Final clinical study report

Randomized single-blind study on the adherence to treatment with topical methylprednisolone aceponate (Advantan®) in different vehicles (AD-HERE)

Prospective, randomized, parallel grouped, single-blinded (investigator), monocentric clinical trial (phase IV) with topical methylprednisolone aceponate (Advantan®) in two different vehicles

Name of the study drug: methylprednisolone aceponate (Advantan®)
Indication: hand eczema
Phase of clinical trial: IV

EudraCT-Number: 2019-001324-35
Trial registration No. in ClinicalTrials.gov: NCT04016025

Date of current version: 04.11.2022
Status of current version: final_latestVersion

Principal Investigator:
Prof. Dr. med. Peter Elsner
Universitätsklinikum Jena
Klinik für Hautkrankheiten
Erfurter Straße 35
07743 Jena, Germany

Sponsor:
Friedrich Schiller University Jena

Authors of the report
Dr. Ulrike Schumacher and Dr. Maria Breternitz-Gruhne
Universitätsklinikum Jena, Zentrum für Klinische Studien
Postfach, 07740 Jena, Germany
E-Mails: ulrike.schumacher@med.uni-jena.de
and Maria.Breternitz-Gruhne@med.uni-jena.de

Dr. Deborah Maria Gregersen
Universitätsklinikum Jena, Klinik für Hautkrankheiten
Erfurter Straße 35, 07743 Jena, Germany
E-Mail: DeborahMaria.Gregersen@med.uni-jena.de

Start of the trial: 04.12.2020
End or termination of the trial: 19.07.2022

Signature page

The signatories endorse herewith the content of the present report summary. The present clinical study has been conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice (GCP), and in compliance with the currently accepted legal regulations.

Principal Investigator	Prof. Dr. med. Peter Elsner	9.11.22 Datum
Biometrician	Dr. Ulrike Schumacher	15.11.2022 Datum
Further contributors	Dr. Maria Breternitz-Gruhne	17.11.2022 Datum
	Dr. Deborah Maria Gregersen	09.11.22 Datum

Synopsis

Sponsor: Friedrich Schiller University Jena	
Study medication: Advantan®	
Drug substance/Active ingredient: methylprednisolone aceponate	
Study title: Randomized single-blind study on the adherence to treatment with topical methylprednisolone aceponate (Advantan®) in different vehicles (AD-HERE)	
Principal investigator: Prof. Dr. med. Peter Elsner	
Study site: Jena University Hospital, Department of Dermatology	
Publication: planned to hand in draft at *British Journal of Dermatology* until 1st December 2022	
first patient in: 04.12.2020 last patient out: 14.04.2022	Phase: IV
Study objective: Objective assessment of the adherence to the treatment with topical methylprednisolone aceponate (Advantan®) depending on the type of vehicle in patients with hand eczema treated according to the current guideline	
Methods: Primary parameters: Adherence defined as percentage of patients applying at least aimed daily dose *Prescribed daily dose* is defined as: planned number of applications per day (1) * surface (measured) * aimed amount per application *Truly applicated daily dose* was evaluated as individual mean amount per dose * individual mean number of applications per day. *Adherence* was assumed, if • truly applicated daily dose is at least 75% of prescribed daily dose and • the individual mean number of applications per day is at least 0.85 Secondary parameters: Improvement of Hand Eczema	
Sample size (projected and analyzed): N = 80	
Indication and inclusion criteria: Hand eczema and as „main inclusion criterion" clinical diagnosis of chronic mild-to-moderate hand dermatitis with or without atopic etiology or background (according to IGA: at least mild at Visit 1)	
Study medication (Dose, Route of administration, Batch No. ADHERE/202028): 1) Advantan® Cream 0.1% (Methylprednisolone aceponate) once a day, dermal application 2) Advantan® Fatty Ointment 0.1% (Methylprednisolone aceponate) once a day, dermal application	
Treatment duration: 28 days	
Comparator product (Dose, Route of administration, Batch No.): -	
1. Comparator product: - 2. Comparator product: -	
Unblinding: none	
Efficacy (Effectiveness) assessment: Adherence definition see above (primary parameters). Secondary the efficacy as measured by improvement of Hand Eczema Severity Index (HECSI) and Investigator´s Global Assessment (IGA) after a 4-week treatment period	
Safety (Tolerability) assessment: clinically, descriptive	
Statistical methods: descriptive, Fishers exact test	

Sponsor: Friedrich Schiller University Jena
Study medication: Advantan®
Drug substance/Active ingredient: methylprednisolone aceponate
Summary of results: Our sample of 80 subjects showed relative equality concerning sex and age. 50% were given Advantan 0,1 % cream, 50% were given Advantan 0,1% fatty ointment. Efficacy (Effectiveness): In total 48% were adherent to the treatment according to our adherence definition. Within the groups we saw a slight tendency towards more adherence with the use of Advantan 0,1% fatty ointment (adherence 54.1%) than with Advantan 0,1% cream (adherence 42.1%) although the differences between the groups were not significant. Via fisher's exact test we were not able to show a tendency towards more adherence in the use of cream or fatty ointment. Assessment of clinical improvement (secondary parameters) supported the suggested treatment in the guideline [1]. Looking at the IGA, at Screening 21.3% had moderate and 76.3% had mild skin lesions, at the last visit 5.2% were clear, 36.4% were almost clear, 53.2 % had mild and 5.2% had moderate skin lesions. Mean HECSI Score at screening was 23.4 with a reduction to 12.5 at last visit. The mean reduction in pruritus, measured by VAS, dropped from 26.3 to 13.0, quality of life assessment was improved from mean QOLHEQ 41.3 at baseline to 24.6 at last visit. Safety (Tolerability): There were no safety considerations throughout the study. Conclusions: Overall adherence was poor. The adherence showed a non-significant tendency depending on the galenics. The treatment effect measured by IGA and HECSI as well as VAS and QOLHEQ showed an overall improvement throughout the study time.
Report date: 04.11.2022

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1 Ethics

1.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

According to § 40 German Medicinal Products Act (AMG), the prerequisite for the initiation of this trial was the approval of the Ethics committee (EC) of Friedrich Schiller University Jena. This EC approved all amendments during the study duration.

1.2 Ethical conduct of the study

The study was conducted in compliance with national legislation (German Medicinal Product Act, German GCP Ordinance), the requirements of the ICH Guideline for Good Clinical Practice (GCP) E6 from June 1996, the Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 from July 2002, and the Declaration of Helsinki (7th revision of Fortaleza 2013).
In accordance with the requirements of the German Medicinal Product Act, an indemnity insurance policy was taken out for all patients who consented to participate in the trial.

1.3 Patient information and consent

Patients meeting the inclusion criteria were considered candidates for participation in this study. Eligible patients were only included in the study after providing written IRB-approved informed consent. Patients who were incapable to understand and/or to provide written informed consent were not suitable for study participation.
Informed consent was obtained before conducting any study-specific procedures (i.e. all of the procedures which were not part of the daily routine). The processes of patient information and date and informed consent and date were documented in the patient source documents.

2 Investigators and study administrative structure: Responsible persons

Sponsor (according to AMG):	Friedrich Schiller University Jena Authorized representative of the sponsor: Prof. Dr. med. Peter Elsner
Principal investigator:	Prof. Dr. med. Peter Elsner Universitätsklinikum Jena, Klinik für Hautkrankheiten Erfurter Straße 35 07743 Jena, Germany Telefon: +49 (0) 3641 9 32 88 00 Telefax: +49 (0) 3641 9 32 88 05 E-Mail: elsner@derma-jena.de
Project management:	Dr. med. Maria Breternitz-Gruhne Universitätsklinikum Jena, Zentrum für Klinische Studien Postfach, 07740 Jena, Germany
Pharmacovigilance/SAE-management	Mariann Städtler Universitätsklinikum Jena, Zentrum für Klinische Studien Postfach, 07740 Jena, Germany
Data management:	Lisa Franke Universitätsklinikum Jena, Zentrum für Klinische Studien Postfach, 07740 Jena, Germany
Biometrics:	Dr. Ulrike Schumacher Universitätsklinikum Jena, Zentrum für Klinische Studien Postfach, 07740 Jena, Germany Tel.: +49 (0) 3641 9396656 Fax: +49 (0) 3641 9399969 E-Mail: ulrike.schumacher@med.uni-jena.de
Monitoring:	Anke Braune Universitätsklinikum Jena, Zentrum für Klinische Studien Postfach, 07740 Jena, Germany
Independent Data Monitoring Committee:	-
Author of the final report:	Dr. Ulrike Schumacher Universitätsklinikum Jena, Zentrum für Klinische Studien Postfach, 07740 Jena, Germany Tel.: +49 (0) 3641 9396656 Fax: +49 (0) 3641 9399969 E-Mail: ulrike.schumacher@med.uni-jena.de Dr. Maria Breternitz-Gruhne Universitätsklinikum Jena, Zentrum für Klinische Studien Postfach, 07740 Jena, Germany Tel.: +49 (0) 3641 9396656 Fax: +49 (0) 3641 9399969 E-Mail: Maria.Breternitz-Gruhne@med.uni-jena.de Dr. Deborah Maria Gregersen Universitätsklinikum Jena, Klinik für Hautkrankheiten Erfurter Straße 35, 07743 Jena, Germany Tel.: +49 (0) 3641 9328848 Fax: +49 (0) 3641 9328836 E-Mail: DeborahMaria.Gregersen@med.uni-jena.de
Investigator(s) of the single study center:	Dr. med. Melanie Peckruhn (Deputy Principal Investigator) Universitätsklinikum Jena, Klinik für Hautkrankheiten

	Erfurter Straße 35, 07743 Jena, Germany Telefon: +49 (0) 3641 93 73 50 Telefax: +49 (0) 3641 93 73 43 E-Mail: melanie.peckruhn@med.uni-jena.de Dr. med. Deborah M. Gregersen Hautphysiologisches Labor, Klinik für Hautkrankheiten Erfurter Str. 35, 07743 Jena, Germany Universitätsklinikum Jena Telefon: +49 (0) 3641 32 88 48 E-Mail: DeborahMaria.Gregersen@med.uni-jena.de

3 Introduction

Chronic hand eczema is a common disease with a heavy burden of disease and long, often frustrane therapeutic outcome. Consequent basic care and topical treatment are advised but often subject to poor adherence [2].
One factor to influence adherence to treatment is the vehicle's galenics; a factor that has been well characterized in psoriaisis treatment [3]. Although a common condition, until today poor scientific data is available on chronic hand eczema treatment. Therefore, the Department of Dermatology of the Jena University Hospital initiated this prospective, monocentric, randomised controlled, single-blinded study on hand eczema to compare the adherence to treatment with first line topical treatment of chronic hand eczema in different galenics (first endpoint). Our secondary endpoint assesses the efficacy of such treatment (via IGA, VAS, QOLHEQ and HECSI score). We analyzed 80 subjects with hand eczema of age 18-65 without further dermatologic conditions on the hand and no acute dermatoses on the rest of the body and no cancer. The investigational period lasted for 35 days: 28 days of therapy and 7 days for follow-up. The subjects applied Bepanthen® Sensiderm over the day in unlimited amount and Methylprednisolonaceponat 0,1% cream (IMP) or fatty ointment (Control) once daily on eczema locations of the hands. Time and frequency of application were measured by a microchip technology via MEMS® Cap (Medication Event Monitoring System, AARDEX). The cream/fatty ointment quantity was measured by weighing before and after use of the tube.
The protocol was written in accordance with the applicable versions of the German Medicinal Products Act (AMG) and the Regulation on the Application of Good Clinical Practice in the Conduct of Clinical Trials of Medicinal Products for Human Use (GCP-V) as well as the principles published in the ICH-GCP Guideline and the ethical principles set out in the Declaration of Helsinki as the recognised ethical basis for clinical trials, as amended in 2013 [4,5,6,7,8,9,10,11].

4 Study objectives

4.1 Primary objective

The primary objective of the study was the objective assessment of the adherence to the treatment with topical methylprednisolone aceponate (Advantan®) depending on the type of vehicle in patients with hand eczema treated according to the current guideline.

4.2 Secondary objective

The secondary objective of the study was the improvement of hand eczema.

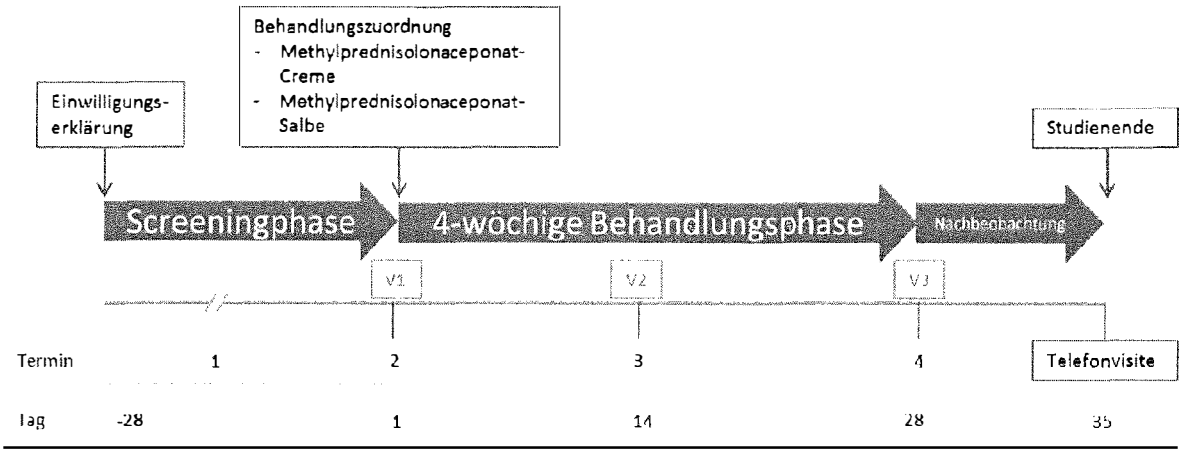
5 Investigational (Observational) plan

5.1 Overall study design and plan

Prospective, randomized, parallel grouped, single-blinded (investigator), monocentric clinical trial (phase IV) on the adherence to treatment with topical methylprednisolone aceponate (Advantan®) in different vehicles.
It was assumed that approximately 10 patients per month with hand eczema would be eligible for an inclusion into the study (ca. 150 in 15 months). It was estimated that 5-6 patients per month could be enrolled in the study. Considering the required number of 80 patients, the study could be concluded within 15 months. Patients with hand eczema were screened and were then informed about the study and enrolled for study treatment after receiving their written informed consent and checking the inclusion and exclusion criteria.

The screening of subjects was possible up to 28 days before enrollment in the study. 80 overall healthy subjects presenting with chronic hand eczema were included. The treatment with Methylprednisolonaceponat 0,1% cream (study medication 1, IMP) or fatty ointment (study medication 2, Control) took place once daily on hand eczema. Unlimited amount of emollient with a break of 2 hours before application of IMP/Control was allowed and no other care cream, topical or cosmetic product was allowed during the 28-day long treatment time. The individual amount of study medication based on the area of lesions on the hands, measured in fingertip units (FTU). One FTU equals 500 mg of topical drug in male and 400 mg in female subjects. The subject was instructed to use possible amounts of study medication product of 0.25 (125/100 mg), 0.5 (250/200 mg), 0.75 (375/300 mg) or 1 FTU (500/400 mg) once daily, best before going to bed. Instructions to only use the study medication and basic care cream via tubes with MEMS® Caps were given each subject on hand out of study medication.

The Investigator was blinded (single blinded design).
Data monitoring happened continuously throughout the study conduction with monitoring visits every 2-3 months as a standardized procedure through our Center for Clinical Studies (ZKS Jena). There was no Data Safety and Monitoring Comittee or Steering Comittee.



5.2 Discussion of study design, including the choice of control groups

Our aim in choosing adult patients was to meet a representative group of the population affected by chronic hand eczema throughout an active life phase and to look at treatment adherence alongside their daily routine. Therefore, our subject inclusion criteria were not

limited to specific causes of hand eczema (e.g. atopic, subtoxic-cumulative, contact allergic) nor to one daily activity or profession. Both IMP and Control, Advantan® Cream 0.1% (Methylprednisolone aceponate) und Advantan® Fatty Ointment 0.1% (Methylprednisolone aceponate), are approved drugs for which extensive safety and tolerance data are available for many years. They can be found in the SmPC for Advantan® Cream 0.1% (Methylprednisolone aceponate) und Advantan® Fatty Ointment 0.1% (Methylprednisolone aceponate). In this regard, we assumed the IMPs would be applied in a safe and proven manner within this study. Nevertheless, although considered empirically safe, we excluded pregnant and breast-feeding women from randomization due to lack of safety data and required thorough birth control and a negative pregnancy test before randomization of potential fertile female subjects.
To prevent overdose and to have a fixed measurable frame to correlate with the amount of IMP/Control we used the Finger Tip Unit (FTU) according to affected area of hand eczema. To simplify the comparability we portioned the hand areas into quarters and advised the patient to use 0,25, 0.5, 0.75 and 1 FTU depending on the total area affected of both hands.
We decided not to prolong the treatment further than 4 weeks allowing a short period of two days without and a period of up to seven days with further notification of the PI and documentation on treatment elongation. The guideline by Diepgen et al. recommends up to six weeks of topical treatment with corticosteroids stating that continuous daily treatment longer than six weeks may lead to persistent corticosteroid-associated side effects in the skin [1].
An application scheme of once or twice daily may influence the treatment adherence. The hand eczema guideline states the possibility that application once daily may show even better results than the application twice daily without further exploration. In this study, we decided for a once daily treatment to keep the scheme as simple as possible, although the control via MEMS® Caps if application happens once or twice is given. Additionally, we can assume a higher drug safety with reduced adverse reactions if IMP and control when only used once daily.
The single-blind design refers only to the investigator to reduce the investigator's outcome expectations; knowing that studies often state a higher patient preference to less fatty vehicles such as gels and creams. We cannot assume any blinding of our chronic hand eczema patients towards the galenics of IMP or control after the first use. The vehicles galenic are clearly perceptible from the first use on. We can furthermore assume that chronic hand eczema patients have undergone a multitude of topical treatments and must be therefore familiar with different vehicles and topical drugs.
To meet our secondary endpoint (improvement of hand eczema), we chose a wash-out phase for pre-treatment of different intervals according to invasivity and mean duration of effects (topical treatment 2 weeks, phototherapy 4 weeks, systemic treatment 8 weeks). Our aim was to attribute our topical treatment towards the effect measured via clinical scores on visits 2 and 3.

5.3 Selection of study population

Patients presumably meeting the inclusion criteria were considered for participation in this study. Patients who were incapable to understand and/or to provide written informed consent were not suitable for study participation.
Before conducting any study-specific study screening interventions or tests (study-specific procedures) which are not part of standard of clinical practice, information of the patient on the clinical trial was performed. After information about the study, the patient had enough time to ask questions and decide about a possible participation in the study. Eligible patients were only included in the study after providing written IRB-approved informed consent.

The process of patient information and date and informed consent and date was documented in the patient source documents.

*5.3.1 **Inclusion criteria***

Male and female adult patients with mild to moderate hand eczema formed the study population of this trial.

- Subject (male or female) aged from 18 to 65 years.

- Obtained signed and dated informed consent.
- Clinical diagnosis of chronic mild-to-moderate hand dermatitis with or without atopic etiology or background (according to IGA: at least mild at Visit 1).
- In overall good health including well controlled diseases as determined by medical history, physical examination, vital signs and clinical laboratory.
- Female subjects must be of either:
    - non-childbearing potential, post-menopausal, or have a confirmed clinical history of sterility or,
    - childbearing potential, provided there is a confirmed negative urine pregnancy test prior to exposure, to rule out pregnancy

  Female subjects of childbearing potential must be willing to use highly effective methods of contraception to avoid causing pregnancy from enrolment and until the last visit (V3).
- Female subjects must not be breastfeeding.

*5.3.2 **Exclusion criteria***

- female who is pregnant or breast-feeding
- Systemic treatment with immunosuppressive drugs, retinoids or corticosteroids within 8 weeks prior to randomization.
- Phototherapy (PUVA or UVB) on the hands within 4 weeks prior to randomization.
- Topical applied treatment with immunomodulators (e.g. pimecrolimus or tacrolimus) or corticosteroids on the hands within 2 weeks prior to randomization.
- Use of other treatment on the hands during the clinical trial except for the use of investigational medicinal product (IMP) and new emollient provided by sponsor during the clinical trial.
- Use of systemic antibiotics or cutaneously applied antibiotics on the hands within 2 weeks prior to randomization.
- Concurrent skin diseases on the hands and/or integument with acute flare and/or skin lesions within the last 8 weeks.
- Current diagnosis of eczema on the integument except for the hands.
- Current diagnosis of exfoliative dermatitis.
- Current diagnosis of glaucoma or cataract.
- Significant clinical infection on the hands that requires antibiotic treatment.
- Known or suspected hypersensitivity to component(s) of the IMP.
- Subjects with history of an immunocompromising disease (e.g. lymphoma, HIV).
- Former participation on this clinical trial.
- Current participation in any other interventional clinical trial.
- Subjects known or, in the opinion of the investigator, are unlikely to comply with the Clinical Trial Protocol (e.g. alcoholism, drug dependency or psychotic state).
- Close affiliation with the investigator or other employees of the trial site (e.g. a close relative) or persons working at LEO Pharma A/S or BAYER Consumer Care GmbH or subject is an employee of Klinik für Hautkrankheiten Jena.

*5.3.3 **Removal of patients from therapy or assessment***

In the following case, a stop of treatment with the IMP/control was predefined as indicated:

- in case of worsening of hand dermatitis with need of increased therapy
- in case of need for forbidden medication (listed under 5.4.7)
- in case of allergically skin reactions
- in case of hypersensitivity
- in case of pregnancy.

It was defined that a patient undergoing discontinuation of study drug treatment (if, in the investigator's or the treating physician's opinion or on request of the sponsor, continuation of the study drug treatment would be detrimental to the patient`s well-being) should not be

considered as being withdrawn from the study. The patient would continue to be observed for endpoints and adverse events and should be assessed at the scheduled follow-ups.

5.4 Treatments

*5.4.1 **Treatments administered***

Topical methylprednisolone aceponate (Advantan®) was used in different vehicles in this trial. Advantan® Cream 0.1% (Methylprednisolone aceponate) serves as IMP; Advantan® Fatty Ointment 0.1% (Methylprednisolone aceponate) was the control. The treatment was topically applicated once a day for 28 days. The aimed daily dose of this application, the *prescribed daily dose,* was defined for each individual patient.

*5.4.2 **Identity of investigational product(s)***

Advantan® Cream 0.1% (Methylprednisolone aceponate) and Advantan® Fatty Ointment 0.1% (Methylprednisolone aceponate) are marketed medicinal products. Details concerning pharmacokinetics are available in the SmPCs (Fachinformation).
Batch: ADHERE/202028
1 g Advantan cream contains 1 mg (0.1%) methylprednisolone aceponate. Further ingredients are Decyl Oleate, Glycerol monostearate (40-55), Cetolstearyl Alcohol, Hard fat, Glycerol fatty acid tri-esters (Softisan 378), Polyoxyl-40-stearate, Glycerol 85% (E422), Disodium edetate Benzyl alcohol, Butylhydroxytoluene (E321), Purified water.
1g Advantan fatty ointment contains 1 mg (0.1%) methylprednisolone aceponate. Further ingredients are White soft paraffin, Paraffin liquid, Microcrystalline wax, Hydrogenated castor oil.
The IMP and the control were provided from the pharmacy of Universitätsklinikum Heidelberg. This institution was responsible for blinding, labelling and packaging processes and the delivery to the Department of Dermatology of the Jena University Hospital.

The trial site was responsible for the storage and the distribution of the IMP and the control to the patients, and the protection against unauthorized access.

The IMP storage happened temperature controlled from 8-25°C. Throughout the study period the temperature never exceeded the above mentioned boundaries.
The IMP and control were only be used in the context of this clinical trial. The expiration date of the medication (30.11.2022) was not achieved, so no medication was used anymore.

Each handout and receipt of IMP/control was documented in the ISF. The responsible investigator ensured the appropriate storage of the IMP/control and only authorized study personnel, as defined in the ISF (delegation and signature log), had access to the trial medication. Unused and returned medication was documented and retained at the trial site.

*5.4.3 **Method of assigning patients to treatment groups***

A central randomization took place in this study. Treatment allocation to IMP or control was performed in a randomized manner. The medication number (= sequence number) was applied on the IMP/control-tubes labelled by the pharmacy of Universitätsklinikum Heidelberg. Each consecutive patient at the trial site was allocated to the treatment with the next medication (=sequence) number. The allocated number was documented as subject ID in the ISF in the subject identification list and in the case report form.
The randomization list for 150 patients in total was generated with the randomization program RITA version 1.31 using permuted blockwise randomization method.
The assignment of chance was fabricated by **Mersenne Twister-Method** (reference: MATSUMOTO and T. NISHIMURA. Mersenne Twister: A 623-dimensionally equidistributed uniform pseudorandom number generator. ACM Trans. on Modeling and Computer Simulation, 8:3–30, 1998).

5.4.4 ***Selection of doses in the study***

The dose of IMP followed strictly the guideline for therapy of chronic hand eczema by Diepgen et al. 2015.

5.4.5 ***Selection and timing of dose for each patient***

The aimed daily dose of the application, the *prescribed daily dose,* was defined as: planned number of applications per day (1) * surface (measured) * aimed amount per application [12,13,14].
According to the above-mentioned guideline the IMP was administered once daily with application before going to bed. The amount of IMP correlated to the hand surface area with eczema measured by FTU (fingertip unit).
Unlimited use of basic care cream throughout the day was encouraged with a two-hour break between the last application of care cream and IMP.

5.4.6 ***Blinding***

The study was performed in a single (investigator) blinded manner. Patient blinding was impossible, since patients reaction on different texture of products is the primary aim of the study. Patients were not informed about their treatment arm, but it must be assumed, that they were able to guess it.

The IMP and the control were provided from the pharmacy of Universitätsklinikum Heidelberg. This institution was responsible for blinding, labelling and packaging processes and the delivery to the Department of Dermatology of the Jena University Hospital.

Unblinding in an emergency was possible at any time. The pharmacy of Universitätsklinikum Heidelberg was responsible for the labelling process of this trial. This institution provided sealed opaque envelopes which contained the treatment allocation for each medication identification number. One set of envelopes was delivered to the trial site, one to the SAE-management of the ZKS Jena. The envelopes were stored at secure locations.

The PI did ensure that all the seals, with exception of those who were used for documented unblinding, have not been broken. There could have been various reasons for unblinding like serious adverse events. In any case of unblinding of the treatment allocation the investigator was promptly document date and time and the reason for the unblinding of the investigational medicinal product. Unblinding for emergency purposes was only be undertaken when knowledge of the allocated treatment is necessary for decisions about the further management of the patient. If possible, the treating physician should have discussed the necessity of unblinding with the PI or his deputy. In every case of unblinding, especially in case of urgent unblinding without possibility of discussion, the SAE-management of the ZKS and PI were to be informed as soon as possible after a case of unblinding.

5.4.7 ***Prior and concomitant therapy***

Standardized use of emollient (Bepanthen® Sensiderm) on the hands during the clinical trial was necessary to avoid bias due to different base therapies. Sponsor made sufficient quantities available to all patients. The frequency of application was recorded and analysed. It was allowed to use any emollient on the rest of the body.

The following medication was forbidden during participation on the study (from day 1 until day 35):

- Systemic treatment with immunosuppressive drugs, retinoids or corticosteroids
- Phototherapy (PUVA or UVB) on the hands
- Topical applied treatment with immunomodulators (e.g. pimecrolimus or tacrolimus) or corticosteroids on the hands
- Use of systemic antibiotics or cutaneously applied antibiotics on the hands

- Significant clinical infection on the hands which requires antibiotic treatment

5.4.8 ***Treatment compliance resp. Treatment adherence***

In this case "compliance" refers specially to adherence. Adherence was the primary endpoint of the study. Adherence and compliance are two terms that are often used in medicine, and it is quite common to see them being used synonymously, although there is a difference between the terms. Adherence refers to the patient, him or herself, adhering to the proper practices of medicine. Compliance is defined as the patient following the instructions of the physician [2].

In this study, adherence was defined as percentage of patients applying at least aimed daily dose.

Prescribed daily dose was defined as: planned number of applications per day (1) * surface (measured) * aimed amount per application and cm^2 [12,13,14].

Truly applicated daily dose was evaluated as individual mean amount per dose * individual mean number of applications per day.

Adherence was assumed, if

- truly applicated daily dose was at least 75% of prescribed daily dose and
- the individual mean number of applications per day was at least 0.85.

Usage of treatment was measured.
Sensors detecting the opening of the containers (medication Event Monitoring Systems, MEMS® TrackCaps, Aardex Ltd, Zug, Switzerland) were used to monitor times and number of openings of the containers. As the MEMS® TrackCaps were designed to fit standard pharmacy bottles and to be used for capsules and tablets, disposable adapters were designed to match the MEMS® TrackCaps and the tube. At the trial site the disposable adapter was locked into position with the MEMS® TrackCap according to Tusa et al. [16]. Patients were instructed to avoid unnecessary openings.
Regular weight measurement (at V1, V2 and V3) of the unused and used containers measured the amount of used medication.

5.5 Efficacy (Effectiveness) and safety (tolerability) variables

5.5.1 ***Efficacy (Effectiveness) and safety (tolerability) measurements assessed and flow-charts***

The following table lists all assessments and schedules, which took place during screening and participation of patients in the trial. Listed assessments were documented in the patient's medical records (source documents), some assessments in the ISF and, for randomized patients in the electronic case report form.

Schedule of study procedures:

Visit	**Screening visit**	**Baseline visit with randomization (V1)**	**Interim visit (V2)**	**Final visit (V3)**	**Follow up (telephone visit)**
Day **Visit window (days)**	up to 28 days prior to V1	1	14 +/- 2	28 +/-2	35 +/- 2
Informed consent	x				
Subject demographics	x				
In-/exclusion criteria	x	x			
Pregnancy test		x			

Concomitant diagnoses + profession	x				
Classification of hand eczema	x				
Concomitant medication/procedures	x	x	x	x	
Medical history	x				
Physical examination	x	x			
Randomization		x			
Collection of Adverse events		x	x	x	x
Vital signs (BP, heart rate, body temperature)		x		x	
Determination of the treatment areas		x			
Clinical assessment of IGA of Disease Severity	x	x	x	x	
Visual analogue scale of pruritus (VAS)		x	x	x	
Clinical assessment of HECSI		x	x	x	
Quality of Life in Hand Eczema Questionnaire QOLHEQ		x		x	
Handout of study medication and emollient		x	x		
Return of study medication			x	x	
Readout of MEMS® Caps			x	x	
Weighing of medication containers		x	x	x	
Measurement of the affected skin area (hand)		x	x	x	

The following activities and/or assessments were performed during study screening (Screening visit) after written informed consent had been obtained:

- Check that patient was informed about study procedures and written informed consent was correctly obtained
- Document subject demographics
- Assess concomitant diagnoses and profession
- Classification of hand eczema
- Assess concomitant medication/procedures
- Assess medical history
- Physical examination
- Clinical assessment of IGA of disease severity

In case screening demonstrated at this visit that a patient was not eligible for study participation (screening failure) participation of this patient in the trial ended here.

Screening of patients and reasons for non-inclusion were documented in the ISF.

The following activities/measurements were performed at Baseline Visit with Randomization (Patient enrolled for study treatment, V1):

- Urine pregnancy test for women with childbearing potential
- Last check of inclusion/exclusion criteria
- Assess concomitant medication/procedures
- Physical examination
- Randomization
- Assess vital signs (BP, heart rate, body temperature)
- Determination of the treatment areas (calculation of hand surface [13,14])
- Clinical assessment of IGA of disease severity [17,18]
- Clinical assessment of HECSI [19]
- Quality of life in hand eczema questionnaire (QOLHEQ) [20]
- Visual analogue scale of pruritus (VAS) [21]
- Handout of study medication and emollient (Bepanthen® Sensiderm)
- Weighing of medication containers
- Measurement of the affected skin

It was possible that the Baseline visit took place at the same day as the screening visit. The patient was left with enough time to consider enrolment of the study. In that case there were no need to collect data twice concerning in-/ exclusion criteria, Concomitant medication/procedures, Physical examination, Clinical assessment of IGA of Disease Severity. The collected data on the screening visit were count for the baseline visit. Adequate documentation was performed.

Dates for all visits following the screening/baseline visit were calculated to occur in relation to this visit, with date of randomization and first treatment being defined as day 1. Randomization and first treatment with IMP/control on the hands was intended to be performed immediately after randomization under the supervision of the investigator or study nurse. The first application acted as a standardized instruction of the patient.

The IMP/control was to be administered once a day until day 28 (end of study treatment). Administration was measured at each application with help of the MEMS® TrackCap.

The following activities and/or assessments were performed at day 14 after start of treatment (Interim Visit):

- Assess concomitant medication/procedures
- Collection of adverse events
- Clinical assessment of IGA of disease severity
- Clinical assessment of HECSI
- Visual analogue scale of pruritus (VAS)
- Quality of life in hand eczema questionnaire (QOLHEQ)
- Return of study medication
- Handout of study medication and emollient (Bepanthen® Sensiderm)
- Weighing of medication containers
- Readout of MEMS® Caps

The following activities and/or assessments were performed at day 28 after start of treatment (Final Visit):

- Assess concomitant medication/procedures
- Collection of adverse events
- Assess vital signs (BP, heart rate, body temperature)
- Clinical assessment of IGA of disease severity
- Clinical assessment of HECSI
- Visual analogue scale of pruritus (VAS)
- Quality of life in hand eczema questionnaire (QOLHEQ)
- Weighing of medication containers
- Return of study medication
- Readout of MEMS® Caps

The following activity was performed at day 35 after start of treatment (Follow-up telephone visit):

- Collection of adverse events

Patients that had received the IMP/control, who had undergone interim visit at day 14, final visit at day 28 and follow-up telephone visit at day 35 were considered as study completers. The investigator provided follow-up medical care for all study completers, or refered them for appropriate ongoing care.

Adverse events (AE) and serious adverse events (SAEs)

A safety management was established, where adverse events in the course of the clinical trial were recorded and assessed.

Definition of adverse events (AE)

An Adverse Event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. According to ICH-GCP an AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

In this trial, the documentation of AEs started with the first administration of the IMP (methylprednisolone aceponate) and ended 7 days after the last dose.

Definition of serious adverse events (SAE)

In the study it was defined that a **serious adverse event** is any adverse event that meets at least one of the following criteria:

- Results in death: an AE that results in death is defined as any patient death within 7 days starting at administration of the last dose of IMP. In this case, this is a SAE with fatal outcome.
- Is life-threatening: this defines an event in which the subject was at risk of death at the time of the event, it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (except hospitalization on basis of surgery that was planned prior to signing consent and admissions as per protocol for a planned medical/surgical procedure).
- Results in persistent or significant disability/incapacity: any substantial disruption of a person`s ability to conduct a normal life.
- Congenital anomaly/birth defect in the offspring of an exposed subject.
- Is to be deemed serious for any other reason, e.g. if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above.

The following events were not considered as SAE although a "serious" criterion is fulfilled:

- Admissions to hospital
  - for diagnostic reasons only
  - for routine control examinations
  - for previously planned operations
  - due to social indication
- SAEs that occur after randomization and before start of treatment with medicinal product.

If one of these events was reported as an SAE, the SAE management of the ZKS Jena contacted the investigator to verify the report. The result of this request was written down. Even when the SAE report was declared as false report, all related documents will be stored in the TMF and declared as false report.

Classification of the AE

The **Severity of adverse events** was classified according to the following 3-point scale:

Severity	**Description**
mild	Clinical symptom or sign; clinical or diagnostic observations only; intervention not indicated
moderate	Clinical symptom or sign, impair daily activities, local or non-invasive intervention may be required
severe	Clinical symptom or sign, leads to severe impairment, disability, inability to perform daily activities, intervention mostly required

If the severity of an event changed, the highest grade of the adverse event had to be documented. If the severity of an adverse event decreases, the highest classification was not allowed to change.

Using the following criteria, the **causality/relationship** of the adverse event to IMP/control was assessed as follows:

Yes = related:

- There is a clinically plausible time sequence between onset of the AE and administration of study treatment
- The AE cannot be reasonably attributed to concurrent/underlying illness, other drugs or procedures
- The event responds to withdrawal of the study medication and/or recurs with re-challenge
- Reasonable temporal relationship between onset of the AE and administration of study treatment
- Other cause could be considered
- The reaction of withdrawal of the study medication and/or the re-challenge are unclear

No = not related

- The time of occurrence of the AE is not reasonably related to administration of study medication
- The AE is to be explained by the patient´s clinical state, underlying disease, concomitant medication, study or non-study procedure

The following factors were considered in the evaluation:

- Temporal context
- Response to discontinuation and reproduction of the IMP/control
- Underlying concomitant and underlying diseases
- Concomitant medication or non-drug treatment
- Pharmacodynamics/pharmacokinetics of the investigational medicinal products

Expectedness of an SAE was decided by the physician based on the current version of the SMPC (summary of product characteristics/Fachinformation). This represents the reference safety information to determine expectedness of serious adverse events for expedited reporting.

Time period and frequency for the assessment of AEs and SAEs

The assessment of AEs and SAEs was performed at all other study visits after application of IMP.

Reporting of AEs

All AEs after the patient started IMP/control administration were promptly documented in the eCRF. Medical or surgical procedures were not documented as AE, but rather the disease that has led to the necessary intervention. Diseases that already exist prior to inclusion in the clinical trial were not documented as an adverse event but as a concomitant disease. Diseases that already existed before, but worsen during study treatment were also documented as AE.

Details of the event must include e.g.:

- AE-term
- Start time point
- Stop time point
- Causality/relationship to study drug
- Severity
- Action taken with study medication
- Action taken with patient
- Outcome of the event
- Seriousness criteria
- SAE number

If the adverse event was serious, the SAE was reported on the appropriate SAE form available in the ISF.

All AEs were followed to resolution or stabilization during the observation period, or were reported as SAEs if they become serious. AEs that completely resolved and then recurred were recorded as a new AE.

The Principal Investigator (PI) was responsible for evaluating all AEs, obtaining supporting documents and determining that documentation of the event is adequate. The PI was able to delegate these duties to Sub-Investigators (documented in the delegation and signature log) and had to assure that these Sub-Investigators are qualified to perform these duties under the supervision of the PI.

Reporting of SAEs

The trial site informed SAE Management, immediately (within 24 hours after knowledge) by means of an SAE form about the occurrence of a serious adverse event. All SAEs, whether related or not related to study medication, were reported after beginning of treatment with IMP/control until 7 days after last administration. The notification was made by a SAE form, which was available in the ISF. The SAE form had to be filled out fully. This form was sent by fax to the SAE management at ZKS Jena.

If further information on the SAE was available later, it had also be reported immediately to the ZKS Jena. The SAE management checked all report forms for completeness and plausibility, and, if necessary, questions had to be asked and tracked.
For all notifications, personal data had to be be pseudonymised (using the patient identification number) prior to transmission to the SAE management. The initial report and all follow-up reports had to be assignable to each other using the patient identification number and gender of the subject. All SAEs had to be followed to resolution or stabilization.
On the SAE form, the reporting investigator rated the event regarding criteria “serious” and “causal relationship”. For each submitted SAE, a physician delegated by sponsor´s representative carried out an assessment based on the criteria of "serious", "causal relationship" and "expectedness".

Reporting of Suspected Unexpected Serious Adverse Reaction, SUSARs

Specifically, every SAE, which was assessed by the sponsor to be suspected to be related to the study drug and assessed to be either “unexpected” or “unexpected with regard to outcome or severity of the event”, according to the relevant SmPC for Advantan® Cream 0.1% (Methylprednisolone aceponate) und Advantan® Fatty Ointment 0.1% (Methylprednisolone aceponate), had to be reported as SUSAR.
In case of a SUSAR (Suspected Unexpected Serious Adverse Reaction) the resulting report had tobe sent by the Sponsor to the BfArM, ethics committee and PI of this clinical trial. Before reporting the SUSAR, the case had to be unblinded.
Fatal or life-threating SUSARs had to be report as soon as possible, but not later than 7 days. Further information to these SUSARs had to be report as follow up within additional 8 days. All other SUSARs had to be report no later than 15 days.

Pregnancy

If, after the first dose of study medication, it was subsequently discovered that the patient or the partner of the patient is pregnant or may have been pregnant at the time of study exposure, including during 7 days after last study medication administration, the investigator had to immediately notify the SAE management. Therefore, the investigator had to complete a Pregnancy Form (which was available in the ISF) and forward it to the SAE management within 24 hours after knowledge of the event and in accordance with SAE reporting procedures.

Annual safety report

Annual safety reports (DSUR) were presented to the responsible Ethic Committee (EC) and national competent authority (BfArM) in accordance with ICH guideline E2F and in the EU Clinical Trial Directive 2001/20/EC.

5.5.2 ***Appropriateness of measurements***

All results were measured by validated scores for chronic hand eczema as

- IGA (Investigator Global Assessment [16,17]
- HECSI (Hand Eczema Severity Index) [19]
- VAS (visual analogue scale) [21]
- QOLHEQ (Quality of Life in Hand Eczema Questionnaire) [20].

5.5.3 ***Primary efficacy (effectiveness) variable(s)***

In this study adherence was defined as percentage of patients applying at least aimed daily dose.

Prescribed daily dose was defined as: planned number of applications per day (1) * surface (measured) * aimed amount per application and cm^2 [12,13,14].

Truly applicated daily dose was evaluated as individual mean amount per dose * individual mean number of applications per day.

Adherence was assumed, if

- truly applicated daily dose was at least 75% of prescribed daily dose and
- the individual mean number of applications per day was at least 0.85.

The improvement of Hand Eczema was the secondary objective. So the secondary endpoint was efficacy as measured by improvement of Hand Eczema Severity Index (HECSI) and Investigator´s Global Assessment (IGA) after a 4-week treatment period [17,18,19].

5.5.4 ***Drug concentration measurements***

Not applicable.

5.6 Data quality assurance

The ZKS Jena performed monitoring according to the local standard operating procedures (SOPs) of ZKS Jena. Monitoring in general was performed on-site. Before the site started with patient enrollment, an initiation visit and training was conducted to ensure the investigator and study team are capable to conduct study specific tasks and further understand and accept the obligations during the clinical investigation. The purpose of the regular monitoring visits was primarily to ensure the protection of the rights and safety of the participating subjects. At the end of the trial, a close-out visit was conducted. The extent and manner of the monitoring visits were described in detail in the study-specific monitoring plan that was specified in accordance with the sponsor requirements.

Investigator responsibilities are set out in the ICH guideline for GCP and in the EU Clinical Trial Directive 2001/20/EC and 2005/28/EC. Representatives of the sponsor that are commissioned for the trial (monitor) were allowed to visit all study site locations periodically to assess the data quality and study integrity. A valid written informed consent of a patient was a precondition for the monitor to have access to all source documents of the patient needed to verify the entries in the CRF and other protocol related documents. On site, the monitor reviewed study records and directly compared them with source documents, discussed the conduct of the study with the investigator, and verified that the facilities remain acceptable. Each monitoring site visit was documented by a written monitoring report to the PI/sponsor's representative.

5.7 Statistical methods planned in the protocol and determination of sample size

5.7.1 ***Statistical and analytical plan***

5.7.1.1 Analysis populations

Full Analysis Set (FAS):

All treated subjects, i.e. all subjects who received at least one dose of IMP/control, were to be included in the FAS and to be analyzed with regard to demography, protocol deviations, baseline characteristics, drug exposure, safety and efficacy parameters according the intention-to-treat principle. Patients were to be analyzed as randomized (Intention-to-treat principle, ITT). The analysis of the FAS was to be regarded the primary analysis.

Per-Protocol Analysis Set (PPS):

Patients without major protocol deviations were to be included in the PPS. A sensitivity analysis for the PPS was to be performed for selected demography and baseline characteristics (i.e. age, sex), primary efficacy and selected secondary efficacy parameters.

Major protocol deviations were defined as protocol deviations, which might influence the primary efficacy. Classification of protocol deviations was to be assessed by the PI and statistician in a data review meeting without knowledge of efficacy results prior to data base closure. For predictable protocol deviations, assessment was to be performed a priory independent from the individual patient data.

Safety Analysis Set (SAS):

The safety analysis set was to include all patients of the FAS. For safety purposes, patients were to be analyzed as treated.

5.7.1.2 General considerations

For all available variables, at least adequate descriptive statistics including at least mean, standard deviation, minimum, quartiles with median and maximum for metric data and frequency analysis for non-metric data were to be provided. Where appropriate, change to baseline/shift analysis was to be evaluated. Analysis was to be performed by treatment group and in total.

5.7.1.3 Analysis of study population/Baseline descriptive statistics

Adequate descriptive statistics including at least mean, standard deviation, minimum, quartiles with median and maximum for metric data and frequency analysis for non-metric data.

Analysis was to be performed by treatment group and in total and was to be provided for all baseline and population describing data including but not restricted to demographic data, compliance/treatment administration data, concomitant medication, protocol deviations.

5.7.1.4 Analysis of primary efficacy endpoint

Prescribed daily dose was defined as: planned number of applications per day (1) * surface (measured) * aimed amount per application (mg/cm²) [12,13,14] .

Truly applicated daily dose was to be evaluated as individual mean amount per dose (measured) * individual mean number of applications per day (measured).

Adherence was to be assumed, if

- truly applicated daily dose is at least 75% of prescribed daily dose and
- the individual mean number of applications per day is at least 0.85

Proportion of adherent patients was to be compared by Fisher's exact test with significance level alpha=0.05 (2-sided).

5.7.1.5 Analysis of secondary efficacy endpoints

Secondary outcome was to be efficacy as measured by improvement of Hand Eczema Severity Index (HECSI) and Investigator´s Global Assessment (IGA) after a 4-week treatment period. Secondary parameters and all other parameters were to be analyzed by means of descriptive statistics.

Adequate descriptive statistics including at least mean, standard deviation, minimum, quartiles with median and maximum for metric data and frequency analysis for non-metric data were to be provided. Where appropriate, change to baseline/shift analysis were to be evaluated.

5.7.1.6 Interim Analyses

Not planned.

5.7.1.7 Evaluation of safety and tolerability

Adverse events were to be listed by the unique patient ID. Frequency of adverse events, serious adverse events and relationship of adverse events were to be provided.

5.7.1.8 Presentation of results and mandatory reports

The results of the statistical analyses were to be provided as a statistical report comprising tables of all planned evaluations.

*5.7.2 **Determination of sample size***

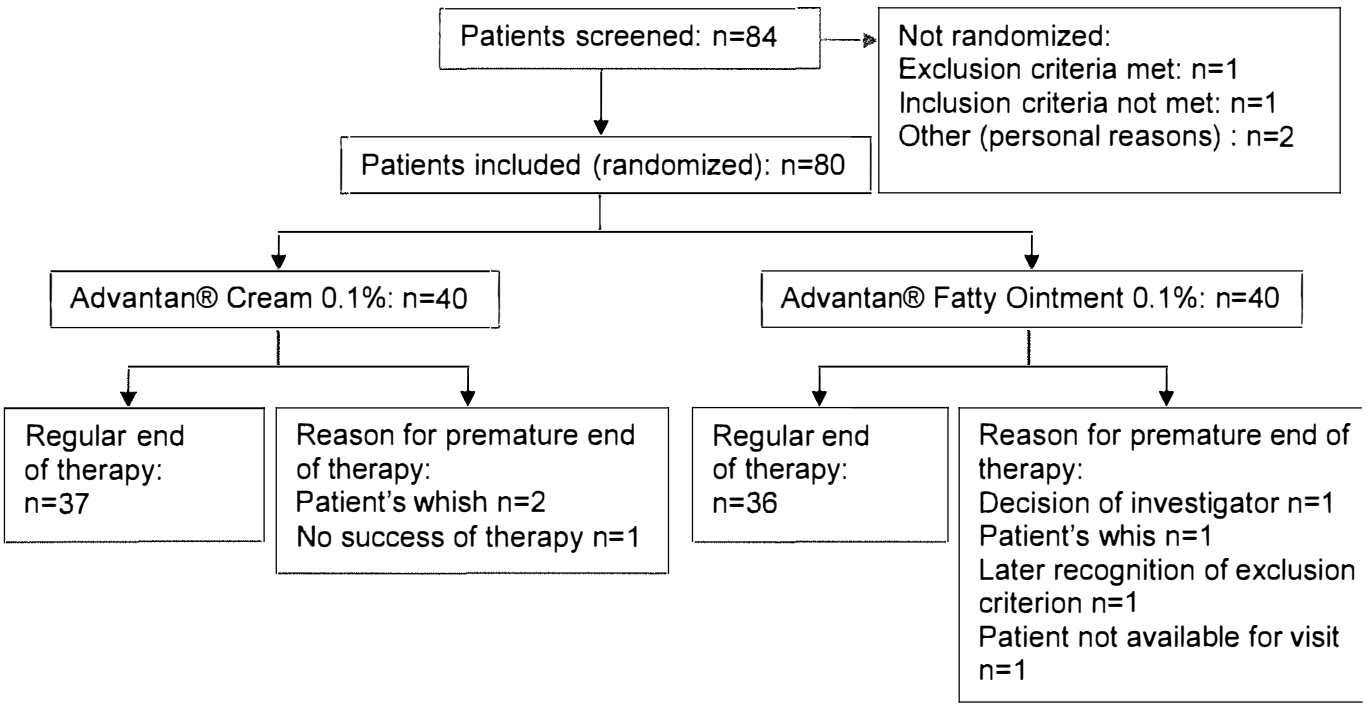
Assuming an adherence of 90% in patients treated with Advantan® Cream and of 60% in patients treated with Advantan® Fatty Ointment, a two-group two-sided Fisher's exact test of equal proportions at significance level alpha=0.05 with 36 patients per group has a power of 80% to detect a difference in adherence.
The power analysis was performed with nQuery Advisor 7.0.
Taking into account a dropout rate of 10%, 80 Patients (40 per group) were to be included.

5.8 Changes in the conduct of the study or planned analyses

A non-substatial formal amendment concerning the exclusion criteria was conducted in 2021. The exclusion criteria of „Close affiliation with the investigator or other employees of the trial site (e.g. a close relative) or persons working at LEO Pharma A/S or BAYER Consumer Care GmbH or subject is an employee of sponsor" was changed that not all employees of sponsor but only employees of the Department of Dermatology are excluded of study participation to improve subject recruitment.

6 Study population

6.1 Disposition of patients



6.2 Protocol deviations

One serious deviation occurred because of inclusion of a patient meeting an exclusion criteria. The error was noticed shortly after inclusion of the patient. The patient was then excluded and the incident documented as such. Throughout the study, we documented only a few other protocol deviations, most of them regarding the study visit dates. None of these protocol deviations was major with respect to statistical analysis of data.

7 Efficacy (Effectiveness) evaluation

7.1 Data sets analyzed

80 patients were randomized in the two treatment groups, 40 each. All patients available were included in the analysis, no major protocol deviations were observed, hence no additional per-protocol analysis was performed. Data for primary efficacy analysis were available for 75 patients, missing data were handled as such and not replaced by estimates.

7.2 Demographic and other baseline characteristics

Patients included had an age of (mean ± standard deviation) 43.8 ± 13.9 years with no remarkable difference between the treatment groups. In both groups, the majority of patients was female (about 61 %). About 34 % of the patients were active smokers in total. Both groups showed a different distribution of smokers (cream group 50%, in the fatty ointment group 42.5%) with the majority presenting with a moderate consumption of 5-10 cigarettes daily (about 41%) and about a further third a consumption of 11-20 cigarettes daily (33.3%, see table 5 and 6). Looking at the profession of patients about a quarter was working in offices and in management (23.8%), about 10% each were working in industry and in a care profession such as nurse (11.3%). The percentage of people working in a bakery and as a hairdresser with hand intensive work was low about 1.3% each. Other professions were present in about half of our patients without remarkable difference in the treatment groups (see table 7). No professional trigger factors for hand eczema symptoms were reported by almost two thirds of our patients (about 61%). The majority of reported trigger factors were irritative such as wet work and water contact with 35.0 % in the cream group and 40.0 % in the fatty ointment group. Almost 3 quarters of the patients reported about wet (humid) work (73.8%) and about 60% to have glove work (58.8%) both without remarkable difference between the groups. The mean duration of wet work comprised of (mean ± standard deviation) 2.9 ± 2.8 and of continuous time work with gloves (mean ± standard deviation) 2.6 ± 2.7 hours.
The mean number of hand washing per day was about (mean ± standard deviation) 11.2 ± 8.0 times without remarkable difference between the groups.

Most patients presented with a cumulative-toxic (cream / fatty ointment: 75.0% / 77.5%) and atopic (65.0% / 62.5%) hand eczema and a dyshidrosiform morphology (60.0% / 65.0%). Contact allergic etiology was less common (20.0% / 7.5%) as well as hyperkeratotic-rhagadiform morphology (25.0% / 37.5%). Only 2 patients (5.0%) presented with a different etiology than the above. Dermatological comorbidities were found in only a third of our patients (31.3%)
According to IGA Score 80% were mild at baseline with a slight difference in the groups (85% in the IMP (cream) group and 75% in the control (fatty ointment) group). Three quarter of our patients were previously treated for their hand eczema (77.5%) in total. The large majority of both groups had received topical treatment with corticosteroids (70.0% and 77.5%) and calcineurininhibitors (45.0% and 45.0%). 40% and 30% of the patients have had a previous light therapie and only a few an oral or parenteral treatment (see table 16). At baseline overall health was explored by a general physical examination including heart, lung, abdomen, neurological state (see table 17)

	Advantan® Cream 0.1% (n=40)	Advantan® Fatty Ointment 0.1% (n=40)	Total
Age [years]*	43.2 ± 14.6	44.4 ± 13.4	43.8 ± 13.9
Male sex**	14 (35.0%)	17 (42.5%)	31 (38.8%)
Smoker**	10 (25.0%)	17 (42.5%)	27 (33.8%)
No Professional trigger factors**	26 (65.0%)	23 (57.5%)	49 (61.3%)
Humid work	29 (72.5%)	30 (75.0%)	59 (73.8%)
Work with gloves	24 (60.0%)	23 (57.5%)	47 (58.8%)
Continuous humid work [hours]*	2.6 ± 2.6	3.1 ± 3.0	2.9 ± 2.8
Continuous time work with gloves [hours]*	2.2 ± 2.5	3.1 ± 2.8	2.6 ± 2.7
Hand washing per day*	10.9 ± 6.3	11.5 ± 9.4	11.2 ± 8.0
Type of hand eczema***			
Atopic	26 (65.0 %)	25 (62.5 %)	
Cumulativ-toxic	30 (75.0 %)	31 (77.5 %)	
Contact allergic	8 (20.0 %)	3 (7.5 %)	
Hyperkeratotic-rhagadiform	10 (25.0 %)	15 (37.5 %)	
Dyshidrosiform	24 (60.0 %)	26 (65.0 %)	
Other etiology	2 (5.0 %)	-	
Severity acc. IGA**			
Mild	34 (85.0 %)	30 (75.0 %)	64 (80.0 %)
Moderate	6 (15.0 %)	10 (25.0 %)	16 (20.0 %)
Previous therapy for hand eczema**	30 (75.0%)	32 (80.0%)	62 (77.5%)

TT1: Important baseline chracteristics
Source: T 5, 6, 7, 8, 9, 10, 11, 13, 15.
* mean ± standard deviation ** n (%) *** n (%), multiple choice possible

7.3 Measurements of treatment compliance

See primary efficacy.

7.4 Efficacy (Effectiveness) analysis and tabulation of individual patient data

7.4.1 Analysis of efficacy (effectiveness)

The primary outcome for adherence to treatment was compared via Fisher's exact test. With a complete sample size of 75 patients we assessed an overall adherence of 48.0% in total with 42.1% in the IMP group and 54.1% in the control group. The difference between both groups showed no significance (p= 0.3588).

We measured from baseline (BL) to V3 the mean daily dose used as (mean ± standard deviation) 515 ±352.7 mg and the mean used daily dose per patient with a total of (mean ± standard deviation) 14693.8 ± 9868.3 mg with a remarkable but not significant difference between the groups (see table 20 and below). The mean number of openings of the MEMS® Cap of IMP and control from BL to V3 was 0.81 ± 0.28 and the mean total number of openings 23.4 ± 7.9 without remarkable difference between the groups.

We looked at the amount taken by the patients via the difference of used dose minus the prescribed dose. The descriptive analysis showed from V1 to V2 a mean amount of 411.2 ± 670.3 mg of IMP/control that was used without remarkable difference between the groups. From V2 to V3 we measured a mean usage of 332.1 ± 832.8 mg more than prescribed.

	Advantan® Cream 0.1%	Advantan® Fatty Ointment 0.1%	Total
Adherence (≥ 75% daily dose and ≥ 0.85 applicatiens per day) **	16 of 38 (42.1%)	20 of 37 (54.1%)	36 of 75 (48.0%)
Mean daily dose used [mg] *	607.0 ± 398.6 [476-738.0]	420.4 ± 272.5 [329.5-511.2]	515.0 ±352.7 [433.8-596.1]
Total dose used [mg]	17306.6 ± 11205.9 [13674.1-20939.1]	12012.2 ± 7515.5 [9541.9-14482.5]	14693.8 ± 9868.3 [12453.9-16933.6]
Mean number of openings per day *	0.79 ± 0.26 [0.71-0.88]	0.83 ± 0.31 [0.73-0.93]	0.81 ± 0.28 [0.75-0.87]
Total number of openings *	23 ± 7.5 [20.6-25.4]	23.8 ± 8.4 [21.0-26.6]	23.4 ± 7.9 [21.6-25.2]
Difference: used dose – prescribed dose [mg] *			
1st fortnight	552.6 ± 754.2 [491.6-613.7]	261.1 ± 528.6 [217.1-305.2]	411.2 ± 670.3 [372.3-450.1]
2nd fortnight	416.0 ± 895.2 [340.1-491.8]	246.2 ± 754.9 [181.4-311.0]	332.1 ± 832.8 [281.9-382.3]

TT2 Adherence results
Source: T 18, 19, 20.
* mean ± standard deviation [95% confidence interval]
** n (%), p=0.3588 (p-value of group comparison by fisher's exact test)

We measured a basic care cream (Bepanthen® Sensiderm) use from baseline (BL) to V3 the mean daily dose used as (mean ± standard deviation) 2042.7 ± 1216.9 mg and the mean used dose per patient with a total of (mean ± standard deviation) 58112.4 ± 35066.7 mg without a remarkable difference between the groups concerning the latter. In total the IMP group used about 100-200 g less than the Control group (not significant, see table 22 and below).

The mean number of openings of the MEMS® Cap of IMP and control from BL to V3 was 2.29 ± 1.84 and the mean total number of openings 66.7 ± 55.1 with slightly (not significant) more openings in the control group. The total of openings reveals a use of 2 to 3 times basic care cream per day.

	Advantan® Cream 0.1%	Advantan® Fatty Ointment 0.1%	Total
Bepanthen® * Mean daily dose used [mg]	1979.3 ± 1196.5 [1574.4-2384.1]	2114.0 ± 1254.7 [1161.6-2566.4]	2042.7 ± 1216.9 [1748.1-2337.2]
Bepanthen® * Total dose used [mg]	58121.6 ± 35008.7 [46449.1-69794.1]	58102.7 ± 35639.0 [45860.3-70345.1]	58112.4 ± 35066.7 [49872.2 -66352.7]
Bepanthen® * Mean number of openings per day	2.18 ± 1.73 [1.61-2.75]	2.4 ± 1.97 [1.73-3.07]	2.29 ± 1.84 [1.86-2.72]

Bepanthen® * Total number of openings	64.3 ± 53.4 [46.8-81.9]	69.2 ± 57.4 [49.8-88.6]	66.7 ± 55.1 [53.9-79.4]

TT3 Adherence measurements
Source: T 22.
mean ± standard deviation [95% confidence interval] * short for Bepanthen® Sensiderm

As an unplanned sensitivity analysis, we analyzed adherence with a generalized linear model analysis with covariates Bepanthen® Sensiderm use, frequency and amount. This analysis showed a better adherence to study treatment, independent of the formulation, in patients using basic care cream more often (p=0.0032), however, correction for this covariate did not reveal any difference in the adherence between the treatment groups.

Regarding the second endpoint we see an overall improvement of hand eczema from BL to V3 with only a few exceptions.
The mean IGA score showed a total of 63 (78.8%) of patients with a mild and 17 (21.3%) with a moderate hand eczema at BL. At V3 the IMP group patients presented with a clear 2 (5.1%), 17 (43.6%) with an almost clear, 19 (48.7%) with a mild and 1 (2.6%) with a moderate hand eczema according to IGA. The control group showed with a clear 2 (5.3%), 11 (28.9%) with an almost clear, 22 (57.9%) with a mild and 3 (7.9%) with a moderate finding.
The mean HECSI showed only half the severity from BL to V3 23.4 ± 17.6.7 to 12.5 ± 16.0.
Improvement of itching was measured with half the VAS score at V3 (13.0 ± 20.4) than at BL (26.3 ± 26.4). Improvement of both HECSI and VAS from BL to V3 showed no remarkable difference (see table below).
Overall Quality of life improved from 41.3 ± 20.6 at BL to 24.6 ± 21.1 at V3.

		Advantan® Cream 0.1 %	Advantan® Fatty Ointment 0.1%	Total
IGA **	V1 Mild Moderate	 34 (85.0%) 6 (15.0%)	 29 (72.5%) 11 (27.5%)	 63 (78.8%) 17 (21.3%)
	V3 Clear Almost clear Mild Moderate	 2 (5.1%) 17 (43.6%) 19 (48.7%) 1 (2.6%)	 2 (5.3%) 11 (28.9%) 22 (57.9%) 3 (7.9%)	 4 (5.2%) 28 (36.4%) 41 (53.2%) 4 (5.2%)
HECSI*	BL/V1	21.4 ± 14.4 [16.8-26.0]	25.3 ± 20.4 [18.8-31.8]	23.4 ± 17.6.7 [19.4-27.3]
	V2	13.2 ± 14.4 [8.5-17.8]	18.7 ± 22.5 [11.2-26.2]	15.9 ± 18.8 [11.6-20.2]
	V3	9.6 ± 9.5 [6.5-12.7]	15.6 ± 20.4 [8.9-22.3]	12.5 ± 16.0 [8.9-16.2]
VAS*	BL/V1	30.4 ± 28.1 [21.4-39.4]	22.1 ± 24.2 [14.4-29.8]	26.3 ± 26.4 [20.4-32.1]
	V2	16.3 ± 22 [9.2-23.5]	14.4 ± 20.0 [7.7-21.1]	15.4 ± 21.0 [10.6-20.2]
	V3	12.3 ± 19.2 [6.1-18.5]	13.6 ± 21.9 [6.4-20.8]	13.0 ± 20.4 [8.3-17.6]
QOLHEQ*	BL/V1	44.2 ± 18.5 [38.3-50.1]	38.4 ± 22.4 [31.2-45.6]	41.3 ± 20.6 [36.7-45.9]
	V2	28.0 ± 21.5 [21.0-35.0]	24.1 ± 21.5 [16.9-31.3]	26.1 ± 21.5 [21.2-31.0]
	V3	25.2 ± 19.3	23.9 ± 23.0	24.6 ± 21.1

		[18.9-31.4]	[16.4-31.5]	[19.8-29.3]

TT4 Efficacy results
Source: T 25, 26, 28, 29.
* mean ± standard deviation [95% confidence interval] ** n (%)

*7.4.2 **Efficacy (Effectiveness) conclusions***

We can conclude that overall adherence was poor in both study groups towards the prescribed treatment. Nevertheless, hand eczema improved over time along with pruritic sensation and quality of life. Looking at variables, we observed that patients who tended to use high amounts of basic care cream tended to be more adherent to the prescribed treatment.

8 Safety (Tolerability) evaluation

8.1 Adverse events (AE)

In total, we observed only few adverse events throughout the investigational period. The majority of the patients stayed AD free: from Baseline visit to V2 we reported no AE for 93.4%, from V2 to V3 83.1% and from V3 to FU 96.1% without remarkable difference between the groups. Of all adverse events, the majority concerned non cutaneous conditions, with acute infections, e.g. common cold, and orthopedic conditions, e.g. back pain, representing the largest number. Of the cutaneous AE we reported on one exanthema and one acute urticaria, both linked to spontaneously occurring infectious triggers.
In the IMP group, one patient and in the control group 2 patients experienced a deterioration of the hand eczema under AD-HERE treatment.
We counted one spontaneous pregnancy that was conceived within the period between V2 and V3. The patient had a completed family planning and aborted the pregnancy on own wish and unrelated to any study procedures within the first trimenon.
We assessed three AEs as being serious adverse events (SAEs), all of them resolved without permanent damage to the patient. Two of them happened as accidents, one of them being a spontaneous syncope. All were unrelated to the study procedure and to IMP/Control application.
Deaths, other serious adverse events, and other significant adverse events
No deaths occurred during the study course. We observed 3 SAEs, one case of traumatic brain injury (outcome recovered/resolved), one case of rib fracture (outcome recovered/resolved) and one case of syncope (outcome recovered/resolved). All three were assessed as not related to the study medication.

8.2 Clinical laboratory evaluation

Not applicable

8.3 (Vital signs, physical findings and other observations related to safety (tolerability)

No relevant changes in blood pressure, heart rate and auricular temperature were observed. For details see T58.

8.4 Safety (Tolerability) conclusions

We observed no relevant safety issues concerning IMP and control throughout the whole investigational period.

9 Discussion and overall conclusions

Within the AD-HERE study, improvement of hand eczema was shown throughout the course of the study according to clinical scores widely used for hand eczema assessment. There were no safety concerns associated with the study treatment (see 8.1, 8.2 and 8.5).
Poor treatment adherence was measured with no significant difference between the IMP and the control group (see 7.4).
Our findings are consistent with pre-existing data and literature, indicating that overall adherence to topical treatment in chronic dermatoses is poor. The majority of studies dealing with adherence to topical treatment assessed psoriasis, followed by atopic dermatitis. One remarkable study dealing with vesicular hand eczema treatment adherence assessed not only topical, but also systemic treatment adherence subjectively by the Morisky Medication Adherence Scale. 50% of the patients presented with a medium treatment adherence in a course of three months and greater reduction of QOLHEQ was associated with a better adherence Of the highly adherent patients, the significant majority was female and used systemic treatment [22].
This study's results are not directly comparable to ours due to the fact of subjective adherence measurement and a mixture of topical and systemic treatment. It underlines, though, our finding of poor treatment adherence to topical therapy in hand eczema patients.
In contrast, the present study showed no adherence dependence on demographic features. Our assessment suggested that patients who used more basic care cream were also more adherent to the topical drug.
A limitation to the present study might be the relatively short observation period, considering that in long-term studies with periods of over a year a deterioration of treatment adherence have been observed and knowing that a clinical study setting might improve treatment adherence [23,24].

We conclude that treatment adherence in chronic hand eczema is not significantly dependent on the galenic vehicle of the preparation. The vehicle's galenics has been one of the factors named to improve treatment adherence in the literature [2,3]. We also conclude the use of methylprednisolone aceponate 0,1% cream or fatty ointment along with basic care (first-line treatment of chronic hand eczema according to guideline [1]) is a safe and effective treatment for hand eczema of various etiologies.

10 Tables, figures and graphs referred to, but not included in the text

10.1 Demographic data

T 5 Demography: Descriptive analysis of age - FAS, N total = 80

	Treatment		
Age [years]	Advantan® Cream 0.1%	Advantan® Fatty Ointment 0.1%	Total
N	40	40	80
NMiss	0	0	0
Mean	43.2	44.4	43.8
StdDev	14.6	13.4	13.9
Min	18	22	18
P25	31	33	32
Median	43	48	46
P75	58	56	57
Max	65	65	65
LCLM	38.5	40.1	40.7
UCLM	47.8	48.7	46.9

LCLM / UCLM: lower / upper limit of 95% confidence interval

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T 6 Demography: Frequency analysis of gender, smoking behaviour, pregnancy test - FAS, N= 80

		Treatment					
		Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
		N	%	N	%	N	%
Sex	Male	14	35.0	17	42.5	31	38.8
	Female	26	65.0	23	57.5	49	61.3
Smoker	No	30	75.0	23	57.5	53	66.3
	Yes	10	25.0	17	42.5	27	33.8
Smoking in history	Missing/na	10	0.0	17	0.0	27	0.0
	No	19	63.3	17	73.9	36	67.9
	Yes	11	36.7	6	26.1	17	32.1
Amount of smoking	Missing/na	30	0.0	23	0.0	53	0.0
	1-4 cigarettes/day	2	20.0	4	23.5	6	22.2
	5-10 cigarettes/day	5	50.0	6	35.3	11	40.7
	11-20 cigarettes/day	2	20.0	7	41.2	9	33.3
	Unknown	1	10.0	0	0.0	1	3.7
Pregnancy test performed	No	26	65.0	26	65.0	52	65.0
	Yes	14	35.0	14	35.0	28	35.0
Pregnancy test result	Missing/na	26	0.0	26	0.0	52	0.0
	Negativ	14	100.0	14	100.0	28	100.0

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T 7 Medical history: Frequency analysis of job anamnesis details - FAS, N= 80

		Treatment					
		Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
		N	%	N	%	N	%
Current profession	Bakery	1	2.5	0	0.0	1	1.3
	Industry	3	7.5	6	15.0	9	11.3
	Office/management	11	27.5	8	20.0	19	23.8
	Care profession	4	10.0	5	12.5	9	11.3
	Hairdresser	1	2.5	0	0.0	1	1.3
	Other	20	50.0	21	52.5	41	51.3
Professional trigger factors?	No	26	65.0	23	57.5	49	61.3
	Yes	14	35.0	17	42.5	31	38.8

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T 8 Medical history: Number of professional trigger factors and number and % of patients by factor - FAS, N= 80

	Treatment	
Type	Advantan® Cream 0.1%	Advantan® Fatty Ointment 0.1%
0 Type	26 (65.0 %)	23 (57.5 %)
1=Mechanical	4 (10.0 %)	9 (22.5 %)
2=Chemical	3 (7.5 %)	6 (15.0 %)
3=Physical	3 (7.5 %)	1 (2.5 %)
4=Irritative (incl. wet work/water contact)	14 (35.0 %)	16 (40.0 %)

*Multiple choice possible, hence patient numbers do not sum up to 100%

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T 9 Medical history: Frequency analysis of eczema and job anamnesis details - FAS, N= 80

		Treatment					
		Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
		N	%	N	%	N	%
Worsening during work time	No	25	62.5	22	55.0	47	58.8
	Yes	14	35.0	17	42.5	31	38.8
	Unknown	1	2.5	1	2.5	2	2.5
Improvement during work time	No	37	92.5	37	92.5	74	92.5
	Yes	1	2.5	2	5.0	3	3.8
	Unknown	2	5.0	1	2.5	3	3.8
Healing during leisure time	No	27	67.5	24	60.0	51	63.8
	Yes	12	30.0	15	37.5	27	33.8
	Unknown	1	2.5	1	2.5	2	2.5
Worsening during leisure time	No	35	87.5	29	72.5	64	80.0
	Yes	4	10.0	10	25.0	14	17.5
	Unknown	1	2.5	1	2.5	2	2.5
Humid work	No	11	27.5	10	25.0	21	26.3
	Yes	29	72.5	30	75.0	59	73.8
Work with gloves	No	16	40.0	17	42.5	33	41.3
	Yes	24	60.0	23	57.5	47	58.8
Skin stressing leisure activities	No	24	60.0	20	50.0	44	55.0
	Yes	16	40.0	20	50.0	36	45.0

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T 10 Medical history: Descriptive analysis of job anamnesis details - FAS, N total = 80

		Treatment		
Parameter	**Statistic**	**Advantan® Cream 0.1%**	**Advantan® Fatty Ointment 0.1%**	**Total**
Continuous humid work time [h]	N	29	30	59
	NMiss	11	10	21
	Mean	2.6	3.1	2.9
	StdDev	2.6	3	2.8
	Min	0.3	0.3	0.3
	P25	0.8	0.5	0.5
	Median	1.5	2	2
	P75	3.5	5	4
	Max	9	10.5	10.5
Continuous time work with gloves [h]	N	24	23	47
	NMiss	16	17	33
	Mean	2.2	3.1	2.6
	StdDev	2.5	2.8	2.7
	Min	0.3	0.3	0.3
	P25	0.5	0.8	0.5
	Median	1	2.5	1.5
	P75	2.3	4	4
	Max	9	10	10
Hand washing/day	N	40	40	80
	NMiss	0	0	0
	Mean	10.9	11.5	11.2
	StdDev	6.3	9.4	8
	Min	2	2	2
	P25	7	6	7
	Median	10	9.5	10
	P75	15	10.5	12.5
	Max	30	50	50

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T 11 Medical history: Number of hand eczema type and number and % of patients by type of hand eczema - FAS, N= 80

	Treatment			
	Advantan® Cream 0.1% , N = 40		Advantan® Fatty Ointment 0.1%, N = 40	
Type of hand eczema	Type	N (%) Patients*	Type	N (%) Patients*
Atopic	26	26 (65.0 %)	25	25 (62.5 %)
Cumulativ-toxic	30	30 (75.0 %)	31	31 (77.5 %)
Contact allergic	8	8 (20.0 %)	3	3 (7.5 %)
Hyperkeratotic-rhagadiform	10	10 (25.0 %)	15	15 (37.5 %)
Dyshidrosiform	24	24 (60.0 %)	26	26 (65.0 %)
Other etiology	2	2 (5.0 %)	.	

*Multiple choice possible, hence patient numbers do not sum up to 100%

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T 12 Medical history: Descriptive analysis of time since first diagnosis of hand eczema - FAS, N total = 80

	Treatment		
Time since 1st diagnosis of hand eczema [months]	Advantan® Cream 0.1%	Advantan® Fatty Ointment 0.1%	Total
N	39	40	79
NMiss	1	0	1
Mean	177.23	148.77	162.82
StdDev	167.89	146.08	156.87
Min	4.52	3.18	3.18
P25	48.56	43.98	48.56
Median	103.48	122.11	116.36
P75	251.51	178.62	218.23
Max	524.16	612.89	612.89

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T 13 Medical history: Frequency analysis of dermatological anamnesis details - FAS, N= 80

		Treatment					
		Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
		N	%	N	%	N	%
Severity acc. IGA	Mild	34	85.0	30	75.0	64	80.0
	Moderate	6	15.0	10	25.0	16	20.0
Known atopy	No	10	25.0	13	32.5	23	28.8
	Yes	30	75.0	27	67.5	57	71.3
Atopic dermatitis	Missing/na	10	0.0	13	0.0	23	0.0
	No	16	53.3	10	37.0	26	45.6
	Yes	14	46.7	17	63.0	31	54.4
Allergic rhinokonjunctivitis	Missing/na	10	0.0	13	0.0	23	0.0
	No	17	56.7	12	44.4	29	50.9
	Yes	13	43.3	15	55.6	28	49.1
Allergic asthma	Missing/na	10	0.0	13	0.0	23	0.0
	No	26	86.7	20	74.1	46	80.7
	Yes	4	13.3	7	25.9	11	19.3
Food allergy	Missing/na	10	0.0	13	0.0	23	0.0
	No	23	76.7	22	81.5	45	78.9
	Yes	7	23.3	5	18.5	12	21.1
Positive family history	Missing/na	10	0.0	13	0.0	23	0.0
	No	4	13.3	6	22.2	10	17.5
	Yes	26	86.7	21	77.8	47	82.5
Eczema at other localization than hands	Never	14	35.0	12	30.0	26	32.5
	In previous time	26	65.0	28	70.0	54	67.5
Other dermatological disease/ new dermatological disease	No	26	65.0	29	72.5	55	68.8
	Yes	14	35.0	11	27.5	25	31.3

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T 14 Medical history: Frequency analysis of allergy details - FAS, N= 80

		Treatment					
		Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
Question	Answer	N	%	N	%	N	%
Known/new Typ I and/or Typ IV allergy	No	16	40.0	15	37.5	31	38.8
	Yes	24	60.0	25	62.5	49	61.3
Allergy pass available	No	21	52.5	22	55.0	43	53.8
	Yes	19	47.5	18	45.0	37	46.3
Prick test during last 3 years	No	35	87.5	35	87.5	70	87.5
	Yes	5	12.5	5	12.5	10	12.5
Prick test result relevant for hand eczema	Missing/na	35	0.0	35	0.0	70	0.0

		Treatment					
		Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
Question	Answer	N	%	N	%	N	%
	No	4	80.0	4	80.0	8	80.0
	Yes	1	20.0	1	20.0	2	20.0
Epicutan testduring last 3 years	No	33	82.5	35	87.5	68	85.0
	Yes	7	17.5	5	12.5	12	15.0
Epicutan test result relevant for hand eczema	Missing/na	33	0.0	35	0.0	68	0.0
	No	1	14.3	3	60.0	4	33.3
	Yes	6	85.7	2	40.0	8	66.7

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T 15 Medical history: Frequency analysis of presence of previous therapy - FAS, N= 80

	Treatment					
	Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
Previous therapy for hand excema	N	%	N	%	N	%
No	10	25.0	8	20.0	18	22.5
Yes	30	75.0	32	80.0	62	77.5

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T 16 Medical history: Number of previous therapies and number and % of patients by therapy - FAS, N= 80

	Treatment	
Therapies	Advantan® Cream 0.1%	Advantan® Fatty Ointment 0.1%
0 Therapies	10 (25.0 %)	8 (20.0 %)
MTX	1 (2.5 %)	1 (2.5 %)
Ciclosporin	5 (12.5 %)	2 (5.0 %)
Azathioprin		1 (2.5 %)
Oral retinoids	3 (7.5 %)	4 (10.0 %)
Oral steroids	6 (15.0 %)	5 (12.5 %)
Dupilumab	1 (2.5 %)	
Light therapy	16 (40.0 %)	12 (30.0 %)
Topic steroids	28 (70.0 %)	31 (77.5 %)
Topic calcineurin inhibitors	18 (45.0 %)	18 (45.0 %)
Topic antibiotics	3 (7.5 %)	1 (2.5 %)
Other	1 (2.5 %)	2 (5.0 %)

*One patient may have had several therapies, hence patient numbers do not sum up to 100%

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T 17 Medical history: Frequency analysis of physical examination results - FAS, N= 80

			Treatment					
			Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
Visit	Question	Answer	N	%	N	%	N	%
Screening	Physical examination performed	Yes	40	100.0	40	100.0	80	100.0
	Heart	Normal	40	100.0	40	100.0	80	100.0
	Lung	Normal	40	100.0	40	100.0	80	100.0
	Abdomen	Normal	40	100.0	40	100.0	80	100.0
	Neurologic state	Normal	40	100.0	40	100.0	80	100.0
	Other conspicuous clinical symptoms	No	40	100.0	40	100.0	80	100.0
V1 (Baseline)	Physical examination performed	Yes	40	100.0	40	100.0	80	100.0
	Heart	Normal	40	100.0	40	100.0	80	100.0
	Lung	Normal	40	100.0	40	100.0	80	100.0
	Abdomen	Normal	40	100.0	40	100.0	80	100.0
	Neurologic state	Normal	40	100.0	40	100.0	80	100.0
	Other conspicuous clinical symptoms	No	40	100.0	40	100.0	80	100.0

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10.2 Efficacy (Effectiveness) data

Primary efficacy

T 18 Adherence: Frequency of adherence to Advantan description by visit - FAS, N= 80

		Treatment					
		Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
		N	%	N	%	N	%
Adherence (>=75% daily dose and >=0.85 applicatiens per day) BL - V2	Missing/na	4	0.0	4	0.0	8	0.0
	No	16	44.4	14	38.9	30	41.7
	Yes	20	55.6	22	61.1	42	58.3
Adherence (>=75% daily dose and >=0.85 applicatiens per day) V2 - V3	Missing/na	6	0.0	5	0.0	11	0.0
	No	22	64.7	17	48.6	39	56.5
	Yes	12	35.3	18	51.4	30	43.5
Adherence (>=75% daily dose and >=0.85 applicatiens per day) BL - V3	Missing/na	2	0.0	3	0.0	5	0.0
	No	22	57.9	17	45.9	39	52.0
	Yes	16	42.1	20	54.1	36	48.0
<ALL>	Total (row %)	40	50.0	40	50.0	80	100.0

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T 191 Adherence: Fishers exact test of adherence by visit and total - FAS

Total: Baseline - Visit 3

Table of treat by adherence_tot			
treat(Treatment)	adherence_tot(Adherence (>=75%% daily dose and >=0.85 applicatiens per day) BL - V3)		
Frequency Percent Row Pct Col Pct	No	Yes	Total
Advantan® Cream 0.1%	22 29.33 57.89 56.41	16 21.33 42.11 44.44	38 50.67
Advantan® Fatty Ointment 0.1%	17 22.67 45.95 43.59	20 26.67 54.05 55.56	37 49.33
Total	39 52.00	36 48.00	75 100.00
Frequency Missing = 5			

Statistics for Table of treat by adherence_tot

Statistic	DF	Value	Prob
Chi-Square	1	1.0723	0.3004
Likelihood Ratio Chi-Square	1	1.0748	0.2999
Continuity Adj. Chi-Square	1	0.6470	0.4212
Mantel-Haenszel Chi-Square	1	1.0580	0.3037
Phi Coefficient		0.1196	
Contingency Coefficient		0.1187	
Cramer's V		0.1196	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	22
Left-sided Pr <= F	0.8975
Right-sided Pr >= F	0.2107
Table Probability (P)	0.1082
Two-sided Pr <= P	0.3588

Column 1 Risk Estimates						
	Risk	ASE	(Asymptotic) 95% Confidence Limits		(Exact) 95% Confidence Limits	
Row 1	0.5789	0.0801	0.4220	0.7359	0.4082	0.7369
Row 2	0.4595	0.0819	0.2989	0.6200	0.2949	0.6308
Total	0.5200	0.0577	0.4069	0.6331	0.4015	0.6369
Difference	0.1195	0.1146	-0.1051	0.3440	-0.1149	0.3429
Difference is (Row 1 - Row 2)						

Column 2 Risk Estimates						
	Risk	ASE	(Asymptotic) 95% Confidence Limits		(Exact) 95% Confidence Limits	
Row 1	0.4211	0.0801	0.2641	0.5780	0.2631	0.5918
Row 2	0.5405	0.0819	0.3800	0.7011	0.3692	0.7051
Total	0.4800	0.0577	0.3669	0.5931	0.3631	0.5985
Difference	-0.1195	0.1146	-0.3440	0.1051	-0.3429	0.1149
Difference is (Row 1 - Row 2)						

Effective Sample Size = 75
Frequency Missing = 5

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Adherence: Fishers exact test of adherence by visit and total - FAS

Baseline - Visit 2

Table of treat by adherence_v2			
treat(Treatment)	adherence_v2(Adherence (>=75%% daily dose and >=0.85 applicatiens per day) BL - V2)		
Frequency Percent Row Pct Col Pct	No	Yes	Total
Advantan® Cream 0.1%	16 22.22 44.44 53.33	20 27.78 55.56 47.62	36 50.00
Advantan® Fatty Ointment 0.1%	14 19.44 38.89 46.67	22 30.56 61.11 52.38	36 50.00
Total	30 41.67	42 58.33	72 100.00
Frequency Missing = 8			

Statistics for Table of treat by adherence_v2

Statistic	DF	Value	Prob
Chi-Square	1	0.2286	0.6326
Likelihood Ratio Chi-Square	1	0.2287	0.6325
Continuity Adj. Chi-Square	1	0.0571	0.8111
Mantel-Haenszel Chi-Square	1	0.2254	0.6350
Phi Coefficient		0.0563	
Contingency Coefficient		0.0563	
Cramer's V		0.0563	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	16
Left-sided Pr <= F	0.7632
Right-sided Pr >= F	0.4057
Table Probability (P)	0.1688
Two-sided Pr <= P	0.8113

Column 1 Risk Estimates						
	Risk	ASE	(Asymptotic) 95% Confidence Limits		(Exact) 95% Confidence Limits	
Row 1	0.4444	0.0828	0.2821	0.6068	0.2794	0.6190
Row 2	0.3889	0.0812	0.2296	0.5481	0.2314	0.5654
Total	0.4167	0.0581	0.3028	0.5305	0.3015	0.5389
Difference	0.0556	0.1160	-0.1718	0.2829	-0.1869	0.2933
Difference is (Row 1 - Row 2)						

Column 2 Risk Estimates						
	Risk	ASE	(Asymptotic) 95% Confidence Limits		(Exact) 95% Confidence Limits	
Row 1	0.5556	0.0828	0.3932	0.7179	0.3810	0.7206
Row 2	0.6111	0.0812	0.4519	0.7704	0.4346	0.7686
Total	0.5833	0.0581	0.4695	0.6972	0.4611	0.6985
Difference	-0.0556	0.1160	-0.2829	0.1718	-0.2933	0.1869
Difference is (Row 1 - Row 2)						

Effective Sample Size = 72
Frequency Missing = 8

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Adherence: Fishers exact test of adherence by visit and total - FAS

Visit 2 - Visit 3

Table of treat by adherence_v3			
treat(Treatment)	adherence_v3(Adherence (>=75%% daily dose and >=0.85 applicatiens per day) V2 - V3)		
Frequency Percent Row Pct Col Pct	No	Yes	Total
Advantan® Cream 0.1%	22 31.88 64.71 56.41	12 17.39 35.29 40.00	34 49.28
Advantan® Fatty Ointment 0.1%	17 24.64 48.57 43.59	18 26.09 51.43 60.00	35 50.72
Total	39 56.52	30 43.48	69 100.00
Frequency Missing = 11			

Statistics for Table of treat by adherence_v3

Statistic	DF	Value	Prob
Chi-Square	1	1.8269	0.1765
Likelihood Ratio Chi-Square	1	1.8364	0.1754
Continuity Adj. Chi-Square	1	1.2294	0.2675
Mantel-Haenszel Chi-Square	1	1.8004	0.1797
Phi Coefficient		0.1627	
Contingency Coefficient		0.1606	
Cramer's V		0.1627	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	22
Left-sided Pr <= F	0.9450
Right-sided Pr >= F	0.1337
Table Probability (P)	0.0787
Two-sided Pr <= P	0.2270

Column 1 Risk Estimates						
	Risk	ASE	(Asymptotic) 95% Confidence Limits		(Exact) 95% Confidence Limits	
Row 1	0.6471	0.0820	0.4864	0.8077	0.4649	0.8025
Row 2	0.4857	0.0845	0.3201	0.6513	0.3138	0.6601
Total	0.5652	0.0597	0.4482	0.6822	0.4404	0.6842
Difference	0.1613	0.1177	-0.0693	0.3920	-0.0779	0.3936
Difference is (Row 1 - Row 2)						

Column 2 Risk Estimates						
	Risk	ASE	(Asymptotic) 95% Confidence Limits		(Exact) 95% Confidence Limits	
Row 1	0.3529	0.0820	0.1923	0.5136	0.1975	0.5351
Row 2	0.5143	0.0845	0.3487	0.6799	0.3399	0.6862
Total	0.4348	0.0597	0.3178	0.5518	0.3158	0.5596
Difference	-0.1613	0.1177	-0.3920	0.0693	-0.3936	0.0779
Difference is (Row 1 - Row 2)						

Effective Sample Size = 69
Frequency Missing = 11

WARNING: 14% of the data are missing.

ZKS Jena Schumacher ADHERE T4_pe.sas 25AUG2022

T 2 Adherence: Descriptive analysis of Advantan use by visit - FAS, N total = 80

		Treatment		
Parameter	**Statistic**	**Advantan® Cream 0.1%**	**Advantan® Fatty Ointment 0.1%**	**Total**
Mean daily dose used [mg] BL - V2	N	36	36	72
	NMiss	4	4	8
	Mean	643	411.7	527.4
	StdDev	500.3	293.6	423.6
	Min	94.6	61.4	61.4
	P25	299.2	225.5	271.7
	Median	523.5	318.5	397.4
	P75	754.6	507	642.9
	Max	2490.8	1330.5	2490.8
	LCLM	473.8	312.4	427.8
	UCLM	812.3	511.1	626.9
Mean daily dose used [mg] V2 - V3	N	34	35	69
	NMiss	6	5	11
	Mean	562.6	430	495.3
	StdDev	391	353.7	375.8
	Min	92.7	32	32
	P25	268.2	186.7	211.5
	Median	448.2	307.7	349.3
	P75	843.1	465.7	743.2
	Max	1549.3	1281.2	1549.3
	LCLM	426.1	308.5	405
	UCLM	699	551.5	585.6
Mean daily dose used [mg] BL - V3	N	38	37	75
	NMiss	2	3	5
	Mean	607	420.4	515
	StdDev	398.6	272.5	352.7
	Min	166.6	46.7	46.7
	P25	270.6	239.2	244.9
	Median	483.5	336.9	425
	P75	892.1	567.6	645.6
	Max	1725.8	1204.9	1725.8
	LCLM	476	329.5	433.8
	UCLM	738	511.2	596.1
Total dose used [mg] BL - V2	N	36	36	72
	NMiss	4	4	8
	Mean	9714	5959	7836.5
	StdDev	7780.2	3939.5	6408.2
	Min	1419	859	859
	P25	4695.5	3535.5	3964.5

		Treatment		
Parameter	**Statistic**	**Advantan® Cream 0.1%**	**Advantan® Fatty Ointment 0.1%**	**Total**
	Median	7673.5	4895	5907.5
	P75	11806.5	7419	9643.5
	Max	37362	18627	37362
	LCLM	7081.6	4626.1	6330.7
	UCLM	12346.5	7292	9342.4
Total dose used [mg] V2 - V3	N	35	36	71
	NMiss	5	4	9
	Mean	7634.1	5902	6755.9
	StdDev	5446	4714.6	5126.4
	Min	1298	448	448
	P25	3824	2747.5	3120
	Median	5712	4711.5	5355
	P75	11148	6711.5	9294
	Max	20141	17937	20141
	LCLM	5763.4	4306.8	5542.5
	UCLM	9504.9	7497.2	7969.3
Total dose used [mg] BL - V3	N	39	38	77
	NMiss	1	2	3
	Mean	17306.6	12012.2	14693.8
	StdDev	11205.9	7515.5	9868.3
	Min	5174	1307	1307
	P25	8569	6857	7566
	Median	13193	9500.5	11299
	P75	24209	16575	19362
	Max	48322	33738	48322
	LCLM	13674.1	9541.9	12453.9
	UCLM	20939.1	14482.5	16933.6

LCLM / UCLM: lower / upper limit of 95% confidence interval

ZKS Jena Schumacher ADHERE T4_pe.sas 25AUG2022

Adherence: Descriptive analysis of Advantan use by visit - FAS, N total = 80

		Treatment		
Parameter	**Statistic**	**Advantan® Cream 0.1%**	**Advantan® Fatty Ointment 0.1%**	**Total**
Mean number of openings per day BL - V2	N	40	39	79
	NMiss	0	1	1
	Mean	0.85	0.89	0.87
	StdDev	0.28	0.29	0.28
	Min	0.08	0.21	0.08
	P25	0.69	0.73	0.69
	Median	0.89	1	0.93
	P75	1	1.06	1
	Max	1.57	1.43	1.57
	LCLM	0.76	0.8	0.81
	UCLM	0.94	0.99	0.93
Mean number of openings per day V2 - V3	N	39	38	77
	NMiss	1	2	3
	Mean	0.73	0.77	0.75
	StdDev	0.29	0.34	0.31
	Min	0.07	0.07	0.07
	P25	0.5	0.5	0.5
	Median	0.73	0.86	0.79
	P75	0.93	1	0.93
	Max	1.5	1.86	1.86
	LCLM	0.63	0.65	0.67
	UCLM	0.82	0.88	0.82
Mean number of openings per day BL - V3	N	39	38	77
	NMiss	1	2	3
	Mean	0.79	0.83	0.81
	StdDev	0.26	0.31	0.28
	Min	0.07	0.14	0.07
	P25	0.64	0.62	0.62
	Median	0.76	0.93	0.86
	P75	0.93	1	0.97
	Max	1.54	1.64	1.64
	LCLM	0.71	0.73	0.75
	UCLM	0.88	0.93	0.87
Total number of openings BL - V2	N	40	39	79
	NMiss	0	1	1
	Mean	12.7	13.2	12.9
	StdDev	4.3	4.2	4.3
	Min	1	3	1

		Treatment		
Parameter	Statistic	Advantan® Cream 0.1%	Advantan® Fatty Ointment 0.1%	Total
	P25	9.5	11	11
	Median	13.5	14	14
	P75	15	16	15
	Max	22	20	22
	LCLM	11.3	11.8	12
	UCLM	14.1	14.5	13.9
Total number of openings V2 - V3	N	39	38	77
	NMiss	1	2	3
	Mean	10.2	10.6	10.4
	StdDev	4.2	5	4.6
	Min	1	1	1
	P25	8	7	8
	Median	10	11.5	11
	P75	12	14	13
	Max	21	26	26
	LCLM	8.8	9	9.4
	UCLM	11.6	12.3	11.5
Total number of openings BL - V3	N	39	38	77
	NMiss	1	2	3
	Mean	23	23.8	23.4
	StdDev	7.5	8.4	7.9
	Min	2	4	2
	P25	19	18	18
	Median	24	26.5	25
	P75	27	28	27
	Max	43	46	46
	LCLM	20.6	21	21.6
	UCLM	25.4	26.6	25.2

LCLM / UCLM: lower / upper limit of 95% confidence interval

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T 23 Adherence: Descriptive analysis of difference of Advantan usage to presciption by visit - FAS, per day, N total = 2326

		Treatment		
Visit	Difference: used dose - prescribed dose [mg]	Advantan® Cream 0.1%	Advantan® Fatty Ointment 0.1%	Total
Visite 2	N	589	555	1144
	NMiss	8	37	45
	Mean	552.6	261.1	411.2
	StdDev	754.2	528.6	670.3
	Min	-375	-375	-375
	P25	2.7	-67.7	-67.7
	Median	367	120.9	200.3
	P75	803.6	436.6	626.8
	Max	5751	2655	5751
	LCLM	491.6	217.1	372.3
	UCLM	613.7	305.2	450.1
Visite 3	N	537	524	1061
	NMiss	30	46	76
	Mean	416	246.2	332.1
	StdDev	895.2	754.9	832.8
	Min	-300	-375	-375
	P25	-100	-125	-100
	Median	270	119.4	142.8
	P75	575.7	334.9	480.9
	Max	10948	12598	12598
	LCLM	340.1	181.4	281.9
	UCLM	491.8	311	382.3

LCLM / UCLM: lower / upper limit of 95% confidence interval
ZKS Jena Schumacher ADHERE T4_pe.sas 25AUG2022

Secondary efficacy

T 22 Adherence: Descriptive analysis of Bepanthen® use by visit - FAS, N total = 80

		Treatment		
Parameter	Statistic	Advantan® Cream 0.1%	Advantan® Fatty Ointment 0.1%	Total
Mean daily dose used [mg] BL - V2	N	33	29	62
	NMiss	7	11	18
	Mean	2174.6	1889.3	2041.1
	StdDev	1372.7	1144.1	1268.9
	Min	443.5	265	265
	P25	1089.6	1221.3	1089.6
	Median	1504	1642.1	1599.3

		Treatment		
Parameter	Statistic	Advantan® Cream 0.1%	Advantan® Fatty Ointment 0.1%	Total
	P75	3366.4	2491.9	2810.4
	Max	4953.1	5090	5090
	LCLM	1687.8	1454.1	1718.9
	UCLM	2661.4	2324.5	2363.4
Mean daily dose used [mg] V2 - V3	N	31	27	58
	NMiss	9	13	22
	Mean	2160.9	2413.4	2278.4
	StdDev	1319.2	1681.1	1490.4
	Min	241.4	193.7	193.7
	P25	1150.7	1224.2	1224.2
	Median	1682	2170.5	2004.9
	P75	3311.5	3157.8	3157.8
	Max	5047.5	7200.3	7200.3
	LCLM	1677	1748.4	1886.6
	UCLM	2644.7	3078.4	2670.3
Mean daily dose used [mg] BL - V3	N	36	32	68
	NMiss	4	8	12
	Mean	1979.3	2114	2042.7
	StdDev	1196.5	1254.7	1216.9
	Min	481.3	261.9	261.9
	P25	1114.5	1316.1	1137.3
	Median	1536.9	2080.8	1779.4
	P75	2845	2665.3	2671.4
	Max	4989.3	6108.8	6108.8
	LCLM	1574.4	1661.6	1748.1
	UCLM	2384.1	2566.4	2337.2
Total dose used [mg] BL - V2	N	33	30	63
	NMiss	7	10	17
	Mean	32283.2	27571.1	30039.3
	StdDev	19911.5	17612.7	18850.8
	Min	6652.9	5949.5	5949.5
	P25	16083	16174	16083
	Median	30081	23409	23444
	P75	48687	37165	44966
	Max	74297	76350	76350
	LCLM	25222.9	20994.4	25291.8
	UCLM	39343.5	34147.8	34786.9
Total dose used [mg] V2 - V3	N	32	29	61
	NMiss	8	11	19
	Mean	31671.6	32084.1	31867.7
	StdDev	21453.5	22229.8	21643.7
	Min	3380	1235	1235

		Treatment		
Parameter	**Statistic**	**Advantan® Cream 0.1%**	**Advantan® Fatty Ointment 0.1%**	**Total**
	P25	14501.5	17138.5	15949
	Median	25681.5	31400	26912
	P75	40064	41457.7	41457.7
	Max	85807	100804.7	100804.7
	LCLM	23936.8	23628.3	26324.5
	UCLM	39406.4	40539.8	37410.9
Total dose used [mg] BL - V3	N	37	35	72
	NMiss	3	5	8
	Mean	58121.6	58102.7	58112.4
	StdDev	35008.7	35639	35066.7
	Min	12513	7596	7596
	P25	31178	27641	30640
	Median	47105	54754	51603.5
	P75	83892	69936	77237
	Max	154667	177154.7	177154.7
	LCLM	46449.1	45860.3	49872.2
	UCLM	69794.1	70345.1	66352.7

LCLM / UCLM: lower / upper limit of 95% confidence interval

ZKS Jena Schumacher ADHERE T4_pe.sas 25AUG2022

Adherence: Descriptive analysis of Bepanthen® Sensiderm use by visit - FAS, N total = 80

		Treatment		
Parameter	**Statistic**	**Advantan® Cream 0.1%**	**Advantan® Fatty Ointment 0.1%**	**Total**
Mean number of openings per day BL - V2	N	40	38	78
	NMiss	0	2	2
	Mean	2.5	2.58	2.54
	StdDev	2.53	2.03	2.29
	Min	0.07	0.13	0.07
	P25	1.28	1.43	1.29
	Median	1.81	2.31	2.06
	P75	2.93	3.07	3.07
	Max	14.87	11.73	14.87
	LCLM	1.69	1.91	2.02
	UCLM	3.3	3.25	3.05
Mean number of openings per day V2 - V3	N	38	36	74
	NMiss	2	4	6
	Mean	1.79	2.19	1.98
	StdDev	1.25	2	1.66
	Min	0.18	0.06	0.06
	P25	0.76	0.89	0.86
	Median	1.48	1.93	1.77
	P75	2.27	3.12	2.73
	Max	4.81	11.86	11.86
	LCLM	1.38	1.51	1.6
	UCLM	2.2	2.87	2.37
Mean number of openings per day BL - V3	N	38	36	74
	NMiss	2	4	6
	Mean	2.18	2.4	2.29
	StdDev	1.73	1.97	1.84
	Min	0.13	0.12	0.12
	P25	1.18	1.22	1.18
	Median	1.79	2.17	1.97
	P75	2.48	2.86	2.64
	Max	9.23	11.79	11.79
	LCLM	1.61	1.73	1.86
	UCLM	2.75	3.07	2.72
Total number of openings BL - V2	N	40	38	78
	NMiss	0	2	2
	Mean	37.3	37.8	37.6
	StdDev	37.7	30.5	34.1
	Min	1	2	1

		Treatment		
Parameter	Statistic	Advantan® Cream 0.1%	Advantan® Fatty Ointment 0.1%	Total
	P25	19.5	20	20
	Median	28	31.5	30.5
	P75	47	45	47
	Max	223	176	223
	LCLM	25.3	27.8	29.9
	UCLM	49.4	47.9	45.3
Total number of openings V2 - V3	N	38	36	74
	NMiss	2	4	6
	Mean	25.6	31	28.2
	StdDev	19.5	29.1	24.6
	Min	3	1	1
	P25	9	12	12
	Median	21	27	24.5
	P75	31	41	36
	Max	77	166	166
	LCLM	19.2	21.2	22.5
	UCLM	32	40.9	33.9
Total number of openings BL - V3	N	38	36	74
	NMiss	2	4	6
	Mean	64.3	69.2	66.7
	StdDev	53.4	57.4	55.1
	Min	4	4	4
	P25	35	36	35
	Median	52	62	58.5
	P75	74	83	76
	Max	286	342	342
	LCLM	46.8	49.8	53.9
	UCLM	81.9	88.6	79.4

LCLM / UCLM: lower / upper limit of 95% confidence interval

ZKS Jena Schumacher ADHERE T4_pe.sas 25AUG2022

T 23 Primary variable: Generalized linear model analysis of adherence to study treatment with fixed factors Bepanthen® Sensiderm use, treatment and time

The LOGISTIC Procedure

Model Information		
Data Set	WORK.PP_PC_TM	
Response Variable	adherence	Adherence (>=75% daily dose and >=0.85 applicatiens per day)
Number of Response Levels	2	
Model	binary logit	
Optimization Technique	Fisher's scoring	

Number of Observations Read	160
Number of Observations Used	145

Response Profile		
Ordered Value	**adherence**	**Total Frequency**
1	No	71
2	Yes	74
	Missing/na	.

Probability modeled is adherence='Yes'.

Note: 15 observations were deleted due to missing values for the response or explanatory variables.

Note: 1 response level was deleted due to missing or invalid values for its explanatory, frequency, or weight variables.

Class Level Information		
Class	**Value**	**Design Variables**
treat	**Advantan® Cream 0.1%**	1
	Advantan® Fatty Ointment 0.1%	-1
time1	**V2 (Day 14)**	1
	V3 (Day 28)	-1

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	202.951	181.236
SC	205.927	199.097
-2 Log L	200.951	169.236

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	31.7145	5	<.0001
Score	23.9661	5	0.0002
Wald	21.1141	5	0.0008

Joint Tests			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
pcdose_true	1	1.6309	0.2016
pcanzday_mean	1	8.6639	0.0032
treat	1	1.4998	0.2207
time1	1	1.8433	0.1746
treat*time1	1	0.0224	0.8809

Note: Under full-rank parameterizations, Type 3 effect tests are replaced by joint tests. The joint test for an effect is a test that all the parameters associated with that effect are zero. Such joint tests might not be equivalent to Type 3 effect tests under GLM parameterization.

Analysis of Maximum Likelihood Estimates							
Parameter			**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept			1	-1.5351	0.3984	14.8474	0.0001
pcdose_true			1	0.000228	0.000178	1.6309	0.2016
pcanzday_mean			1	0.5545	0.1884	8.6639	0.0032
treat	**Advantan® Cream 0.1%**		1	-0.2291	0.1871	1.4998	0.2207
time1	**V2 (Day 14)**		1	0.2688	0.1980	1.8433	0.1746
treat*time1	**Advantan® Cream 0.1%**	**V2 (Day 14)**	1	0.0279	0.1864	0.0224	0.8809

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	76.4	**Somers' D**	0.527
Percent Discordant	23.6	**Gamma**	0.527
Percent Tied	0.0	**Tau-a**	0.265
Pairs	5254	**c**	0.764

Parameter Estimates and Wald Confidence Intervals					
Parameter			**Estimate**	**95% Confidence Limits**	
Intercept			-1.5351	-2.3159	-0.7542
pcdose_true			0.000228	-0.00012	0.000577
pcanzday_mean			0.5545	0.1853	0.9238
treat	**Advantan® Cream 0.1%**		-0.2291	-0.5958	0.1376
time1	**V2 (Day 14)**		0.2688	-0.1192	0.6568
treat*time1	**Advantan® Cream 0.1%**	**V2 (Day 14)**	0.0279	-0.3374	0.3933

Odds Ratio Estimates and Profile-Likelihood Confidence Intervals				
Effect	**Unit**	**Estimate**	**95% Confidence Limits**	
pcdose_true	1.0000	1.000	1.000	1.001
pcanzday_mean	1.0000	1.741	1.224	2.567

Odds Ratio Estimates and Wald Confidence Intervals				
Effect	**Unit**	**Estimate**	**95% Confidence Limits**	
pcdose_true	1.0000	1.000	1.000	1.001
pcanzday_mean	1.0000	1.741	1.204	2.519

LCLM / UCLM: lower / upper limit of 95% confidence interval

ZKS Jena Schumacher ADHERE T4_pe.sas 25AUG2022

T 44 Primary variable: General linear model analysis of usage of study treatment with fixed factors Bepanthen® Sensiderm use, treatment and time

The GLM Procedure

Class Level Information		
Class	**Levels**	**Values**
treat	2	Advantan® Cream 0.1% Advantan® Fatty Ointment 0.1%
time1	2	Visite 2 Visite 3

Number of Observations Read	2326
Number of Observations Used	1998

Dependent Variable: dosediff Difference: used dose - prescribed dose [mg]

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	5	60556038	12111208	21.96	<.0001
Error	1992	1098428004	551420		
Corrected Total	1997	1158984041			

R-Square	Coeff Var	Root MSE	dosediff Mean
0.052249	203.4063	742.5764	365.0706

Source	DF	Type I SS	Mean Square	F Value	Pr > F
pcdose_true	1	17282209.20	17282209.20	31.34	<.0001
pcanzday	1	5111206.73	5111206.73	9.27	0.0024
treat	1	32636757.62	32636757.62	59.19	<.0001
time1	1	3600123.38	3600123.38	6.53	0.0107
treat*time1	1	1925740.58	1925740.58	3.49	0.0618

Source	DF	Type III SS	Mean Square	F Value	Pr > F
pcdose_true	1	23680184.29	23680184.29	42.94	<.0001
pcanzday	1	5283403.83	5283403.83	9.58	0.0020
treat	1	31681919.67	31681919.67	57.46	<.0001
time1	1	3249365.60	3249365.60	5.89	0.0153
treat*time1	1	1925740.58	1925740.58	3.49	0.0618

Parameter	Estimate		Standard Error	t Value	Pr > |t|	95% Confidence Limits	
Intercept	74.8193101	B	46.15773285	1.62	0.1052	-15.7031859	165.3418062
pcdose_true	0.0966638		0.01475069	6.55	<.0001	0.0677354	0.1255922
pcanzday	-23.5601807		7.61137018	-3.10	0.0020	-38.4872619	-8.6330995
treat Advantan® Cream 0.1%	190.6060045	B	48.41031063	3.94	<.0001	95.6658530	285.5461561
treat Advantan® Fatty Ointment 0.1%	0.0000000	B	.	.	.	.	.
time1 Visite 2	20.3518075	B	49.31539593	0.41	0.6799	-76.3633572	117.0669722
time1 Visite 3	0.0000000	B	.	.	.	.	.
treat*time1 Advantan® Cream 0.1% Visite 2	124.9798148	B	66.87782136	1.87	0.0618	-6.1779987	256.1376284
treat*time1 Advantan® Cream 0.1% Visite 3	0.0000000	B	.	.	.	.	.
treat*time1 Advantan® Fatty Ointment 0.1% Visite 2	0.0000000	B	.	.	.	.	.

Parameter	Estimate		Standard Error	t Value	Pr > |t|	95% Confidence Limits
treat*time1 Advantan® Fatty Ointment 0.1% Visite 3	0.0000000	B		.	.	.

Note: The X'X matrix has been found to be singular, and a generalized inverse was used to solve the normal equations. Terms whose estimates are followed by the letter 'B' are not uniquely estimable.

LCLM / UCLM: lower / upper limit of 95% confidence interval

ZKS Jena Schumacher ADHERE T4_pe.sas 25AUG2022

T 55 HECSI: Descriptive analysis of HECSI score by visit - FAS, N= 80

		Treatment		
Visit	HECSI score	Advantan® Cream 0.1%	Advantan® Fatty Ointment 0.1%	Total
V1 (Baseline)	N	40	40	80
	NMiss	0	0	0
	Mean	21.4	25.3	23.4
	StdDev	14.4	20.4	17.6
	Min	3	7	3
	P25	10.5	9.5	10
	Median	18	20	18.5
	P75	33	32	33
	Max	77	95	95
	LCLM	16.8	18.8	19.4
	UCLM	26	31.8	27.3
V2 (Day 14)	N	39	37	76
	NMiss	1	3	4
	Mean	13.2	18.7	15.9
	StdDev	14.4	22.5	18.8
	Min	2	0	0
	P25	5	6	6
	Median	11	9	9.5
	P75	15	19	19
	Max	88	98	98
	LCLM	8.5	11.2	11.6
	UCLM	17.8	26.2	20.2
V3 (Day 28)	N	39	38	77
	NMiss	1	2	3
	Mean	9.6	15.6	12.5
	StdDev	9.5	20.4	16
	Min	0	0	0
	P25	3	5	4
	Median	7	8	7
	P75	13	20	16
	Max	50	100	100
	LCLM	6.5	8.9	8.9
	UCLM	12.7	22.3	16.2

LCLM / UCLM: lower / upper limit of 95% confidence interval

ZKS Jena Schumacher ADHERE T5_se.sas 25AUG2022

T 66 IGA: Frequency analysis of IGA score by visit - FAS, N= 80

		Treatment					
		Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
Visit	IGA Score	N	%	N	%	N	%
Screening	1 - almost clear	2	5.0	0	0.0	2	2.5
	2 - mild	32	80.0	29	72.5	61	76.3
	3 - moderate	6	15.0	11	27.5	17	21.3
V1 (Baseline)	2 - mild	34	85.0	29	72.5	63	78.8
	3 - moderate	6	15.0	11	27.5	17	21.3
V2 (Day 14)	Missing	1	0.0	3	0.0	4	0.0
	0 - clear	0	0.0	1	2.7	1	1.3
	1 - almost clear	13	33.3	5	13.5	18	23.7
	2 - mild	24	61.5	27	73.0	51	67.1
	3 - moderate	2	5.1	4	10.8	6	7.9
V3 (Day 28)	Missing	1	0.0	2	0.0	3	0.0
	0 - clear	2	5.1	2	5.3	4	5.2
	1 - almost clear	17	43.6	11	28.9	28	36.4
	2 - mild	19	48.7	22	57.9	41	53.2
	3 - moderate	1	2.6	3	7.9	4	5.2

ZKS Jena Schumacher ADHERE T5_se.sas 25AUG2022

T 77 IGA: Shift analysis of IGA score baseline versus Visit 3 (Day 28) - FAS, N= 80

		IGA Score, V3 (Day 28)											
		Missing		0 - clear		1 - almost clear		2 - mild		3 - moderate		Total	
Treatment	IGA Score, Screening	N	%	N	%	N	%	N	%	N	%	N	%
Advantan® Cream 0.1%	1 - almost clear	0	0.0	0	0.0	1	5.9	1	5.3	0	0.0	2	5.0
	2 - mild	0	0.0	2	100.0	16	94.1	13	68.4	1	100.0	32	80.0
	3 - moderate	1	100.0	0	0.0	0	0.0	5	26.3	0	0.0	6	15.0
	Total (row %)	1	0.0	2	5.1	17	43.6	19	48.7	1	2.6	40	100.0
Advantan® Fatty Ointment 0.1%	2 - mild	2	100.0	2	100.0	10	90.9	15	68.2	0	0.0	29	72.5
	3 - moderate	0	0.0	0	0.0	1	9.1	7	31.8	3	100.0	11	27.5
	Total (row %)	2	0.0	2	5.3	11	28.9	22	57.9	3	7.9	40	100.0

ZKS Jena Schumacher ADHERE T5_se.sas 25AUG2022

T 28 Itching: Descriptive analysis of 100mm visual analog scale by visit - FAS, N= 80

		Treatment		
Visit	VAS itching	Advantan® Cream 0.1%	Advantan® Fatty Ointment 0.1%	Total
V1 (Baseline)	N	40	40	80
	NMiss	0	0	0
	Mean	30.4	22.1	26.3
	StdDev	28.1	24.2	26.4
	Min	0	0	0
	P25	6	1	1.5
	Median	24	15	20
	P75	43	37	40.5
	Max	99	96	99
	LCLM	21.4	14.4	20.4
	UCLM	39.4	29.8	32.1
V2 (Day 14)	N	39	37	76
	NMiss	1	3	4
	Mean	16.3	14.4	15.4
	StdDev	22	20	21
	Min	0	0	0
	P25	2	1	1.5
	Median	8	5	7
	P75	20	19	19.5
	Max	92	87	92
	LCLM	9.2	7.7	10.6
	UCLM	23.5	21.1	20.2
V3 (Day 28)	N	39	38	77
	NMiss	1	2	3
	Mean	12.3	13.6	13
	StdDev	19.2	21.9	20.4
	Min	0	0	0
	P25	0	0	0
	Median	3	1.5	2.3
	P75	21	17	17
	Max	77	77	77
	LCLM	6.1	6.4	8.3
	UCLM	18.5	20.8	17.6

LCLM / UCLM: lower / upper limit of 95% confidence interval

ZKS Jena Schumacher ADHERE T5_se.sas 25AUG2022

T 89 QOLHEQ: Descriptive analysis of subscales and total score by visit - FAS, N= 80

			Treatment		
Parameter	**Visit**	**Statistic**	**Advantan® Cream 0.1%**	**Advantan® Fatty Ointment 0.1%**	**Total**
Symptomes	V1 (Baseline)	N	40	40	80
		NMiss	0	0	0
		Mean	14.1	12.3	13.2
		StdDev	4.2	6.2	5.3
		Min	3	0	0
		P25	12	7	10
		Median	14	14	14
		P75	16	18	17
		Max	27	22	27
		LCLM	12.7	10.3	12
		UCLM	15.4	14.3	14.4
	V2 (Day 14)	N	39	37	76
		NMiss	1	3	4
		Mean	8.3	7.2	7.8
		StdDev	5.9	6	5.9
		Min	0	0	0
		P25	4	3	3
		Median	7	5	6.5
		P75	11	11	11
		Max	24	20	24
		LCLM	6.3	5.2	6.4
		UCLM	10.2	9.2	9.1
	V3 (Day 28)	N	39	38	77
		NMiss	1	2	3
		Mean	8.2	7.2	7.7
		StdDev	5.6	6.2	5.9
		Min	0	0	0
		P25	3	2	3
		Median	7	6	7
		P75	12	11	11
		Max	20	23	23
		LCLM	6.4	5.2	6.4
		UCLM	10	9.3	9.1
Emotions	V1 (Baseline)	N	40	40	80
		NMiss	0	0	0
		Mean	11	8.9	10
		StdDev	6.7	6.5	6.6
		Min	0	0	0
		P25	6.5	2	5
		Median	9.5	9	9
		P75	15	12.5	14.5
		Max	28	22	28

			Treatment		
Parameter	Visit	Statistic	Advantan® Cream 0.1%	Advantan® Fatty Ointment 0.1%	Total
		LCLM	8.9	6.9	8.5
		UCLM	13.1	11	11.4
	V2 (Day 14)	N	39	37	76
		NMiss	1	3	4
		Mean	6.1	5.1	5.6
		StdDev	6.7	6.1	6.4
		Min	0	0	0
		P25	1	0	0
		Median	3	3	3
		P75	10	7	9.5
		Max	25	21	25
		LCLM	3.9	3	4.2
		UCLM	8.3	7.1	7.1
	V3 (Day 28)	N	39	38	77
		NMiss	1	2	3
		Mean	5.6	4.8	5.2
		StdDev	6.2	6.9	6.5
		Min	0	0	0
		P25	2	0	0
		Median	3	2	2
		P75	8	9	8
		Max	25	25	25
		LCLM	3.6	2.6	3.8
		UCLM	7.6	7.1	6.7
Functioning	V1 (Baseline)	N	40	40	80
		NMiss	0	0	0
		Mean	9.1	8	8.5
		StdDev	5.6	6.3	5.9
		Min	0	0	0
		P25	5	2.5	3
		Median	8	7.5	8
		P75	12.5	13	13
		Max	27	28	28
		LCLM	7.3	6	7.2
		UCLM	10.9	10	9.9
	V2 (Day 14)	N	39	37	76
		NMiss	1	3	4
		Mean	6.3	5.1	5.7
		StdDev	6	6.1	6
		Min	0	0	0
		P25	2	0	1
		Median	5	3	4
		P75	9	7	8.5
		Max	30	22	30
		LCLM	4.3	3.1	4.4

			Treatment		
Parameter	Visit	Statistic	Advantan® Cream 0.1%	Advantan® Fatty Ointment 0.1%	Total
		UCLM	8.3	7.2	7.1
	V3 (Day 28)	N	39	38	77
		NMiss	1	2	3
		Mean	5.1	5	5
		StdDev	5.1	5.9	5.4
		Min	0	0	0
		P25	1	0	1
		Median	4	3	3
		P75	8	6	7
		Max	22	21	22
		LCLM	3.4	3	3.8
		UCLM	6.7	6.9	6.3
Treatment and Behaviour	V1 (Baseline)	N	40	40	80
		NMiss	0	0	0
		Mean	10.1	9.2	9.6
		StdDev	4.6	5.9	5.3
		Min	3	0	0
		P25	7	5	6
		Median	9	8	9
		P75	14	14.5	14
		Max	20	22	22
		LCLM	8.6	7.3	8.4
		UCLM	11.6	11	10.8
	V2 (Day 14)	N	39	37	76
		NMiss	1	3	4
		Mean	7.3	6.7	7
		StdDev	4.8	5.4	5.1
		Min	0	0	0
		P25	4	2	3
		Median	6	4	5
		P75	11	11	11
		Max	21	19	21
		LCLM	5.8	4.9	5.9
		UCLM	8.9	8.5	8.2
	V3 (Day 28)	N	39	38	77
		NMiss	1	2	3
		Mean	6.2	6.9	6.6
		StdDev	4.3	5.7	5
		Min	0	0	0
		P25	3	2	2
		Median	6	5.5	6
		P75	9	12	9
		Max	23	17	23
		LCLM	4.8	5.1	5.4

			Treatment		
Parameter	**Visit**	**Statistic**	**Advantan® Cream 0.1%**	**Advantan® Fatty Ointment 0.1%**	**Total**
		UCLM	7.6	8.8	7.7
QOLHEQ total score	V1 (Baseline)	N	40	40	80
		NMiss	0	0	0
		Mean	44.2	38.4	41.3
		StdDev	18.5	22.4	20.6
		Min	7	1	1
		P25	31.5	17	24
		Median	42	40.5	41.5
		P75	57.5	55	55.5
		Max	102	83	102
		LCLM	38.3	31.2	36.7
		UCLM	50.1	45.6	45.9
	V2 (Day 14)	N	39	37	76
		NMiss	1	3	4
		Mean	28	24.1	26.1
		StdDev	21.5	21.5	21.5
		Min	0	0	0
		P25	11	9	10
		Median	22	19	20
		P75	39	35	38.5
		Max	100	72	100
		LCLM	21	16.9	21.2
		UCLM	35	31.3	31
	V3 (Day 28)	N	39	38	77
		NMiss	1	2	3
		Mean	25.2	23.9	24.6
		StdDev	19.3	23	21.1
		Min	0	0	0
		P25	11	5	10
		Median	20	19.5	20
		P75	39	31	36
		Max	90	84	90
		LCLM	18.9	16.4	19.8
		UCLM	31.4	31.5	29.3

LCLM / UCLM: lower / upper limit of 95% confidence interval

ZKS Jena Schumacher ADHERE T5_se.sas 25AUG2022

T 30 Skin area: Frequency analysis of % of hand area affected by visit - FAS, N= 80

		Treatment					
		Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
Visit	Percentage of affected hand surface (both hands)	N	%	N	%	N	%
V1 (Baseline)	0-25%	23	57.5	18	45.0	41	51.3
	26-50%	12	30.0	13	32.5	25	31.3
	51-75%	5	12.5	9	22.5	14	17.5
V2 (Day 14)	Missing	1	0.0	3	0.0	4	0.0
	0-25%	29	74.4	28	75.7	57	75.0
	26-50%	10	25.6	3	8.1	13	17.1
	51-75%	0	0.0	6	16.2	6	7.9
V3 (Day 28)	Missing	1	0.0	2	0.0	3	0.0
	0-25%	34	87.2	30	78.9	64	83.1
	26-50%	5	12.8	4	10.5	9	11.7
	51-75%	0	0.0	4	10.5	4	5.2

ZKS Jena Schumacher ADHERE T5_se.sas 25AUG2022

10.3 Safety (Tolerability) data

10.3.1 ***Displays of adverse events***

T 31 Status: Frequency analysis of adverse events/pregnancies by visit

			Treatment					
			Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
			N	%	N	%	N	%
AEs since last visit	V2 (Day 14)	Missing	1	0.0	3	0.0	4	0.0
		No	37	94.9	34	91.9	71	93.4
		Yes	2	5.1	3	8.1	5	6.6
	V3 (Day 28)	Missing	1	0.0	2	0.0	3	0.0
		No	30	76.9	34	89.5	64	83.1
		Yes	9	23.1	4	10.5	13	16.9
	Follow up (day 35)	Missing	1	0.0	2	0.0	3	0.0
		No	38	97.4	36	94.7	74	96.1
		Yes	1	2.6	2	5.3	3	3.9
Known pregnancy	V2 (Day 14)	Missing	1	0.0	3	0.0	4	0.0
		No	39	100.0	37	100.0	76	100.0
	V3 (Day 28)	Missing	1	0.0	2	0.0	3	0.0
		No	39	100.0	38	100.0	77	100.0
	Follow up (day 35)	Missing	1	0.0	2	0.0	3	0.0
		No	38	97.4	38	100.0	76	98.7
		Yes	1	2.6	0	0.0	1	1.3

ZKS Jena Schumacher ADHERE T7_ae.sas 25AUG2022

T 329 AE: Number of AE and number and % of patients by localization - FAS, N= 80

	Treatment			
	Advantan® Cream 0.1% , N = 40		Advantan® Fatty Ointment 0.1%, N = 40	
Localization	AE	N (%) Patients*	AE	N (%) Patients*
0 AE	.	27 (67.5 %)	.	32 (80.0 %)
Not cutaneous	11	11 (27.5 %)	6	6 (15.0 %)
Cutaneous lesional	1	1 (2.5 %)	2	2 (5.0 %)
Cutaneous non-lesional	1	1 (2.5 %)	3	3 (7.5 %)

*One patient may have more than one AE, hence patient numbers do not sum up to 100%

ZKS Jena Schumacher ADHERE T7_ae.sas 25AUG2022

T 33 AE: Frequency analysis of details - FAS

		Treatment					
		Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
Question	Answer	N	%	N	%	N	%
Localization	Missing (no AE)	27	0.0	32	0.0	59	0.0
	Not cutaneous	11	84.6	6	54.5	17	70.8
	Cutaneous lesional	1	7.7	2	18.2	3	12.5
	Cutaneous non-lesional	1	7.7	3	27.3	4	16.7
SAE	Missing	27	0.0	32	0.0	59	0.0
	No	12	92.3	9	81.8	21	87.5
	Yes	1	7.7	2	18.2	3	12.5
Intensity	Missing (no AE)	27	0.0	32	0.0	59	0.0
	Mild	9	69.2	5	45.5	14	58.3
	Moderate	4	30.8	5	45.5	9	37.5
	Severe	0	0.0	1	9.1	1	4.2
Relationship to study medication	Missing (no AE)	27	0.0	32	0.0	59	0.0
	No-not probable	13	100.0	11	100.0	24	100.0
Action study medication	Missing (no AE)	27	0.0	32	0.0	59	0.0
	None	10	76.9	9	81.8	19	79.2
	Study medication stopped	1	7.7	0	0.0	1	4.2
	n.a. (study medication already finished)	2	15.4	2	18.2	4	16.7
Outcome	Missing (no AE)	27	0.0	32	0.0	59	0.0
	Recovered/resolved	8	61.5	6	54.5	14	58.3
	Ongoing	5	38.5	5	45.5	10	41.7

ZKS Jena Schumacher ADHERE T7_ae.sas 25AUG2022

T 104 AE: Frequency analysis of dermatological diseases details - FAS

	Treatment					
	Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
Action patient	N	%	N	%	N	%
	27	0.0	32	0.0	59	0.0
0=None	2	15.4	3	27.3	5	20.8
1=Medical treatment	5	38.5	4	36.4	9	37.5
1,2	2	15.4	2	18.2	4	16.7
1,3	1	7.7	0	0.0	1	4.2
2=Non-medical treatment	2	15.4	0	0.0	2	8.3
3=Other	1	7.7	2	18.2	3	12.5

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T 115 CM: Frequency analysis of application and dosing scheme - FAS

		Treatment					
		Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
Question	Answer	N	%	N	%	N	%
Application way	Missing/no medication	10	0.0	12	0.0	22	0.0
	oral	81	86.2	73	77.7	154	81.9
	topic	2	2.1	2	2.1	4	2.1
	subcutan	2	2.1	4	4.3	6	3.2
	transdermal	1	1.1	0	0.0	1	0.5
	inhalativ	7	7.4	14	14.9	21	11.2
	other	0	0.0	1	1.1	1	0.5
	vaginal	1	1.1	0	0.0	1	0.5
Dosing scheme	Missing/no medication	10	0.0	12	0.0	22	0.0
	daily	74	78.7	64	68.1	138	73.4
	once per week	1	1.1	1	1.1	2	1.1
	2-4 x per week	1	1.1	0	0.0	1	0.5
	as needed	17	18.1	27	28.7	44	23.4
	once	0	0.0	2	2.1	2	1.1
	other	1	1.1	0	0.0	1	0.5

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T 126 Therapies and procedures: Frequency analysis of procedure, localization and frequency by visit - FAS

		Treatment					
		Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
Question	Answer	N	%	N	%	N	%
Procedure	Missing/no procedure	17	0.0	11	0.0	28	0.0
	Interventional treatment during last 12 months	18	36.7	19	30.2	37	33.0
	Diagnostic procedure	20	40.8	28	44.4	48	42.9
	Physiotherapy	8	16.3	5	7.9	13	11.6
	Manual lymphatic drainage	1	2.0	0	0.0	1	0.9
	Ergotherapy	0	0.0	1	1.6	1	0.9
	Massage	1	2.0	3	4.8	4	3.6
	Other	1	2.0	7	11.1	8	7.1
Localization	Missing/no procedure	17	0.0	11	0.0	28	0.0
	Hands, lesional	1	2.0	4	6.3	5	4.5
	Upper extremity	16	32.7	28	44.4	44	39.3
	Lower extremity	10	20.4	6	9.5	16	14.3
	Torso	14	28.6	7	11.1	21	18.8
	Head area	5	10.2	12	19.0	17	15.2

		Treatment					
		Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
Question	Answer	N	%	N	%	N	%
	Unknown	3	6.1	6	9.5	9	8.0
Frequency	Missing/no procedure	17	0.0	11	0.0	28	0.0
	once per week	1	2.0	2	3.2	3	2.7
	2-4 x per week	2	4.1	1	1.6	3	2.7
	1-5 x in total	41	83.7	54	85.7	95	84.8
	5-10 x in total	4	8.2	3	4.8	7	6.3
	>10 x in total	1	2.0	2	3.2	3	2.7
	unknown	0	0.0	1	1.6	1	0.9

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T 137 Anamnesis: Frequency analysis of general anamnesis by visit, N= 80

			Treatment					
			Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
			N	%	N	%	N	%
Screening	Actual anamnesis	No complaints	40	100.0	37	92.5	77	96.3
		Other	0	0.0	3	7.5	3	3.8
	Concomitant diseases present/ new concomitant disease?	No	13	32.5	13	32.5	26	32.5
		Yes	27	67.5	27	67.5	54	67.5
	State of disease	Missing/na	13	0.0	13	0.0	26	0.0
		Inactive	3	11.1	2	7.4	5	9.3
		Active	24	88.9	25	92.6	49	90.7
	Concomitant disease controlled?	Missing/na	16	0.0	15	0.0	31	0.0
		Yes	24	100.0	25	100.0	49	100.0
	Drug therapy control?	Missing/na	16	0.0	15	0.0	31	0.0
		No	3	12.5	2	8.0	5	10.2
		Yes	21	87.5	23	92.0	44	89.8
V1 (Baseline)	Actual anamnesis	No complaints	39	97.5	38	95.0	77	96.3
		Infection	1	2.5	0	0.0	1	1.3
		Other	0	0.0	2	5.0	2	2.5
	Concomitant diseases present/ new concomitant disease?	No	40	100.0	40	100.0	80	100.0
	State of disease	Missing/na	40	0.0	40	0.0	80	0.0
	Concomitant disease controlled?	Missing/na	40	0.0	40	0.0	80	0.0
	Drug therapy control?	Missing/na	40	0.0	40	0.0	80	0.0
V2 (Day 14)	Actual anamnesis	Missing	1	0.0	3	0.0	4	0.0
		No complaints	39	100.0	37	100.0	76	100.0
	Concomitant diseases present/ new concomitant disease?	Missing	1	0.0	3	0.0	4	0.0
		No	38	97.4	35	94.6	73	96.1

			Treatment					
			Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
			N	%	N	%	N	%
		Yes	1	2.6	2	5.4	3	3.9
	State of disease	Missing/na	39	0.0	38	0.0	77	0.0
		Active	1	100.0	2	100.0	3	100.0
	Concomitant disease controlled?	Missing/na	39	0.0	38	0.0	77	0.0
		Yes	1	100.0	2	100.0	3	100.0
	Drug therapy control?	Missing/na	39	0.0	38	0.0	77	0.0
		No	0	0.0	1	50.0	1	33.3
		Yes	1	100.0	1	50.0	2	66.7
V3 (Day 28)	Actual anamnesis	Missing	1	0.0	2	0.0	3	0.0
		No complaints	35	89.7	37	97.4	72	93.5
		Infection	1	2.6	0	0.0	1	1.3
		Other	3	7.7	1	2.6	4	5.2
	Concomitant diseases present/ new concomitant disease?	Missing	40	0.0	40	0.0	80	0.0
	State of disease	Missing/na	37	0.0	40	0.0	77	0.0
		Active	3	100.0	0	0.0	3	100.0
	Concomitant disease controlled?	Missing/na	37	0.0	40	0.0	77	0.0
		Yes	3	100.0	0	0.0	3	100.0
	Drug therapy control?	Missing/na	37	0.0	40	0.0	77	0.0
		No	2	66.7	0	0.0	2	66.7
		Yes	1	33.3	0	0.0	1	33.3

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T 148 Anamnesis: Number of concomitant diseases and number and % of patients by type of disease, by visit - FAS, N= 80

		Treatment			
		Advantan® Cream 0.1% , N = 40		Advantan® Fatty Ointment 0.1%, N = 40	
Visit	Concomitant disease	Disease	N (%) Patients*	Disease	N (%) Patients*
Screening	0 Disease	.	13 (32.5 %)	.	13 (32.5 %)
	Internal	16	16 (40.0 %)	23	23 (57.5 %)
	Orthopedic	4	4 (10.0 %)	5	5 (12.5 %)
	Surgical	1	1 (2.5 %)	1	1 (2.5 %)
	Mental	2	2 (5.0 %)	4	4 (10.0 %)
	Other	7	7 (17.5 %)	5	5 (12.5 %)

*Multiple choice possible, hence patient numbers do not sum up to 100%

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T 159 Anamnesis: Number of new concomitant diseases and number and % of patients by type of disease, by visit - FAS, N= 80

		Treatment			
		Advantan® Cream 0.1% , N = 40		Advantan® Fatty Ointment 0.1%, N = 40	
Visit	Concomitant disease	Disease	N (%) Patients*	Disease	N (%) Patients*
V1 (Baseline)	0 Disease	.	40 (100.0 %)	.	40 (100.0 %)

*Multiple choice possible, hence patient numbers do not sum up to 100%

ZKS Jena Schumacher ADHERE T8_os.sas 25AUG2022

Anamnesis: Number of new concomitant diseases and number and % of patients by type of disease, by visit - FAS, N= 80

		Treatment			
		Advantan® Cream 0.1% , N = 40		Advantan® Fatty Ointment 0.1%, N = 40	
Visit	Concomitant disease	Disease	N (%) Patients*	Disease	N (%) Patients*
V2 (Day 14)	0 Disease	.	39 (97.5 %)	.	38 (95.0 %)
	Internal	1	1 (2.5 %)	.	
	Orthopedic	.		1	1 (2.5 %)
	Other	.		1	1 (2.5 %)

*Multiple choice possible, hence patient numbers do not sum up to 100%

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Anamnesis: Number of new concomitant diseases and number and % of patients by type of disease, by visit - FAS, N= 80

		Treatment			
		Advantan® Cream 0.1% , N = 40		Advantan® Fatty Ointment 0.1%, N = 40	
Visit	Concomitant disease	Disease	N (%) Patients*	Disease	N (%) Patients*
V3 (Day 28)	0 Disease	.	40 (100.0 %)	.	40 (100.0 %)

*Multiple choice possible, hence patient numbers do not sum up to 100%

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T 40 Anamnesis: Number of concomitant dermatological diseases and number and % of patients by disease, by visit - FAS, N= 80

			Treatment	
Visit	Disease	diagnosis	Advantan® Cream 0.1%	Advantan® Fatty Ointment 0.1%
Screening	0 diagnosis	---	26 (65.0 %)	29 (72.5 %)
	Autoimmune	Total		1 (2.5 %)
		Collagenosis		1 (2.5 %)
	Proliferative, oncological	Total	1 (2.5 %)	1 (2.5 %)
		BCC	1 (2.5 %)	1 (2.5 %)
	Psoriasiform	Total	2 (5.0 %)	1 (2.5 %)
		Psoriasis vulgaris	1 (2.5 %)	
		Other	1 (2.5 %)	1 (2.5 %)
	Inflammatory	Total	6 (15.0 %)	5 (12.5 %)
		Acne spp.		1 (2.5 %)
		Rosacea	3 (7.5 %)	2 (5.0 %)
		Other	3 (7.5 %)	2 (5.0 %)
	Infectious	Total	4 (10.0 %)	1 (2.5 %)
		Tinea	3 (7.5 %)	
		Verruca vulgaris	1 (2.5 %)	1 (2.5 %)
	Allergological	Total		3 (7.5 %)
		Urtikaria spp.		3 (7.5 %)
	Other	Total	2 (5.0 %)	1 (2.5 %)
		Hair diseases	1 (2.5 %)	
		Other	1 (2.5 %)	1 (2.5 %)

*Multiple choice possible, hence patient numbers do not sum up to 100%

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T 41 Anamnesis: Number of new concomitant dermatological diseases and number and % of patients by disease, by visit - FAS, N= 80

			Treatment	
Visit	**Disease**	**diagnosis**	**Advantan® Cream 0.1%**	**Advantan® Fatty Ointment 0.1%**
V1 (Baseline)	0 diagnosis	---	40 (100.0 %)	40 (100.0 %)

*Multiple choice possible, hence patient numbers do not sum up to 100%

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Anamnesis: Number of new concomitant dermatological diseases and number and % of patients by disease, by visit - FAS, N= 80

			Treatment	
Visit	**Disease**	**diagnosis**	**Advantan® Cream 0.1%**	**Advantan® Fatty Ointment 0.1%**
V2 (Day 14)	0 diagnosis	---	40 (100.0 %)	39 (97.5 %)
	Inflammatory	Total		1 (2.5 %)
		Other		1 (2.5 %)

*Multiple choice possible, hence patient numbers do not sum up to 100%

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Anamnesis: Number of new concomitant dermatological diseases and number and % of patients by disease, by visit - FAS, N= 80

			Treatment	
Visit	**Disease**	**diagnosis**	**Advantan® Cream 0.1%**	**Advantan® Fatty Ointment 0.1%**
V3 (Day 28)	0 diagnosis	---	39 (97.5 %)	37 (92.5 %)
	Proliferative, oncological	Total	1 (2.5 %)	
		Other	1 (2.5 %)	
	Inflammatory	Total		2 (5.0 %)
		Other		2 (5.0 %)
	Allergological	Total		1 (2.5 %)
		Urtikaria spp.		1 (2.5 %)

*Multiple choice possible, hence patient numbers do not sum up to 100%

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T 42 Anamnesis: Frequency analysis of dermatological diseases details by visit - FAS, N= 80

				Treatment					
				Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
Visit	Disease	Diagnosis	Localization	N	%	N	%	N	%
Screening	Missing/no disease	.		26	0.0	29	0.0	55	0.
	Autoimmune	Collagenosis	11,2	0	0.0	1	100.0	1	100.
	Proliferative, oncological	BCC	2,5	1	100.0	0	0.0	1	50.
			5=Head area	0	0.0	1	100.0	1	50.
	Psoriasiform	Psoriasis vulgaris	2,5	1	100.0	0	0.0	1	100.
		Other	4=Torso	0	0.0	1	100.0	1	50.
			5=Head area	1	100.0	0	0.0	1	50.
	Inflammatory	Acne spp.	4=Torso	0	0.0	1	100.0	1	100.
		Rosacea	5=Head area	3	100.0	2	100.0	5	100.
		Other	11,2,5	1	33.3	0	0.0	1	20.
			2=Upper extremity	1	33.3	0	0.0	1	20.
			2,3	0	0.0	1	50.0	1	20.
			3=Lower extremity	1	33.3	0	0.0	1	20.
			3,4	0	0.0	1	50.0	1	20.
	Infectious	Tinea	3=Lower extremity	3	100.0	0	0.0	3	100.
		Verruca vulgaris	12=Hands, perilesional	0	0.0	1	100.0	1	50.
			3=Lower extremity	1	100.0	0	0.0	1	50.
	Allergological	Urtikaria spp.	2=Upper extremity	0	0.0	1	33.3	1	33.
			3=Lower extremity	0	0.0	1	33.3	1	33.
			4=Torso	0	0.0	1	33.3	1	33.
	Other	Hair diseases	5=Head area	1	100.0	0	0.0	1	100.
		Other	4=Torso	1	100.0	1	100.0	2	100.
V1 (Baseline)	Missing/no disease	.		40	0.0	40	0.0	80	0.
V2 (Day 14)	Missing/no disease	.		40	0.0	39	0.0	79	0.
	Inflammatory	Other	2=Upper extremity	0	0.0	1	100.0	1	100.
V3 (Day 28)	Missing/no disease	.		39	0.0	37	0.0	76	0.
	Proliferative, oncological	Other	4=Torso	1	100.0	0	0.0	1	100.
	Inflammatory	Other	12,2,4,5	0	0.0	1	50.0	1	50.
			12,2,5	0	0.0	1	50.0	1	50.
	Allergological	Urtikaria spp.	2=Upper extremity	0	0.0	1	100.0	1	100.

11=Hands, lesional

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Anamnesis: Frequency analysis of dermatological diseases details by visit - FAS, N= 80

				Treatment					
				Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
Visit	Disease	Diagnosis	State	N	%	N	%	N	%
Screening	Missing/no disease	.	Missing/na	26	0.0	29	0.0	55	0.
	Autoimmune	Collagenosis	Inactive	0	0.0	1	100.0	1	100.
	Proliferative, oncological	BCC	Inactive	1	100.0	1	100.0	2	100.
	Psoriasiform	Psoriasis vulgaris	Inactive	1	100.0	0	0.0	1	100.
		Other	Active	1	100.0	1	100.0	2	100.
	Inflammatory	Acne spp.	Inactive	0	0.0	1	100.0	1	100.
		Rosacea	Inactive	1	33.3	1	50.0	2	40.
			Active	2	66.7	1	50.0	3	60.
		Other	Inactive	3	100.0	2	100.0	5	100.
	Infectious	Tinea	Inactive	3	100.0	0	0.0	3	100.
		Verruca vulgaris	Inactive	0	0.0	1	100.0	1	50.
			Active	1	100.0	0	0.0	1	50.
	Allergological	Urtikaria spp.	Inactive	0	0.0	3	100.0	3	100.
	Other	Hair diseases	Active	1	100.0	0	0.0	1	100.
		Other	Inactive	0	0.0	1	100.0	1	50.
			Active	1	100.0	0	0.0	1	50.
V1 (Baseline)	Missing/no disease	.	Missing/na	40	0.0	40	0.0	80	0.
V2 (Day 14)	Missing/no disease	.	Missing/na	40	0.0	39	0.0	79	0.
	Inflammatory	Other	Active	0	0.0	1	100.0	1	100.
V3 (Day 28)	Missing/no disease	.	Missing/na	39	0.0	37	0.0	76	0.
	Proliferative, oncological	Other	Active	1	100.0	0	0.0	1	100.
	Inflammatory	Other	Active	0	0.0	2	100.0	2	100.
	Allergological	Urtikaria spp.	Inactive	0	0.0	1	100.0	1	100.

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T 43 Anamnesis: Frequency analysis of changes in dermatologic anamnesis details by visit - FAS, N= 80

			Treatment					
			Advantan® Cream 0.1%		Advantan® Fatty Ointment 0.1%		Total	
Visit	Question	Answer	N	%	N	%	N	%
V1 (Baseline)	Known/new Typ I and/or Typ IV allergy	No	40	100.0	40	100.0	80	100.0
	Change in Job	No	40	100.0	40	100.0	80	100.0
	Job change relevant for hand eczema	Missing/na	40	0.0	40	0.0	80	0.0
	Change in dermatological anamnesis	No	40	100.0	40	100.0	80	100.0
	Anamnesis change relevant for hand eczema	Missing/na	40	0.0	40	0.0	80	0.0
	Change in leisure activities	No	40	100.0	40	100.0	80	100.0
V2 (Day 14)	Known/new Typ I and/or Typ IV allergy	Missing/na	1	0.0	3	0.0	4	0.0
		No	39	100.0	37	100.0	76	100.0
	Change in Job	Missing/na	1	0.0	3	0.0	4	0.0
		No	39	100.0	37	100.0	76	100.0
	Job change relevant for hand eczema	Missing/na	40	0.0	40	0.0	80	0.0
	Change in dermatological anamnesis	Missing/na	1	0.0	3	0.0	4	0.0
		No	39	100.0	37	100.0	76	100.0
	Anamnesis change relevant for hand eczema	Missing/na	40	0.0	40	0.0	80	0.0
	Change in leisure activities	Missing/na	1	0.0	3	0.0	4	0.0
		No	39	100.0	37	100.0	76	100.0
V3 (Day 28)	Known/new Typ I and/or Typ IV allergy	Missing/na	1	0.0	2	0.0	3	0.0
		No	39	100.0	38	100.0	77	100.0
	Change in Job	Missing/na	1	0.0	2	0.0	3	0.0
		No	39	100.0	38	100.0	77	100.0
	Job change relevant for hand eczema	Missing/na	40	0.0	40	0.0	80	0.0
	Change in dermatological anamnesis	Missing/na	1	0.0	2	0.0	3	0.0
		No	39	100.0	38	100.0	77	100.0
	Anamnesis change relevant for hand eczema	Missing/na	40	0.0	40	0.0	80	0.0
	Change in leisure activities	Missing/na	1	0.0	2	0.0	3	0.0
		No	38	97.4	37	97.4	75	97.4
		Yes	1	2.6	1	2.6	2	2.6

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T 164 Anamnesis: Descriptive analysis of frequency in hand washing by visit - FAS, N= 80

		Treatment		
Visit	Hand washing/day	Advantan® Cream 0.1%	Advantan® Fatty Ointment 0.1%	Total
Screening	N	40	40	80
	NMiss	0	0	0
	Mean	10.9	11.5	11.2
	StdDev	6.3	9.4	8
	Min	2	2	2
	P25	7	6	7
	Median	10	9.5	10
	P75	15	10.5	12.5
	Max	30	50	50
V1 (Baseline)	N	40	40	80
	NMiss	0	0	0
	Mean	11.3	11.5	11.4
	StdDev	6.6	9.4	8.1
	Min	2	2	2
	P25	7	6	7
	Median	10	9.5	10
	P75	15	10.5	12.5
	Max	30	50	50
V2 (Day 14)	N	39	37	76
	NMiss	1	3	4
	Mean	9.4	9.3	9.4
	StdDev	5.5	6.1	5.8
	Min	2	2	2
	P25	5	5	5
	Median	10	8	9
	P75	12	10	11.5
	Max	30	30	30
V3 (Day 28)	N	39	38	77
	NMiss	1	2	3
	Mean	10	9.2	9.6
	StdDev	5.6	5.6	5.6
	Min	2	1	1
	P25	6	5	5
	Median	10	8.5	9
	P75	12	11	12
	Max	30	25	30

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T 175 Vital signs: Descriptive analysis of blood pressure, heart rate and temperature by visit - FAS, N= 80

			Treatment		
Parameter	**Visit**	**Statistic**	**Advantan® Cream 0.1%**	**Advantan® Fatty Ointment 0.1%**	**Total**
Blood pressure systolic [mmHg]	V1 (Baseline)	N	40	40	80
		NMiss	0	0	0
		Mean	133	128.6	130.8
		StdDev	17.5	15.7	16.7
		Min	95	94	94
		P25	121	118.5	120.5
		Median	131	130	130
		P75	143	137.5	139.5
		Max	177	166	177
	V3 (Day 28)	N	39	38	77
		NMiss	1	2	3
		Mean	133.4	129.8	131.6
		StdDev	20.3	15.8	18.2
		Min	98	101	98
		P25	118	118	118
		Median	130	126.5	129
		P75	146	137	141
		Max	214	164	214
Blood pressure diastolic [mmHg]	V1 (Baseline)	N	40	40	80
		NMiss	0	0	0
		Mean	82	79.9	81
		StdDev	12	10.3	11.2
		Min	57	55	55
		P25	76.5	73	74
		Median	82	81	82
		P75	90.5	87.5	89
		Max	107	102	107
	V3 (Day 28)	N	39	38	77
		NMiss	1	2	3
		Mean	83.6	82.6	83.1
		StdDev	12.9	10.6	11.7
		Min	64	66	64
		P25	74	74	74
		Median	83	82.5	83
		P75	90	90	90
		Max	135	110	135
Heart rate [bpm]	V1 (Baseline)	N	40	40	80
		NMiss	0	0	0
		Mean	72.1	69	70.5
		StdDev	9.1	10.8	10.1

			Treatment		
Parameter	Visit	Statistic	Advantan® Cream 0.1%	Advantan® Fatty Ointment 0.1%	Total
		Min	51	51	51
		P25	64.5	60	63
		Median	72	69.5	71.5
		P75	78	76.5	78
		Max	89	91	91
	V3 (Day 28)	N	39	38	77
		NMiss	1	2	3
		Mean	74.3	74.7	74.5
		StdDev	10.1	10.6	10.3
		Min	52	52	52
		P25	69	68	69
		Median	73	75	74
		P75	79	81	80
		Max	104	104	104
Temperature aurikulär [°C]	V1 (Baseline)	N	40	40	80
		NMiss	0	0	0
		Mean	36.6	36.6	36.6
		StdDev	0.5	0.5	0.5
		Min	35.6	34.6	34.6
		P25	36.3	36.3	36.3
		Median	36.6	36.6	36.6
		P75	36.9	36.9	36.9
		Max	37.5	37.4	37.5
	V3 (Day 28)	N	39	38	77
		NMiss	1	2	3
		Mean	36.6	36.6	36.6
		StdDev	0.4	0.4	0.4
		Min	35.8	35.5	35.5
		P25	36.3	36.4	36.4
		Median	36.6	36.6	36.6
		P75	36.9	36.8	36.8
		Max	37.4	37.3	37.4

ZKS Jena Schumacher ADHERE T8_os.sas 25AUG2022

UNERWÜNSCHTE EREIGNISSE: ANZAHL, HÄUFIGKEIT, MIT PATIENTEN-IDENTIFIKATIONSNUMMER

BEHANDLUNGSGRUPPE XY , N=...

	Leicht		Mäßig		Schwer		Gesamt		Gesamt
	Related	NR*	Related	NR*	Related	NR*	Related	NR*	R+NR*
Organsystem A Ereignis 1	2(12%) N11** N12**	1(6%) N13**	0(0%)	3(18%) N14** N15** N16**	...	...	...	...	
Ereignis 2	...								

**NR: not related; related kann erweitert werden: sicher wahrscheinlich, möglich*

*** Patienten-Identifikations-Nr.*

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12 List of abbreviations and definition of terms

AE	adverse event
AMG	Medicinal Product Act (Germany)
BfArM	Federal Institute for Drugs and Medical Devices (Germany)
BL	Baseline Visit
BOB	Federal Agency (here: BfArM or PEI)
CPMP	Committee for Proprietary Medicinal Products (now Committee for Medicinal Products for Human Use)
EC	Ethics Committee
FTU	Finger Tip Unit
FU	Follow Up Visit
GCP	Good Clinical Practice
GCP-V	GCP Ordnance (Germany)
HECSI	Hand Eczema Severity Index
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGA	Investigator Global Assessment
IMP	Investigational Medical Product
IRB	Institutional Review Board
MPG	Medical Device Act (Germany)
QOLHEQ	Quality Of Life in Hand Eczema Questionnaire
PEI	Paul Ehrlich Institute
PI	Principal Investigator
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
V1-V3	Visit 1 – Visit 3
VAS	Visual Analogue Scale
ZKS	Zentrum für Klinische Studien (Center for Clinical Studies)