TREAT-Europe registry

TREatment of severe **AT**opic dermatitis

in children and adults

A multicentre cohort study

January, 30th, 2015

PROTOCOL TITLE PAGE

A 5 year multicentre prospective study evaluating systemic immunomodulating treatments in paediatric and adult patients with atopic dermatitis (AD).

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1. LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (ABR = Algemene Beoordeling en Registratie)
AD	Atopic Dermatitis
AE	Adverse Event
AEoSI	Adverse Event of Special Interest
AMC	Academic Medical Centre, Amsterdam
AZA	Azathioprine
BB-UVB	Broadband ultraviolet B
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; Centrale Commissie Mensgebonden Onderzoek
CDLQI	Children's Dermatology Life Quality Index
CsA	Cyclosporin A
CV	Curriculum Vitae
DMC	Data Monitoring Committee
EASI	Eczema Area and Severity Index
EC-MPS	Enteric-coated mycophenolate sodium
EMA	European Medicines Agency
EQ-5D	European Quality of Life - 5 Dimensions
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC	Informed Consent
IGA	Investigator's Global Assessment
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IUD	Intrauterine device
IUS	Intrauterine system
IVIG	Intravenous immunoglobulins
MedDRA	Medical Dictionary for Regulatory Activities
METC	Medical research ethics committee (MREC); medisch ethische toetsing commissie (METC)
MMF	Mycophenolate mofetil

MPA	Mycophenolic acid
MPS	Mycophenolate sodium
MTX	Methotrexate
NB-UVB	Narrowband ultraviolet B
P3NP	Type III procollagen peptide
PGA	Patient Global Assessment
POEM	Patient Oriented Eczema Measure
PROM	Patient Reported Outcome Measure
RCT	Randomized controlled trial
(S)AE	(Serious) Adverse Event
SCORAD	Severity Scoring of Atopic Dermatitis
SPC	Summary of Product Characteristics (officiële productinfomatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
TPMT	Thiopurine S-methyltransferase
UVA1	Ultraviolet A-1
Wbp	Personal Data Protection Act (Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met Mensen)

2. SUMMARY

2.1 Rationale

Atopic dermatitis (AD) is a chronic pruritic inflammatory skin disorder which is among the most common dermatological conditions and can have a major impact on the quality of life of patients. Most patients with AD can be treated effectively with emollients and topical anti-inflammatory agents. A subgroup of AD patients, the more severe cases, requires more than these treatments to control their skin disease. In these cases photo(chemo)therapy and systemic immunomodulating therapy is used.

Besides some randomized controlled trials (RCT) the evidence for these therapies is sparse, especially in children. There is little to no comparative and prospective data available which can give information about real life patients. Long-term follow-up data are often lacking and many treatments are prescribed off-label. Also novel biologic therapies are currently being tested in early phase clinical trials and will need careful follow-up. Therefore we will conduct a prospective cohort study for evaluating the use of systemic immunomodulating therapies in paediatric and adult patients with AD. The effectiveness and safety will be analyzed. The evaluation of phototherapy and intensive topical therapy will be optional.

2.2 Objectives

To evaluate in daily clinical practice

- Effectiveness
- Safety
- Differences between centres and countries

of systemic immunomodulating therapies in the AD population and in subgroups (e.g. patients with comorbidities, lactating women, pregnant women) at different time points (0, 6 weeks (optional for objective scoring), and then every 3 months, end of treatment and switch of therapy) for 5 years in several medical centres in Europe.

2.3 Study design

A 5-year multicentre prospective observational cohort study to evaluate systemic immunomodulating therapies in patients with AD.

2.4 Study population

All eligible patients, children/adults and male/female, who are started on systemic immunomodulating therapy (conventional agents (e.g. CsA, AZA, MTX, MPA) or new agents (e.g. biologics)) and who are willing to give consent for long-term follow up and access to all medical records.

2.5 Intervention

Systemic immunomodulating therapy given as treatment for AD. Observation period of 5 years.

2.6 Endpoints

- Effectiveness by:
    - Mean absolute and relative change of:
        - *Signs:* EASI;
        - *Symptoms:* POEM;
        - *Composite scale signs & symptoms:* SCORAD;
        - *Global assessment:* IGA, PGA;
        - *Quality of life:* Skindex-17, CDLQI, DLQI (optional).
    - Proportion of patients achieving EASI 50, 75 and 90 and IGA score of <3;
    - Long-term control of disease
        - Mean number of flares;
        - Mean frequency and duration of remission;
        - Mean frequency of rebound.
    - Mean drug survival (defined as duration from start to end) at different time points;
    - Mean time to onset of effect;
    - Type, frequency and potency of concomitant AD medication and rescue medication/intervention (e.g. high potency topical or systemic corticosteroids, antibiotics, hospitalization).
- Safety by:
    - SAEs;
    - AEs that cause stop or switch of therapy or change in dosage;
    - *For the above SAEs and AEs:* sort, frequency, severity, probability of relationship with treatment (coded according to MedDRA).
- Differences between centres and countries by:
    - Types and dosages of systemic immunomodulating therapies;
    - Monitoring of systemic immunomodulating therapies (e.g. TPMT at baseline);
    - Treatment algorithms (sequence of treatments).

2.7 Nature and extent of the burden and risks associated with participation, benefit and group relatedness

Patients will visit the dermatology department based on clinical practice. Before starting systemic immunomodulating therapy as usual, evaluation of medical history, concomitant medications, physical examination, severity of AD, laboratory and urine-analysis will be performed dependent on the therapy chosen. After starting therapy patients will be evaluated as in routine clinical practice, for the study at least at week 0, 6 and then every 3 months and end or switch of treatment. These visits include evaluation of the severity of AD, evaluation of the use of concomitant medications, collection of efficacy and safety data of the treatment used, physical examinations and laboratory and urine-analysis. Additional visits may be required to assess any AD exacerbations reported or if AEs require monitoring.

3. INTRODUCTION AND RATIONALE

3.1 Atopic Dermatitis

AD is a chronic pruritic, inflammatory skin disease which has a fluctuating course [1-3]. It is among the most common dermatological conditions and may have a major impact on the quality of life of patients and their families [4]. The prevalence of AD has increased steadily in recent decades and now varies between 1-10% in adults and up to 20% in children, living in industrialized countries [5, 6].

The disease is characterized by erythema, oedema, and vesicles in the acute stage. In the chronic stage, lichenification often occurs [7]. Variations in localisations of eczema occur with age. AD generally follows a chronic relapsing course, but spontaneous remission may occur or is induced by appropriate treatment [2]. Certain triggers or factors (e.g. contact allergens, stress, infection) can affect and aggravate AD. The disease has a strong and clinicaly relevant association with a range of inflammatory comborbidities, in particular affecting the airways (asthma, hay fever) and food allergies, atopic eye disease, clinical depression and attention-deficit hyperactivity disorder [8].

Two major models currently exist to explain the pathogenesis. Traditionally AD is seen as primarily an immune function disorder in which allergen specific T-cells in the skin are activated [9]. The other model describes AD as a result of an intrinsic defect in epidermal barrier in which a mutation of filaggrin has a central role [10]. There is increasing recognition that AD is a highly complex syndrome with multiple causes and mechanisitic pathways that clinically can be distinguished by age of onset, severity of illness, ethnic modifiers, response to therapy, and extrinsic flare factors (e.g. infections, stress) [11].

3.2 Treatment

Topical treatment with corticosteroids, calcineurin inhibitors like tacrolimus and pimecrolimus and coal tar is often used in combination with emollients to treat the signs and symptoms of AD [12]. When necessary it can be given in combination with antipruritics, like antihistamines, and oral antibiotics. Ideally, long term and continuous treatment with (potent) topical corticosteroids should be avoided because of local (atrophy, telangiectasia) and systemic side effects (inhibition of adrenal hormones or growth hormone). For the more severely affected patients who are only treatable with long term high potency topical steroids or have inadequate response, experience side effects of, or have contraindications for topical therapy, treatment with phototherapy or systemic immunomodulators may be necessary [13].

Phototherapy is used as most patients with AD improve during the summer season [14]. Different types of phototherapy are used for AD, including photochemotherapy (PUVA), Ultraviolet A-1 (UVA1), broad band (BB) - and narrow band (NB) - Ultraviolet B (UVB). However, few well-designed and adequately powered RCTs have been undertaken and therefore conclusions must be drawn carefully [15-17].

For systemic immunomodulating therapy, data from routine clinical care suggest that more than 10% of all patients with AD receive this kind of therapy [12, 18]. Possible systemic immunomodulating therapies are systemic glucocorticosteroids, cyclosporin A (CsA), methotrexate (MTX), azathioprine (AZA), intravenous

immunoglobulin (IVIG), and mycophenolic acid (MPA) [19, 20]. Also new medicines are being tested (phase III studies) and may cause future success [21, 22].

A retrospective study (2001-2011) was conducted in two Dutch Academic hospitals to identify the various forms of systemic immunomodulating therapy given to patients with AD, its effectiveness, tolerability and safety and the treatment algorithms used. A systematic review from 2014 on the efficacy and safety of immunomodulating systemic treatments for moderate-to-severe AD, states that more head-to-head trials or prospective registries are required [23]. This review also states that RCTs on children are missing for many relevant interventions and that more research in this age group is needed. In 2011 the TREAT survey was conducted to identify the current prescribing practice of systemic immunosuppression in refractory paediatric AD [24]. This survey confirmed the wide variation in prescribing systemic immunosuppressives, with first-line drugs of choice being CsA, oral corticosteroids and AZA.

This protocol for an international prospective database will focus on evaluation of systemic immunomodulating therapy. The evaluation of phototherapy and intensive topial therapy will be optional.

3.2.1 Systemic glucocorticosteroids

Systemic glucocorticosteroids are frequently used in clinical practice [18], but evidence from RCTs is scarce and most RCTs investigate short-term efficacy and mainly concern children [25-27] . A trial from 2010 showed that almost all patients treated with prednisolone experienced a significant rebound after the end of active treatment [25]. Currently systemic glucocorticosteroids are not recommended for long-term use [20, 23], but may be used for exacerbations of AD (up to 1 week) [20].

In the previously mentioned TREAT survey systemic glucocorticosteroids were first-line drugs of choice in children and were typically used for short-course flare control [24].

3.2.2 Cyclosporin

CsA is the best evaluated systemic treatment option for adults and children with moderate-to-severe AD [6, 13, 23, 28]. It is also the only systemic immunomodulating treatment approved by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) [20]. For adults CsA was shown to be more effective than placebo in RCTs and in head-to-head trials superior to prednisone, IVIG, UVAB and similar to MMF. Both short- and long-term therapy may be useful, but long-term is guided by clinical efficacy and tolerance of the drug [20]. The most frequently side effects are renal dysfunction and hypertension, which are dose dependent, related to the duration of the therapy and usually reversible [25, 29]. Currently CsA is recommended as first line treatment for short-term therapy in adults with moderate-to-severe AD [23].

For children above 2 years there is less experience and evidence. Treatment up to 1 year seems effective and safe [30]. In a survey it was mentioned to be one of the first-line drugs of choice in children with AD, with an average duration of treatment of 2-4 months with a maximum of 12 months in over half of the respondents [24].

3.2.3 Azathioprine

A systematic review of the off-label use of AZA in dermatology recommends the use in patients with severe AD, to whom other registered medication is not effective or cannot be given because of contraindications or side effects [31, 32]. Besides, a RCT which compared the efficacy and safety of MTX and AZA in adults with severe AD, showed that this treatment can achieve clinically relevant improvement and is safe in the short term [33]. However, thiopurine therapy has been recently associated with an increased risk of lymphoproliferative disorders in inflammatory bowel disease [34, 35]. Side effects most frequently seen are abnormalities in blood count like lymphocytopenia [33].

AZA in adults may be used for moderate-to-severe AD in adults for short-term and long-term use up to 24 weeks [23]. Evidence for long-term use more than 24 weeks is lacking.

For children above 2 years with severe AD there are no published prospective clinical trial data [20], only 4 observational studies [36-39]. In the TREAT survey AZA was a less popular first-line drug of choice for children [24].

3.2.4 Methotrexate

MTX is a safe and effective treatment for chronic inflammatory conditions like psoriasis and arthritis [40]. Last few years MTX is also being used for moderate-to-severe AD. Different studies (only 1 RCT) show that MTX may be an effective treatment and a good alternative for patients with AD when standard therapy with topical corticosteroids and emollients is insufficient [33, 40, 41]. Known side effects include bone marrow suppression, gastrointestinal toxicity and liver function abnormalities [33, 40, 42]. The use of folic acid supplements can reduce the side effects [40, 43]. MTX can be used for short-term use and long-term use of 24 weeks in adults with moderate-to-severe AD [23, 44]. Long-term data are missing.

In children above 8 years with severe AD 1 prospective randomized study showed MTX as an effective treatment [45]. It was especially mentioned as a third-line drug of choice in children in the TREAT survey, with an average duration of treatment of 4-12 months [24]

3.2.5 Intravenous immunoglobulins

IVIG should be considered only in patients with severe disease that cannot be controlled with other systemic therapy, like CsA, MTX or AZA and should be used as adjunctive therapy [46, 47]. The effectiveness of monotherapy with IVIG has not been proved adequately and therefore IVIG is currently not recommended [23].

3.2.6 Mycophenolate acid (incl. mycophenolate mofetil (MMF) and sodium(MPS))

MPA may be considered in adult patients who have inadequate effectiveness of or who have contraindications for CsA. The result of different case series varies, but all showed mild side effects [4, 6, 29, 48-50]. A RCT, which compared MPS with CsA as long-term treatment in adult patients with severe AD, showed that although the clinical improvement with MSA is delayed in comparison with CsA, it is as effective as CsA after ten weeks and can be used as a treatment for patients with AD [29]. The most common side effects are gastrointestinal complaints or haematological abnormalities [3, 29, 44]. Because of only one trial investigating MPA, there is a

weak recommendation for MPA as maintenance treatment of severe AD after induction of remission by CsA [23]. Long-term data, more than 30 weeks, are not available.
In children with severe AD above 2 years there is some evidence for effectiveness of MMF [44]. The TREAT survey noticed that it appeared to be used infrequently by the European physicians [24].

3.3 Rationale

As the prevalence is high (1-10% in adults; up to 20% in children) and quality of life can be seriously affected, AD is an important dermatological condition. In practice, for patients with AD for whom topical therapy is no option, systemic immunomodulating therapies are often prescribed. However high quality evidence for these therapies is sparse besides some RCTs, and also long-term follow-up data are often lacking. Many treatments are prescribed off-label. CsA, besides topical treatments, is the only treatment approved by the EMA and FDA. There is little to no comparative and prospective cohort data available which can help to provide more information in real life patients, especially in children and subgroups. These data are important as it may differ from RCT data, where patients are often more healthy and have less comorbidities, and consequently may not be representative of the whole population [51]. In clinical practice there is a resulting lack of clear management guidance. A prospective cohort study is therefore of vital importance to evaluate the real world use of systemic immunomodulating therapies in paediatric and adult patients with moderate-to-severe AD to provide effectiveness and safety data beyond the confines of short-term RCTs.

4. STUDY OBJECTIVES

To evaluate in daily clinical practice

- Effectiveness
- Safety
- Differences between centres and countries

of systemic immunomodulating therapies in the AD population and in subgroups (e.g. patients with comorbidities, lactating women, pregnant women) at different time points (0, 6 weeks (optional for objective scoring), and then every 3 months, end of treatment and switch of therapy) for 5 years in several medical centres in Europe.

5. STUDY DESIGN

This study is a prospective observational cohort study to evaluate systemic immunomodulating therapies in patients, children and adults, with AD for 5 years in several medical centres in Europe.

6. STUDY POPULATION

The population consists of all patients, children and adults, with AD who start with any type systemic immunomodulating therapy after they were found eligible for these treatments according to the treating dermatologist, taking into account the eligibility criteria for the specific drugs and the in- and exclusion criteria. Patients are considered to have moderate-to-severe AD when starting with systemic immunomodulating therapy.

6.1 Inclusion criteria

- Subject is of any age (adults and children);
- Has a diagnosis of AD, based on the U.K. working party's diagnostic criteria [52] (see appendix A);
- Starts with conventional systemic immunomodulating therapy (CsA, systemic glucocorticosteroids, AZA, MTX, IVIG, MPA) or new/investigational drugs;
- Has voluntarily signed and dated an informed consent prior to any study related procedure and is willing to comply with the requirements of this study protocol which has been approved by an Institutional Review Board (IRB/Independent Ethics Committee (IEC)).

6.2 Exclusion criteria

- Only use of antibiotics or antihistamines;
- Systemic drug(s), that can be given to patients with AD, but is given as medication for diseases other than AD.

6.3 Contraindications

For all contraindications see SPC text.

7. TREATMENT OF SUBJECTS

7.1 Investigational treatments

Patients will be treated with systemic immunomodulating therapy as in daily practice. Therapies will include systemic glucocorticosteroids, CsA, AZA, MTX, MPA, IVIG or new systemic immunomodulating drugs. The type of treatment and dosing regime will be determined by the treating physician/dermatologist. Phototherapy and intensive topical therapy will be optional.

7.2 Concomitant therapy

There is no restriction to concomitant therapy outside drugs that may give interactions with the prescribed therapy. Concomitant drugs will be registered.

7.3 Rescue medication

In case of exacerbation or rebound of AD, additional systemic or topical medication may be required. Rescue treatment may include the use of more potent topical steroids, systemic glucocorticosteroids, change or start of antihistamines and antibiotics. Type, dosing and duration of these drugs will be registered.

8. METHODS

8.1 Study endpoints

- Effectiveness by:
    - Mean absolute and relative change of:
        - *Signs:* EASI;
        - *Symptoms:* POEM;
        - *Composite scale signs & symptoms:* SCORAD;
        - *Global assessment:* IGA, PGA;
        - *Quality of life:* Skindex-17, CDLQI, DLQI (optional).
    - Proportion of patients achieving EASI 50, 75 and 90 and IGA score of <3;
    - Long-term control of disease
        - Mean number of flares;
        - Mean frequency and duration of remission;
        - Mean frequency of rebound.
    - Mean drug survival (defined as duration from start to end) at different time points;
    - Mean time to onset of effect;
    - Type, frequency and potency of concomitant AD medication and rescue medication/intervention (e.g. high potency topical or systemic corticosteroids, antibiotics, hospitalization).
- Safety by:
    - SAEs;
    - AEs that cause stop or switch of therapy or change in dosage;
    - *For the above SAEs and AEs:* sort, frequency, severity, probability of relationship with treatment (coded according to MedDRA).
- Differences between centres and countries by:
    - Types and dosages of systemic immunomodulating therapies;
    - Monitoring of systemic immunomodulating therapies (e.g. TPMT at baseline);
    - Treatment algorithms (sequence of treatments).

8.2 Study procedure/visit assessments

The full assessment schedule is presented at the end of the protocol, see table 1. Visits will be performed at baseline, week 6 (optional for objective scoring, mandatory for PROMs) and subsequently every 3 months. Visit frequency may be reduced to 6 months after 2 years of monitoring. Additional visits may be necessary in case of AD exacerbation or if AEs require close monitoring.

8.2.1 In- and exclusion criteria

Patients will be screened to ensure they meet all inclusion criteria and none of the exclusion criteria specified in section 6.1 and 6.2.

8.2.2 Informed Consent

Signed informed consent will be obtained from the subject before any study-related procedures are undertaken. When there are relevant amendments for a patient, a new informed consent will be signed.

8.2.3 Subject characteristics collected at baseline

The following information will be collected:

- **Demographics**: date of birth, sex, ethnicity, educational status.
- **Relevant medical history and current concomitant medications**: relevant medical history includes malignancies (skin versus others) and medical conditions for which currently medication is taken. Also history of tobacco and alcohol use will be obtained.
- **AD history**: A detailed record of the patient's atopic history (date of onset, how diagnosis is established, number of hospitalizations, number of day care treatments) and former phototherapy or systemic therapy for AD (including frequency, duration, effect of treatment, AEs, reason for stop).
- **Allergies**: This will include known allergies (e.g. inhalation, food, contact). Results and dates of epicutaneous allergy tests will be registered as well as IgE specific serum levels in the past (if present).
- C**urrent AD therapy**: This includes all medication for AD taken (systemic immunomodulators, phototherapy, antihistamines, antibiotics, topical therapy, emollients).

8.2.4 Concomitant and rescue medication

See section 7.2 and 7.3.

8.2.5 Vital signs

Blood pressure, body weight and length will be obtained at baseline. Blood pressure will be followed in time.

8.2.6 Physical examination

This includes skin type (at baseline), examination of the skin and lymph nodes. If indicated the physical examination can be expanded.

8.2.7 Laboratory tests

Blood samples for laboratory testing will be collected. The laboratory tests are listed in table 2. Which tests are being done depends on the prescribed therapy. Unscheduled laboratory safety testing may be performed at any time to assess any perceived safety concern. Clinically relevant deviations should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Laboratory values which are considered an AE are those in which the AD treatment is adjusted, like skipping or lowering dosage or stopping treatment.
A certified local laboratory will process and provide results for the general laboratory tests. All abnormal laboratory test results that are considered clinically significant by the local investigator will be followed to a satisfactory resolution.

8.2.8 Pregnancy test

Pregnancy tests are required for all women of child-bearing potential and if the prescribed therapy requires this. A serum pregnancy test or urine pregnancy test can be performed.

8.2.9 Effectiveness outcome parameters

The following assessments will be performed every visit. Sites should make every attempt to have the same investigators conduct these assessments throughout the study for each patient. Information and instructions on the clinical severity measures will be provided to the investigators.

8.2.9.1 Eczema Area and Severity Index (EASI)

See appendix B.

8.2.9.2 Investigators Global Assessment (IGA)

See appendix C.

8.2.9.3 Patients Global Assessment (PGA)

See appendix D.

8.2.9.4 Scoring of Atopic dermatitis index (SCORAD)

See appendix E.

8.2.9.5 Patient Oriented Eczema Measurement (POEM)

See appendix F, G, H.

8.2.9.6 Skindex-17

See appendix I.

8.2.9.7 Children's Dermatology Life Quality Index (CDLQI)

See appendix J.

8.2.10 Safety outcome parameters

SAEs and AEs who cause stop or switch of therapy or change of dosage will be collected every visit. Sort, frequency, severity (mild, moderate, severe) and probability of the relation with treatment (not, unlikely, possible, probable, definitely) will be collected of these SAEs en AEs. These will be registered according to MedDRA.

Rescue and concomitant medication will be registered, see section 7.2 and 7.3. If concomitant topical steroids are used, potency will be recorded.

8.3 Removal of subject from study

8.3.1 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences.

8.3.2 Replacement of individual subjects after withdrawal

When patients are withdrawn from the study, they will not be replaced but a multiple imputation method will be used to replace missing observations.

8.3.3 Follow-up of subjects withdrawn from treatment

Patients who discontinue their therapy will be followed to investigate long term efficacy and safety during 2 years with visits every 6 months (first visit after 3 months, then every 6 months). Patients with medication related (S)AEs will be followed until the (S)AEs are resolved. Patients who fail to come to their scheduled/necessary control visits (whether or not on medication) will be persuaded to come regularly.

9. SAFETY REPORTING

9.1 AEs, SAEs and SUSARs

9.1.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to any of the investigational products. Only adverse events that cause stop or switch of therapy or change of dosage will be reported by the investigator or his staff.

9.1.2 Serious adverse events (SAEs)

A SAE is any untoward medical occurrence or effect that at any dose:

- Results in death;
- Is life threatening (at the time of the event);
- Requires hospitalisation or prolongation of existing inpatients' hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

All SAEs will be reported to the Data Monitoring Committee (DMC).

9.2 Regular safety report

The investigator will regularly submit a safety report, together with the progress report, to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- A list of all suspected serious adverse reactions, along with an aggregated summary table of all reported SAEs, ordered by organ system, per study;
- A report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.3 Follow-up of adverse events

All related (S)AEs will be followed until they have abated, or until a satisfactory resolution has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

10. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

10.1 Statistical and analytical plan

The objectives of the statistical analyses are to evaluate the efficacy and safety of all systemic immunomodulating therapies included.

10.1.1 Analysis population

The population consists of all subjects who are included in the study and received at least one dose of systemic immunomodulating therapy.

10.1.2 Planned methods of statistical analysis

The statistical tests for the endpoints will be performed at the significance level 0.05. All p-values will be rounded to three decimal places. Descriptive statistics will be provided. These include the number of observations, mean, standard deviation, minimum, first quartile, median, third quartile, and maximum for continuous variables; and counts and percentages for discrete variables. The analyses will be performed using SPSS.

Analyses will be stratified according to age bands, gender, disease severity, AD with and without concomitant allergy, and centre/country.

10.1.3 Analysis of demographic and baseline characteristics

The baseline and demographic variables will be presented by proportions (%) or mean (standard deviation) or median (interquartile range) for categorical and continuous variables, respectively. Categorical variables will be compared using the Pearson's chi-square test (or Fischer's exact test as appropriate). Continuous variables will be tested using the one-way ANOVA test or the Kruskal Wallis test for parametric and nonparametric variables respectively. An alpha significance level of 0.05 (2-side test) will be considered statistically significant.

Statistical tests will be performed to access the comparability of the treatment arms. Continuous variables will be analysed using one-way analysis of variance (ANOVA), and discrete variables will be analysed using Fisher's Exact test.

10.1.4 Analysis of efficacy

The efficacy variables measured at different time points will be compared between the different therapies using the Pearson`s chi-square test (or Fischer's exact test as appropriate) for categorical variables. The one-way ANOVA test or the Kruskal Wallis test for parametric and nonparametric variables respectively.

10.1.5 Analysis of safety

Treatment-emergent AEs will be summarized by treatment group using descriptive statistics. Treatment-emergent AEs are defined as events with an onset date after the first study drug until the end of the study. SAEs with onset after informed consent but before the first drug administration will be considered as pre-

treatment SAEs and reported separately. In case of increasing severity of an existing AE, the worsening will be considered as a new AE with a new onset date.

AEs will be tabulated by system organ class and preferred term, whereby the most current implemented MedDRA dictionary will be used. AEs and SAEs who cause switch or stop of therapy or change of dosage will be summarized. Also, summaries by frequency, sort, severity and relationship to study drug will be done for these AEs and SAEs. Certain (S)AEs leading to premature withdrawal, will be listed and described in detail.

10.1.6 Analysis of drug survival

Drug survival will be analysed with the Kaplan-Meier method. Drug survival between different treatments will be compared using the log rank test.

10.2 Determination of sample size

Based on the results of the TREAT survey [24] we expect that at least 800 patients can be recruited within 5 years, 344 of whom are receiving CsA, 246 systemic glucocorticosteroids, and 173 AZA. With an adjusted alpha-level of 0.01 our study has >99% power to detect clinically relevant group differences in EASI change [53]. 92 patients per group are required for group comparisons with 80% power (adjusted alpha level 0.01).

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be performed in accordance with the protocol, International Conference on Harmonization (ICH) guidelines and the ethical principles that have the origin in the “Declaration of Helsinki”.

11.2 Recruitment and consent

Patients will be recruited using different strategies. Firstly, eligible patients will be recruited from the outpatient clinics of the participating centres. Secondly, local dermatologists will be made aware of the study and requested to recruit and refer eligible patients. The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study.

It is the responsibility of the investigator to obtain written informed consent (according to local legal requirements and regulations). The information is intended to give each participant a thorough understanding of the purpose and the nature of the study, the cooperation required and anticipated benefits and potential hazards of the study.

The following basic elements will be included in the written information for the patient:

- A statement that the study involves research;
- A full and fair explanation of the procedures to be followed;
- A full explanation of the nature, expected duration, and purpose of the study;
- A description of any reasonable foreseeable risks or discomforts to the patient;
- A description of any benefits which may reasonably be expected;
- A statement indicating that the patient agrees to allow authorized personnel of the Coordinating Centre, who are bound to secrecy, to review the patient's records if required;
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits, in which case the patient will receive standard treatment with the same degree of care;
- A consent form to be signed by the patient or his/hers relative will be made available. This form must first be approved by the responsible Ethics Committee.

11.3 Benefits and risks assessment, group relatedness

Patients will visit the dermatology department based on clinical practice. After starting therapy patients will be evaluated as in routine clinical practice, for the study at least at week 0, 6, and then every 3 months. Additional visits may be required to assess any AD exacerbations reported or if AEs require close monitoring.

Extra procedures consist of filling out questionnaires and will require extra time from patients.

Risks are as in common practice. Benefits can be more evaluation of screening, monitoring and treatment.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data will be handled confidentially and if possible anonymously. Where it is necessary to be able to trace data to an individual subject, a subject identification code list will be used to link the data to the subject. The code will not be based on the patient initials and birth-date. The key to the code will be safeguarded by the investigator. The handling of personal data complies with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, Wbp). All study data will be collected using an electronic data capture system.

12.2 Monitoring and Quality Assurance

This study will be monitored following the guidelines of the Academic Medical Centre (AMC).

12.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects of the study;
- The scientific value of the study;
- The conduct or management of the study;
- The quality or safety of any intervention used in the study.

All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the investigator/sponsor.

12.4 Regular progress report

The investigator will regularly submit a summary of the progress of the study to the accredited METC. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the study, AEs/ SAEs, other problems and amendments.

12.5 Public disclosure and publication policy

Core publication(s) will be authored by participating authors of the Departments of Dermatology from the Academic Medical Center Amsterdam, the department of dermatology from who contributed significantly to the implementation and conduct of the study and non-site personnel who contributed substantially to the design, interpretation or analysis of the study. Scientists making significant contributions to the study will be included in the list of authors.

Development of the core publication will be coordinated by a publication committee whose membership will include investigators who provided significant input into study design, implementation, conduct and

interpretation, in addition to the scientific personnel responsible for study conduct. Results will be published regardless the nature of the outcomes.

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TABLES

TABLE 1: ASSESSMENT SCHEDULE/STUDY ACTIVITIES

	Baseline	3 monthly visits	Final visit	Additional visits
In- and exclusion criteria	X			
Informed consent	X			
Demographics	X			
Medical history	X	X	X	X
AD history	X			
Allergies	X			
Concomitant medication	X	X	X	X
Current AD therapy	X	X	X	X
Rescue medication		X	X	X
Adverse events		X	X	X
Vital signs	X	X	X	X
Physical examination	X	X	X	X
Pregnancy test*	X			
Laboratory tests	X	X	X	X
Clinical Evaluation				
EASI	X	X	X	X
IGA	X	X	X	X
SCORAD	X	X	X	X
Patient Reported Outcomes				
PGA	X	X	X	X
POEM	X	X	X	X
Skindex-17	X	X	X	X
CDLQI	X	X	X	X
DLQI (optional)	(X)	(X)	(X)	(X)

* = If applicable

TABLE 2A: MANDATORY LABORATORY TESTS AT BASELINE

	THERAPIES						REFERENCE VALUES		UNIT
	CsA	**AZA**	**MTX**	**IVIG**	**MPA**	**New**	Female	Male	
HEMATOLOGY									
Haemoglobin	X	X	X	X	X		7.5-10.0	8.0-10.5	mmol/L
Leukocytes	X	X	X	X	X		4.0-10.5	4.0-10.5	10^E9/L
Leukocytes differentiation	X	X	X	X	X				
Thrombocytes	X	X	X	X	X		150-400	150-400	10^E9/L
CHEMISTRY									
Sodium	X						135-145	135-145	mmol/LL
Potassium	X						3.5-4.5	3.5-4.5	mmol/L
Creatinin	X	X	X		X		65-95	75-110	µmol/L
Urea	X						3.0-7.2	3.0-7.2	mmol/L
AST			X				<40	< 40	U/L
ALT	X	X	X		X		< 45	< 45	U/L
Gamma GT	X	X	X		X		< 40	< 60	U/L
Alkaline phosphate	X	X	X		X		40-120	40-120	U/L
Bilirubin total	X	X	X		X		< 17	< 17	µmol/L
Triglyceride	X						0.5-2.0	0.5-2.0	mmol/L
Cholesterol total	X						3.9-6.5	3.7-6.5	mmol/L
URINE									
Sediment	X		X		X				
Pregnancy urine	X	X	X		X		Negative -Positive	N.A.	
OTHERS									
IgE*	X	X					0-100	0-100	kU/L
P3NP			X				1.7-4.2	1.7-4.2	µg/L
TPMT**		X					48.9-79.9	48.9-79.9	µmol/g protein/h
Hepatitis B/C, HIV**			X				Negative-Positive	Negative -Positive	
FLG swap**	X	X	X	X	X				

N.A. = not applicable
* = At baseline, only if unknown/never done before
** = optional

TABLE 2B: MANDATORY LABORATORY TESTS AT 3-MONTLY VISITS

	THERAPIES						REFERENCE VALUES		UNIT
	CsA	**AZA**	**MTX**	**IVIG**	**MPA**	**New**	Female	Male	
HEMATOLOGY									
Haemoglobin	X	X	X	X	X		7.5-10.0	8.0-10.5	mmol/L
Leukocytes	X	X	X	X	X		4.0-10.5	4.0-10.5	10^E9/L
Leukocytes differentiation	X	X	X	X	X				
Thrombocytes	X	X	X	X	X		150-400	150-400	10^E9/L
CHEMISTRY									
Potassium							3.5-4.5	3.5-4.5	mmol/L
Creatinin	X	X			X		65-95	75-110	µmol/L
Urea	X						3.0-7.2	3.0-7.2	mmol/L
AST	X	X	X		X		<40	< 40	U/L
ALT	X	X	X		X		< 45	< 45	U/L
Gamma GT	X	X	X		X		< 40	< 60	U/L
Alkaline phosphate	X	X	X		X		40-120	40-120	U/L
Bilirubin total	X	X	X		X		< 17	< 17	µmol/L
Triglyceride	X						0.5-2.0	0.5-2.0	mmol/L
Cholesterol total	X						3.9-6.5	3.7-6.5	mmol/L
OTHERS									
P3NP			X				1.7-4.2	1.7-4.2	µg/L

N.A. = not applicable

APPENDICES

APPENDIX A: U.K. WORKING PARTY'S DIAGNOSTIC CRITERIA

Must have:

- An itchy skin condition (or parental report of scratching or rubbing) in the past 12 months

Plus three or more of the following:

- History of involvement of the skin creases (fronts of elbows, behind knees, fronts of ankles, around neck or around eyes)
- Personal history of asthma or hay fever (or history of atopic disease in first-degree relative if child aged > 4 years)
- History of generally dry skin in the past year
- Onset before the age of 2 years (not used if child aged < 4 years)
- Visible flexural dermatitis (including dermatitis affecting cheeks or forehead and outer areas of limbs in children aged < 4 years)

APPENDIX B: EASI

Patient initials: __ __ __ **Date: __ __ __ __ __ __**
Birth year: __ __ __ __
Visit nr: __ __

	None	Mild	Moderate	Severe			
Surface %	0	1-9	10-29	30-49	50-69	70-89	≥ 90
SCORE	**0**	**1**	**2**	**3**	**4**	**5**	**6**

	Head	**Arms**	**Trunk**	**Legs**	
Surface					
*	*** 0.1**	*** 0.2**	*** 0.3**	*** 0.4**	
BSA	+	+	+	=	

EASI	**Head**	**Arms**	**Trunk**	**Legs**	
Erythema					
Induration/Papulation					
Excoriations					
Lichenification					
Som					
Surface score					
Som * Surface					
*	*** 0.1**	*** 0.2**	*** 0.3**	*** 0.4**	
Total	**+**	**+**	**+**	**=**	

Name investigator: _____

APPENDIX C: IGA

Investigator's Global Assessment

0 clear: no inflammatory signs of AD

1 almost clear: just perceptible erythema and just perceptible papulation/infiltration

2 mild disease: mild erythema and mild papulation/ infiltration

3 moderate disease: moderate erythema and moderate papulation/infiltration

4 severe disease: severe erythema and severe papulation/ infiltration

5 very severe disease: severe erythema and severe papulation/ infiltration with oozing/crusting

APPENDIX D: PGA

Patient's Global Assessment (English)

0 clear

1 almost clear

2 mild disease

3 moderate disease

4 severe disease

5 very severe disease

Patient's Global Assessment (Dutch)

0 geen aandoening

1 bijna geen aandoening

2 milde ziekte

3 matige/middelmatige ziekte

4 ernstige ziekte

5 zeer ernstige ziekte

APPENDIX E: SCORAD

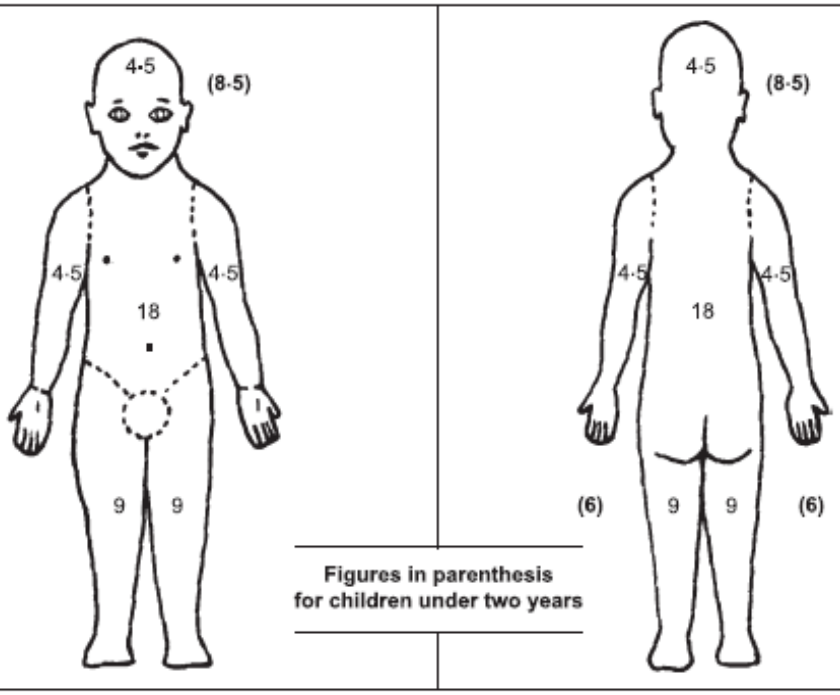
SCORAD INDEX

EUROPEAN TASK FORCE ON ATOPIC DERMATITIS

Last Name | First Name

Date of Birth: DD/MM/YY

Date of Visit:



Figures in parenthesis for children under two years

A: EXTENT Please indicate the area involved	
B: INTENSITY	
C: SUBJECTIVE SYMPTOMS PRURITUS + SLEEP LOSS	

A/5 + 7B/2 + C

CRITERIA	INTENSITY
Erythema	
Oedema/Papulation	
Oozing/crust	
Excoriation	
Lichenification	
Dryness*	

* Dryness is evaluated on uninvolved areas

MEANS OF CALCULATION

INTENSITY ITEMS
(average representative area)
0 = absence
1 = mild
2 = moderate
3 = severe

Visual analog scale (average for the last 3 days or nights)

PRURITUS (0 to 10) 0 10

SLEEP LOSS (0 to 10)

APPENDIX F: POEM (Dutch version)

Instructie

- Beantwoord elk van de onderstaande 7 vragen door het juiste antwoord aan te kruisen
- Bij vragen die u niet kunt beantwoorden, hoeft u niets in te vullen

Vragenlijst

	0 dagen	1-2 dagen	3-4 dagen	5-6 dagen	Elke dag
1. In de afgelopen week, op hoeveel dagen heeft u jeuk gehad door uw eczeem?	☐	☐	☐	☐	☐
2. In de afgelopen week, in hoeveel nachten werd uw slaap verstoord door uw eczeem?	☐	☐	☐	☐	☐
3. In de afgelopen week, op hoeveel dagen heeft uw huid gebloed door uw eczeem?	☐	☐	☐	☐	☐
4. In de afgelopen week, op hoeveel dagen kwam er vocht uit uw huid door het eczeem?	☐	☐	☐	☐	☐
5. In de afgelopen week, op hoeveel dagen waren er barstjes in uw huid door uw eczeem?	☐	☐	☐	☐	☐
6. In de afgelopen week, op hoeveel dagen was uw huid schilferig door uw eczeem?	☐	☐	☐	☐	☐
7. In de afgelopen week, op hoeveel dagen voelde uw huid droog of ruw aan door uw eczeem?	☐	☐	☐	☐	☐

APPENDIX G: POEM (English version, adults)

Patient-Oriented Eczema Measure (POEM)
(Adult version)

Patient details:	Date:
	Total POEM score: (maximum 28)

Please circle one response for each of the seven questions below about your eczema. Please leave blank any questions you feel unable to answer.

1. Over the last week, on how many days has your skin been itchy because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

2. Over the last week, on how many nights has your sleep been disturbed because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

3. Over the last week, on how many days has your skin been bleeding because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

4. Over the last week, on how many days has your skin been weeping or oozing clear fluid because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

5. Over the last week, on how many days has your skin been cracked because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

6. Over the last week, on how many days has your skin been flaking off because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

7. Over the last week, on how many days has your skin felt dry or rough because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

APPENDIX H: POEM (English version, children)

Patient-Oriented Eczema Measure (POEM)
(Infant and young children's version for parents to complete)

Patient details:	Date:
	Total POEM score: (maximum 28)

Please circle one response for each of the seven questions below about your child's eczema. If your child is old enough to understand the questions then please fill in the questionnaire together. Please leave blank any questions you feel unable to answer.

1. Over the last week, on how many days has your child's skin been itchy because of their eczema?

No days 1-2 days 3-4 days 5-6 days Every day

2. Over the last week, on how many nights has your child's sleep been disturbed because of their eczema?

No days 1-2 days 3-4 days 5-6 days Every day

3. Over the last week, on how many days has your child's skin been bleeding because of their eczema?

No days 1-2 days 3-4 days 5-6 days Every day

4. Over the last week, on how many days has your child's skin been weeping or oozing clear fluid because of their eczema?

No days 1-2 days 3-4 days 5-6 days Every day

5. Over the last week, on how many days has your child's skin been cracked because of their eczema?

No days 1-2 days 3-4 days 5-6 days Every day

6. Over the last week, on how many days has your child's skin been flaking off because of their eczema?

No days 1-2 days 3-4 days 5-6 days Every day

7. Over the last week, on how many days has your child's skin felt dry or rough because of their eczema?

No days 1-2 days 3-4 days 5-6 days Every day

APPENDIX I: SKINDEX-17 (Dutch version)

SKINDEX-17

Deze vragen gaan over uw gevoelens van de afgelopen week met betrekking tot de huidaandoening waarvan u (het meeste) last heeft gehad. Kruis per vraag één antwoord aan dat het beste overeenkomt met hoe u zich hebt gevoeld. Het is belangrijk dat u iedere vraag beantwoordt en geen vragen overslaat.

Hoe vaak waren deze omschrijvingen in de afgelopen week op u van toepassing?

		NOOIT	ZELDEN	SOMS	VAAK	ALTIJD
1.	Mijn huid doet pijn	☐1	☐2	☐3	☐4	☐5
2.	Door mijn huidaandoening is het moeilijk mijn werk of hobby's te doen	☐1	☐2	☐3	☐4	☐5
3.	Mijn huidaandoening beïnvloedt mijn sociale leven	☐1	☐2	☐3	☐4	☐5
4.	Mijn huidaandoening maakt me depressief	☐1	☐2	☐3	☐4	☐5
5.	Ik ben geneigd om thuis te blijven door mijn huidaandoening	☐1	☐2	☐3	☐4	☐5
6.	Mijn huid jeukt	☐1	☐2	☐3	☐4	☐5
7.	Mijn huidaandoening belemmert mij intiem om te gaan met de mensen van wie ik hou	☐1	☐2	☐3	☐4	☐5
8.	Ik ben geneigd om dingen in mijn eentje te doen vanwege mijn huidaandoening	☐1	☐2	☐3	☐4	☐5
9.	Water irriteert mijn huidaandoening (baden, douchen, handen wassen)	☐1	☐2	☐3	☐4	☐5
10.	Door mijn huidaandoening is het moeilijk genegenheid of affectie te tonen	☐1	☐2	☐3	☐4	☐5
11.	Mijn huid is geïrriteerd	☐1	☐2	☐3	☐4	☐5
12.	Ik voel me opgelaten en ongemakkelijk door mijn huidaandoening	☐1	☐2	☐3	☐4	☐5
13.	Ik voel me gefrustreerd door mijn huidaandoening	☐1	☐2	☐3	☐4	☐5
14.	Mijn huidaandoening beïnvloedt mijn verlangen om samen met anderen te zijn	☐1	☐2	☐3	☐4	☐5
15.	Ik voel me vernederd door mijn huidaandoening	☐1	☐2	☐3	☐4	☐5
16.	Mijn huidaandoening bloedt	☐1	☐2	☐3	☐4	☐5
17.	Mijn huidaandoening belemmert mijn seksuele leven	☐1	☐2	☐3	☐4	☐5

APPENDIX J: CDLQI

DERMATOLOGY LIFE QUALITY INDEX

DLQI ☐

Hospital No: Visit nr:
Patient initials: Date:
Birth year: Score:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☐ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you.

APPENDIX K: Optional evaluation of phototherapy

Introduction

Phototherapy may be a safe and efficacious option for the treatment of AD in adults [15]. For children younger than 12 years, the European Dermatology Forum Guidelines state that phototherapy should not be applied [20]. It is mostly used for the chronic, pruritic and lichenified forms of AD. NB-UVB has been indicated for these cases [16, 54]. For the acute phase of AD, UVA1 has been mentioned [16, 20]. However in a recent systematic review, which included only RCTs, this recommendations could not be confirmed [15].

Most evidence for effectiveness is found for medium dose UVA1 and NB-UVB [55] and these should be considered as first-choice treatment modalities [15]. PUVA was shown to be equally effective as UVA1 and NB-UVB [15], and compared to medium-dose UVA to give a better short- and long-term response in patients with severe AD [56]. Studies however are of low quality. Full-spectrum UVA, BB-UVB and full spectrum light could not be recommended in this review.

No serious side effects are mentioned in studies, but duration was often short [15]. PUVA has a more long-term risk of developing skin cancer compared to UVB phototherapy and has a number of other important side effects [17, 57]. Another review concludes that BB-UVB, NB-UVB and UVA1 have not yet been directly linked to cutaneous carcinogenesis, but long-term follow-up studies are needed [58].

The benefits vary from person to person with a reasonable number of patients who do not respond or even get worse under phototherapy [17, 20].