Fakultät für Medizin

Klinikum rechts der Isar Technische Universität München

APREMINUM

Eine „Investigator-initiated“, randomisierte, doppel-verblindete, Placebo kontrollierte Studie um die Wirksamkeit von **Apre**milast **i**m **num**mulären Ekzem nachzuweisen

An investigator-initiated, randomized, double-blind, placebo controlled study of Apremilast to demonstrate efficacy in subjects with nummular eczema

Investigational Medicinal Products: Otezla ®

Study Code: AP-CL-ECZ-PI-006539
EudraCT Number: *2016-002351-16*

First Patient First Visit: 01.07.2017 **– Last Patient Last Visit:** 15.09.2021

Sponsor
Technische Universität München, Fakultät für Medizin
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Synopsis

1.	**Sponsor:** Technische Universität München (TUM), Fakultät für Medizin Ismaninger Strasse 22, D- 81675 München, Germany **Sponsor Delegated Person (SDP):** Prof. Dr. med. Kilian Eyerich, Ph.D.
2.	**Name of IMP:** Otezla ®
3.	**Name of Active Ingredient:** Apremilast 30 mg (ATC Code: L04AA32); Apremilast 20 mg (ATC Code: L04AA32); Apremilast 10 mg (ATC Code: L04AA32)
4.	**Individual Study Table:** (only required for submissions) n.a.
5.	**Study Title:** Eine „Investigator-initiated“, randomisierte, doppel-verblindete, Placebo kontrollierte Studie um die Wirksamkeit von Apremilast im nummulären Ekzem nachzuweisen An investigator-initiated, randomized, double-blind, placebo controlled study of Apremilast to demonstrate efficacy in subjects with nummular eczema
	Study Design: An investigator-initiated, single-center, randomised, double-blind, prospective, interventional phase IIb study Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Masking: Double Blind Primary Purpose: Treatment
	Study (Protocol) Code Number: *AP-CL-ECZ-PI-006539*
	Eudra-CT Number: *2016-002351-16*
6.	**Principal Investigators (PI):** Prof. Dr. med. Kilian Eyerich, Ph.D.
7.	**Clinical Trial Sites:** Klinikum rechts der Isar Technische Universität München Department of Dermatology and Allergy Biedersteiner Str. 29 80802 München The clinical trial was planned and conducted as a single-center clinical trial.
8.	**Publication:**

	n.a.
9.	**Study period:** First patient first visit (FPFV): 01.07.2017; Last patient last visit (LPLV): 15.09.2021
	Approvals and Amendments **Approval**: Bundesinstitut für Arzneimittel und Medizinprodukte （BfArM): 10.05.2017; Ethics Committee (EC): 05.05.2017 Clinical Study Protocol (CSP) Version (V) 0.7 23.03.2017 **Amendment 1**: major changes: change of inclusion criteria to include elderly patients Approval AM1: BfArM: 28.11.2017; EC: 02.11.2017, CSP V. 0.8 24.08.2017 **Amendment 2**: major changes: including explorative endpoints on metabolic effects Approval AM1: BfArM: 18.06.2019; EC: 13.06.2019, CSP V. 1.0 06.05.2019 **Amendment 3**: approval of IB Version 23 and 24 Approval AM3: BfArM: 24.09.2021; 18.01.2021 premature recruitment stop due to difficulties in patient recruitment was communicated to HA and EC (already included patients to continue until the end of FU). LPLV 15.09.2021
10.	**Phase of development** Phase II
11.	**Background:** Nummular eczema (NE) is an idiopathic chronic inflammatory skin disease that occurs throughout all life periods. Diagnosis is made primarily clinically in correlation with histological findings. Treatment of NE is difficult. Standard treatment consists of the use of emollients, topical as well as systemic corticosteroids and phototherapy. Nevertheless, remission is hard to achieve and relapse occurs often. Patients usually suffer from severe pruritus and reduced quality of life. Therefore, new therapeutic strategies are urgently needed. So far Apremilast, an inhibitor of PDE-4, has shown efficacy in treating atopic dermatitis (AD). Since there is an overlap between AD and NE with both being caused by impaired epidermal barrier, broad immune-mediated inflammation and microbial skin colonization, using Apremilast in NE seems to be promising
12.	**Objectives:** **Primary Objective:** Number of Patients Achieving an Improvement (Decrease) in PGA (Physician Global Assessment) by two or more points at week 16 as compared to week 0 or achieving an absolute PGA of 0 or 1 at Week 16 **Secondary Objectives:** • EASI 50 score at week 16 and 32 (Eczema Area and Severity Index) • Change From Baseline in Transepidermal Waterloss (TEWL) at week 16 and 32 • Significant histological improvement at week 16 • Change From Baseline in the Reduction of the Use of Topical Steroids at week 16 and 32 • Change in PGA score compared to baseline and week 16 for patients in Arm 2 at

	week 32 • Change From Baseline in the Dermatology Life Quality Index (DLQI) Total Score at Week 16 and 32 • Change From Baseline in Pruritus Visual Analog Scale (VAS) Score at Week 16 and 32 • Change From Baseline in the Global Satisfaction Subscale of the Treatment Satisfaction Questionnaire for Medication (TSQM) Score at Week 16 and 32 • Safety of Apremilast will be Assessed by Evaluating Adverse Events (AEs) **Exploratroy Objective:** Change From Baseline in metabolic functions at Week 16 and 32
13.	**Methodology** This is an investigator-initiated, single-center, prospective, randomized, double-blind, interventional phase IIb study. Forty patients with clinically and histologically confirmed NE will be enrolled according to inclusion and exclusion criteria. Patients will be included after written informed consent is obtained. Prior to randomization, average application rate of class II topical steroids per day will be measured for 4 weeks. Subsequently, patients will be randomized in a 1:1 ratio into one arm to receive Apremilast 30 mg BID (following titration phase) for 16 weeks or a second arm receiving identically matching placebo for 16 weeks. From beginning of week 17, all patients will start an open-label treatment with Apremilast 30 mg BID until week 32. Concomitant use of topical steroids (class II) is allowed during the study. During the treatment period both placebo and Apremilast will be applied p.o. from week 0 until week 32.
14.	**Sample size (planned/analysed):** <u>Planned:</u> 40 patients <u>Included / analysed:</u> 33 / 31 patients, 2 patients excluded from all analyses (not randomized); Safety Analysis Set (SA) is identical with full analysis set (FAS)
15.	**Patient Population (Diagnosis):** Nummular eczema; ICD-classification L30.0
	Main criteria for inclusion • Clinically confirmed diagnosis of NE • Biopsy-proven, meaning histology consistent with eczema (including PAS-staining) • PGA ≥ 3 on a 5 point scale • History of continuous use of topical steroids for the last 8 weeks • Age 18-85 years of age, body weight ≥ 40 kg and ≤ 160 kg • Signed informed consent from patient **Main criteria for exclusion** • Permanent severe diseases, especially those affecting the immune system • Pregnancy or breast feeding

	• History or presence of epilepsy, significant neurological disorders, depression, suicidal ideation and behaviour, cerebrovascular attacks or ischemia • History or presence of myocardial infarction or cardiac arrhythmia which requires drug therapy • Evidence of severe renal dysfunction • Evidence of significant hepatic disease • History of lymphoproliferative disorders
16.	**Test product, dose and mode of administration** **Study treatment, arms:** Experimental: Apremilast Patients randomized to this arm will start Apremilast with a titration phase of 5 days, followed by 30 mg Apremilast tablets twice daily (BID) by mouth (PO) for a total of 32 weeks (including titration phase). Experimental: Placebo + Apremilast Patients randomized to this arm will receive identically matching placebo (including the titration phase) by mouth for first 16 weeks. Placebo participants will be switched to receive Apremilast 30 mg BID from beginning of Week 17 for another 16 weeks. In this arm Apremilast will be started without titration
17.	**Blinding:** This is a blinded study. Patients and study site personnel performing assessments of outcomes are blinded to study treatment until the end of the study. Patients are randomised to the treatment arms at visit 0 by the means of assigning the next available randomization number.
18.	**Investigational plan:** This is an investigator-initiated, single-center, prospective, randomized, double-blind, placebo controlled, interventional Phase II study. Forty patients with confirmed NE will be enrolled according to inclusion and exclusion criteria. Patients will be included after written informed consent is obtained. Prior to randomization, average application rate of class II topical steroids per day will be calculated (Screening Phase). Subsequently, patients will be randomized in a 1:1 ratio into one arm to receive Apremilast 30 mg BID (following titration phase) for 16 weeks or a second arm receiving placebo for 16 weeks (Blinded Phase). Beginning with week 17, all patients will start an open-label treatment with Apremilast 30 mg BID until week 32 (Open-Label-Phase). Concomitant use of topical steroids (class II) is allowed during the study. The following treatment groups will be assessed in this study: • Verum: After a titration phase of 5 days, 30 mg Apremilast PO BID for a total of 32 weeks. • Placebo: Identically matching placebo tablets for 16 weeks, from week 17 on Apremilast 30 mg PO BID (open label phase), no titration phase, for a total of 16 weeks. The study will consist of 4 periods: • Period 1: Screening Period (Visits1 and 2) to measure average baseline application

	rate of concomitant medication class II topical steroids, occurring from week -4 up to week 0. • Period 2: Blinded Phase occurring from week 0 (baseline) up to and including week 16. • Period 3: Open Label Phase occurring from beginning of week 17 to week 32. • Period 4: Follow-up Phase 28 days after last dose of IMP (phone contact)
19.	**Analysis sets:** All analyses will be performed on the full analysis set (FAS), consisting of all patients who were randomized into the trial and received at least one dose of study medication and who have at least baseline PGA values. Analysis will be done as randomized, regardless of the treatment which the patient actually received (ITT analysis). Missing primary endpoint data will be imputed conservatively, using the highest measured change in PGA score for missing values in the placebo group and 0 (no change) in the Apremilast group. **Primary endpoint analysis:** The two groups will be compared with respect to the absolute change in PGA score at week 16 after therapy begin. The two-sided Wilcoxon test will be used to test for differences between the two groups. The significance level will be set to 5%. If there is a baseline difference in the mean PGA scores between the groups, then a linear regression model will be computed for the primary endpoint, containing treatment and baseline value as independent variables. Only data from the first 16 weeks of the study will be used for the analysis of the primary endpoint. **Secondary endpoint analysis:** Analyses of baseline data and secondary endpoints will be done using appropriate descriptive statistics and independent samples tests for difference between the two study groups. Tests for related samples have to be employed for the analysis of the within Arm 2 changes between the first and the second 16 weeks of the trial. All tests will be two-sided with an exploratory significance level of 5%. No adjustment for multiple comparisons will be done. **Safety:** All AEs will be recorded and coded using MedDRA. The absolute and relative incidences of AEs, related to Apremilast AEs, SAEs, and related to Apremilast SAEs will be reported by preferred term and system organ class and compared between the two study groups within the first 16 weeks of trial using the Fisher exact test **Sample size:** Sample size calculation was done using the primary endpoint. It is assumed, estimated on the efficacy of Apremilast in NE and psoriasis that the change in PGA score during the first 16 weeks of the trial will be with mean 2 points in Arm 1 and 0 points in Arm 2. The common standard deviation is assumed to be 1.7 points. A sample size of 17 patients in each group will have 85% power to detect a difference in median PGA scores of 2, assuming that the common standard deviation is 1.7 and using the two-sided Wilcoxon test with 5% significance. Assuming an additional drop-out rate of 15%, it is reasonable to allow for 20 patients per group to be entered in the study, a total of 40 patients. The study was stopped after recruiting 33 patients.

20.

Summary - Conclusions:

Patient demographics and patient disposition
In total 33 patients were included; two patients withdrew concent before they could be randomized and therefore received no IMP. Consequently, 31 patients were treated in the study (FPFV: 13.07.2017, LPI: 09.12.2020, LPLV: 15.09.2021).
Of the 31 patients included in the analyses, 19 patients completed study participation including the follow up visit. 12 patients discontinued the study prematurely. Reasons for discontinuation were adverse events (n=5), withdrawal of consent during the course of the study (n=7) and other reasons (n=1). One patient left the study due to two reasons.
A total of 15 patients were included in the verum arm and 16 patients in the placebo + apremilast arm. The blinded phase of the study was completed by 11/15 (73.3%) patients in the aplremilast arm and 15/16 (93.8%) in the placebo + apremilast arm. The open label phase of the study was completed by 10/15 (66.7%) patients in the apremilast arm and 9/16 (56.3%) patients in the placebo + apremilast arm.
This study included 22 adult (18-64 years, 71%) and 9 elderly (65-84 years, 29%) patients. The median age was 62 years [range: 27 – 81] in the verum group and 55.5 years [range: 23 – 78] in the placebo + apremilast group. The apremilast group included 5/15 (33.3%) and the placebo + apremilast group 2/16 (12.5%) female patients. Distributions of relevant demographics at baseline are given in Table 1 (Appendix).

Compliance:

There were no violations of inclusion or exclusion criteria.

Protocol Violation (PV):
93 PVs were reported in 27/31 patients: All PV were rated as minor (i.e. TEWL could not be performed due to malfunction of the machine (n=36); prednicarbate cream was not returned by the patient (n=27)).

Study medication:
Overall compliance for IMP intake were as expected following clinical routine.

Safety Assessments (all patients included)
Annual Safety Reports have been provided to BfArM and EC for the following periods:

DSUR 1: 13.07.2017-10.05.2018
DSUR 2: 11.05.2018-10.05.2019
DSUR 3: 11.05.2019-10.05.2020
DSUR 4: 11.05.2020-10.05.2021
DSUR 5: 10.05.2021-09.05.2022

Adverse Events and Serious Adverse Events were classified according to CTCAE V. 4 and coded according to MedDRA V. 20.0 English.

Safety Results (AE, SAE, SUSAR)

Adverse Events (AE)
A total of 59 AEs were reported in 20 (64.5%) of 31 patients see Table 2 (Appendix). During Phase I 10/15 (67%) patients experienced 22 AEs in the apremilast arm and 10/16 patients experienced 21 AEs in the placebo arm. During phase II, while taking apreminum, 9/25 (36%) of the patients experienced 16 AEs.
Alltogether 22/59 (37.3%) AEs were deemed related to treatment administered (AR).
36/59 (61.0) AEs were rated Grade 1 (mild), 21/59 (35.6%) Grade 2 (moderate), 2/59 (3.4%) Grade 3 (severe), 0/59 Grade 4 (life-threatening), 0/59 Grade 5 (death).

Serious AE (SAE)
One mild (according to CTCAE) SAE was reported in one patient while under Apremilast in phase I of the trial. The SAE was coded under MedDRA system organ class “Skin and subcutaneous tissue disorders” and preferred term “Eczema”. The original terma was “worsening of nummular eczema”.

Suspected Serious Adverse Reactions (SAR)
No SAR was reported.

Suspected Unexpected Serious Adverse Reactions (SUSAR)
No SUSAR was reported in the study.

Non-serious Adverse Events (AE)
A total of 58 non-serious AEs on 20 patients were reported during the study. During phase I 21 events in 10/15 (67%) patients acurred in the apremilast group and 21 events in 10/16 (63%) patients in the placebo group. While taking apremilast during phase II of the study, 9/25 (36%) patients experienced 16 events (see Appendix Tables 3 and 4 for details).

Efficacy Results

Primary Endpoint

The distribution of PGA scores at baseline was similar in both treatment groups.
The primary endpoint was analysed on the FAS. Four patients in the apremilast group and two patients in the placebo + apremilast group did not deliver PGA values at week 16. The change in PGA between baseline and week 16 was imputed as planned using zero in the apremilast group and -3 points in the placebo group. After imputation the number of patients with PGA improvement within 16 weeks of treatment was 1/15 (6.7%) in the apremilast group and 4/16 (25.0%) in the placebo group. This difference was not statistically significant ($p = 0.369$).
Two sensitivity analyses of the primary endpoint were performed on the set of complete PGA data (without imputation). The linear regression model, containing treatment and baseline values as independent variables delivered a p-value of 0.862 for the t-statistic of variable treatment goup. The Wilcoxon rank sum test could not find differences between the two treatments ($p = 0.812$). Results of the primary endpoint analyses are shown in the appendix Table 5.

Secondary Endpoints

None of the analyzed secondary endpoints showed a significant difference between the verum and placebo + apremilast arm at week 16 or week 32.

Of the 31 patients in the FAS, 25 delivered results on EASI50 response after 16 weeks (11 in the apremilast group and 14 in the placebo + apremilast group) and 22 patients after 32 weeks. Mean ±SD EASI in the verum arm at baseline was 12.75 ±4.70 vs 13.75 ±7.91 in the placebo arm. At week 16 mean EASI was 9.1 ±7.15 in the apremilast arm vs. 6.96 ±5.18 in the placebo arm. At week 32 mean EASI was 8.94 ±7.19 in the apremilast arm vs. 5.92 ±4.74 in the placebo + apremilast arm. There was no significant difference between the two treatment groups in terms of improvement in EASI50 with more than 50% (see Table 6).

Additionally, there was no difference in the change of transepidermal waterloss between the two treatment groups (see Table 7).

	Histological improvement assessed by reduction in epidermal thickness and inflammatory cell count at week 16 showed no difference between the apremilast and the placebo + apremilast arm. 4/11 patients in the apremilast group and 5/14 patients in the placebo group showed improvement after week 16. Mean epidermal thickness in the verum arm at baseline was 318.7 ±88.8 µm vs. 291.3 ±114.4 µm in the placebo arm. At week 16 epidermal thickness decreased to 230.3 ±59.3 µm in the apremilast arm and 200.6 ±127.1 µm in the placebo arm. Mean inflammatory cell count at baseline was 192.8 ±59.1 in the verum arm vs. 193.1 ±69.1 in the placebo arm. At week 16 it decreased to 115.6 ±82.7 in the apremilast group vs. 112.0 ±89.4 in the placebo group (see Table 8). Daily use of topical steroids showed a reduction compared to the screening phase during Phase I from a mean 4.2 ±3.8 g to 3.2 ± 3.0 g in the verum arm compared to 2.6 ±1.4 g to 2.8 ±1.9 g in the placebo arm. During phase 2 the mean daily usage of topical steroids was 1.3 ±1.1 g in the apremilast vs. 1.6 ±1.1 g in the placebo + apremilast group. There was no statistical difference between the two arms in both phases of the clinical trial (see Table 9). Mean change in PGA score compared to baseline was -0.73 both in week 16 (SD 0.90) and week 32 (SD 0.65) in the apremilast arm. In the placebo + apremilast group mean change in PGA was -0.57 ±0.86 after 16 weeks and -0.82 ±0.75 after 32 weeks. There was no statistically significant difference between the two treatment phases (see Table 10). According to patient based outcome measures, quality of life (DLQI), pruritus (VAS) and treatment satisfaction (TSQM) was assessed. In the verum arm, DLQI showed a mean change compared to baseline of -3.82 ±4.92 and -4.45 ±9.46 after 16 and 32 weeks, respectively. In the placebo + apremilast arm mean change in DLQI was -2.36 ±3.39 after 16 weeks and -4.64 ±5.71 after 32 weeks. There was no significant difference between the two groups (see Table 11). Pruritus visual analog scale showed a mean change of -0.27±2.38 and -1.00 ±4.04 at week 16 and week 32, respectively in the apremilast arm vs. -0.18 ±1.69 and -1.55 ±2.94 in the placebo + apremilast arm. There was no significant difference between the two groups (see Table 12). In addition, none of the four subscores of the TSQM (effectiveness, side effects, convenience and global satisfaction) did show a statistical difference between the two treatment arms after 16 and 32 weeks (see Table 13). Exploratory: To assess change in metabolic functions BMI, girth, glucose, HbA1c, cholesterol, HDL, LDL and Lipoprotein A were assessed at baseline, week 16 and week 32. There was no significant difference for any parameter between the two treatment arms.
	Overall Conclusion: Both in the primary and in the secondary endpoints, significance could not be demonstrated. Reported AE/SAE were in accordance with the known safety profile of Apremilast in the approved indication Psoriasis administered according to clinical routine. In conclusion, this study provides no evidence that Apremilast is effective in the treatment of nummular eczema.

APPENDIX

Table 1: Demographics and Baseline Characteristics

		Treatment group	
		Apremilast (N = 15)	*Placebo + Apremilast (N = 16)*
Sex (n, %)	*Female*	5 (33.3%)	2 (12.5%)
	Male	10 (66.7%)	14 (87.5%)
Age group (n, %)	*Adults (18 - 64 years)*	11 (73.3%)	11 (68.8%)
	Elderly (65 – 84 years)	4 (26.7%)	5 (31.5%)
Age (years)	*Mean*	54.5	54.6
	Std	17.0	15.5
	Min	27.0	23.0
	Median	62.0	55.5
	Max	81.0	78.0
Ethnicity (n, %)	*Asian*	1 (6.7%)	1 (6.3%)
	Caucasian	13 (86.7%)	15 (93.8%)
	Other	1 (6.7%)	0
Weight (kg)	*Mean*	87.7	87.5
	Std	19.2	16.7
	Min	62.0	55.0
	Median	88.0	88.0
	Max	135.0	126.0
Height (cm)	*Mean*	174.5	175.3
	Std	11.9	8.2
	Min	155.0	160.0
	Median	175.0	175.0
	Max	197.0	192.0
BMI	*Mean*	28.7	28.6
	Std	4.8	6.0
	Min	21.6	19.0
	Median	28.3	27.8
	Max	40.8	39.8

Table 2: All AEs, all phases

System Organ Class Preferred Term	*Phase I*						*Phase II*		
	Exposed to Apremilast N=15			*Exposed to Placebo N=16*			*Exposed to Apremilast N=25*		
		Subjects affected			*Subjects affected*			*Subjects affected*	
	Events	*n*	*(%)*	*Events*	*n*	*(%)*	*Events*	*n*	*(%)*
All AEs	22	10	(67)	21	10	(63)	16	9	(36)
SAE	1	1	(7)	0	0		0	0	
Non-SAE AEs	21	10	(67)	21	10	(63)	16	9	(36)

Table 3: Non-SAE AEs – Phase 1

	Exposed to Apremilast N=15			*Exposed to Placebo N=16*		
		Subjects affected			*Subjects affected*	
System Organ Class Preferred Term	*Events*	*n*	*(%)*	*Events*	*n*	*(%)*
OVERALL	21	10	(67)	21	10	(63)
Gastrointestinal disorders	9	7	(47)	2	2	(13)
Abdominal distension	1	1	(7)	0	0	(0)
Abdominal pain upper	1	1	(7)	0	0	(0)
Diarrhoea	3	3	(20)	1	1	(6)
Flatulence	1	1	(7)	0	0	(0)
Nausea	3	3	(20)	1	1	(6)
General disorders and administration site conditions	2	1	(7)	1	1	(6)
Chest pain	0	0	(0)	1	1	(6)
Fatigue	2	1	(7)	0	0	(0)
Infections and infestations	7	7	(47)	4	3	(19)
Hordeolum	1	1	(7)	0	0	(0)
Pneumonia	0	0	(0)	1	1	(6)
Viral upper respiratory tract infection	6	6	(40)	3	3	(19)
Investigations	1	1	(7)	0	0	(0)
Hepatic enzyme increased	1	1	(7)	0	0	(0)
Metabolism and nutrition disorders	1	1	(7)	0	0	(0)
Decreased appetite	1	1	(7)	0	0	(0)
Musculoskeletal and connective tissue disorders	0	0	(0)	1	1	(6)
Musculoskeletal pain	0	0	(0)	1	1	(6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	(0)	1	1	(6)
Keratoacanthoma	0	0	(0)	1	1	(6)
Nervous system disorders	1	1	(7)	3	2	(13)
Dizziness	1	1	(7)	0	0	(0)
Headache	0	0	(0)	1	1	(6)
Migraine	0	0	(0)	2	1	(6)
Skin and subcutaneous tissue disorders	0	0	(0)	9	3	(19)
Eczema	0	0	(0)	1	1	(6)
Eczema weeping	0	0	(0)	4	1	(6)
Pruritus	0	0	(0)	4	2	(13)

Table 4: Non-SAE AEs – Phase 2

	Exposed to Apremilast N=25		
		Subjects affected	
System Organ Class Preferred Term	*Events*	*n*	*(%)*
OVERALL	16	9	(36)
Eye disorders	1	1	(4)
Cataract	1	1	(4)
Gastrointestinal disorders	6	4	(16)
Abdominal discomfort	1	1	(4)
Diarrhoea	3	2	(8)
Nausea	1	1	(4)
Vomiting	1	1	(4)
General disorders and administration site conditions	1	1	(4)
Oedema peripheral	1	1	(4)
Infections and infestations	2	2	(8)
Viral upper respiratory tract infection	2	2	(8)
Nervous system disorders	2	2	(8)
Headache	2	2	(8)
Skin and subcutaneous tissue disorders	4	2	(8)
Eczema	1	1	(4)
Photodermatosis	1	1	(4)
Pruritus	2	2	(8)

Table 5: Primary endpoint: PGA

PGA improvement from Baseline to …		*Treatment group* *Apremilast*	*Placebo + Apremilast*	*P-value*
		(N = 15)	*(N = 16)*	
Week 16 (Missing values imputed)	*No improvement*	14 (93.3%)	12 (75.0%)	0.369
	Improvement	1 (6.7%)	4 (25.0%)	
		(N = 11)	*(N = 14)*	
Week 16 (Complete case)	*No improvement*	10 (90.9%)	12 (85.7%)	0.812
	Improvement	1 (9.1%)	2 (14.3%)	

Table 6: EASI 50 score at week 16 and 32

EASI 50 improvement from Baseline to …		*Treatment group* *Apremilast*	*Placebo + Apremilast*	*P-value*
		(N = 11)	*(N = 14)*	
Week 16	*No improvement*	6 (54.5%)	8 (57.1%)	1.000
	Improvement	5 (45.5%)	6 (42.9%)	
		(N = 11)	*(N = 11)*	
Week 32	*No improvement*	6 (54.5%)	5 (45.5%)	0.670
	Improvement	5 (45.5%)	6 (54.5%)	

Table 7: Change in mean TEWL (transepidermal waterloss)

Change in mean TEWL between Baseline and …		*TRT_rand*		
		Apremilast	*Placebo + Apremilast*	*P-value*
meanTEWL_change_w16	*N*	9	9	0.185
	Mean	-26.04	-12.24	
	Std	10.29	21.47	
	Min	-40.73	-40.37	
	Median	-27.37	-16.97	
	Max	-3.13	18.73	
meanTEWL_change_w32	*N*	8	6	0.847
	Mean	-19.08	-16.85	
	Std	19.46	29.73	
	Min	-43.53	-58.03	
	Median	-28.68	-12.52	
	Max	8.50	11.67	

Table 8: Histological improvement – Epidermal thickness

Histological improvement		*TRT_rand*		*P-value*
		Apremilast	*Placebo + Apremilast*	*(Fisher Exact Test)*
Overall histological improvement at Week 16	*No improvement*	7 (63.6%)	9 (64.3%)	1.000
	Improvement	4 (36.4%)	5 (35.7%)	
Epidermal thickness at Baseline	*N*	11	14	
	Mean	318.73	291.29	
	Std	88.84	114.44	
	Min	207.50	176.00	
	Median	300.50	257.75	
	Max	442.00	505.00	
Epidermal thickness at Week 16	*N*	11	14	
	Mean	230.32	200.57	
	Std	59.29	127.07	
	Min	140.00	77.00	
	Median	231.50	132.25	
	Max	357.00	481.50	
Immun cell count at Baseline	*N*	11	14	
	Mean	192.77	193.11	
	Std	59.08	69.08	
	Min	117.50	93.50	
	Median	163.00	195.25	
	Max	279.50	310.00	
Immun cell count at Week 16	*N*	11	14	
	Mean	115.55	112.00	
	Std	82.74	89.38	
	Min	19.50	21.50	
	Median	136.50	86.75	
	Max	265.00	300.00	

Table 9: Use of Topical Steroids (Mean Daily Use during Screening, Phase I, and Phase II)

Mean daily steroid use during …		*TRT_rand*		
		Apremilast	*Placebo + Apremilast*	*P-value*
Screening	*N*	13	13	0.538
	Mean	4.23	2.63	
	Std	3.79	1.44	
	Min	0.60	0.13	
	Median	3.28	2.63	
	Max	13.75	5.23	
Phase I	*N*	13	15	0.854
	Mean	3.18	2.84	
	Std	3.02	1.85	
	Min	0.56	0.72	
	Median	2.22	2.40	
	Max	11.22	6.34	
Phase II	*N*	11	10	0.597
	Mean	1.31	1.61	
	Std	1.10	1.10	
	Min	0.00	0.00	
	Median	1.04	1.50	
	Max	3.08	3.36	

Table 10: PGA Distribution - changes between blinded and open label parts of the study

Change in PGA between …		*TRT_rand*	
		Apremilast	*Placebo + Apremilast*
P-value (Wilcoxon Signed Ranks Test) Comparing blinded and unblended period within treatment group		0.391	0.625
Baseline and Week 16	*N*	11	14
	Mean	-0.73	-0.57
	Std	0.90	0.85
	Min	-3.00	-2.00
	Median	-1.00	-0.50
	Max	0.00	1.00
Baseline and Week 32	*N*	11	11
	Mean	-0.73	-0.82
	Std	0.65	0.87
	Min	-2.00	-2.00
	Median	-1.00	-1.00
	Max	0.00	0.00
Week 16 and Week 32	*N*	11	11
	Mean	0.00	-0.55
	Std	1.18	0.82
	Min	-1.00	-2.00
	Median	0.00	-1.00
	Max	3.00	1.00

Table 11: DLQI - Change From Baseline in the Dermatology Life Quality Index (DLQI)

Change in DLQI between Baseline and …		*TRT_rand*		
		Apremilast	*Placebo + Apremilast*	*P-value*
Week 16	*N*	11	14	0.678
	Mean	-3.82	-2.36	
	Std	4.92	3.39	
	Min	-14.00	-7.00	
	Median	-2.00	-2.00	
	Max	2.00	5.00	
Week 32	*N*	11	11	0.792
	Mean	-4.45	-4.64	
	Std	9.46	5.71	
	Min	-21.00	-14.00	
	Median	-2.00	-4.00	
	Max	12.00	5.00	

Table 12: Pruritus Visual Analog Scale (VAS) Score at Week 16 and 32

Change in VAS between Baseline and …		*TRT_rand*		
		Apremilast	*Placebo + Apremilast*	*P-value*
Week 16	*N*	11	14	0.617
	Mean	-0.27	-0.18	
	Std	2.38	1.69	
	Min	-3.50	-3.00	
	Median	-1.00	-0.25	
	Max	6.00	3.00	
Week 32	*N*	11	11	0.741
	Mean	-1.00	-1.55	
	Std	4.04	2.94	
	Min	-8.00	-7.00	
	Median	-1.00	-1.50	
	Max	6.00	3.00	

Table 13: TSQM Score

Change in TSQM sub-score between Baseline and …		*TRT_rand*		
		Apremilast	*Placebo + Apremilast*	*P-value*
Effectiveness Week 16	*N*	9	10	0.152
	Mean	-3.71	-12.24	
	Std	20.22	30.75	
	Min	-27.80	-44.50	
	Median	-11.10	-25.05	
	Max	38.90	50.00	
Effectiveness Week 32	*N*	9	8	0.194
	Mean	-0.01	19.84	
	Std	32.62	24.44	
	Min	-44.40	-11.00	
	Median	-5.60	13.85	
	Max	50.00	66.70	
Side effects Week 16	*N*	9	10	0.428
	Mean	-6.94	2.50	
	Std	52.70	29.93	
	Min	-100.00	-50.00	
	Median	0.00	0.00	
	Max	100.00	75.00	
Side effects Week 32	*N*	9	8	0.285
	Mean	-13.88	-34.11	
	Std	52.73	37.75	
	Min	-100.00	-100.00	
	Median	0.00	-26.05	
	Max	87.50	0.00	
Convenience Week 16	*N*	9	10	0.775
	Mean	15.42	10.04	
	Std	32.11	29.32	
	Min	-16.60	-22.20	
	Median	5.60	0.00	
	Max	83.30	56.00	

Change in TSQM sub-score between Baseline and …		*TRT_rand*		
		Apremilast	*Placebo + Apremilast*	*P-value*
Convenience Week 32	*N*	9	8	0.661
	Mean	9.87	14.59	
	Std	48.00	26.76	
	Min	-50.00	-22.30	
	Median	0.00	5.55	
	Max	88.90	55.70	
Global satisfaction Week 16	*N*	9	10	0.367
	Mean	-10.31	-21.36	
	Std	25.77	42.59	
	Min	-35.70	-85.70	
	Median	-14.30	-25.00	
	Max	50.00	72.00	
Global satisfaction Week 32	*N*	9	8	0.665
	Mean	-2.38	2.72	
	Std	37.61	36.63	
	Min	-35.70	-42.90	
	Median	-14.30	0.20	
	Max	71.40	78.60	