured. The highest temperature at which a wheal reaction was observed was recorded as CTT. In patients who did not develop a wheal at the lowest temperature tested (4°C) the CTT was recorded as $<$4°C. To evaluate the effectiveness of treatment all patients were divided into 3 groups according to their response on CTT after provocation with TempTest® 3.0: "complete responders" who did not show any wheals on provocation, "partial responders" who showed a reduction in CTT $\geq$4°C compared with placebo treatment and "non-responders" who showed a reduction in CTT less than 4°C in comparison with CTT on placebo.

CsTT was evaluated using the same instrument by exposing the skin to 4°C for 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5 and 5.0 min. Ten min after the instrument was removed the resulting wheals were observed. The lowest of the 10 time-points at which a wheal appeared was recorded as the CsTT. If no wheal was apparent after 5 min of provocation, the CsTT was recorded as >5 min. According to their response on CsTT the patients were divided into 3 groups: "complete responders" who did not develop any wheals on provocation testing, "partial responders" who showed an increase in CsTT $\geq$ 0.5 min in comparison with placebo treatment and "non-responders" who did not show any differences in CsTT compared with placebo.

At each visit patients were asked if they had experienced any adverse events (AEs) over the previous week and during washout periods. AEs were classified according to severity and relationship to therapy. No formal approach for the assessment of somnolence was used. General physical examination, ECG and laboratory blood analyses including differential blood count, sodium, potassium, chloride, calcium liver enzymes, creatin kinase, creatinine and urea were performed at the screening and the final visit.

### *Statistical analysis*

The results for CTT and CsTT are expressed as median (with range) and the significance of differences calculated using Wilcoxon non-parametric test. The significance values for the numbers of individual patients responding or not responding to treatments were calculated using Fisher's exact test.