Ergebnisbericht gemäß §42b AMG

1) Name of Sponsor/Company
Medical Faculty, TU Dresden
Jochen Schmitt
Fetscherstr. 74
01307 Dresden

2) Name of Finished Product
Immunosporin® 50mg
Toctino® 30mg

3) Name of Active Substance
Ciclosporin 50mg
Alitretinoin 30mg

4) Individual Study Table: Referring to Part of the Dossier (Volume, Page)
(entfällt)

5) Title of Study
Title: Ciclosporin vs. Alitretinoin for severe atopic hand dermatitis. A randomized controlled investigator-initiated double-blind trial.
Prüfplancode: TUD-TOCYDD-044
Version: 5.0, 21. Juli 2010
Amendments: -

6) Investigators

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8) Publication (reference)

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9) Studied period (years): date of first enrolment, date of last completed

Date of first enrolment: December 14, 2010
Date of last completed: March 22, 2012

The failure to recruit the planned number of patients had several reasons: While we were planning the study we had identified approximately 40 patients with severe atopic hand eczema who were candidates for systemic treatment. Due to a delayed start of the trial, several of the potentially eligible patients from our department had already been treated with one of the trial medications, which both have market authorization. Recruitment was therefore achieved through specific referrals of resident physicians (network of local surgeries) and newspaper advertisements.

Since both treatment options already have market authorizations, much fewer patients than expected were willing to participate in the study, because they could not be convinced of a personal benefit from study participation. The study medication expired by March 31, 2012, and a further extension of the expiry date was not possible. Extending the study to more study sites and producing additional study medication was not possible due to the limited finances of this investigator-initiated trial. The principal investigator therefore stopped the trial on March 22, 2012. No patient was still included in the trial at that date.

10) Phase of development

Phase 4

11) Objectives

To investigate the comparative efficacy and safety of ciclosporin microemulsion and alitretinoin in the treatment of severe atopic hand dermatitis in adults.

12) Methodology

In an investigator-initiated double-blind randomized controlled trial, adults with severe chronic atopic hand dermatitis were randomly allocated 1:1 to receive ciclosporin or alitretinoin, treated accordingly for 24 weeks, and followed for another 24 weeks.

Primary endpoint was the proportion of patients with complete or almost complete clearance of hand dermatitis according to the Investigator Global Assessment (IGA) within 24-week active therapy in both groups.

Analysis was by intention-to-treat.

13) Number of patients (planned and analyzed)

Planned total enrollment: 78
14 patients were randomized and analyzed.

14) Diagnosis and main criteria for inclusion

Study inclusion criteria were:

- Male and female patients age ≥ 18 years and ≤ 75 years
- Body weight 50 to 100 kg
- Chronic hand dermatitis (duration ≥ 6 months)
- Atopic constitution according to
    - Erlanger Atopiescore and/or
    - positive personal history for atopic eczema, allergic rhinitis, allergic asthma and/or
    - elevated serum IgE
- Severe hand dermatitis not responding to treatment with potent topical steroids for at least 4 weeks within the past 6 months due to IGA
- Written informed consent

Exlusion criteria:

- Participation in other clinical trial within past 4 weeks
- Pregnancy/breastfeeding
- Women within reproductive age except those women who fulfil at least one of the following criteria throughout the total study and until at least 5 weeks after active study treatment in case of early study termination:
    - post-menopausal women (12 months physiological amenorrhoea or 6 months amenorrhoea with serum FSH level > 40 mIU/ml),
    - postoperative (6 weeks after bilateral ovariectomy with or without hysterectomy)
    - regular and proper use of at least two methods of contraception, including at least one method of contraception with a failure rate < 1% per year (eg, implants, depot preparations, oral contraceptives, IUD).
    - vasectomy of the partner.
- Women within reproductive age, who do not meet all of the following criteria throughout the whole study or – in case of early study termination – up to 5 weeks after active therapy:
    - The patient understands the teratogenic risk associated with taking the study medication.
    - The patient understands the need for strict monthly monitoring, the need for a reliable, continuous contraception and the need for regular pregnancy tests throughout the study and – in case of early study termination – up to 5 weeks of active therapy.
    - The patient is able to adequately and reliably apply methods of contraception.
    - The patient is informed about the possible consequences of pregnancy and knows that she must immediately contact her physician in case of suspected pregnancy.
    - The patient gives informed consent about knowing the potential risks and necessary measures to avoid pregnancy.
- Blood and/or plasma donation during the whole study period. In case of early study termination blood and plasma donation is not allowed until 1 month after the end of active study treatment
- UV-therapy within past 3 months
- Concurrent photo- and / or photochemotherapy
- Known hypersensitivity / intolerance against ciclosporin, alitretinoin or any other ingredients of Immunosporin® or Toctino®

- Known allergy against peanuts or soya
- Known hereditary fructose intolerance
- Acute and/or uncontrolled chronic infectious disease
- Known congenital or acquired immune deficiency
- Malignant tumor (past or present)
- Uncontrolled arterial hypertension (RR systolic ≥ 160 mm Hg and/or RR diastolic ≥ 90 mm Hg despite anti-hypertensive treatment)
- Renal insufficiency (Serum creatinine above normal range)
- Liver insufficiency (CHILD ≥ Stadium B)
- Not sufficiently controlled hyperlipidemia (LDL/HDL ratio > 4 despite medical treatment)
- Clinically significant thyroid hypofunction
- Known hypervitaminosis A
- Concurrent supplementation of vitamin A or treatment with other retinoids
- Concurrent tetracycline therapy
- Concurrent therapy with St. John's wort ("Johanniskraut")
- Known genetic diseases causing increased UV light sensitivity such as Xeroderma pigmentosum, Cockayne-syndrome, Bloom syndrome
- Known drug- and/or alcohol abuse
- Known significant psychiatric morbidity

15) Test product, dose and mode of administration, batch number
Ciclosporin 50mg p.o., batch number 102010

16) Duration of treatment
Ciclosporin 24 weeks

17) Reference therapy, dose and mode of administration, batch number
Alitretinoin 30mg p.o., batch number 102010; duration: 24 weeks
Placebo p.o., batch number 102010; duration: 24 weeks

18) Criteria for evaluation: Efficacy, Safety
The primary endpoint was defined as the proportion of patients with complete or almost complete clearance according to the Investigator Global Assessment (IGA) within 24 weeks of active therapy in both groups.
A validated and well-established photographic atlas with exemplary medical finding for the respective degrees of severity was used as a tool to standardize the assessment of the IGA. The assessment of the primary endpoints was performed by experienced and trained investigators.

Secondary endpoints were:

- Time to complete or almost complete clearance according to IGA in both groups
- Proportion of patients with complete or almost complete clearance according to the Patient´s Global Assessment (PGA) at week 12 and at week 24 of active therapy
- Mean relative change in the Hand Eczema Severity Index (HECSI) between baseline and week 4, 8, 12, 16, 20, 24 in both groups

- Mean relative change in quality of life (Skindex-17) between baseline and week 24 in both groups
- Cost-effectiveness of the studied treatment options (cost/QALY gained; assessed by means of the EQ-5D)
- Mean relative change in work productivity (assessed by means of the Work Limitation Questionnaire (WLQ)) in both groups
- Mean utilization of topical steroids within the follow-up period in both groups
- Patient satisfaction with treatment in both groups (assessed using a 100 mm VAS Scale)
- Proportion of patients with relaps (≥ 75% of baseline HECSI) within 24-week follow-up after previous complete/almost complete clearance
- In patients with atopic dermatitis on the body: percentage of patients with at least 50% improvement in disease severity with the active therapy using the SCORing Atopic Dermatitis (SCORAD)
- Tolerability and safety in both study groups

19) Statistical methods

Statistical analysis:

The primary study endpoint was the proportion of patients with complete or almost complete remission within 24 weeks of active therapy in both treatment groups. Therefore, the chi-square test for independent samples was used. With a power of 80%, a two-sided significance level of 0.05 and a suspected response rate of 66% and 33% in the ciclosporin and alitretinoin group, 35 patients are needed in each group. Assuming a drop-out rate of randomized patients prior to first application of the study drug (Baseline-Visit; V2) (criterion for ITT-population) of maximal 10% we are planning to randomize 39 patients per group, i.e. include a total number of 78 participants.

Definition of analysis collective:

All analyses were performed on the Intention-to-Treat (ITT) population. This population includes all patients that completed the baseline visit and used the trial medication at least once during the study. Statistical analyses of this population determines whether the results of the trial are of statistical significance or not.

Planning of the confirmatory statistical assessment:

The trial was designed to answer the following question: *Is there a difference in efficacy of ciclosporin versus alitretinoin in the therapy of severe atopic hand dermatitis?* Efficacy is measured by the number of patients with complete or almost complete clearance according to IGA at the end of the active treatment (week 24). According to the null hypothesis both therapy options are similar effective. A clinically relevant difference between both treatments was defined as efficacy variation of 33%. The primary endpoint will be analyzed by utilising a chi-square-test.

Planed explorative analysis:

Analysis of secondary endpoints is performed in a descriptive and explorative way. Measured values are calculated with a t-test, or if appropriate with a Mann-Whitney-U-Test. Prevalences were compared with a chi-square-test, or if appropriate with the Fisher's exact test.

Handling of missing values:
Missing values were replaced by the last observed value of the variable (last observation carried forward (LOCF)).

Economic analysis:
In addition to efficacy and safety comparisons of both trial medications, the study also aimed to test for efficiency of ciclosporin vs. alitretinoin in patients suffering from severe chronic hand dermatitis. The planned economic analysis was not performed due to the limited number of patients recruited. Out-of-pocket expenses were compared descriptively between the two study groups.

20) Summary - Conclusions: Efficacy Results, Safety Results, Conclusion

A) Baseline characteristics / study population

Soziodemographic data

	Treatment group	
	ciclosporin (n = 7)	alitretinoin (n = 7)
Age (years)	42.1 (13.9)	33.1 (12.7)
Female sex	1/7 (14.3%)	4/7 (57.1%)

Table 1: Age (mean and standard deviation) and sex

A total of 14 patients were randomized and received at least one dose of study treatment. From those patients, seven patients were allocated to ciclosporin, and 7 to alitretinoin treatment. Table 1 shows informations about age and gender of both study groups. Patients in the ciclosporin group were about 9 years older and less frequently female than patients allocated to alitretinoin.

	Treatment group	
	ciclosporin (n = 7)	alitretinoin (n = 7)
Characteristics of atopic disease (ever)		
- Atopic dermatitis	5/7 (71.4%)	6/7 (85.7%)
- Asthma bronchiale	2/7 (28.6%)	2/7 (28.6%)
- Rhinitis	3/7 (42.9%)	7/7 (100%)
- Conjunctivitis	1/7 (14.3%)	5/7 (71.4%)
- IgE ≥ 100 kU/l	4/7 (57.1%)	7/7 (100%)

Table 2: Characteristics of atopic disease

Table 2 summarizes atopic comorbidities and IgE-levels of both treatment groups. No statistically significant differences were observed. Atopic rhinitis and conjunctivitis tended to be more prevalent in the alitretinoin group.

Table 3 informes about characteristics of hand eczema. In all cases both hands were affected. Episodic disease within last 12 months (i.e. disease-free intervals) were reported in two patients of the alitretinoin group, and in none of the patients allocated to ciclosporin. Per treatment group 5 patients out of 7 suffer from eczema not only at both hands but also at other parts of their body.

	Treatment group	
	ciclosporin (n = 7)	alitretinoin (n = 7)
Characteristics of hand eczema		
- One hand/both hands	0%/100%	0%/100%
- Duration of hand eczema (months)	136 (184)	146 (129)
- Continuous disease within 12 months	7/7 (100%)	5/7 (71.4%)
- Other parts of the body involved	5/7 (71.4%)	5/7 (71.4%)

Table 3: Characteristics of hand eczema

Previous treatment of hand eczema covers external and internal medication as well as UV therapy and reception of antihistaminics (table 4).

Previous treatment of eczema	**Treatment group**	
	ciclosporin (n = 7)	alitretinoin (n = 7)
External		
- Glucocorticosteroids (class 3/4)	6/7 (85.7%)	7/7 (100%)
- Pimecrolimus	2/7 (28.6%)	3/7 (42.9%)
- Tacrolimus	3/7 (57.1%)	4/7 (57.1%)
- Skin care	7/7 (100%)	5/7 (71.4%)
UV therapy	1/7 (14.3%)	3/7 (42.9%)
Internal		
- Systemic Glucocorticosteroids	1/7 (14.3%)	2/7 (28.6%)
- Ciclosporin A	0	1/7 (14.3%)
- Alitretinoin	1/7 (14.3%)	0
- Acitretin	1/7 (14.3%)	1/7 (14.3%)
Antihistaminics	4/7 (57.1%)	4/7 (57.1%)

Table 4: Previous treatment of hand eczema

Characteristics of the hand eczema at baseline

The severity of atopic hand eczema and its impact on quality of life and wellbeing were characterized by the following scores at baseline:

Erlanger Atopy Score

Hand Eczema Severity Index (HECSI)

SCORing Atopic Dermatitis (SCORAD)

Investigator global assessment of disease severity (IGA)

Quality of life score (Skindex-17)

Patient Satisfaction Score (VAS with 0 indicating absolute unsatisfaction, and 10 maximum satisfaction)

As detailed in table 5, baseline characteristics concerning hand eczema were similar in both groups.

	Treatment group	
	ciclosporin (n = 7)	alitretinoin (n = 7)
Erlanger Atopy Score	14.6 (4.7)	21.1 (8.2)
Severity of hand eczema (HECSI)	106.1 (36.3)	104.7 (37.6)
Severity of atopic eczema (SCORAD)	32.9 (23.0)	37.1 (24.4)
Investigator global assessment of disease severity (IGA) - mild - moderate - severe	 0 0 7/7 (100%)	 0 0 7/7 (100%)
Quality of life (Skindex-17)	30.3 (18.8)	32.3 (14.3)
Patient satisfaction (VAS)	2.0 (1.2)	4.3 (4.5)

Table 5: Scores at the beginning of the study (mean and standard deviation, IGA excepted)

Covariables

Furthermore, at the beginning of the study cardiovascular risk factors like systolic and diastolic blood pressure and body mass index (derivated from length and weight of the patient) were documented (table 6).

	Treatment group	
	ciclosporin (n = 7)	alitretinoin (n = 7)
General morbidity - Body mass index - Blood pressure systolic (mmHg) - Blood pressure diastolic (mmHg) - Hypertension (BP ≥ 140/90 mmHg)	 25.2 (4.3) 122.0 (8.3) 75.1 (6.3) 0	 24.8 (3.0) 126.7 (5.7) 80.0 (6.5) 0

Table 6: Cardiovascular risk factors at baseline (mean and standard deviation)

B) Efficacy results:

Primary endpoint

Primary study endpoint was the proportion of patients with complete or nearly complete healing of hand eczema (measured by Investigator Global Assessment) until week 24 in the ciclosporin and the alitretinoin treatment groups. Table 7 shows the results.
4 out of 7 patients (57.1%) allocated to ciclosporin and 2 out of 7 (28.6%) allocated to alitretinoin achieved the primary endpoint (p = 0.592).

	Duration of treatment									
	Baseline	week 4	week 8	week 12	week 16	week 20	week 24	week 29	week 36	week 48
Investigator Global Assessment (IGA): Percent of complete or nearly complete healing										
ciclosporin	0	3/7 (42.9%)	2/7 (28.6%)	3/7 (42.9%)	4/7 (57.1%)	3/7 (42.9%)	3/7 (42.9%)	2/7 (28.6%)	1/7 (14.3%)	1/7 (14.3%)
alitretinoin	0	0	1/7 (14.3%)	1/7 (14.3%)	1/7 (14.3%)	0	2/7 (28.6%)	2/7 (28.6%)	1/7 (14.3%)	2/7 (28.6%)

Table 7: Investigator Global Assessment (IGA): Percent of complete or nearly complete healing

Secondary efficacy endpoints

Due to the failure to recruit the required amount of patients as determined by sample size calculation before the initiation of the study, statistical tests are not considered as appropriate and p-values will not be reported in the following paragraphs.
As detailed in table 7, 3 out of 7 patients (42.9%) allocated to ciclosporin and 1 out of 7 (14.3%) allocated to alitretinoin achieved an IGA clear/almost clear at week 12, respectively. At week 24, the IGA-response rates were 42.9% in the ciclosporin group and 28.6% in the alitretinoin group.

	Duration of treatment									
	Baseline	week 4	week 8	week 12	week 16	week 20	week 24	week 29	week 36	week 48
Patient's Global Assessment (PGA): Percent of complete or nearly complete healing										
ciclosporin	0	3/7 (42.9%)	3/7 (42.9%)	3/7 (42.9%)	4/7 (57.1%)	3/7 (42.9%)	4/7 (57.1%)	2/7 (28.6%)	2/7 (28.6%)	1/7 (14.3%)
alitretinoin	0	0	0	1/7 (14.3%)	1/7 (14.3%)	1/7 (14.3%)	2/7 (28.6%)	1/7 (14.3%)	1/7 (14.3%)	2/7 (28.6%)

Table 8: Patient's Global Assessment (PGA): Percent of complete or nearly complete healing

As shown in table 8, the response rates based on PGA were similar to those based on IGA with higher proportions of patients allocated to ciclosporin benefitting from therapy compared to alitretinoin.

In both treatment groups, the severity of hand eczema measured by means of the HECSI was substantially reduced. Patients in the ciclosporin group tended to respond faster (table 9). The absolute magnitude of effect until week 24 was similar in both groups (mean HECSI decrease ciclosporin 80.9%; alitretinoin 69.8%). None of the patients relapsed within 24 week follow-up (table 10).

	Duration of treatment									
	Baseline	week 4	week 8	week 12	week 16	week 20	week 24	week 29	week 36	week 48
Variation during treatment (mean and standard deviation)										
ciclosporin	120.9 (38.2)	53.4 (53.8)	42.0 (73.9)	35.0 (33.8)	22.3 (22.9)	12.6 (16.3)	23.1 (24.4)	26.4 (22.4)	28.0 (21.5)	25.4 (21.1)
alitretinoin	115.7 (37.8)	78.4 (42.1)	55.0 (45.1)	35.7 (35.5)	36.6 (36.5)	51.9 (44.8)	35.0 (39.3)	25.6 (38.1)	31.6 (38.4)	30.3 (36.2)
Percent of baseline										
ciclosporin	100%	44.2%	34.7%	28.9%	18.4%	10.4%	19.1%	21.8%	23.2%	21.0%
alitretinoin	100%	67.8%	47.5%	30.8%	31.6%	44.8%	30.2%	22.1%	27.3%	26.2%

Table 9: Severity of hand eczema (HECSI)

	Treatment group	
	ciclosporin (n = 7)	alitretinoin (n = 7)
Patients with HECSI score of at least 75% of baseline score	0/7 (0%)	0/7 (0%)

Table 10: Severity of hand eczema (HECSI): Percent of patients with HECSI score of at least 75% of baseline score in week 48

	Duration of treatment									
	Baseline	week 4	week 8	week 12	week 16	week 20	week 24	week 29	week 36	week 48
ciclosporin	28.9 (18.8)	15.0 (16.7)	17.9 (20.7)	15.1 (21.8)	18.7 (20.4)	18.0 (20.1)	19.1 (21.5)	20.9 (21.8)	22.1 (24.3)	25.3 (25.1)
alitretinoin	23.7 (13.8)	23.0 (14.0)	16.4 (10.5)	15.7 (11.5)	19.6 (10.4)	19.7 (10.3)	20.0 (10.5)	19.1 (11.6)	20.0 (12.7)	26.7 (11.5)

Table 11: Quality of life (Skindex-17)

The effects of treatment on quality of life were more pronounced in the ciclosporin group (mean change in Skindex-17 from baseline to week 24 ciclosporin 33.9%; alitretinoin 15.6%)

Tables 12 and 13 summarize SCORAD reduction from baseline until 48 week follow up. The SCORAD response tended to be more pronounced in the ciclosporin group.

	Duration of treatment									
	Baseline	week 4	week 8	week 12	week 16	week 20	week 24	week 29	week 36	week 48
ciclosporin	29.8 (20.0)	25.4 (19.9)	20.1 (15.9)	18.1 (14.9)	16.2 (15.9)	20.5 (14.0)	27.8 (13.2)	27.8 (13.2)	30.6 (13.4)	29.8 (12.4)
alitretinoin	37.6 (27.6)	38.8 (29.0)	35.0 (23.8)	29.8 (23.7)	29.9 (22.6)	38.6 (25.5)	33.8 (23.2)	33.2 (25.7)	27.1 (24.2)	33.0 (19.2)

Table 12: Severity of atopic eczema (SCORAD)

	Treatment group	
	ciclosporin (n = 7)	alitretinoin (n = 7)
Patients with SCORAD reduction	2/7 (28.6%)	1/7 (14.3%)

Table 13: Severity of atopic eczema (SCORAD): Percent of patients with SCORAD reduction of at least 50% during intervention (baseline to week 24)

	Duration of treatment									
	Baseline	week 4	week 8	week 12	week 16	week 20	week 24	week 29	week 36	week 48
ciclosporin	2.7 (1.5)	5.8 (3.7)	7.3 (3.3)	6.2 (3.2)	6.9 (3.6)	7.0 (2.2)	6.7 (3.2)	5.4 (3.0)	4.5 (3.3)	3.1 (3.1)
alitretinoin	3.2 (3.6)	4.9 (3.0)	4.8 (3.1)	5.7 (2.6)	5.1 (2.4)	5.0 (1.7)	4.9 (2.1)	5.0 (2.2)	4.5 (2.4)	2.9 (2.6)

Table 14: Patient's satisfaction (VAS)

In both treatment groups, satisfaction with care increased within active treatment with more pronounced effects in the ciclosporin group. At week 48, the average VAS satisfaction scores almost equaled those from the baseline visit indicating that treatment satisfaction increased only during active treatment (table 14).

The quality of life questionnaire EuroQol (EQ-5D) involves 5 subscales supplemented by a global assessment of subjective health state. The subscales are mobility, to be able to care for myself, to be able to fulfill common duties and the fields of pain and somatic disorders and anxiety and depressiveness. This questionnaire was applied every 12 weeks. As shown in table 15, patients of both therapy groups report no problems in self-care and only less problems in mobility. Otherwise, moderate or extreme occurrence of pain and somatic disorders were mentioned by patients from both groups. Half of the patients reported problems with the fulfilling of common duties as well as anxiety and depressive symptoms. Overall, study treatment did not have an effect on generic quality of life as measured by the EQ-5D (table 15).

	Duration of treatment									
	Baseline	week 4	week 8	week 12	week 16	week 20	week 24	week 29	week 36	week 48
Mobility: few problems/impossible										
ciclosporin	1/7 (14.3%) 0			1/7 (14.3%) 0			0 0		1/7 (14.3%) 0	1/7 (14.3%) 0
alitretinoin	0 0			0 0			1/7 (14.3%) 0		1/7 (14.3%) 0	1/7 (14.3%) 0
Self-care: few problems/unable										
ciclosporin	0 0			0 0			0 0		0 0	0 0
alitretinoin	0 0			0 0			0 0		0 0	0 0
Common duties: few problems/unable										
ciclosporin	3/7 (42.9%) 0			1/7 (14.3%) 0			0 2/7 (28.6%)		2/7 (28.6%) 1/7 (14.3%)	2/7 (28.6%) 2/7 (28.6%)
alitretinoin	1/7 (14.3%) 0			0 0			1/7 (14.3%) 0		1/7 (14.3%) 0	2/7 (28.6%) 0
Pain, somatic disorders: moderate/extreme										
ciclosporin	5/7 (71.4%) 1/7 (14.3%)			1/7 (14.3%) 0			3/7 (42.9%) 1/7 (14.3%)		5/7 (71.4%) 1/7 (14.3%)	6/7 (85.7%) 1/7 (14.3%)
alitretinoin	5/7 (71.4%) 0			5/7 (71.4%) 0			5/7 (71.4%) 0		5/7 (71.4%) 0	6/7 (85.7%) 0
Anxiety, depressiveness: moderate/extreme										
ciclosporin	1/7 (14.3%) 0			0 1/7 (14.3%)			1/7 (14.3%) 0		2/7 (28.6%) 0	3/7 (42.9%) 0

alitretinoin	1/7 (14.3%) 0			1/7 (14.3%) 0			0 0		0 0	3/7 (42.9%) 0
EuroQol-Score (actual subjective health status): mean and standard deviation										
ciclosporin	65.7 (25.1)			73.9 (14.7)			68.3 (32.0)		59.7 (31.8)	48.1 (33.0)
alitretinoin	73.7 (21.7)			66.3 (17.0)			76.4 (13.5)		74.3 (12.1)	68.6 (17.0)

Table 15: Subjective health status (EuroQol)

The Work limitations questionnaire (WLQ) was assessed ervery 12 weeks throughout the study. Since WLQ was developed to measure the ability to meet occupational requirements, patients who do not work are not integrated into this consideration. This reglementation leads to patient numbers of 5 in both therapy groups (4 actually not working patients, 2 in every group, had to be excluded). Table 16 summarizes the results of work limitations in both groups. No effects of treatment on work limitations were observed.

	Duration of treatment									
	Baseline	week 4	week 8	week 12	week 16	week 20	week 24	week 29	week 36	week 48
Time demands (mean and standard deviation)										
ciclosporin	22.6 (2.9)			25.0 (3.2)			21.4 (4.9)		21.0 (4.4)	20.8 (4.2)
alitretinoin	21.6 (1.3)			20.8 (4.5)			22.4 (3.6)		20.4 (5.0)	20.2 (5.3)
Physical demands (mean and standard deviation)										
ciclosporin	18.0 (8.6)			20.8 (10.4)			18.4 (11.0)		18.4 (11.0)	17.8 (10.4)
alitretinoin	14.2 (4.1)			12.8 (10.0)			14.4 (9.9)		12.2 (6.6)	12.4 (8.2)
Mental-interpersonal demands (mean and standard deviation)										
ciclosporin	39.2 (5.3)			45.4 (4.9)			41.8 (4.1)		41.8 (4.1)	41.2 (3.7)
alitretinoin	42.2 (3.1)			41.4 (3.5)			40.8 (4.1)		39.6 (5.0)	40.0 (5.2)
Outcome demands (mean and standard deviation)										

ciclosporin	19.2 (8.2)			23.8 (3.9)			21.2 (5.5)		21.2 (5.5)	20.8 (5.3)
alitretinoin	20.2 (5.0)			20.2 (5.9)			20.6 (6.4)		21.0 (5.0)	19.6 (5.8)

Table 16: Work limitation questionnaire (WLQ, n = 5 in both treatments)

Out of pocket expenses

	Duration of treatment									
	Baseline	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks	29 weeks	36 weeks	48 weeks
ciclosporin	84.29 (43.15)			42.17 (47.33)			8.67 (13.66)		27.33 (15.37)	32.75 (27.87)
alitretinoin	63.29 (69.53)			37.00 (46.97)			55.83 (85.23)		88.33 (92.58)	99.83 (77.72)

Table 17: Patient's out of pocket expenses (Euro): mean and standard deviation

Table 17 summarizes patients' out of pocket expenses during therapy and 24 weeks follow up. Patients were asked for their private costs over the past 12 weeks. Each mean value in table 17 summarizes expenses for the previous 12 weeks. Expenses decreased to a greater extent in the ciclosporin group compared to the alitretinoin group.

C) Safety results:

A total of 6 adverse events (AE) were documented with 5 patients experiencing at least one adverse event (table 18). Two patients in the ciclosporin group had an exacerbation after the end of active treatment leading to study withdrawal (tables 18 and 19). No SAEs were recorded throughout the trial. Table 18 details the severity, relatedness and result of each adverse event that was recorded throughout the study.

Treatment	Patient number	name / description	resolved at last study visit	resolved as of March 19, 2013	Severity	Relatedness	Result
ciclosporin							
	3	fatigue, bone-ache, dry lips	yes		mild	possible	discontinuation of treatment
	11	Exacerbation of hand eczema	no	yes	severe	no	study withdrawal
	19	exacerbation of atopic eczema	no	yes	moderate	possible	study withdrawal
	19	viral infection, headache, exhaustion	yes		mild	Not reported	discontinuation of treatment
alitretinoin							
	5	cystitis	yes		mild	no	continuation per protocol
	13	tonsillitis	yes		moderate	unlikely	continuation per protocol

Table 18: Adverse events

	Duration of treatment									
Patient number	Baseline	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks	29 weeks	36 weeks	48 weeks
1	p	p	p	p	p	p	p	p	p	p
2	p	p	p	p	p	p	p	p	p	p
3	p	p	p	p	p	p	p	np	np	p (earlier last visit)
4	p	p	p	p	p	p	p	p	p	p
5	p	p	p	p	p	p	p	p	p	p
8	p	p	p	p	np	np	np	np	np	np
9	p	p	p	p	p	p	p	p	p	p
10	p	p	p	p	p	p	p	p	p	p
11	p	p	p	p	p	p	p	np	np	np
12	p	p	p	p	p	p	p	p	p	p
13	p	p	p	p	p	p	p	p	p	p
15	p	p	p	p	p	p	p	p	p	p
16	p	p	np	np	np	np	np	np	np	np
19	p	p	p	p	p	p	p	np	np	np

Table 19: Duration of study: participation of patients: p: patient participated; np: patient did not participate (dropout)

D) Conclusions:
This investigator-initiated RCT was designed to compare the efficacy and safety of ciclosporin and alitretinoin, the two systemic treatments currently approved for severe atopic hand eczema.

Unfortunately, the trial could not recruit the number of patients needed to answer the research questions with sufficient statistical power. The failure to recruit the planned number of patients had several reasons: While we were planning the study we had identified approximately 40 patients with severe atopic hand eczema who were candidates for systemic treatment. Due to a delayed start of the trial, several of the potentially eligible patients from our department had already been treated with one of the trial medications, which both have market authorization. Recruitment was therefore achieved through specific referrals of resident physicians (network of local surgeries) and newspaper advertisements.

Since both treatment options already have market authorizations, much fewer patients than expected were willing to participate in the study, because they could not be convinced of a personal benefit from study participation. The study medication expired by March 31, 2012, and a further extension of the expiry date was not possible. Extending the study to more study sites and producing additional study medication was not possible due to the limited finances of this investigator-initiated trial. The principal investigator therefore stopped the trial on March 22, 2012. No patient was still included in the trial at that date.

Due to the low number of patients recruited, any conclusions from this study are very limited, and statistical hypothesis testing was considered inadequate. In accordance with our hypothesis, the efficacy of ciclosporin tended to be higher than the efficacy of alitretinoin, and the response rates were in the hypothesized range (please refer to sample size considerations above). The secondary endpoints also indicate that ciclosporin might be superior to alitretinoin in the treatment of severe chronic atopic hand eczema, but firm conclusions cannot be drawn. In accordance with the literature, some patients receiving ciclosporin experienced disease exacerbation after discontinuation of active therapy. These two patients were withdrawn from the trial. No severe adverse event occurred.

Future research is still needed to clarify the comparative efficacy and safety of ciclosporin and alitretinoin in the treatment of severe atopic hand eczema

21) Date of report.
Initial Submission: March 22, 2013