# Standard for Outcome Measures in Clinical Trials for the treatment of plaque psoriasis supporting Labelling Claim and their application in practice – a critical review of the EMA Guideline CHMP/EWP/2454/02corr and a proposal for future development

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# 1 List of Abbreviations

| | |
|---|---|
| BSA | Body Surface Area |
| CHMP | Committee for Medicinal Products for Human Use |
| CDLQI | Children's Dermatology Life Quality Index |
| CTD | Clinical Trials Directive |
| DLQI | Dermatology Life Quality Index |
| EMA | European Medicines Agency |
| EPAR | European public assessment report |
| EU | European Union |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| HRQL | Health-related Quality of Life |
| ICH | International Conference on Harmonisation |
| IMP | Investigational Medicinal Product |
| Itch NRS | Itch Numeric Rating Scale |
| LS-PGA | Lattice System Physician's Global Assessment |
| MAA | Marketing Authorisation Application |
| MAb | Monoclonal antibody |
| OTC | Over the counter |
| PaGA/PatGA | Patient's Global Assessment |
| PASI | Psoriasis Area and Severity Index |
| PASS | Psoriasis Assessment Severity Score |
| PDI | Psoriasis Disability Index |
| PEASI | Psoriasis Exact Area and Severity Index |
| Peds QL | Pediatric Quality of Life Inventory |
| PGA | Physician's Global Assessment |
| PLASI | Psoriasis Long-based Area and Severity Index |
| PLSI | Psoriasis Life Stress Inventory |
| PRO | Patient Reported Outcome |
| PSORIQol | Psoriasis Index of Quality of Life |
| Q&As | Questions and Answers |
| QIDS-SR16 | Quick Inventory of Depressive Symptomatology-Self Reported 16 items |
| QoL | Quality of Life |

| | |
|---|---|
| SAPASI | Self-administered PASI |
| SF-36 | 36-item Short Form Health Survey |
| SIAQ | Self-Injection Assessment Questionnaire |
| SPASI | Simplified PASI |
| SPI | Salford Psoriasis Index |
| TNF | Tumour necrosis factor |
| TSS | Total Severity Sign Score |
| VAS | Visual Analogue Scale |
| WPAI-PSO | Work Productivity Activity Impairment Questionnaire-Psoriasis |

# 2 Introduction

## 2.1 Regulatory environment for clinical trials for the treatment of plaque psoriasis in Europe in the light of continuous market growth

The evaluation of new medicinal products targeting marketing authorisation follow a complex regulatory framework in which requirements for the three main criteria

- Quality,
- Safety and
- Efficacy

are defined and regulated in detail. While data on quality and safety will normally be generated from the early stages of the drug development on, efficacy data will be primarily collected at a later development stage, namely in clinical development phases II and III.
The general binding rules for the marketing authorisation of medicinal products for human use in Member States of the European Union are laid down in Directive 2001/83/EC [1]; more specifically, the “Clinical Trials Directive” 2001/20/EC” [2] rules out the framework for clinical trials supporting marketing authorisation application and procedures. However, as both Directives set the framework for marketing authorisation and clinical trials in very general terms, several guidelines have been issued by the EMA to provide guidance for the conduct of clinical trials in specific indications.

Over the past 20 years, a number of new compounds have been developed for the treatment of different dermatologic indications. The vast majority of newly marketed drugs target the inflammatory disease plaque psoriasis. To address this situation, Guideline CHMP/EWP/2454/02 corr has come into operation in 2005 to provide guidance on the clinical investigation of new medicinal products indicated for the treatment of psoriasis [3]. Among other aspects of clinical trials in psoriasis, this guideline specifies the requirements for primary outcome parameter and comments on Patient Reported Outcomes (PROs) Further guidance on the use of PROs is given in a Reflection Paper issued by the Committee for Medicinal Products for Human Use (CHMP) on the use of Health Related Quality of Life (HRQL) Measures [4]; however, while the FDA has released a Reflection Paper on PROs [5], no Guideline aiming to regulate the requirements for the assessment of key disease symptoms from the patient’s perspective has been released by the EMA yet.

The continuous development of medicinal products for the treatment of plaque psoriasis over the last decade (2005-2015) has led to a changed usage of efficacy parameters and PROs used in clinical trials conducted to support a marketing authorisation. Plaque psoriasis still is one of the two top indications showing the most dynamic clinical research activities with a growth of 9% in IND submissions [6]. Being an auto-immunological inflammatory disease, plaque psoriasis is regarded as model disease for a variety of conditions studied in new drug developments targeting at inflammation processes in humans.
Based on the comparison between regulatory requirements on the one hand and the usage of primary efficacy parameter and PROs in clinical trials for marketing purposes on the other, a revision of the EMA-guideline CHMP/EWP/2454/02 corr with regards to potential outcome

parameter will be discussed and a proposal will be made on how to address these aspects in future research activities in psoriasis trials.

# 3 Objectives of the master thesis

This master thesis has the following objectives:

1. Description and assessment of European regulatory guidelines and reflection papers dealing with the development of medicinal products for the treatment of psoriasis. In this context, the European Clinical Trials Directive 2001/20/EC will be consulted for suitable guidance for dermatological trials. Recommendations for efficacy parameters originating from physician's as well as from patient's perspective shall be identified.
2. Performance of a literature research aiming at the identification of suitable efficacy parameters to be used in clinical trials on psoriasis.
3. Identification of parameters actually used in pivotal clinical phase III trials that have led to a marketing authorisation in the time period between issuing of relevant guidelines for clinical trials in psoriasis and today.
4. Based on the collected information, the topicality and usefulness of relevant guidelines for clinical trials in psoriasis shall be discussed.

Since the implementation of the 'Guideline on Clinical Investigation of medicinal products indicated for the treatment of psoriasis' in 2005, several new medicinal products including a new class of biological therapies have obtained approval for Marketing Authorisation.

The present master thesis aims at comparing the regulatory requirements for primary efficacy objectives as laid down in the European Guideline CHMP/EWP/2454/02 corr with the actual practice in clinical trials in the indication plaque psoriasis.

In order to prove the hypothesis, applicable Guidelines or other supporting documents applicable for the conduct of clinical trials aiming to reach marketing authorisation for the treatment of plaque psoriasis in Europe as well as guidance documents for the use of PROs have been searched and analysed.

Furthermore all clinical trials supporting labelling claim for medicinal products treating the medical condition plaque psoriasis have been identified and evaluated with regard to their efficacy parameter and PROs.

# 4 Current Regulatory Environment for Clinical Trials for dermatologic indications within the European Union

## 4.1 Legal Situation in the EU: Regulation, Directive and Guideline

Within the European Union, Regulations are legal acts that immediately become an enforceable law in all member states. For the conduct of clinical trials, the European Commission has issued Regulation 536/2014 [7]. It will be implemented as soon as the necessary technical prerequisites have been installed and audited and plays no role today yet. It is assumed that Regulation 536/2014 will be implemented in late 2018.

A Directive needs to be transposed into national law by the EU members. This in turns means that local adaptations will be possible, which is not the case for a Regulation. The European Clinical Trials Directive, 2001/20/EC [2] is the leading Directive for the EU when it comes to the conduct of clinical trials. It will be regarded in more detail in chapter 4.2.

Guidelines and Guidances are issued by e.g. the Committee for Medicinal Products for Human Use (CHMP) or the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and are intended serving as guidance for the topic that they deal with. For dermatology, three guidelines have been issued so far:

- “Clinical investigation of corticosteroids intended for use on the skin” (1987, reference number 3CC26a) [8]
- “Questions and answers on Guideline Title: Clinical investigation of corticosteroids intended for use on the skin” (CHMP/EWP/21441/2006) [9]
- “Guideline on Clinical Investigation of Medicinal Products indicated for the treatment of psoriasis” (CHMP/EWP/2454/02 corr) [3]

Contents of these guidelines will be described in more detail in chapter 4.3. Furthermore, chapter 4.4 will provide details on two guidance publications on Patient Reported Outcomes as outcome parameters in clinical trials in general.

## 4.2 The European Clinical Trials Directive 2001/20/EC

The Clinical Trials Directive (CTD) 2001/20/EC [2], having been issued on 4 April 2001, establishes general requirements for the conduct of clinical trials on medicinal products. In particular, the conduct of clinical trials in accordance with Good Clinical Practice, GCP, is one of the directive’s main objectives. In the CTD’s scope it is clearly stated that design, conduct and reporting of all clinical trials, regardless of the clinical development phase they are

attributed to, shall be in accordance with the principles of GCP. The CTD is not applicable to non-interventional trials.

The Member States were prompted to adopt the CTD to national laws before 1 May 2004.

The CTD is understood as collection of definitions and stipulations that need to be observed in any clinical trial. The CTD sets the scene for the GCP-compliant preparation and conduct of clinical trials. It does not contain any specific stipulation or any detailed requirement for e.g. the trial- or disease-specific selection of efficacy parameters. In contrast, it covers the broader prerequisites for clinical trials.

## 4.3 Guidelines on Clinical Investigation of Medicinal Products specifically indicated for dermatologic conditions

### 4.3.1 Clinical investigation of corticosteroids intended for use on the skin

The guideline (reference number 3CC26) came into force in August 1987. In its introduction, the guideline is stated to "(…) hold good in principle for all topical corticosteroids which are intended to be used on the skin." The guidance given on clinical investigations addresses few aspects with regard to efficacy, such as the study design should be randomised and double-blind as well as different treatment groups need to be comparable in terms of the medical conditions. No detailed guidance is given on outcome measures. As topically applied corticosteroids play a role in several dermatologic conditions, no disease-specific guidance is given either.

### 4.3.2 Questions and answers on Guideline Title: Clinical investigation of corticosteroids intended for use on the skin

In 2006, Guideline 3CC26a [8] was updated in the form of a Question and Answers publication [9] (CHMP/EWP/21441/2006). The paper reflects the main issues that have come along with the guideline since its coming into force in practice from a regulatory point of view. It deals with issues around vasoconstriction testing and safety; however, clinical investigation issues including outcome measures are not considered.

### 4.3.3 Guideline on Clinical Investigation of Medicinal Products indicated for the treatment of psoriasis

The disease-specific 'Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis' by the Committee for Medicinal Products for Human Use (CHMP) [3] focuses on the development and the evaluation of topical and systemic therapies for the treatment of chronic plaque psoriasis. Thereby, it provides guidance for design and performance of clinical development studies and gives detailed recommendations on different aspects of clinical trials such as study design, methods to assess efficacy and safety as well as special populations.

The guideline gives full particulars on several aspects around study design applicable for clinical trials supporting labelling claim including the use of placebo, blinding, duration, long-term efficacy and safety and conditions for registration.

**Design of Clinical Trials in Psoriasis Patients**

The guideline provides exact and clear guidance on the design of trials split into the development phases. Besides pharmacodynamics and pharmacokinetics, special focus is laid on phase II and phase III trials. For both, therapeutic exploratory and therapeutic confirmatory trials, reflections and proposals on the use of efficacy parameters apply; these are summarised below.

**Phase II Trials in Psoriasis**

Therapeutic exploratory studies should preferably be designed as randomised, double-blind, placebo-controlled comparisons. For topically applied medicinal products, an intra-individual approach is accepted while for systemically applied medication, a parallel-group design is to be chosen for obvious reasons. Several drug concentrations should be tested and the optimal application frequency should be subject to the therapeutic exploratory development phase. For systemically applied drugs, at least three concentrations should be tested, and the determination of plasma concentrations is considered useful.

**Phase III Trials in Psoriasis**

Therapeutic confirmatory studies should preferably be designed as randomised, double-blind, parallel group comparisons. Intra-individual comparisons are not deemed acceptable. Studies may be designed as non-inferiority or superiority trials. Non-inferiority trials should be three-armed comparing the new agent with placebo and an active comparator. A superiority trial of the new drug versus an active comparator is acceptable if conducted without placebo arm. However, if superiority over standard should not be reached, non-inferiority cannot be claimed. For systemically active agents, three-arm comparisons (new agent vs. placebo vs. active comparator) are explicitly recommended. Short-term assessments after 8-12 weeks should be complemented by a 3-6 months follow-up after treatment cessation.

**Target Population and Selection of Patients**

The target population generally should be defined by the type of psoriasis as well as its duration, severity and previous treatments.

The guideline comments on the ideal psoriasis severity assessment consisting of

- Extent of affected body regions/area,
- Intensity of local signs (erythema, elevation, scale) and
- Intensity of symptoms (e.g. pruritus).

In practice, Body Surface Area (BSA) and Psoriasis Area and Severity Index (PASI) are the most frequently used assessments of the severity of psoriasis and thereby for the definition of the trial target population. From a validity point of view, the use of PASI is associated with some inter-rater variability. Therefore, a training of investigators is explicitly recommended by the CHMP.

The guideline notes that BSA and PASI do not necessarily correlate strongly, but patients may reveal a high BSA with a low PASI and vice versa.

Static Physician's Global assessment on a 6-7 point scale is mentioned as further severity grade measure.

As summarised in Table 4.3.3-1, the guideline comments on the definition and categories of psoriasis severity.

Table 4.3.3-1

| | Severity of plaque psoriasis | | | |
|---|---|---|---|---|
| | Mild to moderate psoriasis | Moderate psoriasis | Moderate to severe psoriasis | Severe psoriasis |
| Clinical description | Good control of lesions with topical therapy alone. | Topical therapy still possible to control the disease. | Topical therapies fail to control the disease. | A justified need for systemic treatment to control the disease. |
| PGA Category | "Mild to moderate" | "Moderate" | "Moderate to severe" | "Severe" |
| PASI/ BSA | BSA <10% or PASI <10 | BSA >10% or PASI ≥10 | BSA >10% or PASI 10-20. Very thick lesions located in "difficult to treat" regions with BSA involvement <10% may also be considered. | BSA >20% or PASI >20; Very important local signs with very thick lesions with BSA involvement >10% may also be considered. |

**Efficacy Measures**

The guideline presents methods to assess efficacy both from investigator's and patient's perspective.

For short-term efficacy measurements, response to treatment should be assessed as the difference between baseline and post-treatment score of " (…) *both body surface area affected with psoriasis and the three main skin signs (erythema, scale and elevation*)" (EMEA/CHMP/EWP/2454/02, Section 4.1.1, Page 7/18), whereas for long-term efficacy measurements, remission and recurrence measures are requested in addition.

As response to treatment measures the following assessments are listed in the guideline:

1. Visual assessment of index lesions (endpoint particularly adapted to proof-of-concept and early therapeutic exploratory trials with topical agents)
2. BSA measurement
3. Clinical signs score: Total severity sign score (TSS)
4. Physician's global assessment of improvement
5. Psoriasis area and severity index (PASI)

Special attention is paid to PASI as the most frequently used severity assessment: *"PASI score has been the most frequently used primary endpoint in therapeutic confirmatory trials both for topical and systemic agents. However, clinical significance of observed changes is not always well understood. This is further complicated by multiplying the obtained result by the constant weighted value assigned to each body part. Moreover, PASI scores >30 are rare, such that almost half the range is of little value. In addition, in patients with PASI=10 at baseline, final score is rarely 0 due to residual erythema. However, a comparison of efficacy data between new and old clinical trials will benefit from keeping PASI as one of the measures."* (EMEA/CHMP/EWP/2454/02, Section 4.1.1, Page 8/18).

In summary, the guideline's recommendation on the choice of endpoints is as follows:

- PASI alone is not deemed sufficient to evaluate psoriasis severity at baseline and on treatment
- It is strongly recommended to use two endpoints to assess efficacy, namely a validated, standardised global score (e.g. PGA) in conjunction with PASI.

This recommendation applies to all therapeutic studies performed on agents targeting at psoriasis. It is not of relevance whether the medicinal product is to be applied topically or systemically. The mode of administration only has impact on the trial design as summarised above.

**Definition of Treatment Responders**

In case PASI will be used as efficacy parameter in a therapeutic exploratory or confirmatory psoriasis trial, a clinically relevant response is defined as a PASI $\geq$ 90% (clinically equivalent to "clear to almost clear", shorthand PASI 90). Patients reaching PASI 90 may thus be considered treatment responders.

PASI $\geq$ 50% (shorthand PASI 50) and PASI $\geq$ 75% (shorthand PASI 75) improvements are considered as clinically meaningful. If defined prospectively in the study protocol, patients with PASI 75 might be considered being treatment responders in clinical trials on patients with severe psoriasis.

Patients achieving less than PASI 50 should be considered as treatment non-responders.

**Patient Reported Outcomes**

The assessment of the treatment efficacy or health-related quality of life (HRQL) by the patients themselves might be a secondary or tertiary endpoint if the clinical trial is considered pivotal. Inventories such as the self-administered PASI (SAPASI), the Dermatology Life Quality Index (DLQI), Skindex, the Psoriasis Disability Index (PDI) and the Psoriasis Life Stress Inventory (PLSI) are suggested.

In summary, the 'Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis' provides detailed guidance on the evaluation of new medicinal products that are indicated for the treatment of psoriasis.

## 4.4 Guidances on the use of Patient Reported Outcomes (PRO) in clinical trials

### 4.4.1 Reflection Paper on the Regulatory Guidance for the Use of Health-Related Quality of Life (HRQL) Measures in the Evaluation of Medicinal Products; 27 July 2005.

The EMA issued a reflection paper discussing the role of health-related quality of life (HRQL) measures, a subtype of PRO, in the drug evaluation process [4] (Committee for Medicinal Products for Human Use, 2005). The paper also gives brief recommendations on its use referring to published guidelines. Furthermore, aspects with regards to study design for HRQOL assessments as well as statistics are described.

HRQL are considered being a subtype of PRO due to its multi-dimensionality:

*"Indeed, HRQL is a broad concept which can be defined as the patient's subjective perception of the impact of his disease and its treatment(s) on his daily life, physical, psychological and social functioning and well-being." (Reflection paper 2004)*

Other patient assessed items such as single core symptom assessments or other multi-item single concept parameter (intermediate PRO measures) are not covered by the refection paper.

The reflection paper emphasizes that in the context of drug approval, which focuses on the evaluation of efficacy and safety, a HRQL assessment basically is optional. Should HRQL claims be intended for a certain treatment, the improvement of HRQL needs to be supported by validated instruments suitable for the medical condition, either by generic or disease-specific questionnaires.

Prior to its application within the framework of a study, the reflection paper suggests a previous validation of the instrument. In principle, two options exist: If the medicinal product has no marketing authorisation, both efficacy and HRQL can be chosen as primary endpoints. A hierarchical testing may be appropriate. If the product has already gained market approval or has shown efficacy and safety in a former clinical trial conducted in the target population, it is suggested to collect HRQL data in a parallel group design comparing the test drug and an active comparator.

Hypotheses about a product should be based on former study results and a literature review and should be formulated prior to the conduct of the actual study. The methodology to assess HRQL is very similar to that for efficacy and safety testing e.g. with respect to randomisation, blinding, handling of missing data, duration of the clinical trial and analysis plan. For the control of multiplicity, hierarchical testing is recommended: Only if the results for efficacy are significant, HRQL results may statistically be tested.

It is worth noting that especially in chronic diseases, HRQL measures may help patients and physicians to choose one medicinal product over the other if efficacy and safety are similar.

### 4.4.2 Qualification of novel methodologies for drug development: guidance to applicants; 09 January 2012. [10]

This guidance document describes a new and voluntary process for pharmaceutical companies to obtain qualification opinion by the EMA on the acceptability of the use of novel methodologies. The guidance document is also applicable for novel HRQL/PRO instruments [11]. Isaac et al. [11] confirm the regulatory perspective of the EMA on HRQL-related claims being still valid as outlined in the Reflection Paper of 2004 [4] and identify a need to give recommendations with regard to intermediate PRO measures. The authors emphasize the need to harmonise FDA and EMA regulatory requirements and hold out the prospect of a case-to-case basis acceptance of new PROs as primary outcome if “clear and detailed justification” is given.

These conclusions, however, still have to be realised. As long as of the reflection paper is not revised or a PRO guideline is published, the main differences between FDA (U.S Department of Health and Human Services: PRO guideline 2009) [5] and EMA standards with regard to PROs will not be balanced. This leads to a higher acceptance of PROs comprising single, intermediate and multi-disciplinary assessments by the FDA as well as the potential acceptance of PROs as primary outcome measures.

Although the regulatory authorities EMA and FDA share the view on the patients’ perspective being important for the development and approval process of new medicinal products [12], they differ with regard to the kind of PROs that are accepted and the consideration of PROs as primary outcome measures.

This higher acceptance is also reflected by the fact that the FDA has released a Guidance on PRO Measures that defines requirements for the development of novel PROs whereas no comparable efforts from the EMA have been undertaken.

## 4.5 Evaluation of the Guidelines applicable for dermatology trials in the European Union

The ‘Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis’ by the Committee for Medicinal Products for Human Use [3] (CHMP/EWP/2454/02 corr) provides clear recommendations on various issues regarding clinical investigations for the treatment of psoriasis, e.g. aspects around strategy and design of both, exploratory and confirmatory trials, recommendations on clinical trials in special populations as well as safety aspects.

However, the assessment of psoriasis severity as well as the methods to assess efficacy reveal some uncertainties: The guideline recommends that psoriasis severity classification should ideally integrate measures of body surface affection, clinical symptoms as well as signs (e.g. pain), while in practice BSA and PASI, that do not consider signs of the medical condition plaque psoriasis, are the most frequently used measures for disease severity.

So far no consensus on a clear definition for psoriasis severity has been reached. Commonly, the following four categories are used:

- Mild to moderate
- Moderate
- Moderate to severe
- Severe

The assessment of the use of PASI is connected to several limitations that are commented by the guideline's authors, which are listed in the following:

- The score shows a considerable inter-rater variability,
- the clinical significance of observed changes are not always well understood,
- PASI values of more than 30 are rarely observed,
- a PASI of 0 as treatment response is hardly reachable and
- the assessment is not suitable for certain locations (nail, scalp etc).

Nevertheless, due to the considerable number of clinical trials over the past years having used PASI as primary endpoint, the guideline recommends to keep PASI as one of the measures in future clinical trials in order to compare efficacy data between new and past clinical trials.

This pragmatic compromise results in the statement that PASI alone is insufficient, but PASI together with BSA could serve as endpoint: *"it is strongly recommended to use two endpoints to assess efficacy" "* (EMEA/CHMP/EWP/2454/02; p. 8). It remains however unclear how both endpoints should be connected, i.e. as co-primary endpoints or alternatively as primary and secondary endpoint and how the results of both endpoints should be interpreted (especially in case the results differ: "*In some cases, a degree of BSA/PASI involvement does not reflect psoriasis severity: some patients with low BSA involvement have severe psoriasis and some patients with high BSA involvement have mild psoriasis measure")* (EMEA/CHMP/EWP/2454/02; p. 6)*).*

In summary, there are several uncertainties linked to the performance of clinical trials for the treatment of psoriasis patients due to the lack of a well-validated severity score comprehensively covering all relevant aspects.

Regarding PROs, both Guideline CHMP/EWP/2454/02 corr as well as the Reflection paper on the Regulatory Guidance for the Use of Health-Related Quality of Life (HRQL) Measures in the Evaluation of Medicinal Products make clear that PROs can be considered as outcome measure. However, labelling claim does not depend on PRO such as HRQL inventories. Nevertheless, PRO assessments have gained growing attention over the last years.

The following section aims at elucidating how the guideline was interpreted and adopted in design and conduct of pivotal trials for the purpose of marketing authorisation for medicinal products for the treatment of psoriasis. The analysis covers medicinal products marketed after the implementation of the guideline. It will be presented how efficacy outcome measures in psoriasis trials have developed and what the current practice is.

# 5 Psoriasis vulgaris

## 5.1 Clinical aspects

Psoriasis is a chronic immune-mediated inflammatory skin disorder affecting approximately 2 to 3 percent of the world's population [13]. According to a large, multinational, population-based survey in Europe and North America, the prevalence of psoriasis ranges from 1.4% to 3.3% [14, 15]. Plaque psoriasis is the most common clinical form of psoriasis with a 80% share of the affected patients [16].

The disease typically takes a chronic course of progression and relapses, thereby having a major impact on patients' lives. As in half of the cases the onset is before the age of 22, numerous patients suffer over several decades. Today psoriasis is regarded as a systemic disorder with characteristic skin involvement and association with other disorders. Psoriasis thus goes along with a high risk of comorbidities. The severe chronic forms, in particular, require life-time therapy [16].

In any case, psoriasis requires severity adjusted treatment, which should take into account both the skin symptoms and the improvement of patient's quality of life.

## 5.2 Treatment options for psoriasis

The majority of psoriasis patients suffer from mild to moderate disease and are treated with topical agents, which is the mainstay of treatment [17]. For moderate to severe forms of plaque psoriasis, therapies with systemic agents (conventional small molecules and biologics) are indicated [18]. Still, those patients treated with phototherapy or systemic agents including biologics may also use topical agents as adjuvant therapy [16].

The following section provides an overview of topical and systemic treatments for the indication psoriasis vulgaris.

The overview of topical treatments is based on the most recent systematic reviews of Laws and Young (2010) [19] and Samarasekera and colleagues (2013) [20]. The selection of these papers was based on a literature search in the PubMed database by the following terms: 'topical treatment' AND 'plaque psoriasis'. With filters in publication dates (10 years), text availability (free full texts) and article types (review), the search provided 11 hits. These articles were screened and evaluated regarding comprehensiveness and accuracy. Samarasekera's review focused on the efficacy of topical agents as shown in head-to-head-trials with approved topical therapies for the treatment of plaque psoriasis in the UK. Comprehensive searches of Medline, Embase, Cinahl and The Cochrane Library, last updated on 8 March 2012, restricted to articles published in English, were performed. In total, 63 studies were analysed.

The overview of systemic treatment is based on the European S3-Guidelines on the systemic treatment of plaque psoriasis published by Pathirana and colleagues (2009) [21]. It provides a detailed overview of existing treatment options including evaluations and recommendations based on clinical practice and the inspection of clinical data. The guideline was developed by

39 international dermatological experts who compared and evaluated three existing evidence-based national guidelines from United Kingdom, Germany and the Netherlands. Subsequently, an extensive database and literature search was conducted for in the European countries marketed systemic therapies.

Although European Treatment Guidelines are legally non-binding, the classification “S3” implies the highest development stage of medical guidelines with a variety of evidence-based analyses, evaluation of clinical relevant trials, and periodic review.

Medicinal products for the treatment of plaque psoriasis, that are not reflected in the European psoriasis guideline since they have entered the European market from 2009 onwards are added to the treatment chapters 5.2.1 and 5.2.2.

### 5.2.1 Topical treatment

Topical treatments—medications applied to the skin—are usually the first line of therapy in treating psoriasis. Topicals slow down or normalise excessive cell reproduction and reduce psoriasis inflammation.

There are several effective topical treatments for psoriasis. While many can be purchased over the counter (OTC), others are available by prescription only.

Corticosteroids, or just "steroids," are the most frequently used treatment for psoriasis. They are referred to as anti-inflammatory agents, because they reduce the swelling and redness of lesions. Anthralin, synthetic vitamin D3, and vitamin A are also used in prescription topical treatments to control psoriasis lesions.

OTC topicals come in many different forms. Two active ingredients, salicylic acid and coal tar, are approved by the FDA for the treatment of psoriasis. There are other products that contain substances such as aloe vera, jojoba, zinc pyrithione and capsaicin, which are used to moisturize, soothe, remove scale or relieve itching [22].

The following descriptions of topical treatments are extracted from the review paper of Laws and Young [19] about topical treatment of psoriasis. The authors have written the review on the basis of comprehensive literature searches targeting adult patients with chronic plaque psoriasis and topical treatment via PubMed and Embase including a Cochrane review:

#### Corticosteroids

Corticosteroids are a class of steroid hormones that are produced in the adrenal cortex of vertebrates, as well as the synthetic analogues of these hormones. Two main classes of corticosteroids, glucocorticoids and mineralocorticoids, are involved in a wide range of physiologic processes, including stress response, immune response, and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior [23].

As drugs treating inflammatory diseases, Corticosteroids are classified in four potency groups (mild, moderately potent, potent and very potent or class I to IV corticosteroids) and are prescribed determined by disease severity, affected area and patient preference [19]. Topical corticosteroids show efficacy rates of up to 92% in clinical trials of short term [24]. The S3-guideline of Nast and colleagues (2011) [25] evaluates the efficacy of corticosteroids on the basis of 122 clinical studies as “25-77% of the patients reaching a significant improvement of

the lesions or a complete remission" [25]. According to the review or Samarasekera and colleagues, the most rapid improvement in response amongst all topical therapies occurred during the first 2–4 weeks for corticosteroids.

Side effects of a therapy with corticosteroids comprise skin atrophy, telangeiectasia, striae distensae, acne and purpura [19].

Corticosteroids of potent class III are recommended as induction therapy for patients with mild to moderate plaque psoriasis [25].

**Vitamin D analogs**

Three vitamin D analogs are available in Europe since 1992: calcitriol, tacalcitol and calcipotriol.

Calcitriol is an active form of vitamin D and is prescribed as ointment only [19]. The treatment with calcitriol shows long term efficacy and safety but can lead to a slight hypercalcemia in particular patients [26].

Calcipotriol, a substance derived from vitamin D, acts through receptors in the skin to prevent the multiplication of cells that cause the scaly patches in psoriasis; it is available as ointment only. Tacalcitol is a synthetic form of vitamin D analogue.

The most frequently occurring side effects include skin irritation like burning or itching, dryness, scaling and edema [27]. Furthermore, there is a risk of an increased calcium homeostasis when treating psoriasis with higher doses than 210 g calcitriol 3 µg/g, 70 g tacalcitol 4 µg/g and 100 g calcipotriol 50 µg/g.

**Calcineurin inhibitors**

Two preparations of calcineurin inhibitors have been marketed, both in 2002, tacrolimus (0.03 and 0.1%) and pimecrolimus (1.0%), which have been used primarily in the treatment of eczema on flexural or facial skin [19]. Calcineurin inhibitors are immunmodulating agents, they reduce skin inflammation accordingly. Side effects such as burning and stinging after application occur but seem to decrease with ongoing application (ibid.).

Both products are not marketed for the treatment of psoriasis, however, as the response to treatment in patients with plaque psoriasis ranges between 40-50% significant improvement or complete remission respectively, calcineurin inhibitors are often used off-label.

**Dithranol**

Dithranol is a synthetic tar derivate that suppresses cell proliferation.

After Dithranol entered the market in 1916 it has become the most frequently prescribed therapy for psoriasis until the early 1980ies, when Corticosteroids captured the market.

Dithranol has several drawbacks such as negative skin reactions and the risk of contamination on furniture and clothing [19]. There are two ways to treat psoriasis with dithranol: the cream can be applied as a short-term treatment on an outpatient basis or as for 24 hours as an inpatient. The first version is more feasible while the second offers better efficacy [28].

### Coal tar

With more than 100 years, coal tar is the oldest treatment option for psoriasis [19] and furthermore very effective, especially in combination with UVB [29]. Like dithranol, coal tar preparations may stain furniture and clothing and are not cosmetically favoured. Side effects include skin irritation and contact dermatitis [19].

Nowadays coal tar is not anymore recommended as mono-therapy but only in combination with UV-therapy on an individual case basis.

### Tazarotene

With its development in the 1990s, tazarotene is a rather young therapeutic approach for the treatment of psoriasis [19] and belongs in the group of retinoids. By binding the retinoic acid receptor, tazarotene minimises epidermal hyperproliferation and decreases inflammation.

Two trials comparing 0.1 and 0.05% cream provided satisfying results [30, 31]. A third of patients treated with tazarotene may suffer from burning, stinging and itch [31].

Tazarotene is still on the market in Germany, however is not actively marketed anymore and does not play an important role in the topical treatment of psoriasis anymore.

### Keratolytics

Keratolytics are helpful on hyperkeratosis that may reduce the efficacy of other topical therapies [19]. Among others, keratolytics include salicylic acid and urea which are briefly described in the paper. Salicyl acid is often used in combination with other treatments due to a better absorption of the second drug. Urea minimises transepidermal water loss.

## 5.2.2 Systemic treatment

For the treatment of moderate to severe forms of plaque psoriasis, therapies with systemic agents (conventional agents and biologics) are indicated [18]. The following summary on systemic treatments is based on the extensive European S3-guidelines on the systemic treatment of plaque psoriasis by Pathirana and colleagues (2009) [21] who outline the State of the Art treatment of plaque psoriasis. It provides a detailed overview of existing treatment options including evaluations and recommendations based on clinical practice and the inspection of clinical data. The guideline was developed by 39 international dermatological experts who compared and evaluated three existing evidence-based national guidelines from United Kingdom, Germany and the Netherlands. The guideline was updated in 2015 by Nast and colleagues [25]. It presents the most profound and valid presentation of all systemic treatments available on the European market.

Novel therapies identified through a research of most recent Marketing Authorisations for the treatment of plaque psoriasis on the EMA homepage have been added.

Small molecules

**Methotrexate**

MTX is a folic acid analogue that competitively inhibits the enzyme dihydrofolate reductase and other folate-dependent enzymes. The administration of MTX thus leads to a reduced synthesis of thymidylate and purine, resulting in a decreased production of DNA and RNA. In activated T cells and in keratinocytes, this mechanism is believed to lead to the antiproliferative and immunomodulatory effects of MTX, which are crucial to the treatment of psoriasis [21].

The drug was approved for the treatment of moderate to severe plaque psoriasis in 1958 and is employed all over Europe (ibid.). It can be applied orally, subcutaneously, or intramuscularly with different points of action. A dose of 5-10 mg per week as initial dose and 5-30 mg weekly as maintenance dose are recommended, although clinically relevant response is expected after 4 to 12 weeks. Due to this relatively slow onset, methotrexate should not be used on short term. Frequently occurring side effects are nausea, malaise and hair loss (ibid.).

**Ciclosporin**

Ciclosporin is an immunosuppressant agent that lowers the activity of the immune system by reducing the activity of T cells. The application of ciclosporin in the therapy of psoriasis gained approval in Europe in 1993 [21]. It is recommended as a short-term therapy for 8 to 16 weeks, whereas clinically relevant improvement can be expected after 4 weeks. The initial dosage is 2.5 – 5 mg/kg daily, the recommended maintenance therapy is an interval therapy with a dose reduction at the end of induction therapy. Important side effects include renal failure, reversible hepatogastric complaints (both dose dependent) tremor, headache and weariness (ibid.).

**Retinoids**

Retinoids in the treatment of psoriasis include etretinate, acitretin and isotretinoin, of which only acitretin is available in most countries in Europe. Since 1992 retinoids are an approved treatment for psoriasis in Germany [21]. The mechanisms of action are not completely investigated but it is clarified that retinoids have antiproliferative and immunomodulatory qualities. In a studie of Moy and colleagues 1985 etretinate has shown higher effectiveness rates than acitretin [25] but at the same time it has a shorter half-life and lower lipophilia [32].

The side effects of retinoids in psoriasis are mild (except for bone toxicity and teratogenicity).

Compared to the other systemic agents, acitretin should not be selected as monotherapy for the treatment of psoriasis (ibid.).

### Fumaric acid esters

While the clinical effect of fumaric acid esters on psoriasis has been recognised in 1959, it was not approved in Germany until 1994 [21]. The active component, dimethylfumarate (DMF), is a key factor in the development and retention of immunologic reactions and accordingly the inflammatory response of the skin. It also plays and important role in the induction of apoptosis (ibid.). In nine studies considered by the authors of the guideline, 50 to 70% of the patients treated with fumarates showed PASI 75 after 16 weeks. Adverse effects during the therapy are gastrointestinal conditions and flushing. Fumarates are suggested as an effective induction therapy for moderate to severe psoriasis.

### Apremilast

Apremilast is an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4) specific for cyclic adenosine monophosphate (cAMP). PDE4 inhibition results in increased intracellular cAMP levels which is thought to indirectly modulate the production of inflammatory mediators [33].

Otezla® was approved for the treatment of psoriasis at the beginning of 2015. In two efficacy studies around a third of the patients treated with Otezla® achieved PASI 75 after 16 weeks. Adverse events might occur in the digestive system and cause diarrhoea and nausea, other side effects are colds and headaches [21].

Biologic therapies

### Adalimumab

In December 2007, Adalimumab (Humira®) was approved for the treatment of psoriasis by the EMA [21]. Adalimumab is recombinant human immunoglobulin G1 monoclonal antibody, inhibits TNF-α and so reduces inflammation of the skin.

Adalimumab is delivered subcutaneously. The loading dose at baseline contains 80 mg, the maintenance dose 40 mg every other week. It shows frequent adverse effects such as itching, swelling, erythema and pain in the site of injection. Adalimumab shows high efficacy with a reached PASI by 53-80% of the study population [34, 35]. If skin lesions did not improve (at least PASI 50) at week 12, Adalimumab should be discontinued [21].

### Etanercept

Etanercept was considered an approved therapy for psoriasis by the EMA in September 2004 [21]. Etanercept is a human dimeric fusion protein and a TNF-α inhibitor that helps to reduce the inflammation of the skin. It is administered with 25 or 50 mg biweekly and showed PASI 75 in 33% and 49% of the study population in week 12 [e.g. 36, 37]. The long-term safety of etanercept is not well studied, but it is suggested for the treatment of moderate to severe psoriasis on short-term.

### Infliximab

Infliximab was approved for the treatment of psoriasis in 2005 [21].

Infliximab is the most effective biologic for the treatment of moderate to severe psoriasis with a PASI 75 response rate of approximately 80% in the studies recorded by the guideline (ibid.). Actually, more than 50% achieved PASI 90 after 10 weeks of treatment.

Frequent side effects are infusion reactions and infections: infusion reactions such as flush, pruritus, headache and chills were observed in 20% of the patients in all clinical trials [e.g. 38, 39]. 52% of the treated patients experienced at least one infection [40].

### Ustekinumab

Ustekinumab is a biological agent treatment targeting p40 (IL-12 and IL-23). The drug was approved in 2009 and is, according to the European treatment Guideline for psoriasis [25] recommended as a second-line therapy for psoriasis. The dosage depends on the body weight: Patients of over 100 kg receive 90mg per injection while patients with 100 kg and less receive 45 mg.

### Alefacept

Alefacept was approved in 2004 for the treatment of psoriasis in Switzerland with a regular dosing of 15 mg weekly [21]. Alefacept is a recombinant human LFA-3 IgG1 fusion protein. It combines two mechanisms of action, the inhibition of T-cell activation and proliferation and T-cell apoptosis that leads to the minimisation of inflammatory reactions of the skin.

In the recorded studies, PASI 75 was achieved by 21% (intramuscular injection) and 33% (intravenous injection) of the patients after 14 weeks [41, 42]. Frequent side effects include malignancies, serious infections and allergic reactions [21].

Among the biologics, alefacept is not recommended as a first-choice treatment by the authors of the guideline [21].

### Efalizumab

Efalizumab is a recombinant humanised monocloncal antibody and acts as an immunosuppressant. Approved in 2004, the EMEA recommended the suspension of the marketing authorisation for efalizumab in 2009 because of the high risks when administered to patients [21]. In studies considered in the guideline, 30 % of the patients achieved PASI 75 after 12 weeks [43, 44].

### Secukinumab

Secukinumab is a human IL-17A antagonist that was approved for the treatment of psoriasis across all European countries in 2015 [45]. It is administered as subcutaneous injection (300 mg weekly for four weeks followed by 300 mg every four weeks). Four big efficacy and safety studies (s. Chap. 7.2) for secukinumab were conducted: over 75 % of the patients who received 300 mg secukinumab showed a PASI 75 improvement after 12 weeks. The treatment with secukinumab might cause side effects such as nasopharyngitis, diarrhea and colds; less common reactions are rhinitis, oral herpes and urticaria (ibid.).

### Ixekizumab

Ixekizumab is a humanised monoclonal immunoglobulin G antibody and a specific inhibitor of interleukin-17A (IL-17A), a pro-inflammatory cytokine [46]. In spring 2016 ixekizumab was approved by the EMA for the treatment of psoriasis. In three main studies patients received ixekizumab (initial dose 160 mg, then 80 mg biweekly), 89 % of them showed a PASI 75 improvement after 2 weeks. The most often occurring side effects are pain and redness at the injection site, nose, throat or chest infections (ibid.).

# 6 Outcome Parameter for efficacy evaluation in psoriasis trials

According to the S3 guideline, there are no generally valid definitions of treatment goals in psoriasis, but a variety of ideas [21]. The aim of the Guideline is to help dermatologists in optimising patient care by providing benchmarks on the Psoriasis Area and Severity Index (PASI) and the Dermatology Quality of Life Index (DLQI) to estimate the degree of improvement and the patient's view of the disease's influence on his life. Thus, the most suitable therapy for each individual psoriasis patient should be found.

In practice, there are three conceivable situations:

- treatment successful,
- treatment unsuccessful and
- treatment classified neither successful nor unsuccessful.

If the commenced treatment is assessed as being successful, there is no need for modification. If the treatment does not work for a patient, the dose should be adjusted or combined with another therapy. In some cases the treatment should be replaced by another treatment.

Clinically, the improvement should be assessed after 10 to 16 weeks of treatment and every 8 weeks thereafter with the help of the PASI. Although complete clearance of the skin should be the primary treatment goal, an improvement of 75 % is realisable and generally accepted as clinically relevant by dermatologists. An instrument for measurement of the impact of the disease on the patient's health-related quality of life, the DLQI is assessed. DLQI was the first instrument introduced to measure life quality in patients with dermatological diseases [47]. It is still the most frequently used one. Patients can achieve a score from 0 to 30, with lower scores reflecting better quality of life. The goal for an individual psoriasis patient is to achieve a DLQI score of 0 to 1, indicating that the patient's quality of life is no longer impacted by psoriasis.

Although the PASI and the DLQI do not correlate directly, there seems to be a connection between the improvement of the PASI score and improvement of the DLQI.

## 6.1 Current Efficacy parameters in psoriasis trials

### 6.1.1 Symptom scores

A systematic literature search of the Pubmed database was conducted in August 2016 with the aim to identify reviews of clinical outcome measures in clinical trials on plaque psoriasis. The search terms included occurrences for (severity) outcome measures for plaque psoriasis: ((((("review"[Publication Type] AND ("outcome assessment (health care)"[MeSH Terms] OR "outcome measures"[All Fields]) AND ("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields]) AND scores[All Fields]) OR "evaluation"[All Fields]) AND ("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields]) AND severity[All Fields])), which provided 27 hits.

Citation titles and abstracts were screened to identify relevant articles. Amongst them, two reviews [48, 49] were identified. The aim of both of these reviews was to evaluate the degree of validation of the most commonly used outcome measures for psoriasis. In 2010 Puzenat

and colleagues identified twelve eligible clinical severity scores of which six were chosen and analysed (PASI, BSA, the Physician's Global Assessment (PGA), the Lattice System Physician's Global Assessment (LS-PGA), the Salford Psoriasis Index (SPI) and SAPASI). Except for the SPI, Spuls and colleagues analysed these instruments as well, but expanded their work on six further measurements (the Patient's Global Assessment (PaGA), the Psoriasis Assessment Severity Score (PASS), the Simplified PASI (SPASI), the Psoriasis Exact Area and Severity Index (PEASI), the Psoriasis Long-based Area and Severity Index (PLASI) and the Signs). Brief descriptions of the analysed instruments are shown in Table 6.1.1-1.

Table 6.1.1-1: Overview of the twelve current psoriasis assessment analysed by Puzenat *et al.* (2010) and Spuls *et al.* (2010) [48, 49].

| **Severity scores** | **Description** |
|---|---|
| BSA | Assessment of affected body surface area [50] |
| LS-PGA | Similar to the PGA, integrates ranges of BSA and total plaque morphology [51] |
| PaGA | Five to seven point rating scale from "clear" to "very severe" assessed by the patient [49] |
| PASI | Assessment of redness, thickness and scaling (severity), as well as percentage of affected area [52] |
| PASS | Assessment divided into two steps: estimation of percentage BSA, three point scale for erythema, desquamation and induration [53] |
| PEASI | Derivation of the PASI with BSA percentage |
| PGA | Five to seven point rating scale from "clear" to "very severe" [27] |
| sPGA | Physician's determination of the patient's psoriatic lesions overall assessed on a 6 point scale (0 (clear), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe), or 5 (very severe)) |
| PLASI | Derivation of the PASI using six BSA groupings |
| SAPASI | Patients color affected body areas on a body silhouette |
| Signs | Assessment of erythema, scaling und induration |
| SPASI | Simplified derivation of the PASI |
| SPI | Combination of a modified PASI, a score for psychological disability and a score based on historical information [54] |

Although literature classifies up to eleven inventories as eligible to assess severity of psoriasis and therapy-related improvement [48, 49], only three of them are well established in clinical trials since years. The most commonly used inventories are the PASI, the PGA and the BSA [18]. These will be described in more detail in the following.

Psoriasis area and severity index (PASI) (App. 1)

PASI was developed in 1978 and was initially applied to assess the effect of retinoids in the treatment in plaque psoriasis [52].

The PASI evaluates the intensity and the extent of the lesions separately. The degree of erythema, desquamation and induration of the psoriasis is assessed on a scale from 0 to 4 (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe). The extent of the lesions is rated for four anatomical regions (head, trunk, upper and lower extremities) and assigned a value of 0 to 6 (0 = no involvement, 1 = 1-9%, 2 = 10-29%, 3 = 30-49%, 4 = 50-69%, 5 = 70-89% and 6 = 90-100% body surface area involvement). The total score thus can achieve values between 0 and 72 with higher scores indicating a more severe condition. Response rates to therapeutic interventions in clinical trials are frequently stated by the percentage of PASI reduction (PASI 50, PASI 75, PASI 90, and PASI 100).

Despite the fact that the PASI is handled as “gold standard” in clinical trials for psoriasis [55], it has been criticised for being complex and inaccurate, lacking sensitivity and usability of only half the scale [51, 53]. Certainly, a big advantage of the PASI being applied in most of the conducted studies in psoriasis is the possibility to compare the results over the past decades. Although the PASI has never been formally validated, it is the score most validated by practice [18, 48].

Modified inventories such as the simplified PASI (SPASI), the psoriasis log-based area and severity index (PLASI) and the psoriasis exact area and severity index (PEASI) were derived from the PASI to provide a more accurate assessment of improvement and a simplified application in practice [49].

Physician’s global assessment (PGA) (App. 2)

The physician’s global assessment (PGA) was an FDA-initiated attempt to provide a broader estimate of psoriasis severity based on a global judgment of the physician summarising the different features of lesions into one figure. The PGA is the second most widely used symptom score.

It is unknown who the inventor of the PGA is, but the earliest report of such a scale was a plaque psoriasis study by Katz and colleagues in 1991 [56]. Since then multiple versions of the PGA have been described ranging from 4 point to 11 point scales. Additionally, there are several definitions regarding the wording allocated to the particular scores and substantially different instructions how to use the PGA. This might be regarded as the greatest weakness of this score. Furthermore, none of the several existing PGAs has been formally validated. Certainly, the PGA shows good correlation with other symptom and health-related quality of life psoriasis measurements [51, 57].

Body surface area index (BSA) (App. 3)

The BSA was developed to estimate the area of skin affected by psoriasis. One percent of BSA is approximately equal to the patient's palm (from wrist to finger tips) with fingers tucked together and the thumb tucked to the side, as stated in the Koo-Menter Psoriasis Instrument [58]. The investigator adds up the number of palms required to cover the affected skin thereby estimating the percentage in each of the four body regions: Head (including scalp) and neck (10%), upper extremities (20%), trunk (30%), lower extremities (40%). The BSA thus ranges from 0 to 100%.

The weakness of this assessment is that it is very imprecise as one hand actually represents 0.70 - 0.76 % of the body surface [59]. Furthermore, the BSA does not assess severity as it does not include the intensity of the lesions. Nevertheless, the BSA correlates strongly with the PGA [57].

### 6.1.2 Patient Reported Outcomes

The psychosocial impact of psoriasis is commonly assessed by Quality of Life measures (QoL), some of which follow a generic approach (short-form (36) health survey (SF-36), [56]), whereas others assess the burden of disease either dermatology-specific (DLQI, Skindex) or even psoriasis-related (Psoriasis Index of Quality of Life (PSORIQol) [61], Psoriasis Disability Index (PDI) [62], Psoriasis Life Stress Inventory (PLSI) [63]). The most comprehensive overview over PRO measures in psoriasis is given by Bhosle and colleagues (2006) [64].

The most established and dermatology-specific measure to assess quality of life in patients is the dermatology quality of life index (DLQI), followed by the Skindex-29 [65]. These will be briefly described in the following.

Dermatology quality of life index (DLQI) (App. 4)

The DLQI, developed by Finlay and colleagues in 1994 [47], is a skin-specific QoL instrument designed to assess the impact of any dermatological disease on the patient's daily life. This 10-item questionnaire measures how skin problems have affected patient's life over the past week. The questionnaire covers six different areas of life:

- Symptoms and feelings,
- leisure,
- daily activities,
- work or school performance,
- personal relationship and
- treatment.

Except for item 7, the questions provide the answer options "very much" (3), "a lot" (2), "a little" (1), "not at all" (0) and "not relevant" (0). (The option "not relevant" is not available for items 1 and 2). Item 7 can be answered with "yes" or "no". In case the answer is "no", further specifications "a lot", "a little" and "not at all" can be chosen..

The DLQI total score reaches from 0 (no impairment) to 30 (maximum impairment). The DLQI has become the standard in QoL assessment in dermatology and has in the meantime been translated into more than 100 languages.

Skindex-29

An alternative QoL questionnaire for skin diseases is the Skindex-29, developed in 1997 [66]. Skindex-29 contains 30 items of which 29 are associated to three scales (emotions, functioning and symptoms) as well as one global score. The answering categories range from 1 to 5 on a Likert scale (1 = never, 2 = rarely, 3 = sometimes, 4 = often, 5 = all the time).

# 7 Clinical Development and Research in Psoriasis vulgaris

Global drug development spending has continuously increased over the past years, within the last 10 years from 112.5 billion USD in 2005 to 135.9 billion USD in 2013. Growth in therapeutic areas varies significantly and has shifted during the past five years, with psoriasis being amongst the indications showing increased levels of activity.

The number of INDs (Investigational New Drugs) for dermatology development has increased around 9% in the years 2007-2012, as research in oncology and inflammation has allowed new therapies to be developed across a variety of diseases. The spending for INDs in the area of Dermatology is estimated to be $ 7.75 billion USD.

## 7.1 Marketing Authorisations for the treatment of psoriasis

This subchapter presents the marketing authorisations for medicinal products in psoriasis approved in Europe between Jan 01, 2005 and Nov 16, 2016; the time period was defined in order to select all medicinal products after the Guideline CHMP/EWP/2454/02 corr has been issued (18th Nov 2004).

To identify these products, Marketing Authorisations for the therapeutic indication “plaque psoriasis” have been searched on the EMA homepage [67].

Furthermore, GlobalData, a provider of data and analysis for consumer technology and healthcare business, was consulted.

The search resulted in 8 hits, amongst them four products that have reached marketing authorisation as originators and four medicinal products that have been marketed as generic biological (Biosimilars), see Tab.7.1-1:

Table 7.1-1: Medicinal products for the treatment of plaque psoriasis marketed between 2005 and 2016.

| No | Medicine Name | Product Number | Active Substance | Marketing Authorisation Holder | Authorisation date | Bio similar |
|---|---|---|---|---|---|---|
| 1 | Stelara® | EMEA/H/C/000958 | ustekinumab | Janssen-Cilag International NV | 16/01/2009 | no |
| 2 | Cosentyx® | EMEA/H/C/003729 | secukinumab | Novartis Europharm Ltd | 15/01/2015 | no |
| 3 | Otezla® | EMEA/H/C/003746 | apremilast | Celgene Europe Limited | 15/01/2015 | no |
| 4 | Taltz® | EMEA/H/C/003943 | ixekizumab | Eli Lilly Nederland B.V. | 25/04/2016 | no |
| 1 | Inflectra® | EMEA/H/C/002778 | infliximab | Hospira UK Limited | 10/09/2013 | yes |
| 2 | Remsima® | EMEA/H/C/002576 | infliximab | Celltrion Healthcare Hungary Kft. | 10/09/2013 | yes |
| 3 | Benepali® | EMEA/H/C/004007 | etanercept | Samsung Bioepis UK Limited | 14/01/2016 | yes |
| 4 | Flixabi® | EMEA/H/C/004020 | infliximab | Samsung Bioepis UK Limited | 26/05/2016 | yes |

Three out of 4 originators are classified as biological and one product was marketed as small molecule.

## 7.2 Marketing Authorisation/pivotal clinical studies Phase II and III

In order to identify the pivotal studies that have been evaluated by the Competent Authorities in the marketing authorisation approval process, the European public assessments reports (EPARs) generated by the Committee for Medicinal Products for Human Use (CHMP) for all marketed products listed above have been reviewed.

In addition to the comments on efficacy data in the EPARs, the database of clinicaltrials.gov was searched for each product by the terms “chronic plaque psoriasis”, “phase III” and “interventional study” to receive relevant papers of the particular pivotal and safety and efficacy trials. Studies were selected if the status was “completed” and “Has results” and if data collection for primary outcome measure was before the date of approval.

Further information to correctly select the Phase III trials the marketing authorisation approval was based on, was obtained from the companies press releases [68].

In the following, the products will be introduced with a brief profile (table 7.2-1 to 7.2-8); for each newly marketed product the relevant outcome measures as assessed in the Phase III trials in the indication chronic plaque psoriasis will be summarised in order to later compare the practice of outcome parameter in pivotal trials with the requirements as laid down in CHMP/EWP/2454/02 corr.

Table 7.2-1: Basic data for Stelara®.

| **Name (Trademark)** | **Stelara® (ustekinumab)** |
|---|---|
| **Profile** | A human anti-interleukin 12 (IL-12) and anti-interleukin 23 (IL-23) monoclonal antibody (MAb) |
| **EPAR**<br><br>**EMA/383370/2015**<br>**EMEA/H/C/000958** | Efficacy studies:<br><br>*Adults*<br><br>In the treatment of moderate to severe plaque psoriasis, Stelara® has been compared with placebo (a dummy treatment) in two main studies involving a total of 1,996 adults with the condition.<br><br>Both studies looked at two doses of Stelara® (45 and 90 mg). The main measure of effectiveness was the number of patients who ‘responded’ to treatment after 12 weeks, meaning that symptom scores improved by 75% or more.<br><br>*Adolescents*<br><br>An additional study also looked at 110 children with moderate to severe plaque psoriasis aged between 12 and 18 years. The children either received placebo or Stelara® and the main measure of effectiveness was the number of patients who responded to treatment after 12 weeks as shown by an improvement in symptom scores.<br><br>Benefit of Stelara®: |

| **Name (Trademark)** | **Stelara® (ustekinumab)** |
|---|---|
| | *Adults*<br>- Superiority of Stelara® compared to placebo at improving the symptoms of plaque psoriasis.<br>- Two Phase III studies: 69% of the patients receiving Stelara® reached PASI75 after 12 weeks, compared with around 3% of the patients receiving placebo.<br>- There was no difference in response rates between the two doses of Stelara® in patients weighing below 100 kg. Patients weighing over 100 kg had a better response to the 90 mg dose.<br>- The longer-term results showed that with continuous treatment, the response to Stelara® is maintained over 5 years.<br>- The comparative study has shown that Stelara® is more effective than etanercept after 12 weeks of treatment.<br><br>*Adolescents*<br>- 69% of children (25 out of 36) who received Stelara® reached PASI75 compared with 5% of patients receiving placebo (2 out of 37). |
| **Pivotal clinical trials (Phase III)** | *Adults*<br><br>**<u>Phoenix I</u>**<br>A Phase III, Multicenter, Randomised, Double-blind, Placebo Controlled Trial Evaluating the Efficacy and Safety of Ustekinumab (CNTO 1275) in the Treatment of Subjects With Moderate to Severe Plaque-type Psoriasis – PHOENIX I<br>ClinicalTrials.gov Identifier: NCT00267969<br>*Inclusion criteria:*<br>- PASI $\geq$ 12 and at least 10% BSA involvement<br>*Primary Outcome Measures*<br>- PASI75 Improvement From Baseline at Week 12<br>*Secondary Outcome Measures*<br>- Three secondary endpoints, amongst them one PRO:<br>- Change From Baseline in Dermatology Life Quality Index (DLQI) at Week 12<br><br>**<u>Phoenix 2</u>**<br>A Phase III, Multicenter, Randomised, Double-blind, Placebo-controlled Trial Evaluating the Efficacy and Safety of CNTO 1275 in the Treatment of Subjects With Moderate to Severe Plaque-type Psoriasis.ClinicalTrials.gov<br>ClinicalTrials.gov Identifier: NCT00307437<br>*Inclusion criteria:*<br>- PASI $\geq$ 12 and at least 10% BSA involvement<br>*Primary Outcome Measures* |

| Name (Trademark) | Stelara® (ustekinumab) |
|---|---|
| | - Proportion of patients achieving PASI 75 at week 12<br>- Number of Participants With Psoriasis Area and Severity Index (PASI) Score of 75 Percent or Above at Week 12<br>*Secondary Outcome Measures:*<br>- Change in Dermatology Life Quality Index (DLQI) at Week 12<br><br>*Adolescents*<br><br>**CADMUS**<br>Phase III CADMUS registration study, which evaluated the efficacy and safety, as well as improvements in quality of life, among adolescents (pediatric patients ages 12 to 17) receiving STELARA compared with patients receiving placebo<br>ClinicalTrials.gov Identifier: NCT01090427<br>*Inclusion criteria:*<br>- Have a diagnosis of plaque-type psoriasis with or without psoriatic arthritis (PsA) for at least 6 months<br>- Are candidates for phototherapy or systemic treatment of psoriasis<br>*Primary Outcome Measures*<br>- PGA score of cleared (0) or minimal (1) at week 12.<br>*Secondary Outcome Measures*<br>- PASI 75 or PASI 90 at week 12<br>- improvement in quality of life, as measured by the Children's Dermatology Life Quality Index (CDLQI)<br>- Change From Baseline in Pediatric Quality of Life Inventory (PedsQL) Total Scale Score, Psychosocial Health Summary Score, and Physical Health Summary Score at Week 12 |

Leonardi CL, Kimball AB, Papp KA, et al. (May 2008). "Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1)". Lancet. 371 (9625): 1665–74. doi:10.1016/S0140-6736(08)60725-4. PMID 18486739.

Papp KA, Langley RG, Lebwohl M; et al. (May 2008). "Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2)". Lancet. 371 (9625): 1675–84. doi:10.1016/S0140-6736(08)60726-6. PMID 18486740.

Landells I, Marano C, Hsu MC, Li S, Zhu Y, Eichenfield LF, Hoeger PH, Menter A, Paller AS, Taieb A, Philipp S, Szapary P, Randazzo B. Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: results of the randomised phase 3 CADMUS study. J Am Acad Dermatol. 2015 Oct;73(4):594-603. doi: 10.1016/j.jaad.2015.07.002. Epub 2015 Aug 7.

Table 7.2-2: Basic data for Otezla®.

| **Name (Trademark)** | **Otezla® (apremilast)** |
|---|---|
| **Profile** | An oral small-molecule inhibitor of phosphodiesterase 4 (PDE4) specific for cyclic AMP (cAMP) |
| **EPAR**<br><br>**EMA/727043/2014**<br>**EMEA/H/C/003746** | Efficacy studies<br><br>*Adults*<br><br>Otezla® has been investigated in 2 main studies involving a total of 1,257 patients with moderate to severe plaque psoriasis, in which treatment with Otezla® was compared with placebo (a dummy treatment). Response to treatment was defined as patients having a 75% or more reduction in a symptom score known as Psoriasis Area Severity Index (PASI-75) after 16 weeks.<br><br>*Adolsecents*<br><br>Otezla is not used for the treatment of children.<br><br>Benefit of Otezla®<br><br>- Of the patients given Otezla® in the two studies, 33% (168 of 562) and 29% (79 of 274) responded to treatment. This compared with 5% (15 of 282) and 6% (8 of 137) given placebo<br><br>- evidence of maintained benefit in the treatment of psoriasis and psoriatic arthritis when treatment was extended (to 32 and 52 weeks) |
| **Pivotal clinical trials** | ESTEEM 1 and 2 are two large pivotal Phase III randomised, placebo-controlled studies evaluating apremilast in patients with a diagnosis of moderate to severe plaque psoriasis for at least 12 months prior to screening, and who were also candidates for phototherapy or systemic therapy. Approximately 1,250 patients were randomised 2:1 to receive either apremilast 30 mg twice daily or placebo after an initial five-day titration period, for the first 16 weeks, followed by a maintenance phase from weeks 16-32 in which placebo patients were switched to apremilast 30 mg twice daily through week 32. The trial also consisted of a randomised withdrawal phase for responders from week 32 to week 52 based on their initial apremilast randomisation and Psoriasis Area and Severity Index (PASI) response.<br><br>http://smp.businesswire.com/pages/oral-otezla-apremilast-approved-european-commission-treatment-both-patients-psoriasis-and-psor<br><br>**Esteem 1**<br><br>A Phase III, Multicenter, Randomised, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Apremilast (CC-10004) in Subjects With Moderate to Severe Plaque Psoriasis (ESTEEM 1)<br>ClinicalTrials.gov Identifier: NCT01194219<br><br>*Inclusion criteria:*<br><br>- PASI $\geq$ 12 and SPGA $\geq$ 3 and BSA $\geq$ 10% |

| **Name (Trademark)** | **Otezla® (apremilast)** |
|---|---|
| | *Primary Outcome Measures:*<br>- PASI 75 at week 16<br>*Secondary Outcome Measures:*<br>- In total 12, amongst them 3 PROs (Mental Component Summary (MSC) Score of the Medical Outcome Study Short Form 36-item (SF-36) Health Survey Version 2.0, DLQI, Visual Analog Scale (VAS) at week 16)<br><br>**<u>Esteem 2</u>**<br>A Phase III, Multicenter, Randomised, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Apremilast (CC-10004) in Subjects With Moderate to Severe Plaque Psoriasis<br>ClinicalTrials.gov Identifier: NCT01232283<br><br>*Primary Outcome Measures*<br>- PASI 75 at week 16<br>*Secondary Outcome Measures*<br>- In total 11, amongst them 3 PROs (Mental Component Summary (MSC) Score of the Medical Outcome Study Short Form 36-item (SF-36) Health Survey Version 2.0, DLQI, Visual Analog Scale (VAS) at week 16) |
| Paul, C., Cather, J., Gooderham, M., Poulin, Y., Mrowietz, U., Ferrandiz, C, Day, R. M. (2015). Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomised controlled trial (ESTEEM 2). *British Journal of Dermatology*, *173*(6), 1387-1399.<br>Papp, K., Reich, K., Leonardi, C. L., Kircik, L., Chimenti, S., Langley, R. G, Korman, N. J. (2015). Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomised, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). *Journal of the American Academy of Dermatology*, *73*(1), 37-49. | |

Table 7.2-3: Basic data for Cosentyx®.

| **Name (Trademark)** | **Cosentyx® (secukinumab)** |
|---|---|
| **Profile** | A human monoclonal antibody that selectively neutralises IL-17A |
| **EPAR**<br><br>**EMA/780949/2015**<br>**EMEA/H/C/003729** | <u>Efficacy studies</u><br>*Adults*<br>In 4 psoriasis studies involving 2,403 patients, 79% of those on Cosentyx achieved a 75% reduction in their PASI scores (a measure of disease severity and area of skin affected) after 12 weeks of treatment. This compares with 44% of those on a comparator medicine etanercept and 4% of those on placebo.<br>*Adolescents*<br>The safety and efficacy of *Cosentyx*® in *children* below the age of 18 years has |

| Name (Trademark) | Cosentyx® (secukinumab) |
|---|---|
| | not yet been established.<br><br>Benefit of Costenyx®<br>- Superiority of Cosentyx® compared to placebo and etanercept at improving the symptoms of plaque psoriasis<br>- 65% of patients given Cosentyx® had clear or nearly clear skin, compared with 27% of patients given etanercept and 2% of those given placebo. |
| **Pivotal clinical trials** | Feature<br>First Study of Secukinumab in Pre-filled Syringes in Subjects With Chronic Plaque-type Psoriasis: Response at 12 Weeks (FEATURE)<br><br>ClinicalTrials.gov Identifier: NCT01555125<br><br>*Inclusion criteria:*<br>- diagnosis of plaque psoriasis ≥ 6 months<br>- PASI ≥ 12, IGA ≤ 3, BSA ≥ 10%<br><br>*Primary Outcome Measures:*<br><br>- PASI 75 and IGA with 0 or 1 response after 12 weeks<br><br>*Secondary Outcome Measures:*<br>- In total 5, amongst them 1 PRO (Self-administered Self-Injection Assessment Questionnaire (SIAQ) score and investigator / site staff observation)<br><br>**Juncture**<br>Judging the Efficacy of Secukinumab in Patients With Psoriasis Using AutoiNjector: a Clinical Trial Evaluating Treatment Results (JUNCTURE)<br><br>ClinicalTrials.gov Identifier: NCT01636687<br><br>*Inclusion criteria:*<br>- diagnosis of plaque psoriasis >= 6 months<br>- PASI ≥ 12, IGA ≤ 3, BSA ≥ 10%<br><br>*Primary Outcome Measures:*<br>- PASI 75 score and IGA with 0 or 1 response<br><br>*Secondary Outcome Measures:*<br>- In total 11, amongst them 2 PROs (Self-administered Self-Injection Assessment Questionnaire (SIAQ) and investigator / site staff observation, Efficacy of secukinumab with respects to the DLQI)<br><br>**Fixture**<br>Safety and Efficacy of Secukinumab Compared to Etanercept in Subjects With Moderate to Severe, Chronic Plaque-Type Psoriasis (FIXTURE)<br><br>ClinicalTrials.gov Identifier: NCT01358578 |

| **Name (Trademark)** | **Cosentyx® (secukinumab)** |
|---|---|
| | *Inclusion criteria:*<br>- diagnosis of plaque psoriasis ≥ 6 months<br>- PASI ≥ 12, IGA ≤ 3, BSA ≥ 10%<br><br>*Primary Outcome Measures:*<br>- PASI 75 score and IGA with 0 or 1 response at week 12<br><br>*Secondary Outcome Measures:*<br>- In total 8, amongst them 2 PROs: Psoriasis Symptom Diary Items Itching, Pain and Scaling vs placebo, Psoriasis Symptom Diary Items Itching, Pain and Scaling in AIN457 vs Etanercept vs etanercept |
| Blauvelt, A., Prinz, J. C., Gottlieb, A. B., Kingo, K., Sofen, H., Ruer-Mulard, M., Cooper, S. (2015). Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomised controlled trial in psoriasis (FEATURE). *British Journal of Dermatology*, *172*(2), 484-493.<br>Paul C, Lacour JP, Tedremets L, Kreutzer K, Jazayeri S, Adams S, Guindon C, You R, Papavassilis C; JUNCTURE study group.. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomised, controlled trial (JUNCTURE). J Eur Acad Dermatol Venereol. 2015 Jun;29(6):1082-90. doi: 10.1111/jdv.12751.<br>Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, Puig L, Nakagawa H, Spelman L, Sigurgeirsson B, Rivas E, Tsai TF, Wasel N, Tyring S, Salko T, Hampele I, Notter M, Karpov A, Helou S, Papavassilis C; ERASURE Study Group.; FIXTURE Study Group. Secukinumab in plaque psoriasis--results of two phase 3 trials. N Engl J Med. 2014 Jul 24;371(4):326-38. doi: 10.1056/NEJMoa1314258. | |

Table 7.2-4: Basic data for Taltz®.

| **Name (Trademark)** | **Taltz® (ixekizumab)** |
|---|---|
| **profile** | A monoclonal antibody, a protein designed to attach to interleukin 17A |
| **EPAR**<br><br>**EMA/246394/2016**<br>**EMEA/H/C/004020** | Efficacy studies:<br><br>*Adults*<br>3 main studies involving over 3,800 patients with psoriasis<br><br>In 2 studies, treatment was continued in patients whose psoriasis improved with Taltz® given every 2 weeks for 12 weeks.<br><br>*Adolescents*<br>It is not known if *Taltz*® is safe and effective in *children* under 18 years of age.<br><br>Benefit of Taltz®<br>- 89% of those treated every two weeks with Taltz attained a PASI 75 after 12 weeks, compared with 4% of those given placebo and with 48% of patients given etanercept in 2 of the main studies<br>- 82% of patients given Taltz had clear or nearly clear skin after 12 weeks, compared with 4% of patients given placebo and 39% of patients given etanercept<br>- follow up treatment with Taltz® every 4 weeks for 48 weeks, 78% of patients had clear or nearly clear skin. |

| **Name (Trademark)** | **Taltz® (ixekizumab)** |
|---|---|
| **Pivotal clinical trials** | **<u>Uncover-1</u>**<br><br>A Multicenter Study With a Randomised, Double-Blind, Placebo-Controlled Induction Dosing Period Followed by a Randomised Maintenance Dosing Period and a Long- Term Extension Period to Evaluate the Efficacy and Safety of LY2439821 in Patients With Moderate-to-Severe Plaque Psoriasis<br><br>ClinicalTrials.gov Identifier: NCT01474512<br><br>*Inclusion criteria*<br>- At least 10% Body Surface Area (BSA) of Psoriasis, Static Physician Global Assessment (sPGA) score of at least 3 and PASI of at least 12<br><br>*Primary Outcome Measure*<br>- (sPGA) of 0 or 1<br>- PASI 75<br><br>*Secondary Outcome Measure*<br>- In total 15, amongst them 6 PRO (Itch Numeric Rating Scale (Itch NRS), DLQI, Work Productivity Activity Impairment Questionnaire-Psoriasis (WPAI-PSO), SF-36, Quick Inventory of Depressive Symptomatology-Self Reported 16 Items (QIDS-SR16), Patient's Global Assessment (PatGA))<br><br>**<u>Uncover-2</u>**<br><br>A Multicenter, Randomised, Double-Blind, Placebo-Controlled Study Comparing the Efficacy and Safety of LY2439821 to Etanercept and Placebo in Patients With Moderate-to-Severe Plaque Psoriasis<br><br>ClinicalTrials.gov Identifier: NCT01597245<br><br>*Inclusion criteria*<br>- At least 10% Body Surface Area (BSA) of Psoriasis, Static Physician Global Assessment (sPGA) score of at least 3 and PASI of at least 12<br><br>*Primary Outcome Measure*<br>- (sPGA) of 0 or 1<br>- PASI 75<br><br>*Secondary Outcome Measure*<br>- In total 15, amongst them 6 PRO (Itch Numeric Rating Scale (Itch NRS), DLQI, Work Productivity Activity Impairment Questionnaire-Psoriasis (WPAI-PSO), SF-36, Quick Inventory of Depressive Symptomatology-Self Reported 16 Items (QIDS-SR16), Patient's Global Assessment (PatGA))<br><br>**<u>Uncover-3</u>**<br><br>A 12-Week Multicenter, Randomised, Double-Blind, Placebo-Controlled Study Comparing the Efficacy and Safety of LY2439821 to Etanercept and Placebo in Patients With Moderate to Severe Plaque Psoriasis With a Long-Term Extension Period |

| **Name (Trademark)** | **Taltz® (ixekizumab)** |
|---|---|
| | ClinicalTrials.gov Identifier: NCT01646177<br><br>*Inclusion criteria*<br>- At least 10% Body Surface Area (BSA) of Psoriasis, Static Physician Global Assessment (sPGA) score of at least 3 and PASI of at least 12<br><br>*Primary Outcome Measure*<br>- (sPGA) of 0 or 1<br>- PASI 75<br><br>*Secondary Outcome Measure*<br>- In total 15, amongst them 6 PRO (Itch Numeric Rating Scale (Itch NRS), DLQI, Work Productivity Activity Impairment Questionnaire-Psoriasis (WPAI-PSO), SF-36, Quick Inventory of Depressive Symptomatology-Self Reported 16 Items (QIDS-SR16), Patient's Global Assessment (PatGA)) |
| Gordon, K. B., Blauvelt, A., Langley, R., Luger, T., Ohtsuki, M., & Cameron, G. (2015, March). Ixekizumab for treatment of moderate-to-severe plaque psoriasis: 60-week results from a double-blind phase 3 induction and randomised withdrawal study (UNCOVER-1). In *73rd Annual Meeting of the American Academy of Dermatology* (pp. 20-24).<br>Griffiths, C. E., Reich, K., Lebwohl, M., van de Kerkhof, P., Paul, C., Menter, A., ... & Ball, S. (2015). UNCOVER-2 and UNCOVER-3 investigators. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet*, *386*(9993), 541-551. | |

Table 7.2-5: Basic data for Inflectra®.

| **Name (Trademark)** | **Inflectra® (Infliximab)** |
|---|---|
| **profile** | Inflectra® is a 'biosimilar' medicine; the reference medicine for Inflectra® is Remicade |
| **EPAR**<br><br>**EMA/402688/2013**<br>**EMEA/H/C/002778** | <u>Efficacy studies:</u><br>Inflectra® was studied to show that it is comparable to the reference medicine, Remicade®. Inflectra® was compared with Remicade® in one main study involving 606 adult patients with rheumatoid arthritis. Patients received either Inflectra® or Remicade® in addition to methotrexate for 30 weeks. The main measure of effectiveness was the change in symptoms.<br>An additional study was also carried involving 250 patients with ankylosing spondylitis out to show that Inflectra® produces levels of the active substance in the body that are comparable to the reference medicine, Remicade®.<br><br><u>Benefit of Inflectra®:</u><br>Inflectra® is as effective as Remicade® with around 60 % of patients responding to treatment with either medicine (after 30 weeks) |

Table 7.2-6: Basic data for Flixabi®.

| **Name (Trademark)** | **Flixabi® (Infliximab)** |
|---|---|
| **profile** | A 'biosimilar' medicine; the reference medicine for Flixabi® is Infliximab |

| **Name (Trademark)** | **Flixabi® (Infliximab)** |
|---|---|
| **EPAR**<br><br>**EMA/246394/2016**<br>**EMEA/H/C/004020** | Efficacy studies:<br><br>Flixabi® was compared with Remicade® in one main study involving 584 patients with moderate to severe rheumatoid arthritis who had received previous treatment with methotrexate. The main measure of effectiveness was the proportion of patients who achieved at least a 20% reduction in ACR scores after 30 weeks.<br><br>Benefit of Flixabi®<br>Results showed that Flixabi® was as effective as Remicade® in reducing symptoms of rheumatoid arthritis: 64% of those treated with Flixabi® (148 of 231 patients) had at least a 20% reduction in ACR scores, compared with 66% of those given Remicade® (163 out of 247). |

Table 7.2-7: Basic data for Benepali®.

| **Name (Trademark)** | **Benepali® (Etanercept)** |
|---|---|
| **profile** | A 'biosimilar' medicine; the reference medicine for Benepali® is Etanercept. |
| **EPAR**<br><br>**EMA/786638/2015**<br>**EMEA/H/C/004007** | Efficacy studies:<br>Benepali® was also compared with Enbrel® in one main study involving 596 patients with moderate to severe rheumatoid arthritis despite treatment with methotrexate. The main measure of effectiveness was the proportion of patients who achieved at least a 20% reduction in ACR scores (a measure of painful, swollen joints and other symptoms) after 24 weeks of treatment.<br><br>Benefit of Benepali®:<br>Results of this study showed that Benepali® is as effective as Enbrel® at reducing symptoms of rheumatoid arthritis: 78% of patients given Benepali® (193 out of 247) achieved at least a 20% reduction in ACR scores after 24 weeks of treatment, compared with 80% of patients given Enbrel® (188 out of 234). |
| Emery, P., Vencovský, J., Sylwestrzak, A., Leszczyński, P., Porawska, W., Baranauskaite, A. & Rodriguez, A. A. B. (2015). A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. *Annals of the rheumatic diseases*, annrheumdis-2015. | |

Table 7.2-8: Basic data for Remsima®.

| **Name (Trademark)** | **Remsima® (Infliximab)** |
|---|---|
| **profile** | A 'biosimilar' medicine; the reference medicine for Remsima® is Remicade®. |
| **EPAR**<br><br>**EMA/407240/2013**<br>**EMEA/H/C/002576** | Efficacy studies:<br>Inflectra® was studied to show that it is comparable to the reference medicine, Remicade®. Inflectra was compared with Remicade® in one main study involving 606 adult patients with rheumatoid arthritis. Patients received either Inflectra® or Remicade® in addition to methotrexate for 30 weeks. The main measure of effectiveness was the change in symptoms.<br>An additional study was also carried involving 250 patients with ankylosing spondylitis out to show that Inflectra® produces levels of the active substance in the body that are comparable to the reference medicine, Remicade®.<br><br>Benefit of Inflectra®:<br>Inflectra® is as effective as Remicade® with around 60 % of patients responding<br><br>to treatment with either medicine (after 30 weeks) |

# 8 Discussion of Guideline requirements and recommendations with current practice in clinical trials supporting labelling claim

Since the EMA has issued Guideline on Clinical Investigations of Medicinal Products indicated for the treatment of psoriasis (CHMP/EWP/2454/02 corr), eight medicinal products have entered the European market, all containing the label “for the treatment of moderate to severe plaque psoriasis”.

These medicinal products are all systemic therapies, thus no topical agents for the treatment of plaque psoriasis have newly been approved. There are three originator biological for systemic administration (ustekinumab/Stelara®, secukinumab/Consetyx®, ixekizumab/Taltz®), one small molecule for systemic oral treatment (apremilast/Otezla®) and four generic biologicals, so called biosimilars (infliximab/Inflectra®, Remsima®, Flixabi®; etanercept/Benepali®).

All biosimilars have performed the phase III trial supporting labelling claim in the indication rheumatoid arthritis; none of them has performed a phase III trial in patients with plaque psoriasis.

Among the four originators that have been marketed between 2009 and 2016, three products based their marketing authorisation application (MAA) upon two phase III trials each. For one product (ustekinumab), three phase III trials (two trials in adults, one trials including adolescents aged 12-17 years) were filed. In the following these trials will be analysed for their concordance with the Guideline with respect to the outcome parameter as outlined in Chapter 4. These are:

- Primary endpoint and Categories for response to treatment (chapter 8.1)
- Severity categories (chapter 8.2)
- PROs (chapter 8.3)

## 8.1 Primary endpoint and categories for response to treatment

Primary endpoint in all pivotal trials supporting labelling claim for ustekinumab and apremilast in adult patients was PASI75 (for ustekinumab at week 12, for apremilast at week 16) (see table 8.1-1). For the ustekinumab trial in adolescents, cleared (0 or 1) PGA at week 12 was defined as primary endpoint. The most recently approved originator biologics (secukinumab and ixekizumab) used a co-primary endpoint, both PASI 75 and a Physician Global Assessment (IGA/sPGA with 0 or 1 response) at week 12. With the exception for the ustekinumab study conducted in adolescents, the definition of the primary endpoints was consistently applied for all pivotal studies conducted for the respective active ingredient.

Table 8.1-1: Overview of primary endpoints.

| Active ingredient | Primary endpoints |
|---|---|
| **ustekinumab** | PASI75 Week 12*<br>PGA score of cleared (0) or minimal (1) at week 12** |
| **secukinumab** | Co-primary end points :PASI75 and IGA with 0 or 1 response |
| **apremilast** | PASI 75 at week 16 |
| **ixekizumab** | Co-primary end points :PASI75 and sPGA with 0 or 1 response |

*Clinical trial in adults; ** Clinical trial in adolescents

There is a difference regarding the time point of the primary response measurement between the Phase III trials with week 12 being the read-out time point for all three biologicals and week 16 for the clinical phase III trials conducted on the small molecule apremilast.

The Guideline recommends a response to treatment latest at week 12 and even earlier, but the practice has shown, that for biologics week 12 is the most suitable time point to assess the primary endpoint whereas small molecules need more time to become fully effective. Therefore assessment of the response to treatment should be adapted to 16 weeks for these conventional systemic products.

Clear guidance differentiating between different classes of active ingredients could be adopted in the guideline.

## 8.2 Severity categories at patient inclusion

In all referenced pivotal studies - both for supporting labelling claim in biologicals as well as in conventional treatments - primarily moderate to severe psoriasis patients were the target population. These were defined by the extent of affected body surface area ($\geq$10%), the manifestation of symptoms (PASI $\geq$12) and the Physician's Global Assessment (moderate, $\geq$ 3, which correlates with a moderate manifestation of the disease). The definition of the underlying disease's severity was consistently applied for all pivotal studies conducted for each active ingredient.

Table 8.2-1: Definition of psoriasis severity per ingredient (PASI, SPGA, BSA).

| Active ingredient | Definition of psoriasis severity at study entry |
|---|---|
| **ustekinumab** | PASI $\geq$ 12 and at least 10% BSA involvement |
| **secukinumab** | PASI $\geq$ 12 and SPGA $\geq$ 3 and BSA $\geq$ 10% |
| **apremilast** | PASI $\geq$ 12 and SPGA $\geq$ 3 and BSA $\geq$ 10% |
| **ixekizumab** | PASI $\geq$ 12 and SPGA $\geq$3 and BSA $\geq$ 10% |

The major drawback of using (S)PGA is that there are several versions with different definitions regarding the wording allocated to the score. Different categories are used that range from 5-7, and furthermore instructions differ substantially. This may lead to different definitions of the

disease severity of the targeted population and might make it less reliable to compare trial data between the different medicinal products. The latter is difficult in any case as reliable data con only be obtained by a direct comparison of two (or more) active ingredients in a single trial setting.

The Guideline states that no consensus regarding severity grading had been reached at the time of issuing the recommendations. However, standards have been established in the meantime, but they are not fully in line with what the Guideline defined as “moderate to severe” affection: While the guideline defines PASI ≥10 as threshold for moderate psoriasis, it has been agreed upon in the meantime that PASI ≥12 is a more suitable definition to be used in trials supporting labelling claim for “moderate to severe” manifestations of plaque psoriasis.

## 8.3 Patient Reported Outcomes

DLQI is the established QoL questionnaire for clinical trials in dermatologic indications and has been used in all analysed Phase III trials. Regarding other PROS, mainly addressing patient assessable signs of the disease, there’s more diversity in terms of outcome measures as compared with the use of the primary parameter.

Table 8.3-1: Definition of psoriasis severity per ingredient (DLQI).

| Active ingredient | Definition of psoriasis severity at study entry (all the same in all pivotal trials per substance) |
|---|---|
| **ustekinumab** | DLQI at Week 0-12<br>DLQI at Week 0-12<br>diagnosis of plaque-type psoriasis with or without psoriatic arthritis (PsA) for at least 6 months<br>improvement in quality of life, as measured by the Children’s Dermatology Life Quality Index (CDLQI)<br>Change From Baseline in Pediatric Quality of Life Inventory (PedsQL) Total Scale Score, Psychosocial Health Summary Score, and Physical Health Summary Score at Week 12 |
| **secukinumab** | Self-Injection Assessment Questionnaire (SIAQ) score<br>Score From Baseline to Week 12 in Psoriasis Symptom Diary Items Itching, Pain and Scaling |
| **apremilast** | 12 in total, amongst them 3 PROs: SF36 week 0-16, DLQI week 0-16, Pruritus VAS week 0-16<br>11 in total, amongst them 3 PROs: SF36 week 0-16, DLQI week 0-16, Pruritus VAS week 0-16 |
| **ixekizumab** | PROs in all 3 studies: Itching Severity, DLQI, Quick Inventory of Depressive Symptomatology-Self Report 16 Items (QIDS-SR16); Work Productivity Activity Impairment Questionnaire-Psoriasis (WPAI-PSO), 36-Item Short Form Health Survey (SF-36), Patient's Global Assessment (PatGA) of Disease Severity |

In order to enable a comparison between ‘old’ and ‘new’ clinical trials, the use of DLQI could be more clearly recommended in the Guideline.

Guideline CHMP/EWP/2454/02 corr states that PROs should not be used as a primary endpoint, but might be used as secondary or tertiary endpoint. Thus the assessment of PROs in clinical trials supporting labelling claim has not been strengthened. A reflection paper issued in 2005, one year after the Guideline has been released only referred to HRQL. This lack of guidance regarding relevant signs of the disease assessed by patients’ needs to be filled especially in the light that Guideline CHMP/EWP/2454/02 corr emphasises that the ideal psoriasis severity assessment should cover the extent of affected body regions/area, the intensity of local signs (erythema, elevation, scale) and the intensity of symptoms (e.g. pruritus).

Current attempts in clinical trials have been made to add PROs for the assessment of patient relevant clinical signs, however, they are neither systematic nor integrated in a certain assessment rationale that allows an integrated analyses of relevant outcome measures.

Guideline CHMP/EWP/2454/02 corr would profit from clear recommendations on PROs that are important to assess as outcome measures for clinical trials in patients with plaque psoriasis.

# 9 Conclusion and outlook

Within the framework of the master thesis presented here, Guideline CHMP/EWP/2454/02 corr ('Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis') has been reviewed and, together with applicable guidelines and reflection papers, been put into perspective with medicinal products indicated for the treatment of psoriasis, that have been marketed after CHMP/EWP/2454/02 corr has come into force.

PASI seems to be the mainstay in the assessment of clinical efficacy of therapies addressing psoriasis. This is reflected in Guidelines CHMP/EWP/2454/02 corr as well as in systematic reviews. Although PASI shows known limitations as e.g. its inter-rater variability, the lack of understanding of the observed changes and its non-suitability for disease aspects affecting scalp and nails, it is widely used in clinical trials and is still the primarily recommended severity score to be used. A review of the systemic psoriasis therapies having been introduced to the European market since 2009 shows that PASI75 was used in all pivotal clinical trials, in many cases together with a PGA and/or the BSA.

In addition to the assessment of the extent of manifestation (BSA, Body Surface Area) of psoriasis as well as the clinical symptoms, which are covered by PASI, further important severity aspects as apparent clinical signs would add to the complete picture of the severity. Most recently performed pivotal phase III trials supporting labelling claims have addressed those signs in different ways without using any standard, thereby making it difficult to compare results of different trials and leading to an individual, patient-centred assessment of the suitability of the treatments.

A meaningful assessment of psoriasis severity by taking all aspects of phenotype and symptoms into consideration has not yet been established which can be regarded as a major drawback for daily practice/management of psoriasis patients and also for evaluation of the potential of new measures to treat the disease.

It is recommended by the author that such a standard should be developed. This can be best achieved by integrating clinical sings reported by the patient into the classic physician's assessment of extent of disease manifestation and clinical symptoms.

There is an attempt currently undertaken by a group of researchers to develop a novel holistic patient-centered scoring tool: in order to ensure the validity of the newly created tool, all requirements outlined by the FDA Guidance on the development of PROs [5] have been taken into account and the severity score has been developed according to the following development steps:

1. To identify items relevant to both patients and dermatology experts, a literature-based evaluation of existing scores was done. Next, to ensure international usability of the new score, two dermatology expert panels including five dermatology experts from Argentina, Australia, China, Japan and USA (International Expert Group) and five from France, Germany, Ireland, Poland, Spain (European Core Expert Group) were established. Interviews with patients at the sites of the ten experts were performed in their native languages, translated into English by the experts and collected at a CRO. Furthermore, the European Core Group was asked select items that are relevant from a dermatologist's perspective when assessing the severity of psoriasis.

2. Patient interviews were conducted with a total of 18 patients from the sites of the experts. The questions were collected and items classified and divided in four areas considering the severity of symptoms, social impairment, cognitive evaluation and aims, wished and fears of the patients. Especially the grade of itching and visibility on face, scalp and hands constitute important burdening factors as well as the impact on their social lives, sport and leisure activity. The patients' wish for the assessment of the severity of psoriasis was the consideration of extent, visibility, itchiness and scal-ing.
3. The interviews of the dermatology experts from the European Core Group covered current definitions and characterisation of severity and activity, and an evaluation of clinical symptoms that should have been be considered for the new severity score.
4. A panel of experts from outside of the medical field, termed Interdisciplinary Expert Group, but with expertise in process structuring, informatics/biostatistics, neuronal net-working has been invited to join the program. They were informed about the disease, provided with the list of items and asked for their approach to generate an easy-to-use scoring system which takes all or most items into consideration.
5. At the end of the development process, a pilot version of the new severity score was created: A total of seven items covering the most relevant severity symptoms of psoriasis were decided to be included and the severity categories were defined.
6. The pilot study for the implementation of the new severity score was conducted and analysed for their item characteristics as well as the correlation with the other scores are achieved with the rating of the '*extent'* of psoriasis (PASI, PGA, BSA)
7. Based on the results of the pilot study a global validation study is currently ongoing to validate the new severity score on a global scale.

Assuming a positive outcome of the validation study the new severity score might become the first to be validated severity score in the assessment of psoriasis to be used in clinical trials supporting labelling claim. In addition to the superior validation standard the assessment of patient related symptoms as well as all by physicians agreed relevant severity symptoms will then be covered. The hope is that in the long run the assessment of psoriasis severity will become more standardised and the information value through the assessment of the new score will be more comprehensive.

Whereas the development over the last years has been a shift from purely physician related assessment of severity scores to a physician based severity assessment serving as primary endpoint measures and the potential assessment of PROs as secondary/tertiary endpoints, future development should envisage the integration of physician and patient assessed aspects of severity scoring in one holistic tool.

In this regards the reflection paper issued on HRQL in 2005 would profit from becoming a more comprehensive PRO Guideline applicable for clinical trials in Europe. Furthermore the Guideline on Clinical Investigation of Medicinal Products indicated for the treatment of psoriasis should be amended by defining the requirement of integrating all relevant symptoms scores assessed by the patient and the physician in a comprehensive severity score to be used in clinical trials.

# 10 Summary

Marketing authorisation of medicinal products within the European Union follow a complex regulatory framework comprising regulations, directives and guidelines. For some medical conditions Guidelines have been released aiming to provide concrete guidance for the planning of clinical development studies to evaluate efficacy and safety of new compounds.

In June 2005 the EMA-Guideline on Clinical Investigation of medicinal products for the treatment of psoriasis has come into operation. Among other aspects regarding clinical trials in psoriasis this guideline specifies the requirements for primary outcome parameter and comments on Patient Reported Outcomes (PROs).

Since the release of the Guideline the indication plaque psoriasis has been subject to intensive research activities and eight new compounds have been marketed, amongst them four products have reached marketing authorisation as originators and four medicinal products have been marketed as generic biological (Biosimilars).

The present master thesis aims at comparing the regulatory requirements for primary efficacy objectives as laid down in the European Guideline CHMP/EWP/2454/02 corr with the actual practice in clinical trials in the indication plaque psoriasis. As state of the art study designs to evaluate safety and efficacy in the indication of plaque psoriasis have changed over time it is assumed that recommendations given more than ten years ago in the Guideline CHMP/EWP/2454/02 corr could benefit from a revision.

In the present master thesis an overview is given of regulatory requirements applicable for clinical trials for the treatment of plaque psoriasis, followed by on outline regarding the medical condition itself and current treatment options.

All pivotal trials that have been conducted for new compounds under development between 2005 to 2015 in the indication plaque psoriasis have been analysed with respect to outcome parameter.

The analyses revealed that a high level of consistency has been reached with regards to the selection of PASI as primary outcome parameter; however, studies differ with regards to its use as primary or co-primary endpoint as well as to the time point of the assessment of the primary outcome measure. The definition of the severity grading of plaque psoriasis according to PASI as established is not fully in line with the Guideline. In addition to that, Patient Reported Outcome Measures have a much higher relevance in clinical research compared to its meaning as outlined in the Guideline.

Given the fact, that the Guidelines stresses the restrictions that come along with several aspects of the PASI as well as the increased relevance of Patient Reported Outcome as admitted by the EMA, a new attempt should be made to develop outcome measures in the treatment of plaque psoriasis further.

Future development should envisage the integration of physician and patient assessed aspects of severity scoring in one holistic severity score. One attempt, that is currently undertaken by a group of researchers to develop a novel holistic patient-centered scoring tool is presented; it could in the future close the gap between physician’s and patient’s assessment

of the severity as two separate outcome measures as well as overcome the limitations of the currently used Outcome Measures.

In this sense, the Guideline on Clinical Investigation of Medicinal Products indicated for the treatment of psoriasis would profit from a revision.

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# 12 Appendices

### Appendix 1: Psoriasis Area and Severity Index (PASI)

| Score | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| Erythema, Infiltration, Desquamation | none | mild | moderate | severe | Very severe | | |
| Area involved (%) | 0 | 1 – 9 | 10 – 29 | 30 – 49 | 50 – 69 | 70 – 89 | 90 - 100 |

| | **Head** | **Trunk** | **Arms** | **Legs** | **PASI** |
|---|---|---|---|---|---|
| **Erythema** | I___I | I___I | I___I | I___I | |
| **Infiltration** | I___I | I___I | I___I | I___I | |
| **Desquamation** | I___I | I___I | I___I | I___I | |
| **Sum-Score 1** | | | | | |
| **x Area Score** | I___I | I___I | I___I | I___I | |
| **Sum-Score 2** | | | | | |
| | **x 0,1** | **x 0,3** | **x 0,2** | **x 0,4** | |
| **Total Score** | **+** | **+** | **+** | **=** | |

## Appendix 2: Physician's Global Assessment (PGA), examples for the most common grades of evaluation

**Example for 7-point-scale** [57]

| Category | Description | Score |
|---|---|---|
| **Clear** | No signs of psoriasis (post inflammatory hyper-pigmentation may be present) | ☐ 0 |
| **Almost clear** | Intermediate between mild and clear | ☐ 1 |
| **Mild** | Slight plaque elevation, scaling, and/or erythema | ☐ 2 |
| **Mild to moderate** | Intermediate between moderate and mild | ☐ 3 |
| **Moderate** | Moderate plaque elevation, scaling and/or erythema | ☐ 4 |
| **Moderate to severe** | Marked plaque elevation, scaling and/or erythema | ☐ 5 |
| **Severe** | Very marked plaque elevation, scaling and/or erythema | ☐ 6 |

**Example for 5-point-scale** [70]

| Category | Description | Score |
|---|---|---|
| **Clear** | No signs of psoriasis (post inflammatory hyper-pigmentation may be present) | ☐ 0 |
| **Almost clear** | Just perceptible erythema and just perceptible scaling | ☐ 1 |
| **Mild** | Light pink erythema with minimal scaling with or without pustules | ☐ 2 |
| **Moderate** | Dull red, clearly distinguishable erythema with diffuse scaling, some thickening of the skin, with or without fissures, with or without pustule formation | ☐ 3 |
| **Severe** | Deep, dark red erythema with obvious and diffuse scaling and thickening as well as numerous fissures with or without pustule formation | ☐ 4 |

**Appendix 3: Body Surface Area (BSA)** [50]

The patient's palm, including the five digits is used as reference (representing 1% of the total BSA) and is used to repeatedly cover the lesions on the body.
BSA values can be entered with a precision of 0.5%.

| **Body region** | **Number of Palms** |
|---|---|
| Head (including scalp) and neck | \|___\|___\|.\|___\| |
| Upper extremities | \|___\|___\|.\|___\| |
| Trunk | \|___\|___\|.\|___\| |
| Lower extremities | \|___\|___\|.\|___\| |

**BODY SURFACE AREA (BSA) SCORE** |___|___|.|___| %

**Appendix 4: Dermatology Quality of Life Index (DLQI)** [47]

| | | | |
|---|---|---|---|
| **1.** | Over the last week, how itchy, sore, painful or stinging has your skin been? | ☐ Very much<br>☐ A lot<br>☐ A little<br>☐ Not at all | |
| **2.** | Over the last week, how embarrassed or self-conscious have you been because of your skin? | ☐ Very much<br>☐ A lot<br>☐ A little<br>☐ Not at all | |
| **3.** | Over the last week, how much has your skin interfered with you going shopping or looking after your home of garden? | ☐ Very much<br>☐ A lot<br>☐ A little<br>☐ Not at all | ☐ Not relevant |
| **4.** | Over the last week, how much has your skin influenced the clothes you wear? | ☐ Very much<br>☐ A lot<br>☐ A little<br>☐ Not at all | ☐ Not relevant |
| **5.** | Over the last week, how much has your skin affected any social or leisure activities? | ☐ Very much<br>☐ A lot<br>☐ A little<br>☐ Not at all | ☐ Not relevant |
| **6.** | Over the last week, how much has you skin made it difficult for you to do any sport? | ☐ Very much<br>☐ A lot<br>☐ A little<br>☐ Not at all | ☐ Not relevant |
| **7.** | Over the last week, has your skin prevented you from working or studying? | ☐ Yes<br>☐ No | ☐ Not relevant |
| | If “No”, over the last week, how much has your skin been a problem at work or studying? | ☐ A lot<br>☐ A little<br>☐ 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<br>☐ A lot | ☐ Not relevant |

| | | | |
|---|---|---|---|
| | | ☐ A little<br>☐ Not at all | |
| **9.** | Over the last week, how much has your skin caused any sexual difficulties? | ☐ Very much<br>☐ A lot<br>☐ A little<br>☐ 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<br>☐ A lot<br>☐ A little<br>☐ Not at all | ☐ Not relevant |

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Unterschrift_____