

Safety and Activity of UR-1505 in Atopic Dermatitis: A Randomized, Double-blind Phase II Exploratory Trial

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ABSTRACT

Purpose: UR-1505 is a new small molecule with immune modulator properties intended for the topical treatment of inflammatory skin diseases that has shown anti-inflammatory effects in models of skin inflammation. We compared the activity of UR-1505 ointment against its vehicle in the treatment of atopic dermatitis. Secondary objectives included exploring dose response, safety, and local tolerability of UR-1505.

Methods: Patients with AD lesions on 2 symmetrical topographic areas (arms, leg, or trunk) were included in this unicenter randomized, double-blind, within-patient, controlled Phase II exploratory trial and received simultaneously 2 different treatments (0.5%, 1%, or 2% UR-1505 and vehicle or 0.1% tacrolimus ointment) once daily during 28 days. The primary efficacy end point was the change from baseline in the Investigator Global Assessment score at Day 28. Secondary end points were percentage of area clearance, local Eczema Area Severity Index (local EASI), and local tolerability. A linear mixed model was used, fitting treatment, body side, and group (treatment at the contralateral side) as fixed factors and the patient as a random effect.

Findings: Twenty-eight patients were randomized and 25 patients were included in the per protocol analysis, with 50 evaluable lesions ($n = 13$ for vehicle, $n = 8$ for UR-1505 0.5%, $n = 9$ for 1% UR-1505, $n = 8$ for 2% UR-1505, and $n = 12$ for tacrolimus). The mean Investigator Global Assessment score change from baseline at Day 28 was -1.7 for vehicle, -1.0 , -1.2 , and -1.5 for 0.5%, 1%, and 2% UR-1505, respectively, and -2.6% for tacrolimus ($P = 0.002$). No serious nor causal adverse reactions were reported in this study, but patients reported numerous local symptoms after product applications, especially itching, tingling, tightness, and heat/burning sensations

at frequencies that were similar for vehicle, 1% UR-1505, and 2% UR-1505; more frequent with 0.5% UR-1505; and lowest for tacrolimus.

Implications: This study found that UR-1505 may not be a suitable option for the treatment of atopic dermatitis due to its lack of clinically relevant effect compared with its vehicle and 0.1% tacrolimus ointment. EudraCT No.: 2007-002550-27. (*Clin Ther.* 2015;37:1955–1965) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key words: anti-inflammatory agents, atopic, clinical trial, dermatitis, eczema, Phase II.

INTRODUCTION

Atopic dermatitis (AD) is a common inflammatory skin disorder¹ with chronic relapsing course and varying intensity. Although genetic susceptibility and a clear skin barrier defect have been described, the exact pathogenesis remains partially unknown, limiting the development of new drugs causally targeting the specific mechanisms of the disease.² The therapy for mild to moderate AD has been focused on reducing skin inflammation and tackling pruritus and other skin symptoms through topical treatment with corticosteroids or calcineurin inhibitors.^{3,4} However, long-term application of corticosteroids is associated with skin atrophy; depigmentation; acneic eruptions; and the risks of systemic absorption, including hypothalamic-pituitary axis suppression and growth retardation in children.⁵ Concerns of increased risk of lymphoma and skin cancer with long-term use of

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topical calcineurin inhibitors, although unwarranted, have limited the use of pimecrolimus and tacrolimus.^{6–9} Oral immunosuppressants are efficacious in short-term treatment of flares, but are associated with severe toxicity and side effects.¹⁰ Besides, the disease often rebounds when treatments are stopped, especially after corticosteroid use.¹⁰ Emollients increase the hydration of the epidermis, their systematic use has been shown to reduce the need for topical treatments, and they are recommended as the basis of treatment, even if they have no direct effect on the course of the eczema, although they should not be considered as monotherapy during flares.¹¹ Thus there is yet room for improved treatment alternatives for the long-term treatment of mild to moderate AD. Despite the efforts to find new therapeutic targets in AD, no new drugs with innovative mechanisms have come to the market in the past 10 years.²

UR-1505 is a new salicylate-related small molecule with immune modulator properties intended for the topical treatment of inflammatory skin diseases in adults, in particular AD and psoriasis. Its mechanism of action is related to the increase in the expression of proteins' arresting cell cycle, such as p27, and a blockade of T-cell activation resulting in the inhibition of both T-cell proliferation and cytokine production, which seem to be mediated through T-cell receptor/nuclear factor of activated T-cells signalling path.^{12–15} UR-1505 showed anti-inflammatory effects in models of skin inflammation (ie, an oxazolone-induced delayed hypersensitivity model and a model of psoriasis consisting of uninvolved psoriasis patient skin transplanted onto immune-deficient BNX mice and activated with superantigen-stimulated peripheral blood mononuclear cells), although at high concentrations (eg, 10%) some of the effects were compromised by local irritant effects. Only predictable dose-dependent adverse effects related to the salicylate-related structure and to the fluorine content of the moiety were observed after oral administration of UR-1505 during 28 days to dogs and rats at doses above 500-fold those expected to be topically applied in humans; in particular, no systemic immunosuppression was observed. In preliminary clinical trials, strengths of 0.5% and 2% of UR-1505 showed good skin tolerability (Palau Pharma S.A., unpublished data).

Because UR-1505 would theoretically be devoid of calcineurin or corticosteroid safety concerns for

long-term topical use, its clinical efficacy was explored in adult patients with mild to moderate AD.

MATERIALS AND METHODS

Design

A proof of concept study in patients with AD was designed as a randomized, double-blind, within-patient, vehicle and tacrolimus (0.1% ointment) controlled Phase II exploratory trial. The main objective was to compare the activity of the topical application of 3 different strengths of a UR-1505 ointment against its vehicle in the treatment of AD during 28 days. Secondary objectives of the study included exploring dose response, safety, and local tolerability of UR-1505.

The trial was conducted in 1 investigational center (Pharmascan; Groupe DermScan, Villeurbanne, Lyon, France), according to the study protocol and protocol amendments, which were previously approved by the corresponding independent ethics committee (Comité de Protection de Personnes Sud – Est IV, Centre Léon Bérard, Lyon, France) and the Agence Française de Sécurité Sanitaire des Produits de Santé and in accordance with the Helsinki Declaration of 1975, as revised in 1983. The trial was registered at the EU Clinical Trials Registry (EudraCT No.: 2007-002550-27).

Patients

Men and women aged 18 to 65 years and with Fitzpatrick skin phototype I to IV were eligible for the study. For inclusion in the trial, patients had to have AD lesions on at least 2 symmetrical topographic areas (arms, legs, or trunk). The diagnosis was established by the investigator according to the UK Working Party's Diagnostic Criteria for Atopic Dermatitis.¹⁶ Patients were required to have a mild to moderate disease severity (SCORing Atopic Dermatitis¹⁷ value between 8 and 30). The sum of the size of each of the areas selected could not exceed 20% of the body. Women with childbearing potential were required to be using an effective means of contraception. Patients with any systemic or topical therapy for AD within the previous 8 weeks or 2 weeks from study entry, respectively, were excluded, as were those who had used anti-inflammatory drugs, antihistamine drugs, or antibiotic agents during the previous week, immuno-suppressant and/or corticosteroid drugs during the previous month, or systemic retinoid drugs during the previous 6 months.

Recruitment was limited to the period between September and April to avoid major seasonal influence on signs and symptoms.^{18,19}

Before any study-related procedure, patients were given comprehensive information on the study objectives, procedures, and risks, and written informed consent was obtained from all patients.

Interventions

All patients simultaneously received 2 different treatments, 1 in each of the symmetric affected areas, applied once daily up to 28 days. Patients were treated on 1 of the areas with 1 out of 3 different UR-1505 ointment strengths (0.5%, 1%, or 2%) (J Uriach & Cía S.A., Palau Solità i Plegamans, Spain) and on the contralateral side with either vehicle of UR-1505 (J Uriach & Cía S.A.) or 0.1% tacrolimus ointment (Protopic; Astellas Pharma Europe, B.V., Leiden, the Netherlands). The amount of ointment to be applied was roughly the size of a pea for each product, which was equivalent to 300 to 500 mg product and was considered enough to treat approximately 5% of body skin surface (eg, internal surface of arm).

Outcomes and Measurements

Efficacy and safety parameters were measured at pretreatment (Day 0) and weekly thereafter until 1-week posttreatment (Day 35). All parameters were measured independently for each of the 2 symmetrical eczema areas in each patient.

The primary efficacy end point was the change from baseline in the Investigator Global Assessment (IGA) score after 4 weeks of treatment (Day 28) for each treated area.

Secondary efficacy end points included the percentage of area clearance and a local Eczema Area Severity Index (EASI)²⁰ assessed for each studied area and calculated as the sum of scores for each of the symptoms (eg, redness, thickness, scratching, and lichenification). Subjective patient assessments on different symptoms and treatment in general were assessed through a questionnaire at the end of treatment.

Local tolerability was assessed for erythema, edema, skin dryness, desquamation, and roughness by the investigator for each of the symmetrical areas, taking as reference the pretreatment status. When signs were present, clinical relevance and causal relationship to the product were assessed. Functional and physical signs (eg, tightness, stinging, itching,

warm/ burning sensation, and roughness) were rated by patients from 0 (none) to 4 (very severe) at each visit. Blood and urine safety analyses were performed at baseline and at the end of treatment, and patients were asked about any adverse events or new medications at each visit.

Sample Size

Due to the lack of available data on point estimates and data variability from similar studies, no formal sample size estimation was performed. However, based on investigator experience it was expected that 10 patients per each pair of comparisons would provide enough data stability to allow detecting of differences for IGA changes in the inpatient comparisons at Day 28. Based on these calculations, a sample size of 60 patients was anticipated. Eventually, the failure to recruit the target population after 8 months led to termination of the trial when 28 patients had been recruited.

Randomization and Blinding

Patients were randomized in blocks of 6 with an equal probability to 1 of 6 treatment groups (Figure 1). Each group was assigned to a pair of different treatments according to a randomization list issued by the manufacturer of the investigation product. Additionally, each patient was randomized to 1 of the 2 side sequences (left–right or right–left) that assigned the side of the body for each of the 2 treatments assigned to the patient.

The study was double blinded. To keep masking, treatments were supplied in identical outer packages containing 2 ointment tubes each, overlabeled with randomization number and side of the body to be treated (left–right). All ointments were pale greyish and transparent oily and fluid pastes, with minimal and not evident viscosity or spreadability differences. To ensure compliance, lack of side confusion, cross-contamination, or potential treatment identification by patients with previous experience using tacrolimus, patients either went daily to the study site to receive treatment or were treated daily at their home. In both cases, treatments were applied by a trained nurse not involved in the study assessments to ensure that clinical investigators and other study personnel remained blind to treatment identity until the study database was locked.

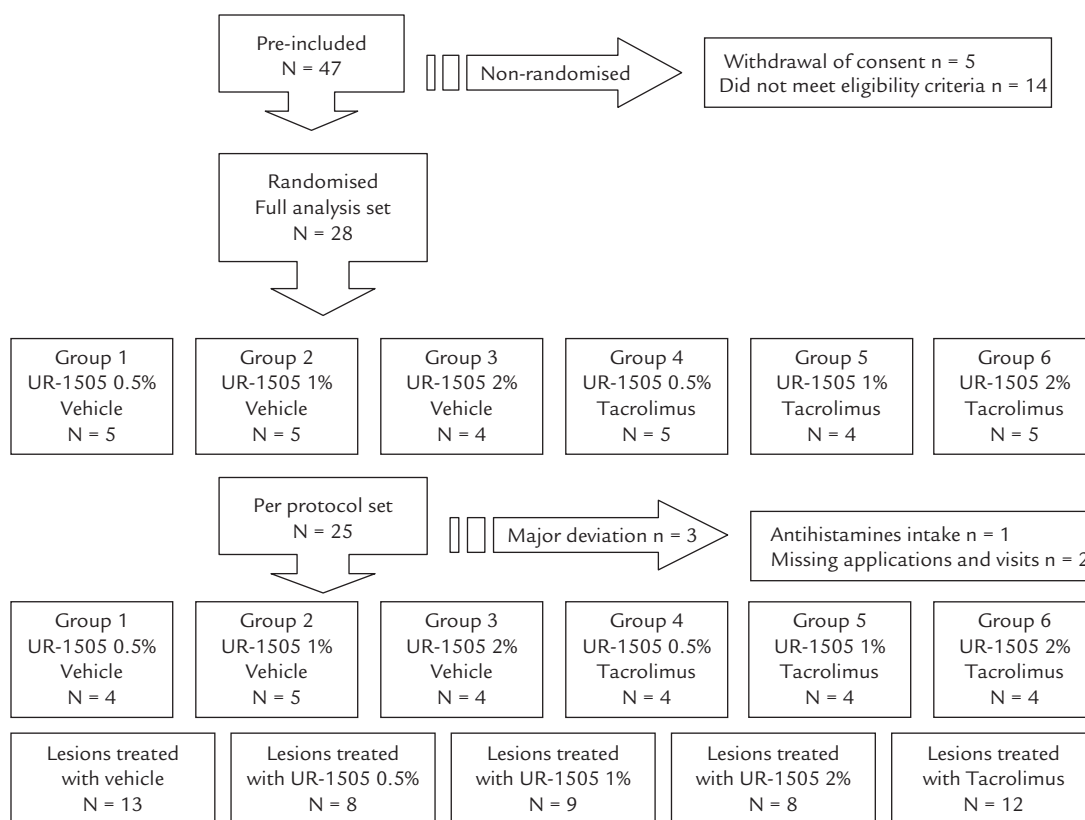


Figure 1. Study design and disposition of patients.

Statistical Methods

Eligibility criteria and populations for analysis were defined during the data blind review meeting (June 2008) before declaring the database locked and before unveiling the randomization assignment list.

For the primary efficacy end point, each individual lesion was considered in the analyses, so that lesions treated with vehicle were pooled in 1 group, and the same for every different treatment administered. A linear mixed model was used, fitting treatment, body side, and group (treatment assigned at the contralateral side) as fixed factors. Random effects by patients were introduced into the statistical model to account for patients' heterogeneity. For secondary end points, time and treatment by time were considered.

A hierarchical approach was adopted for the main analysis to keep a maximum power for tests and to preserve type I error (Figure 2). The significance level was $\alpha = 0.05$ for all tests.

According to the exploratory nature of the trial, the primary analysis was that conducted in the set of patients without relevant protocol deviations (per protocol [PP] set). A sensibility analysis on the full analysis set was also done. No missing data imputation was done. The statistical analysis was conducted using SAS version 9.0 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Patient Characteristics and Treatments

From September 2007 to April 2008, 47 patients with AD were identified at the investigative site and screened for study participation of whom 28 were finally randomized. Three patients were considered to have major protocol deviations and were excluded from the PP set. Figure 1 indicates the number of patients assigned to each treatment group and reasons for not being randomized, for discontinuation, and for

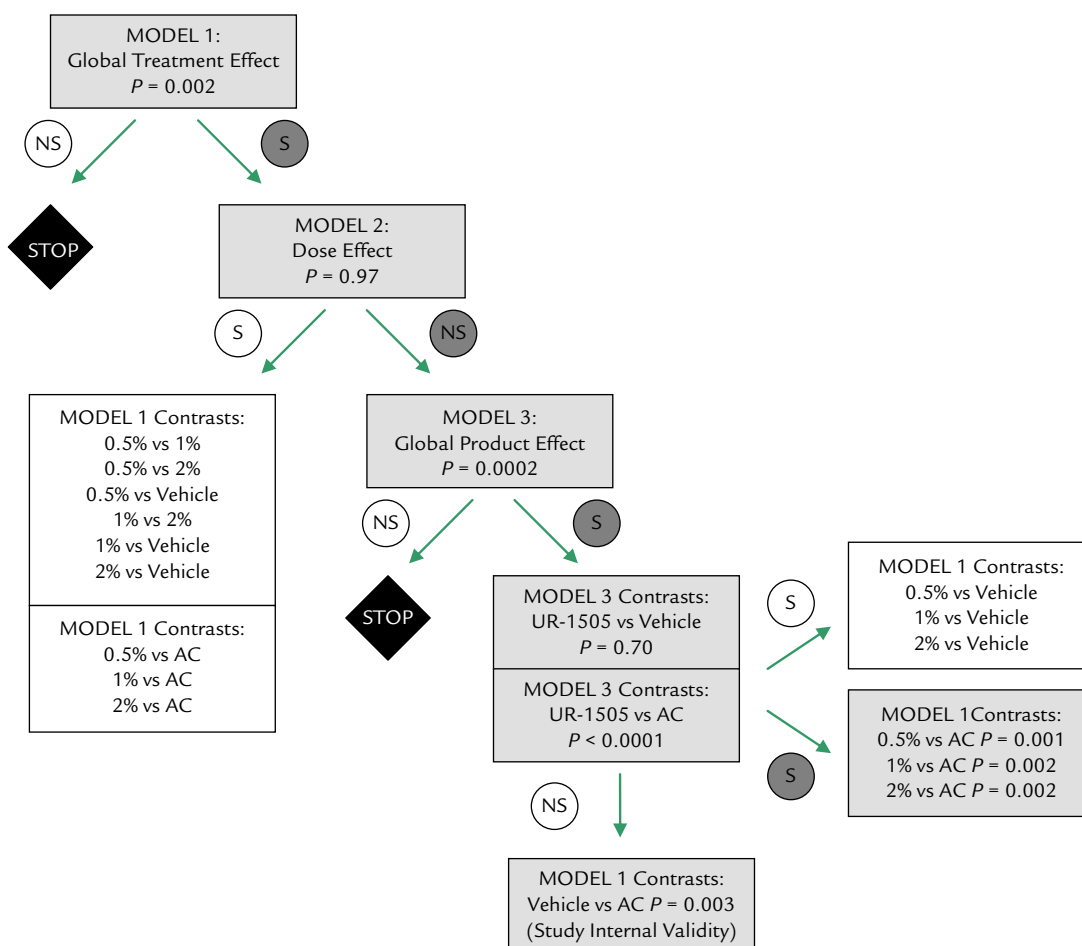


Figure 2. Hierarchical hypothesis testing. Model 1: Global treatment effect. Model 2: Dose-response effect (considering vehicle as dose = 0). Model 3: Global product effect (pooling all UR-1505 doses). Starting at top, level Model 1 for global treatment effect, the applicability of each step is decided on the basis of the results in the previous step. Shaded boxes indicate the actual results of the study and include actual results for P values. AC= active control; NS = nonsignificant P value; S = significant P value.

exclusion from PP analysis. Baseline characteristics of participants are described in [Table I](#).

Efficacy

A significant global treatment effect at Day 28 was observed, but further testing of dose-response effects for UR-1505 did not reveal significant results. Testing of product effect was significant, but whereas testing of pooled treatment effect of UR-1505 versus vehicle did not show a significant effect, testing of pooled treatment effect of UR-1505 versus tacrolimus was significant. Further testing resulted in significance for

the comparison of each UR-1505 concentration versus tacrolimus, in favor of tacrolimus, concluding the sequence of the hierarchical analysis ([Figure 2](#)).

A significant global effect of treatments on IGA change from baseline was evident from the first week of treatment. All treatment options showed significant decreases in IGA values from baseline at all time points, except for 2% UR-1505 at Week 1 and 0.5% and 1% UR-1505 at Week 2. The greatest change in IGA was observed for patients treated with the active control tacrolimus ([Table II](#)). Results for local EASI (total and individual EASI components) and percentage of area

Table I. Baseline characteristics

Description of patients

Gender, n (%)

Male 12 43%

Female 16 57%

Fitzpatrick phototype

I 2 7%

II 12 43%

III 12 43%

IV 2 7%

Mean age (range), y 28 (19–56)

UR-1505

	Total	vehicle	0.5%	1%	2%	Tacrolimus
Lesions, n	50	13	8	9	8	12
Mean Investigator Global Assessment score* (range)	3.3 (1–5)	3.1 (1–5)	3.3 (2–5)	3.2 (1–5)	3.3 (2–4)	3.4 (2–5)
Mean local Eczema Area Severity Index† (range)	6.2 (1–11)	5.8 (1–10)	6.0 (2–11)	5.7 (1–9)	6.7 (4–10)	6.8 (4–11)
Itching, n (%)						
None/slight	12 (21)	2 (14)	2 (20)	2 (22)	2 (22)	4 (29)
Moderate	22 (39)	7 (50)	4 (40)	4 (44)	2 (22)	5 (36)
Severe/very severe	22 (39)	5 (36)	4 (40)	3 (33)	5 (56)	5 (36)

*0 = clear, no inflammatory signs of AD; 1 = almost clear, just perceptible erythema and just perceptible papulation/infiltration; 2 = mild disease, mild erythema, and mild papulation/infiltration; 3 = moderate disease, moderate erythema, and moderate papulation/infiltration; 4 = severe disease, severe erythema, and severe papulation/infiltration; 5 = very severe disease, severe erythema, and severe papulation/infiltration with oozing/crusting.

†Sum of scores assigned by the dermatologist for each area from 0 to 3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe) for intensity of erythema, infiltration/population, excoriation, and lichenification.

clearance were consistent with the main variable (Table II and Figure 3). The percentage of lesions rating as devoid of pruritus in patients' assessments after 4 weeks was 36% for vehicle, 50%, 22%, and 44% for 0.5%, 1%, and 2% UR-1505, respectively, and 93% for tacrolimus. Results from the subjective evaluation questionnaire on Day 28 by patients revealed better results for tacrolimus than UR-1505 and vehicle (data not shown).

Tolerability

No serious adverse events were reported in this study, and none of the adverse events reported were considered to have a causal relationship with the study drugs. Blood and urine analysis at the study end did not reveal any relevant abnormal results considered as potentially related to the study drugs.

Local tolerability was worse for 0.5% UR-1505, with higher frequency of reported local signs or symptoms (13 signs for 10 treated areas), including itching, tingling, tightness, and heat/burning sensations not present at baseline or worsening during the treatment period. Signs and symptoms were reported with similar frequencies for 1% and 2% UR-1505 and vehicle, whereas 0.1% tacrolimus had the lowest incidence (5 signs for 14 treated areas), with none of these signs or symptoms leading to the discontinuation of treatments.

DISCUSSION

The main objective of our study was to explore the clinical efficacy of UR-1505 (0.5%, 1%, and 2%) applied once daily during 4 weeks comparing it with a vehicle without active ingredients and an active

Table II. Global treatment effect for Investigator Global Assessment (IGA) changes and Eczema Area Severity Index (EASI) changes from baseline (Day 0) and mean scores for EASI components at Day 28

	Vehicle n = 13	0.5% UR-1505 n = 8	1% UR-1505 n = 9	2% UR-1505 n = 8	0.1% Tacrolimus n = 12	P value*
←mean (95% CI)→						
IGA [†] changes from baseline						
Day 7	-1.3 (-1.9 to -0.7)	-0.9 (-1.7 to -0.0)	-0.7 (-1.3 to -0.0)	-0.8 (-1.8 to 0.3)	-1.4 (-1.8 to -1.0)	0.01
Day 14	-1.5 (-2.2 to -0.9)	-1.1 (-2.3 to 0.0)	-0.8 (-1.8 to 0.3)	-1.1 (-2.1 to -0.2)	-2.0 (-2.8 to -1.2)	0.02
Day 21	-1.8 (-2.6 to -1.0)	-1.4 (-2.4 to -0.4)	-1.2 (-2.2 to -0.2)	-1.6 (-2.7 to -0.5)	-2.4 (-3.2 to -1.7)	0.001
Day 28 [‡]	-1.7 (-2.6 to -0.8)	-1.0 (-2.4 to 0.4)	-1.2 (-2.4 to -0.0)	-1.5 (-2.7 to -0.3)	-2.6 (-3.3 to -1.9)	0.002
Day 35	-1.8 (-2.6 to -1.0)	-1.3 (-2.6 to -0.0)	-1.0 (-1.9 to -0.1)	-1.6 (-2.8 to -0.4)	-2.2 (-3.2 to -1.1)	0.04
Local EASI [§] changes from baseline						
Day 7	-2.7 (-3.8 to -1.6)	-0.6 (-2.5 to 1.3)	-1.6 (-2.8 to -0.3)	-1.4 (-3.8 to 1.0)	-3.8 (-4.5 to -3.0)	< 0.001
Day 14	-3.4 (-5.0 to -1.8)	-1.5 (-4.7 to 1.7)	-2.0 (-3.9 to -0.1)	-2.4 (-4.4 to -0.4)	-4.8 (-6.3 to -3.2)	0.01
Day 21	-3.6 (-5.5 to -1.7)	-2.9 (-5.3 to -0.5)	-2.6 (-4.4 to -0.7)	-2.9 (-5.1 to -0.6)	-5.6 (-6.7 to -4.5)	< 0.001
Day 28	-3.6 (-5.5 to -1.8)	-1.9 (-5.2 to 1.4)	-2.1 (-4.4 to 0.2)	-2.5 (-4.8 to -0.2)	-5.9 (-7.1 to -4.7)	< 0.001
Day 35	-3.4 (-4.9 to -1.9)	-2.3 (-5.7 to 1.2)	-1.9 (-4.1 to 0.3)	-3.3 (-6.3 to -0.2)	-4.5 (-6.6 to -2.3)	0.08
Local EASI [§] components at Day 28						
Erythema	0.92 (0.54 to 1.31)	1.25 (0.51 to 1.99)	1.22 (0.88 to 1.56)	1.38 (0.75 to 2.00)	0.58 (0.16 to 1.01)	
Infiltration	0.54 (0.14 to 0.94)	1.13 (0.08 to 2.17)	0.89 (0.43 to 1.35)	1.13 (0.43 to 1.82)	0.25 (-0.14 to 0.64)	
Excoriation	0.31 (0.02 to 0.60)	0.88 (-0.26 to 2.01)	0.67 (0.12 to 1.21)	1 (0.23 to 1.77)	0.08 (-0.10 to 0.27)	
Lichenification	0.54 (0.07 to 1.01)	1 (-0.09 to 2.09)	0.78 (0.03 to 1.52)	0.75 (0.01 to 1.49)	0.25 (-0.14 to 0.64)	

*Adjusted ANOVA for global treatment effect: Linear mixed model taking into account the body side and the randomized group as fixed factors, and the patient as a random effect.

[†]0 = clear, no inflammatory signs of atopic dermatitis; 1 = almost clear, just perceptible erythema and just perceptible papulation/infiltration; 2 = mild disease, mild erythema, and mild papulation/infiltration; 3 = moderate disease, moderate erythema, and moderate papulation/infiltration; 4 = severe disease, severe erythema, and severe papulation/infiltration; and 5 = very severe disease, severe erythema, and severe papulation/infiltration with oozing/crusting.

[‡]Main efficacy variable.

[§]Sum of scores assigned by the dermatologist for each area from 0 to 3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe) for intensity of erythema, infiltration/papulation, excoriation, and lichenification.

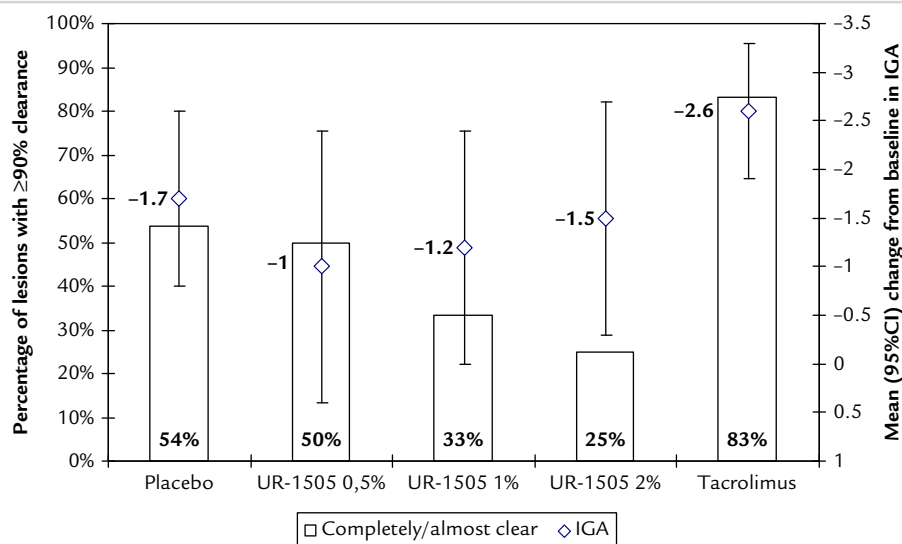


Figure 3. Investigator Global Assessment (IGA) change from baseline and percentage of lesions rated 0 or 1 in percentage of area clearance by Day 28. Total number of lesions = 50, vehicle = 13, 0.5% UR-1505 = 8, 1% UR-1505 = 9, 2% UR-1505 = 8, and tacrolimus = 12. IGA: 0 = clear; 1 = almost clear; 2 = mild disease; 3 = moderate disease; 4 = severe disease; 5 = very severe disease. Percentage of area clearance (0 = completely clear; 1 = almost clear (about 90%); 2 = marked improvement (about 75%); 3 = moderate improvement (about 50%); 4 = slight improvement (about 25%); 5 = condition unchanged; and 6 = condition worsened).

treatment, in adult patients with mild to moderate AD. The results of the efficacy parameters showed that whatever the concentration used, the effect of UR-1505 on AD was similar to that of vehicle alone, and significantly worse than the effect of tacrolimus.

Lesions improved during the first week of treatment whichever treatment the patient received. After that, only lesions treated with tacrolimus improved further, whereas lesions treated with vehicle and UR-1505 flattened their progress. The clinical course of AD is characterized by remissions and exacerbations,¹⁰ and thus a natural remission of the symptoms could be expected over time. Also, a beneficial effect of the vehicle of UR-1505 may have contributed to the initial improvement. This is further supported by the fact that in some cases vehicle alone showed better IGA results than UR-1505, a fact that may parallel a potential irritating effect of UR-1505 overcoming the beneficial vehicle effect, as suggested by the local tolerability assessments by patients.

The posology used in our study (once daily application for 28 days), which was determined in part by the requirement of treatment application by a third

party to preserve the study blinding, can be regarded as inferior in frequency to the usual twice-daily schedules. In fact, once-daily application of 0.1% tacrolimus is only indicated as maintenance treatment in patients who have already responded to a twice-daily schedule.²¹ However, the studied population was highly selected, with a maximum degree of skin involvement limited to 20%, an AD severity score limited to <30, and exclusion of facial involvement, and this fact likely determined that lesions were more likely to respond even to a low frequency of treatment application. Actually, despite the frequency of application, this study confirmed previously reported efficacy of 0.1% tacrolimus ointment in AD²² by demonstrating a significant, consistent, and clinically relevant improvement of AD lesions versus vehicle, and thus confirming the internal validity of the trial. In this context, the lack of significant differences of UR-1505 with respect to vehicle allows us to conclude that UR-1505, applied as a topical ointment, has no relevant intrinsic activity in AD at any of the concentrations tested, despite the favorable results observed in preclinical models. No serious nor causal adverse

reactions were reported in our study, but patients reported numerous symptoms after product applications—especially itching, tingling, tightness, and heat/burning sensations—at frequencies that were similar for vehicle, 1% UR-1505, and 2% UR-1505, more frequent with 0.5% UR-1505, and lowest for tacrolimus. Although in AD the discrimination of local adverse effects as a consequence of the treatment itself or as a consequence of the lack of efficacy of the treatment (eg, itching) is difficult, a better efficacy of tacrolimus may have accounted for its better local tolerability, and may explain the inverse dose response observed in symptoms for UR-1505 doses (Figure 3).

To avoid major influence on disease signs and symptoms associated with seasonal changes,^{18,19} study recruitment was interrupted before the summer season when 28 patients had been treated. Despite the fact that the target number of patients was not reached, the study found statistically significant differences between tacrolimus and vehicle, and tacrolimus and UR-1505, confirming the internal validity of the study, and thus allowing us to make reliable decisions on the clinical development of UR-1505 for AD. In that sense, the design of this study can be considered an efficient approach for Phase IIa proof of concept studies in AD. The double randomization scheme (ie, pairs of treatments and then body side) allowed us to control the “side” effect, and the fact that every patient received 2 treatments in symmetric lesions increased the statistical power by considering independent lesions but including patient and treatment at the contralateral site as random effects. This design has been previously and successfully applied in similar settings.^{23–25} However, the requirement of 2 equivalent symmetrical lesions hindered study recruitment, as did the requirement of treatment application by a third party. These disadvantages should be weighed against controlled compliance, reduced errors in application, and avoiding cross-contamination of results. Recruitment was further slowed down by the fact that the study involved 1 investigational site only, with limited available population, although the benefits of homogeneity in procedures and assessments contributed to the ability of the study to detect differences between treatments.

As a Phase II trial, the main objective was to assess activity of the compound and discard frequent relevant adverse reactions. The study design and the duration of the treatment and follow-up were considered adequate

for this purpose. Based on the study results, a decision was made to discontinue the clinical development of UR-1505 ointment for the topical treatment of AD, regardless of any further exploration of UR-1505 in other inflammatory dermatologic diseases.

CONCLUSIONS

Our randomized, double-blind clinical trial concluded that UR-1505 may not be a suitable option for the treatment of AD due to its lack of clinically relevant effect compared with its vehicle and 0.1% tacrolimus ointment. A small but robust study with both inter- and inpatient comparisons and a hierarchical approach to efficacy analysis made it possible to obtain useful results for further drug development decision making in a relatively short period of time and based on a minimum number of patients exposed to the experimental treatments.

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R. Vives implemented the study, contributed to the statistical analysis plans and interpretation of results and wrote the manuscript. C. Pontes designed the study, supervised the implementation of the study and contributed to the statistical analysis plans and interpretation of results and wrote the manuscript. M. Sarasa contributed to study design, implementation of the study, interpretation of results and review of the manuscript. A. Millier did the data management and statistical analysis of the study and contributed to the interpretation of results and review of the manuscript.

CONFLICTS OF INTEREST

R. Vives, C. Pontes, and M. Sarasa were full-time employees of Palau Pharma S.A. at the time that the study was conducted.

A. Millier was full-time employee of Stateliss, a company outsourced by Pharmascan for data management and statistics, at the time that the study was conducted.

The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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