Diploma Thesis

IL-23 and IL-17 inhibitors in the therapy of psoriasis

submitted by

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to attain the Academic Degree

Doctor medicinae universae

(Dr. med. univ.)

at the

Medical University of Graz

conducted at the

Department of Dermatology and Venerology

under the supervision of

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Graz, 12.05.2022

Declaration on oath

Herewith I declare to have written the present Diploma Thesis independently on my own as well as in absence of any assistance proceeding from third parties. Furthermore, I confirm to not have utilized in the preparation of the Thesis sources other than those specified as well as to have indicated the sources, cited or in terms of content, as such.

Graz, 12.05.2022 *Stephan Tschavgov eh.*

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List of Abbreviations

AE	Adverse event
BSA	Body surface area
C/EBPb	CCAAT enhancer-binding protein b
CASPAR	Classification of Psoriatic Arthritis
CBAD	C/EBPβ activation domain
CD4+ T-cells	Cluster of differentiation 4+ t-cells
CD8+ T lymphocytes	Cluster of differentiation 8+ t lymphocytes
CNV	Copy number variation
COPD	Chronic obstructive pulmonary disease
CTLA-8	T lymphocyte-associated antigen 8
CXCL1	C-X-C motif chemokine ligand 1
CXCL8	C-X-C motif chemokine ligand 8
CXCL12	C-X-C motif chemokine ligand 12
CXCR1	C-X-C motif chemokine receptor 1
CXCR2	C-X-C motif chemokine receptor 2
DEFB	Beta-defensin
DLQI	Dermatology Life Quality Index
e.g.	exempli gratia
Ebi3	Epstein-Barr virus induced gene 3
G-CSF	Granulocyte colony-stimulating factor
GWAS	Genome-wide association studies
GPP	Generalized pustular psoriasis
HDL	High Density Lipoprotein
HLA	Human leukocyte antigen
HuR	Human antigen R
i.e.	id est
i.v.	intravenous
IBD	Inflammatory bowel disease
IFN	Interferon
IFN-γ	Interferon gamma
IGA	Investigator's Global Assessment

IgG1	immunoglobulin G1
IgG1κ	immunoglobulin G1κ
IgG4	immunoglobulin G4
IL	Interleukin
IL-17RA	interleukin-17 receptor A
IL-1R	IL-1 receptor
IL-6	Interleukin-6
IL-6Rα	Interleukin-6 receptor subunit alpha
IL-12	Interleukin-12
IL-12Rβ1	Interleukin 12 receptor, beta 1 subunit
IL-12Rβ2	Interleukin 12 receptor, beta 2 subunit
IL-17	Interleukin-17
IL-17R	Interleukin-17 receptor
IL-21	Interleukin-21
IL-22	Interleukin-22
IL-23	Interleukin-23
IL-23R	Interleukin 23 receptor
IL-27	Interleukin-27
IL-35	Interleukin-35
ILC3s	Innate lymphoid cells type 3
Itch NRS	Itch Numeric Rating Scale
JAK	Janus kinase
Jak2	Janus kinase 2
kb	Kilobase
LTi	Lymphoid tissue inducer cells
MACE	Major adverse cardiac event
MAPK	Mitogen-activated protein kinase
mDC	Myeloid dendritic cells
MHC	Major histocompatibility complex
MS	Multiple sclerosis
n.a.	not applicable
NAPSI	Nail Psoriasis Severity Index

NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NGS	Next generation sequencing
NK cells	Natural killer cells
NMSC	Non-Melanoma Skin Cancer
PASI	Psoriasis Area and Severity Index
PsA	Psoriasis arthritis
PGA	Physician global assessment
PGA-F	Physician's Global Assessment of Fingernail Psoriasis
PPP	Palmoplantar pustular psoriasis
PPPASI	Palmoplantar Psoriasis Area and Severity Index
PSORS loci	Psoriasis susceptible loci
PSSI	Psoriasis Scalp Severity Index
PUVA	Psoralen and ultraviolet A
Q2W	Every 2 Weeks
Q4W	Every 4 Weeks
ROR- γt	Retinoid-related orphan receptor- γt
SEA	Serious adverse event
SEFIR	Similar expression of fibroblast growth factor genes and IL 17R
SF2(ASF)	Serine/arginine-rich splicing factor 1
SNP	Single nucleotide polymorphism
sPGA	Static Physician Global Assessment
ss-IGA	Scalp-Specific Investigator’s Global Assessment
STAT	Signal transducer and activator of transcription
STAT3	Signal transducer and activator of transcription 3
STAT4	Signal transducer and activator of transcription 4
TEAE	Treatment-emergent adverse events
TGF-β	Transforming growth factor beta
TH1 cell	T Helper 1 cells
TH17 cell	T Helper 17 cells
TIR	Toll/interleukin-1 receptor

TLR	Toll-like receptor
TLR 9	Toll-like receptor 9
TRAF2	TNF receptor-associated factor 2
TRAF3	TNF receptor-associated factor 3
TRAF4	TNF receptor-associated factor 4
TRAF5	TNF receptor-associated factor 5
TRAF6	TNF receptor-associated factor 6
TNF-α	Tumor necrosis factor alpha
type I IFN	Interferon type I
UV	Ultraviolet
UVB	Ultraviolet B
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor

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Figure 1 Treatment algorithm for healthy adult men with chronic plaque psoriasis (> 5% BSA) without psoriatic arthritis (BB-broadband, BSA-body surface area, NB-narrowband, PUVA-psoralen plus UVA, UV-ultraviolet) (44)..... 32

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Zusammenfassung

Hintergrund: Da es sich bei der Psoriasis um eine chronische, immunvermittelte Krankheit handelt und die Lebensqualität der Patienten/Patientinnen durch die Krankheit massiv beeinträchtigt werden kann, ist eine wirksame Therapie erforderlich, die sowohl ein schnelles und effizientes Ansprechen innerhalb der ersten 12-16 Wochen als auch eine langfristige Behandlung der Krankheit ermöglicht. **Zielsetzung:** Ziel dieser Arbeit ist es, die Wirksamkeit von IL-17- und IL-23-Antagonisten im Hinblick auf ihr PASI75/90/100-Ansprechen sowohl in der Induktionstherapie als auch in der Langzeittherapie zu vergleichen. Ebenso wird untersucht, ob es Unterschiede im Therapieansprechen an schwer zu behandelnden Stellen (z. B. Nägel, Kopfhaut usw.) oder im Sicherheitsprofil zwischen den beiden Substanzklassen gibt. Ein weiterer Aspekt der vorliegenden Arbeit ist es, zu zeigen, ob es möglich ist, eine Therapieempfehlung für den/die einzelnen/einzelne Psoriasis-Patienten/Patientin zu formulieren. **Methoden:** Es wurde eine umfassende Literaturrecherche durchgeführt, um die relevanten Daten für den Zeitraum zwischen 1997 und 2022 zu sammeln. **Ergebnisse:** Alle Biologika haben eine gute Wirksamkeit bei Patienten/Patientinnen mit Psoriasis gezeigt und können somit die Läsionen und die Lebensqualität der Betroffenen verbessern. Dies gilt insbesondere für Secukinumab, Ixekizumab, Brodalumab, Bimekizumab, Guselkumab und Risankizumab. Insgesamt weisen diese neuen Medikamente ein günstiges Nebenwirkungsprofil auf, obwohl man sagen kann, dass die IL-23-Inhibitoren ein etwas günstigeres Nebenwirkungsprofil aufweisen, da bei den IL-17 -Inhibitoren vermehrt Candida-Infektionen, IBD und Injektionsnebenwirkungen aufgetreten sind. Hinsichtlich spezieller Lokalisationen und Juckreiz wurde festgestellt, dass es leider noch nicht genügend Studien gibt und diese zu unterschiedlich sind, um Unterschiede zwischen den Gruppen festzustellen. Allerdings hat sich die Situation sowohl mit IL-17- als auch mit IL-23-Hemmern verbessert.

Konklusion: IL-17-, IL-23- und IL12/23-Inhibitoren haben neue Maßstäbe in der Therapie dieser lebenslangen Erkrankung gesetzt und können so das Leben vieler Betroffener verbessern. Es sind jedoch weitere Informationen erforderlich, um die Unterschiede zwischen diesen Medikamenten vollständig zu verstehen.

Abstract

Background: As psoriasis is a chronic immune-mediated disease and the quality of life of patients can be massively affected by the disease, effective therapy is required, both in terms of a rapid and efficient response within the first 12-16 weeks and in terms of long-term management of the disease. **Objective:** The aim of this work is to compare the efficacy of IL-17 and IL-23 antagonists in terms of their PASI75/90/100 response both in induction therapy and in long-term therapy. Likewise, it will be investigated whether there are differences in treatment response at difficult-to-treat sites (e.g., nails, scalp, etc.) or in the safety profile between the two classes of treatment agents. Another aspect of the present work is to show whether it is possible to formulate a therapy recommendation for the individual psoriasis patient. **Methods:** A thorough literature review was performed to collect the relevant data for the time period between 1997 and 2022. **Results:** All biologicals have shown good efficacy in patients suffering from psoriasis and are thus able to improve the lesions and the quality of life of those affected. This is especially true for secukinumab, ixekizumab, brodalumab, bimekizumab, guselkumab and risankizumab. Overall, these new drugs have a favorable side effect profile, although it can be said that the IL-23 inhibitors have shown a slightly more favorable side effect profile, as there has been an increased incidence of candida infections, IBD, and injection side reaction with the IL-17 inhibitors. Regarding special locations and itching, it has been found that unfortunately there are not enough studies yet and they are too different to detect differences between the groups. However, there has been improvement with both IL-17 and IL-23 inhibitors. **Conclusion:** IL-17, IL-23and IL12/23 inhibitors have reached new standards in the therapy of this life-long condition and can thus improve the lives of many sufferers. However, more information is needed to fully understand the differences between these drugs.

1 Introduction

1.1 Psoriasis

1.1.1 Definition

Psoriasis is a common, immune mediated, chronic inflammatory skin disease that manifests in people with a genetic predisposition. (1) The global prevalence, depending on the region, is around 2%. (1) Psoriasis can affect the skin, the joints or both and is often associated with comorbidities. (2) Due to its visibility patients often bear a huge physical and psychological burden. (2)

1.1.2 Clinical forms

1.1.2.1 Psoriasis vulgaris

The most prevalent type of psoriasis is chronic plaque psoriasis, also known as psoriasis vulgaris. (2) Around 90 percent of those affected suffer from this type. (2) In the chronic stadium the clinical picture of psoriasis is characterized by the efflorescence of erythematosquamous plaques and especially during exacerbation psoriasis can itch. (3) The typical morphology corresponds to an erythematous plaque with attached, loosely adhering silvery-white coarse scaling. (3) The extensor sides of the extremities, the sacral region and the scalp are predilection sites. (3) In special cases it can occur in flexural and intertriginous areas and is then called psoriasis inversa. (2)

1.1.2.2 Guttate psoriasis

In acute phases, often after streptococcal infections, disseminated psoriasis foci are released, which quickly reach drop size. (3) Most of the time guttate psoriasis affects children or adolescents and occurs equally often in both genders. (4) Out of all psoriasis cases less than one-third account for guttate psoriasis. (4) A third of children suffering from guttate psoriasis will develop psoriasis vulgaris. (2)

1.1.2.3 Pustular psoriasis

Another variant of psoriasis is pustular psoriasis. (5) In the course of acute attacks of psoriasis, pustular eruptions may occur. (3) These multiple, white,

intraepidermal pustules on reddened skin are usually grouped and often confluent and painful to touch. (3) With a massively increased activation and immigration of neutrophilic granulocytes into the epidermis, the Munro microabscesses become clinically visible pustules. (6) The pustules are basically sterile and can develop in an erythema or in clinically healthy skin. (6) According to the course and location of the pustules, different variants are distinguished: (6)

- Generalized
    - Generalized pustular psoriasis (GPP), also known as psoriasis type von Zumbusch: (6)

      Generalized pustular psoriasis is a potentially life-threatening variant of pustular psoriasis. (6) The prevalence of GPP varies and is around 1-9/1 million. About 30% of GPP is associated with psoriasis vulgaris. (6) GGP occurs acutely to subacutely, is possible as a single event, but tends to recur chronically, with very long intervals without symptoms. (6) On the trunk and extremities, disseminated pustules are found on sharply to blurredly defined flat erythema, which can confluent into blisters or pustule. (6)

      In the course of the disease, spontaneous or mechanical opening of the pustules causes erosion, which can lead to a combustion-like image. (6) Mucous membranes and the upper respiratory tract are often affected. (6) General symptoms such as fever, shivering, a feeling of illness and fatigue occur as part of the obligatory systemic inflammatory reaction. (6) GPP may be accompanied by electrolyte shifts, hypoalbuminemia and hypoparathyroidism, and complications may include infection and renal failure. (6)
    - Annular pustular psoriasis:

      It mainly affects the trunk and extremities, while the face, palms and soles of the feet are almost always spared. (6) Clinically, the individual lesions of the annular pustular psoriasis spread centrifugally with a central healing tendency, resulting in a three-zone structure. (6) The course of the disease is often intermittent and generally much milder than in other forms of GPP. (6) Children seem

to be affected disproportionately often. (6)

- Impetigo herpetiformis:
  Impetigo herpetiformis is a serious complication that occurs mainly in the third trimester of pregnancy. (7) It leads to an acute spread of the pustules and to potentially live threatening complications like hypoparathyroidism and hypocalcemia. (7)

- Localized
  - Acrodermatitis continua suppurativa – Hallopeau's disease:
    Hallopeau's disease is a rare pustular disease of the fingers and/or toes, often with pronounced nail involvement and is considered a rare and disabling variant of pustular psoriasis, that is often resistant to normal therapies. (8)(6) Clinically, one or more end limbs of the fingers and/or toes show acute to subacute pustules, erythema, overheating, swelling and pain. Nail dystrophy and parungual involvement are typical. (6)
  - Psoriasis pustulosa palmaris et plantaris
    This phenotype with pustules is restricted to the palms of the hands and/or the soles of the feet, often on erythematous and scaly skin. (6) In about 18- 25% of the cases, there are also typical psoriasis plaques, whereby the kinetics of pustular palmoplantar skin changes and the plaque type psoriasis can be asynchronous.(6) (8)

1.1.2.4 Erythrodermic psoriasis

The maximum form affects almost the entire body, it is called psoriatic erythroderma. (3) It is characterized by a generalized, scaly and inflammatory red skin. (3) Typically this form occurs in patients with active plaque psoriasis, but rarely it can take place without recent symptoms. (9) The most common cause of erythroderma is psoriasis, accounting for a quarter of all cases. (10) This type can show a big variety of symptoms on the skin such as erythema, edema, pruritus, psoriatic plaques and furthermore can be accompanied by serious systemic symptoms like fever, tachycardia and dehydration. (10)

1.1.2.5 Nails

The most common signs of nail psoriasis are small, sharply defined depressions in the nail surface, the so-called pits. (11) Parakeratosis is caused by small psoriatic foci in the apical matrix, which tear off when they grow under the proximal nail fold and leave pits. (11) If the entire matrix attachment is affected, a complete nail destruction with crumbling of the plate happens. (11) When the middle to distal matrix is affected, leukonychia occurs, parakeratotic cells are deposited in the nail plate, making it opaque. (11) If psoriatic plaques are present in the most distal matrix and in the nail bed, so-called oil stains will appear. (11) Psoriatic arthritis has a particularly strong negative influence on the quality of life. (11) Very often it has a severe nail involvement, up to a complete nail destruction (psoriatic paronychia) and is often accompanied by a swelling of the distal interphalangeal joint. (11)

1.1.2.6 Anti TNF-α induced psoriasis

Tumor necrosis factor alpha (TNF-α) inhibitors are used for diseases like inflammatory bowel diseases or psoriasis. (12) But there have been reports which have pointed out that the usage of TNF-α inhibitors has led to cutaneous side effects such as psoriasis. (12) These lesions have been found to be similar to psoriasis, but clinically and histologically more similar to eczema. (12) This is why they are also called "psoriasiform eczema" or "psoriasiform dermatitis". (12) The lesions are not as sharply defined and the silvery white scaling of psoriasis is missing, but both have erythema. (12) No predisposing factors were identified. (12) Both sexes seem to be equally affected and no preferred age group was found. (12) A family or personal history of psoriasis could not be detected in most cases. (13)

1.1.2.7 Psoriatic arthritis

Psoriasis arthritis is an inflammatory disease, that affects a lot of different body areas but primarily musculoskeletal parts and thus can lead to arthritis, enthesitis and dactylitis. (14) Chances of developing psoriatic arthritis in patients with

psoriasis are 20-30%. (15) With an estimated prevalence for psoriasis of around 3% in the USA, the prevalence of patients with psoriatic arthritis is between 30-100 per 10.000 people in the USA. (16) PsA usually manifests between the age of 30 and 50. (17) Pain, edema and stiffness of joints, ligaments and tendons are typical symptoms and are often caused by enthesitis and dactylitis. (17) These characteristics may worsen or improve over time and can even result in permanent inflammation. (17) Five clinical subtypes are described in the literature. (16) The oligoarticular subtype manifests asymmetrically in four or less joints. (16) Comparable to rheumatoid arthritis the poly-articular subtype may occur symmetrically, and 5 or more joints are affected. (16) The distal subtype normally occurs with other subtypes, and affects the distal interphalangeal joints of the hands, feet, or both. (16) Arthritis mutilans leads to marked bone resorption or osteolysis and thus results into deformations and destruction. (16) Characteristics for this subtype are telescoping and flail digits. (16) The spine and sacroiliac joints are mainly affected in the axial or spondyloarthritis subtype. (16) As the duration of the disease progresses, these patterns may change. (16)
The Classification of Psoriatic Arthritis (CASPAR) criteria is a group of criteria that is used to diagnose PsA: (18)
Table 1. CASPAR Criteria (18)

(The CASPAR criteria have specificity of 98.7% and sensitivity of 91.4%.)
(Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.)

To meet the CASPAR (Classification criteria for Psoriatic Arthritis) criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from the following 5 categories:

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis.

Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.

A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider.

A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report.

2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination.

3. A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range.

4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist.

5. Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

1.1.3 Genetics

Psoriasis has a strong genetic component, which is shown by the fact that there is an increased number of cases in families with people who already have the disease. (1) (19) The incidence is higher in the first and second generation of psoriasis patients than in the general population. (1) (19) Monozygotic twins have a 20-73% risk of developing psoriasis and dizygotic twins have a 12-30% risk of developing psoriasis. (1) (19) Genome-wide association studies (GWAS) and next generation sequencing (NGS) have recently shown that psoriasis sensitivity and expression are strongly impacted by genomic changes such as SNPs (single nucleotide polymorphisms), CNVs (copy number variations) and epigenetic

alterations. (19) Distributed over 22 autosomes, 424 genes with SNPs associated with psoriasis were found. (19) The 424 genes comprise genes in PSORS loci (Psoriasis susceptible loci). (19) Fifteen PSORS loci have been identified in the human genome. (19) PSORS loci are the areas of chromosomes that have been shown to harbor psoriasis genes. (19) The most important genetic determinant of psoriasis is PSORS1, which contributes to the disease's genetics between 30 and 50%. (19) This region of about 300 kb is located in the major histocompatibility complex (MHC). (19) The SNPs revealed about fifteen genes in the PSORS1 region, that are highly related to psoriasis. (DDR1, DPCR1, MUC21, MUC22, HCG22, C6orf15, PSORS1C1, CDSN, PSORS1C2, CCHCR1, TCF19, POU5F1, PSORS1C3, HCG27, HLA-C) (19) The HLA-C gene plays a role in the immune defense because it codes for an MHC class I receptor. (20) This receptor presents antigens to CD8+ T lymphocytes. (20) Different alleles are expressed by SNPs in the promoter region of HLA-C and thus can affect the self-antigenic tolerance. (19) One of them is HLA-Cw0602*, 10-15% of the population carries this gene and about 60% of psoriasis patients carry it. (19) It is considered to be a risk allele, as the risk of psoriasis is 20 times higher in people with this allele. (19) HLA-Cw*0602 positive psoriasis patients tend to have a younger manifestation age of psoriatic arthritis and plaque-type psoriasis vulgaris, more extensive plaques on arms, legs and the trunk and a higher incidence of the Koebner phenomena. (21) Association between psoriatic arthritis and HLA-Cw6 is very complex. (21) Patients with psoriatic arthritis with HLA-Cw6 show cutaneous symptoms before musculoskeletal symptoms, and the symptoms manifest earlier in life, but the relationship between HLA-Cw6 and psoriatic arthritis severity is still unclear. (21) In contrast to PSORS1, 14 other PSORS regions (PSORS2-15) outside the MHC were also found to be associated with psoriasis. (19) Several studies have shown that the presence of multiple PSORS loci and the resulting interactions increase the risk of psoriasis. (19)

In addition to the SNPs, the number of DNA copies also plays an important role. (19) These copy number variations represent a major contribution of the human genomic polymorphism. (19) CNVs of beta-defensin genes (DEFB) are associated with a risk of psoriasis. (19) For instance, the risk increases fivefold in persons

with a DEFB copy number > 5 compared to persons with a copy number of 2. (19) Other genes associated with psoriasis by CNVs are IL22 gene exon and FCGR3B. (19)

Furthermore, epigenetic mechanisms also play a crucial role in the pathogenesis of psoriasis. (19) These includes DNA methylation and histone modifications, for example the demethylation of the promoter 2 region of the SHP-1 isoform II mRNA, or Global histone H4 hypoacetylation are involved in psoriatic skin lesions. (19)

1.1.4 Pathogenesis

Psoriasis is an inflammatory skin disease in which an interaction of environmental, genetic and immune-mediated risk factors plays a role as a disease-triggering event. (19) The PSORS loci predisposing to psoriasis cause immune dysregulation. (3) This results in the activation of dendritic cells of the skin, which in turn stimulate subgroups of T-helper cells (TH17, TH1 cells) by means of messenger substances (TNF-α, IL-23). (3) Keratinocytes release antimicrobial peptides as a result of injury. (1) Examples of antimicrobial peptides associated with psoriasis are LL37, beta-defensins and S100. (1) LL37 that is bound to DNA leads to the activation of plasmacytoid dendritic cells by binding to their toll-like receptor 9 (TLR 9). (1) The onset of psoriatic plaque development is characterized by the formation of Interferon type I (type I IFN), which is produced by the activated plasmacytoid dendritic cells. (1) Type I IFN signals lead to production of IFN-γ and IL-17 and are part of the differentiation and function of Th1 and Th17. (1) Furthermore, myeloid dendritic cells (mDC) are promoted by type I IFN signals. (1) When mDCs are activated, they migrate into draining lymph nodes and secrete TNF-α, IL-23 and IL-12. (1) The different T cell subsets activate the adaptive immune response which then drives the maintenance phase of psoriatic inflammation. (1) Keratinocyte proliferation in the epidermis is activated by the cytokines of TH 17 cells (IL-17, IL-21, IL-22). (1) There are six IL17 ligands (IL-17A to IL-17E) and five receptors (IL-17RA to IL-17RE). (22) IL-17 promotes the release of antimicrobial peptides, proinflammatory cytokines and chemokines. (22) Thus, it participates in the immune response against, for example, various

Candida species. (22) IL-17A is secreted by innate immune cells such as natural killer cells (NK cells), gamma-delta T cells, mast cells and neutrophils, whereas IL-17C is secreted from keratinocytes in lesioned skin. (22) Experiments in mice suggest that IL-17C is more strongly expressed in psoriatic lesions than IL-17A, further experiments in mice have shown that the development of lesions occurs when IL-17C is specifically overexpressed from keratinocytes in mice. (22)
TNF-α is a central cytokine in many autoimmune diseases and in psoriasis, although the connection between TNF-α and the development of Psoriasis has not yet been completely clarified. (22) TNF-α in combination with IL-17A and IL-17C and other cytokines forms strong synergies that enhance responses. (22) It is therefore an important element of the cytokine storm in psoriasis. (22) The strong synergism between TNF-α and IL-17A is based on the stabilization of IL-17A mRNA by TNF-α, which enhances the effects of IL-17A. (22)
IL-23 has an important role in the production of IL-17 and thus in the development of psoriasis. (23) Antigen-presenting Langerhans cells, dendritic cells and monocytes/macrophages of the innate immune system secrete IL-23 in response to an inflammatory or biochemical insult. (23) When IL-23 binds to its receptors, it leads to phosphorylation and activation of janus kinase 2 (Jak2) and Signal transducer and activator of transcription 3 (STAT3). (23) This leads to an increased expression of IL-17 and the transcription factor retinoid-related orphan receptor (ROR)-γt, the latter of which promotes the expression of IL-17A and IL-23 receptors. (23) IL-23 thus leads to a maintenance of pathogenic Th17 cell populations. (23) IL-23 represents a bridge between the innate and adaptive immune system. (23) In the innate part, it stimulates IL-17 production of natural killer cells and neutrophils and can thus control an infection. (23) In the adaptive part, however, T-cells are stimulated to produce IL-17, which leads to an inflammatory autoimmune reaction. (23)

1.1.4.1 IL-17 and IL-23: two key cytokines in the pathogenesis of psoriasis

1.1.4.1.1 IL-17

Cytokines are messenger substances that perform their work by binding to specific cell surface receptors. (24) Interleukins are cytokines produced by

leukocytes and act mainly on other white blood cells. (24) The gene of Interleukin 17A was discovered in 1993. (25) Until 1995 the protein was called T lymphocyte-associated antigen 8 (CTLA-8) due to the large difference in sequence compared to other cytokines. (25) Only then its specific receptor was discovered, and it was counted among the cytokines. (25) In 1996, an important role of IL-17 in the development of rheumatoid arthritis was found, as it induces the production of the downstream cytokines (IL-6 and IL-8) by synoviocytes. (26) This discovery was an important indication of the role of IL-17 in the development of immune inflammatory diseases. (26) The proinflammatory nature of IL-17 plays a crucial role in the host protective defense against extracellular bacterial and fungal infections. (26) (27) However, increased production is associated with immunopathology and autoimmune disease. (26) (27) The cytokines of the IL-17 group are called IL-17A (IL-17), IL-17B, IL-17C, IL-17D, IL-17E (IL-25) and IL-17F. (25) The corresponding receptors of the cytokines are named IL-17RA, IL-17RB, IL-17RC, IL-17RD and IL-17RE. (25) IL 17F has the most similar sequence structure to IL-17A of all cytokines. (28) They signal as homodimers or heterodimers through IL-17R, a receptor complex of IL-17RA and IL-17RC subunits. (28)
There are three domains at the IL-17 receptors. (28) A fibronectin III-like domain, a SEFIR domain (similar expression of fibroblast growth factor genes and IL-17Rs) and a distal activation domain (CBAD). (28) The SEFIR domain is related to the TIR (toll/interleukin-1 receptor) domain in toll-like receptors (TLRs) and IL-1 receptors (IL-1Rs), therefore it is assumed that there are similarities between the IL-17 and TLR signaling cascades. (28) (29) Act1 (NF-κB activator 1, also known as CIKS) is a cytosolic protein, which also carries the SEFIR domain and is essential for all IL-17-mediated signaling cascades. (29) Act1 catalyzes the ubiquitization of TNF receptor-associated factor 6 (TRAF6). (25) This enables TRAF6 to activate the mitogen-activated protein kinase (MAPK), the CCAAT enhancer-binding protein b (C/EBPb) and the NF-κB. (25) In this way, transcriptional activation of downstream target genes is triggered. (25) These include proinflammatory cytokines, chemokines and antimicrobial peptides. (25) NFκB is only weakly activated by IL-17A alone, but IL-17 is able to form a synergy with other cytokines, thereby promoting and prolonging the inflammatory response. (29) An example would be

TNF-α, a strong NFκB activator. (29) TNF-α induces the expression of highly unstable pro-inflammatory mRNAs. (29) Stabilization of these mRNAs by IL-17A enhances chemokine expression. (29) Therefore, further signaling is based on the stabilization of mRNA transcripts coding for intrinsically unstable targets such as cytokines and chemokines. (25) This signal path is based on 2 complexes, the Act1/TRAF2/TRAF5/SF2(ASF) complex and the Act1/TRAF2/TRAF5 and HuR complex. (29) SF2(ASF) is an mRNA destabilizing factor that is sequestered by TNF receptor-associated factor 2 (TRAF2) and TNF receptor-associated factor 5 (TRAF5). (25) The mRNA-stabilizing factor HuR, however, is recruited. (25) The proinflammatory capabilities of IL-17A, IL-17F and IL-17A/F are triggered by these two paths. (25) Negative feedback loops prevent overdriven signaling. (30) This happens in different ways. (30) Firstly, the formation of the IL-17R-Act1-TRAF6 complex is disturbed by recruiting TNF receptor-associated factor 3 (TRAF3) to the IL-17 receptor, secondly, the Act1-TRAF6 signaling pathway is inhibited by TNF receptor-associated factor 4 (TRAF4) interacting with Act1. (30) Furthermore, phosphorylation of Act1 also results in a downregulation of the IL-17 signaling pathway. (30)

Transforming growth factorβ (TGFβ), IL6 and IL21 stimulate naïve CD4+ T-cells which then turn into Th17 cells. (26) The majority of IL-17 is then produced by Th17 cells. (26)

Other cellular sources of IL-17 are:

- γδ T cells (28)
- lymphoid tissue inducer cells (LTi) (28)
- innate lymphoid cells type 3 (ILC3s) (28)
- natural killer cells (26)
- macrophages (26)
- neutrophils (26)
- mast cells (26)

At the site of infection, IL-17A and IL17F are released by TH17 cells when they encounter antigens. (31) These cytokines cause neutrophil cell proliferation and recruitment. (31) The receptor for IL-17A and IL17F is expressed on many cells,

such as epithelial cells, fibroblasts, and keratinocytes. (31) IL-17 stimulates these cells to produce various cytokines, such as IL-6, which enhances the TH-17 response, and the hematopoietic factor granulocyte colony-stimulating factor (G-CSF), which enhances the formation of neutrophil cells in bone marrow. (31) The production of the chemokines CXCL8 and CXCL12 is also stimulated by IL-17. (31) Their receptors ,CXCR1 and CXCR2, are expressed exclusively by neutrophils. (31) Therefore, it is shown that IL-17 induces local cells to release cytokines and chemokines that attract neutrophils at sites of infection.(31)
High levels of IL-17A have been demonstrated in various inflammatory and autoimmune diseases such as psoriasis, rheumatoid arthritis, multiple sclerosis (MS), asthma and Crohn's disease, suggesting that IL-17A plays a major role in these diseases. (29) Single nucleotide polymorphisms have been found in the genome of psoriasis patients through genome-wide association studies, thereby indicating that the IL-17 cytokine network is associated with vulnerability to psoriasis. (29) In the inflammatory psoriasis infiltrate, IL-17-producing T cells are present. (30) The main source of this seems to be neutrophils and mast cells. (30) After administration of anti-IL-17 treatment with secukinumab, there is a clearance of neutrophils from psoriatic plaques and at the same time normalization of psoriatic keratinocytes and loss of neutrophil chemoattractants (CXCL1, CXCL8). (30) Thus, an association of IL-17 and psoriasis with pathological neutrophilic activities is associated. (30)

1.1.4.1.2 IL-12 and IL-23

The interleukin 12 (IL-12) family consists of IL-12, IL-23, IL-27 and IL-35. (32) The interleukin 12 family is distinct because it contains heterodimeric cytokines.(32) The cytokines of the IL-12 family consist of an alpha chain and a beta chain. (32) The alpha chain can consist of p19, p28 or p35 and the beta chain of p40 or Ebi3. (32) The IL-12 family belongs to the IL-6 superfamily, members of this superfamily have an alpha chain with a characteristic four-helix bundle structure. (32) The beta chains on the other hand have a common homology with class I receptor chains for cytokines, such as IL-6Rα. (32) IL-12 consists of a linked p40 and p35 subunit, whereas p40 and p19 form IL-23. (32) Furthermore, the receptor chains are also

used by several cytokines. (32) IL-12 transmits its signals via IL-12Rβ1 and IL-12Rβ2 and IL-23 via IL-12Rβ1 and IL-23R. (32) The p35 and p40 genes are regulated independently of each other. (33) The p40 subunit is produced in larger amounts than the p35 subunit, which means that the p35 subunit is speed limiting. (33) Likewise, the synthesis of p19 and p40 subunits leads to biologically active IL-23 within the same cell. (33) Macrophages and dentritic cells produce IL-12 and IL-23. (33) Receptors for IL-12 and IL-23 are located on T cells, natural killer cells and some antigen-presenting cells such as macrophages and dentritic cells. (33) IL-12 and IL-23 play a decisive role in the development of the TH1 and TH17 subgroup of T-helper cells and have mainly proinflammatory and prostimulatory characteristics. (32)

IL-12 activates natural killer cells and, in conjunction with adaptive immunity, promotes the differentiation of CD4 T cells into Th1 cells. (31) The attachment of naive T-cells to the Th17 line is triggered by contact with TGF-β and IL-6. (31) The first determination of Th1 cells is by IFN-γ. (31) However, these initial conditions are not sufficient to initiate complete and effective Th17 or Th1 reactions. (31) In addition, each T cell requires stimulation by another cytokine: IL-23 for the Th17 cells and IL-12 for the Th1 cells and the Th17 cells. (31) Defined Th17 cells express a receptor for IL-23 and, in small amounts, the receptor for IL-12, Th1 cells express the receptor for IL-12. (31) Like many other cytokines they act via the intracellular JAK-STAT signaling pathway. (31) In the cell, IL-23 signals primarily activate the transcription activator STAT3, but also STAT4. (31) In contrast, IL-12 activates STAT4 particularly strongly, but STAT3 only slightly. (31) IL-23 does not induce the attachment of naive CD4 T cells to the Th-17 line but stimulates their proliferation and contributes to their survival. (31) IL-12 regulates the effector activity of fixed Th1 cells at infection sites. (31)

The task of the Th1 cells formed by IL-12 and IFN- gamma consists of the release of proinflammatory cytokines. (33) These are needed to control bacterial pathogens by direct bacterial lysis and activation of B cells. Furthermore, IL-12 and IFN- γ promote the bactericidal effect of macrophages. (33) The role of IL-23 is to provide immunity against intracellular pathogens but is still not fully understood. (33) In the absence of IL-12, the effect of IL-23 appears to be enhanced. (33)

1.1.4.2 Trigger factors in psoriasis

In psoriasis, the intrinsic factors mentioned so far play a major role. (34) But external factors are also decisive. (34) Extrinsic triggers can lead to the manifestation of lesions in patients who carry the intrinsic conditions. (34) An example of this is the so-called Koebner phenomenon. (34) There are a large number of such factors that can serve as triggers but can also lead to a worsening of the condition. (34)

Examples for these trigger factors are:

- Infections: mainly infections of the upper airways with beta hemolyzing Group A Streptococci. (3) A possible cause could be a homology of the M proteins of the streptococcal capsule to keratins of the epidermis. (3) This type of infection-triggered psoriasis is usually found in children and adolescents. (3) Skin colonization with Staphylococcus aureus can lead to immune stimulation by superantigen expression and thus to the development of psoriasis plaques. (3)
- Some drugs can also be a trigger, examples of this would be beta-blockers lithium, interferon, chloroquine. (3)
- In the summer months, the lesions improve because of increased UV exposure, UV light has an immunosuppressive and anti-inflammatory effect on the skin. (3)
- Psychological factors can also lead to exacerbation, typically stress. (3)
- Triggers for the Koebner phenomenon would be mechanical irritations, for example minor trauma, scratching or sunburns. (3) (34)

1.1.5 Epidemiology

1.1.5.1 Incidence

People in the USA under the age of 18 years have a sex- and age- adjusted annual incidence of psoriasis of 40.8 per 100.000. (35) This number was generated from a study between 1970 and 1999 and the diagnosis was made by general physicians or dermatologists. (35) Another study investigating the incidence of psoriasis among children took place in Italy. (35) In 2006 60 out of 100.000

children were diagnosed with psoriasis and in 2012 57 out of 100.000. (35) All diagnoses were made by primary health physicians. (35) The incidence of psoriasis in adults varies depending on the country. (35) A sex- and age- adjusted study in the USA between 1970-2000 has shown an annual incidence of 78.9 per 100.000. (35) In 2001 321 and in 2005 230 out of 100.000 were diagnosed with psoriasis according to an observational study in Italy. (35) A study from 2012 in north Africa has shown higher numbers. (35) In Algeria, Morocco and Tunisia the incidences were 1026, 1504 and 1326 out of 100.000. (35)

1.1.5.2 Prevalence

The prevalence of psoriasis under the age of 18 ranges from 0% in Taiwan to 1.37 % in Germany. (35) In adults, prevalence is lowest in the USA at 0.51% and highest in Norway at 11.4%. (35) Although different studies in America range from 0.51% up to 3.10%. (35) In Europe the lowest prevalence was found in the United Kingdom (1.3%) and the highest in Norway (11.4%). (35)

1.1.6 Histology of psoriasis

Histologically psoriasis is visible as a continuous hyperkeratosis with "Munro-microabscesses", epidermal acanthosis, a loss of the stratum granulosum, a narrowing of the suprapapillary epidermis and in the papillary dermis a thin leukolymphocytic infiltrate. (36) Another histological characteristic of psoriasis are dilated and contorted blood vessels in the dermis. (37) Epidermal keratinocytes produce angiogenic factors such as vascular endothelial growth factor (VEGF). (37) These are significantly increased in plaques of psoriasis and lead to abnormal dermal angiogenesis. (37) Serum concentrations correlate with the clinical severity of psoriasis. (37) Normally, keratinocytes need 28-30 days to migrate from the stratum basale to the horny layer. (38) In psoriatic skin this process is increased by up to 50 times and the keratinocytes need 3 to 5 days for the same process. (38) This shortened time leads to an altered differentiation which leads to the absence of the granular layer and to parakeratosis. (38) Keratinocyte nuclei may still be visible in the thickened horny layer. (38)

1.1.7 Comorbidities

People suffering from psoriasis often have comorbidities such as psoriatic arthritis, inflammatory bowel diseases, depression, non-alcoholic fatty liver disease, metabolic syndrome and cardiovascular diseases. (17) These comorbidities play a big role in the reduced life expectancy of people suffering from psoriasis. (2) The probability of developing psoriasis as a patient with Crohn's disease is 7 times higher compared to the general population. (17) On the other hand, the risk of getting Crohn's disease increases 2.9 times if you have psoriasis. (17) Both diseases have common inflammatory pathways and shared genetic risks, which explains why patients with both diseases are more likely to have comorbidities such as seronegative arthritis, thyroiditis, diabetes and lymphoma compared to those with psoriasis alone. (17) The metabolic syndrome is a major risk factor for arterial diseases, especially coronary heart disease. (17) It is characterized by the following four factors: Abdominal obesity, hypertension, lipometabolic disorder with hypertriglyceridemia and low HDL cholesterol, insulin resistance. (17) Patients suffering from psoriasis also more often have a metabolic syndrome. (17) This connection exists especially in patients with severe psoriasis. (17) The metabolic syndrome is closely related to cardiovascular diseases. (17) A study from 2006 showed that the adjusted relative risk for a myocardial infarction for a 30-year old patient with mild psoriasis is 1.29 times higher and 3.10 times higher in patients with severe psoriasis. (39) This study therefore indicated that psoriasis is an independent risk factor for myocardial infarctions. (39) This increased risk was also still present in older patients. (39) At 60 years, the relative risk was 1.08 times higher in patients with mild psoriasis and 1.36 higher in those who suffer from severe psoriasis. (39) Psoriatic arthritis and Crohn's disease have genetic similarities to psoriasis. (39) The genes of coronary diseases and metabolic syndrome are similar, but the genes of psoriasis are not related to them. (39) Therefore, the connection between the development of coronary disease and metabolic syndrome is seen in a chronic inflammation. (39) The so-called psoriatic march is considered to be the cause of increased cardiovascular mortality in psoriasis patients. (2) It states that psoriasis is a systemic inflammation and this inflammation leads to a reduced sensitivity of

insulin receptors for insulin. (2) As a result of this resistance, fewer vasodilating factors such as nitric oxide are released in endothelial cells. (2) This results in vascular stiffening called endothelial dysfunction, which contributes to the formation of atherosclerotic plaques by the expression of adhesion molecules. (2) It is also believed that anti-inflammatory therapy reduces the risk of cardiovascular comorbidities by inhibiting systemic inflammation. (40)

1.1.8 Management of psoriasis

The basic therapy is used for the light form (BSA <10%, PASI ≤ 10 points) as well as for the medium and severe form (BSA >10%, PASI ≥ 10 points). (41) One part of the basic therapy is the topical application of active substance-free ointment bases. (41) Urea (3-10%) and salicylic acid (3-10%) are used for this purpose. (41) In mild forms, other drugs can be administered topically in addition to the basic therapy. (41) These include calcineurin inhibitors (tacrolimus and pimecrolimus), glucocorticoids and vitamin D-3 analogues. (41) In order to use fewer steroids, a combination of vitamin D analogues and corticosteroids is often used in topical therapy. (42) Combination preparations of calcipotriol and betamethasone dipropionate were developed to simplify handling. (42) These also increase patient compliance. (42) Glucocorticoids and vitamin D-3 analogues are also used for scalp psoriasis. (41) (2) Skin atrophy, telangiectasias and suppression of the hypothalamic–pituitary–adrenal axis are some of the adverse events that are possible to occur in patients treated with topical glucocorticoids and therefore should be used for a short time or intermittent. (42) Typical adverse events that might occur from vitamin D analogs are localized skin irritation and pruritus. (42) Use should be averted in areas with thin skin as for example the face. (42) Another possibility to avert the long treatment with steroids is the use of calcineurin inhibitors. (42) Calcineurin inhibitors showed a good effect against psoriasis and pruritus was the only side effect observed. (42) Calcineurin inhibitors are used in the face and intertriginous areas. (2) Simultaneous use with phototherapy or strong sunlight should be prevented in order not to increase the probability of skin cancer and lymphoma. (42) In severe cases light therapy is used and also systemic therapy. (41) Light therapy usually consists of UVB therapy or PUVA

therapy. (41) In systemic therapy, mainly immunosuppressive drugs such as acitretin, ciclosporin, fumaric acid or methotrexate are used. (41) In case of insufficient therapy success, intolerance or contraindications, apremilast, e tanercept and biologics are additionally used. (41) However the European Medical agency proposed to use biologics also as first line therapy in patients with moderate to severe psoriasis. (43)

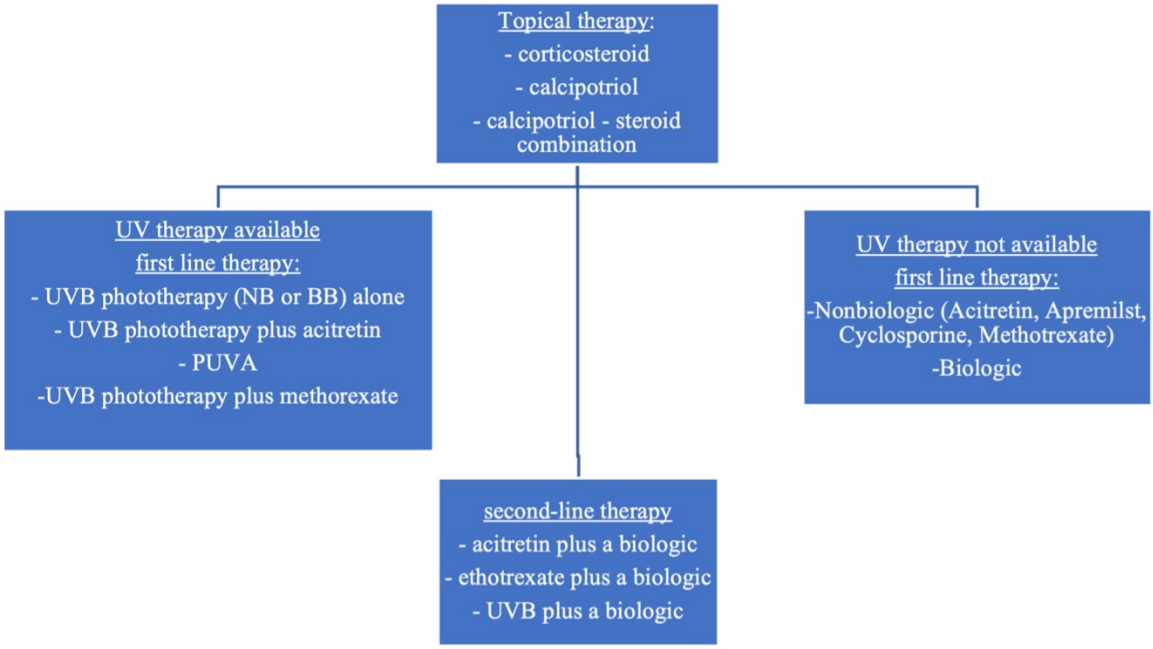

Figure 1 Treatment algorithm for healthy adult men with chronic plaque psoriasis (> 5% BSA) without psoriatic arthritis (BB-broadband, BSA-body surface area, NB-narrowband, PUVA-psoralen plus UVA, UV-ultraviolet) (44)

1.1.9 Psoriasis Area and Severity Index

The most commonly used method for determining the severity of psoriasis is the Psoriasis Area and Severity Index (PASI). (45) Furthermore, the PASI score is used in clinical studies to detect changes and to distinguish them from placebo. (46) In 1978 the PASI was developed by Fredriksson and Pettersson to recognize the effect of retinoid treatment in chronic plaque psoriasis. (47) The affected body surface area (BSA), severity of erythema (redness), induration (thickness) and desquamation (scale) are determined. (46) (47) These are determined separately for head, trunk, upper and lower extremities. (46) (47) A percentage of the body

surface area is allocated to each of these four areas. (46) The head and neck make up 10%, the upper extremity 20%, the trunk 30% and the lower extremity 40%. (46) The severity of erythema, induration, and desquamation in each area is determined by 0-4, 0 indicating no involvement, 1 slight, 2 moderate, 3 severe and 4 very severe characteristics. (47) (46) For each region, a score is determined by adding the 3 parameters and then multiplying by the percentage of BSA associated with it. (46)
A score between 0 and 72 is determined, the higher this value the more severe the clinical picture is. (47)
The PASI is also a graduation score concerning the severity of the disease. In 2005 Schmitt J et al proposed the following grading categories for the severity of psoriasis: (47)
PASI <7: mild chronic plaque-type psoriasis
PASI 7-12: moderate chronic plaque-psoriasis
PASI >12: severe chronic plaque psoriasis

In 2011 Mrowietz et al defined the severity of psoriasis as follows: PASI ≤ 10 and BSA ≤10 were defined as mild disease, whereas PASI > 10 and BSA > 10 were defined as moderate to severe disease. (59) This classification is also used in the current S3 guidelines for the treatment of psoriasis (43) and is nowadays widely used by dermatologists.
Improvement of psoriasis has been defined as PASI 75/90/100 compared to the baseline PASI. (48) A PASI 75 means that the PASI has improved by 75% compared to the PASI determined at the baseline, PASI 90 and PASI 100 are defined as a 90 and 100% improvement compared to the baseline PASI. (48) PASI 75 is often used in clinical trials to determine the success of a therapy. (48) It also serves as an evidence-based efficacy parameter. (48)

1.1.10 Physician global assessment (PGA) / Investigator's Global Assessment (IGA)

Another tool for evaluating the severity is the physician global assessment, or sometimes referred to as Investigator's Global Assessment (IGA). (49) (50) The PGA can be measured at a single point or as a dynamic form. (49) The standard is

measured at a single point and is called the static Physician Global Assessment (sPGA). (49) The sPGA usually consists of 7 points: score 0 = clear; scores 1–6 = increasing severity. (49)

1.1.11 Itch Numeric Rating Scale (Itch NRS)

The Itch NRS is a self-administrated single-item 11-point scale ranging from no itch (0) to worst itch imaginable (10). (51) An improvement of ≥ 4 points is considered clinically meaningful. (51)

1.1.12 The Nail Psoriasis Severity Index (NAPSI)

The Nail Psoriasis Severity Index is a score to measure the severity of nail bed psoriasis and nail matrix psoriasis. (52) The nail is divided into 4 quadrants, and it is looked whether in the individual quadrants signs of nail bed psoriasis and nail matrix psoriasis are found. (52) Per square 1 point is distributed if there are one or more signs of nail bed psoriasis and 1 point if there are one or more signs of nail matrix psoriasis. (52) This means that one can reach 2 points per square and thus 8 points per nail. (52) So, it is possible to reach a total of 80 points on both hands together. (52) Signs of nail matrix psoriasis would be pitting, leukonychia red spots in the lunula and crumbling. (52) Onycholysis, splinter hemorrhages, subungual hyperkeratosis and oil drop would be signs of nail bed psoriasis. (52)

1.1.13 The Physician's Global Assessment of Fingernail Psoriasis (PGA-F)

The Physician's Global Assessment of Fingernail Psoriasis is a measurement tool for psoriatic nail disease. (53) With the score, there are 5 severity levels: 0 - clear; 1 - minimal; 2 - mild; 3 - moderate; and 4 - severe. (53)

1.1.14 Psoriasis Scalp Severity Index (PSSI)

The Psoriasis Scalp Severity Index (PSSI) is a scalp-specific modification of the PASI. (54) Similar to the PASI, the PSSI is based on the extent of involvement and the severity of erythema, intrusion, and scaling. Depending on the severity, 0-72 points can be assessed. (54)

1.1.15 Scalp-Specific Investigator's Global Assessment (ss-IGA)

The ss-IGA evaluates the degree of redness, thickness, and scaling of lesions on a 5-point scale, with 0 corresponding to no disease and 4 indicating severe disease. (55)

1.1.16 Quality of life in patients with psoriasis and DLQI

Psoriasis can have a major impact on the quality of life, both physical and psychological. (56) Although psoriasis is only in very few cases life-threatening, those affected often state a more severe limitation of their quality of life than patients suffering from diabetes mellitus or ischemic heart disease and COPD. (37) In about one third of cases, psoriasis manifests itself in the age under 18 years. (56) Since this young adulthood is a critical and delicate phase, young patients often suffer particularly severely from the consequences of the disease. (56) Psoriasis is often accompanied by social isolation and a lifestyle of avoidance. (37) Patients who show an improvement of symptoms due to a therapy are often still uncertain and anxious because they are afraid of relapses. (37) Due to the fear of relapses, it is possible that patients respond less well to therapies such as photochemotherapy. (37) The recognition and treatment of depression and anxiety is still a major problem in the treatment of psoriasis. (37)

The Dermatology Life Quality Index (DLQI) is used to measure the impact of life quality due to different dermatologic conditions. (48) (46) Impacts on quality of life include effects on work, leisure activities, personal relationships and feelings, which are assessed by a 10-item questionnaire. (46) For each question the patient has 4 answers: "not at all," "a little," "a lot," and "very much, the possible answers correspond to points between 0 and 3. (46) (48) After addition the DLQI ranges between 0 and 30, whereby higher scores illustrate worse quality of life: (48)

0–1: no effect

2–5: small effect

6–10: moderate effect

11–20: very large effect

21–30: extremely large effect

There is no correlation between PASI and DLQI, however, a connection between the improvement of the PASI and the improvement of the DLQI was observed. (48) Drugs, which led to a higher PASI reduction, also led to a reduction of the DLQI. (48) The therapy aims at a DLQI of 0 or 1. (48)

1.2 Biologicals

There are new drugs that act on the interleukins involved in the pathogenesis of psoriasis, e.g. interleukin-17 and interleukin-23, and offer a new and highly efficient treatment option for patients suffering from psoriasis. (57) (58) This new group of drugs has shown very high efficacy in achieving PASI 75, which has been proposed as the treatment goal to be achieved in induction period of biological therapy within the first 12-16 Weeks of treatment. (58) (59) The proportion of the patients achieving PASI 90 as well as 100 has been so high that more and more dermatologists concluded that PASI 75 should no longer be regarded as the benchmark for therapy. (58) (59)With the use of this highly effective new group of drugs, PASI 90 or even PASI 100 may be considered as a new and realistic treatment goal in psoriasis patients.(58)
In the following sections the focus will first be put on the efficacy and safety of the IL-17 and IL-23 in the treatment of psoriasis, the head-to-head studies comparing IL-17 and IL-23 inhibitors and on the efficacy of these drugs in the treatment of psoriatic arthritis, special locations (e.g. nails, palmoplantar psoriasis, scalp psoriasis), symptoms (e.g. itch) and special populations (e.g. children).

2 Methods

A comprehensive literature search was conducted using PubMed databases. Articles related to the treatment of psoriasis with biologicals were collected. In particular, articles were collected on all phase 3 pivotal trials and on head-to-head studies of IL-17, IL-23, IL-12/23 inhibitors used in the treatment of psoriasis. Furthermore, case reports, metanalyses, and reviews were also searched. All relevant scientific articles were published in English, German, or Spanish between 1997 and 2022.

The following terms were included in the search “psoriasis”, “phase 3”, ”nail“, „itch”, “arthritis”, “scalp”, “palmoplantar”, pustulosis”, ”pregnancy”, ”children”, ”pediatrics”, “head-to-head”, “adverse events”, “side effects”, “secukinumab”, “ixekizumab”, “brodalumab”, “guselkumab”, “tildrakizumab”, “risankizumab”, “ustekinumab”, “bimekizumab”, “IL-17”, “IL-23”, “IL-12/23”, “inhibitor” and “biologicals”.
In the relevant scientific papers found, all reference lists were additionally searched to identify further published articles that were not recognized by the database search tools. All phase 3 pivotal studies for the above biologics were selected, as well as head-to-head studies comparing these drugs, review articles were also included. Among the factors of interest was the degree of improvement in psoriasis patients' symptoms when treated with different biologicals. This improvement was indicated by scores such as the PASI score, DLQI and PGA/IGA. Attention was also paid to the length of time it took for improvement to occur. Another important point was the adverse events that occurred during the therapy. Particular attention was paid to differences between the drugs of the different modes of action (IL-17, IL-23, IL-12/23 inhibitors). Missing data were noted as not available (n.a.). A simple descriptive analysis was performed.

3 Results

3.1 IL-17 Inhibitors

3.1.1 Secukinumab

Secukinumab is the first IL-17A-inhibitor used for the treatment of psoriasis. (60) It has been approved for the treatment of moderate to severe psoriasis in the year 2015. (60) Secukinumab, formerly known as AIN457, is a highly specific, human immunoglobulin G1κ (IgG1κ) monoclonal antibody. (61) After IL-17A binds to its receptor, there is usually a release of pro-inflammatory cytokines and chemokines. (60) This signaling cascade plays an important role in the development of psoriasis and is successfully interrupted by secukinumab. Secukinumab binds to circulating and tissue IL-17A, thereby inhibiting its interaction with the IL-17A receptor. (60)

3.1.1.1 Secukinumab Phase III Trials

Secukiumab has been extensively studied in a great phase III study program. (62) (63) (64) (65) (66) (67) In the ERASURE and FIXTURE studies subcutaneous doses of secukinumab 300mg and 150mg were compared with placebo alone (ERASURE) or etanercept 50mg and placebo (FIXTURE). (62) In the ERASURE study at week 12 patients treated with secukinumab reached significantly higher PASI 75, PASI 90, PASI 100 (results see table 2) and IGA response rates than patients that were given placebo. (62) In FIXTURE, there were also significantly higher response rates in all these measures in both secukinumab groups compared with etanercept (PASI values at week 12 see table 2). (62) In both studies, infections were more common in patients treated with secukinumab and etanercept than in patients treated with placebo. (62)

In the FEATURE study self-administration of secukinumab with pre-filled syringes has been proven to be effective with an acceptable safety profile and a high usability. The PASI results of the FEATURE are displayed in table 2. (63) Participants in this study received secukinumab 300mg, secukinumab 150mg or placebo in a 1:1:1 ratio. (63) At baseline and weeks 1, 2, 3 and then every 4 weeks, both secukinumab doses and the placebo were administered with pre-filled syringes. (63)

The efficacy, safety, and usability of secukinumab in patients applying an autoinjector/pen was investigated in the JUNCTURE trial. The results of the study also proved the efficacy (For PASI results see table 2) , safety and usability in patients applying secukinumab by autoinjector/pen. (64)

In the so-called SCULPTURE trial the efficacy of secukinumab in a retreatment-as-needed (Dosage groups: 150 and 300 mg secukinumab) versus a fixed-interval regimen of secukinumab (Dosage groups: 150 and 300 mg secukinumab) was compared. (65) At week 12, 67.7% (secukinumab 300mg) and 52.4% (secukinumab 150mg) of the patients in the retreatment as needed group achieved PASI75 as well as 78.2% (secukinumab 300mg) and 62.1% (secukinumab 150mg) on fixed interval achieved PASI75. (65) PASI 90 response rates at week 52 were 13.8% in the retreatment-as-needed group in patients receiving 300mg and 11.2% in patients receiving 150mg. (65) In the fixed-interval

group, the rates were 59.7% and 45.8%, respectively. (65) Throughout the maintenance period (52 weeks) the fixed interval group that received 300mg consistently achieved higher PASI 75, PASI 90, PASI 100 and IGA response rates, compared to the retreatment as needed group. (65) The authors also noted that PASI 90 responses at week 52 were higher in the fixed interval group (secukinumab 300 mg: 59.7% vs secukinumab 150 mg 45.8%) compared to the retreatment-as -needed group (secukinumab 300 mg 13.8% vs secukiumab 150 mg 11.2%). (65)

The aim of the SIGNATURE study was to determine the efficacy and safety of secukinumab in patients with TNF-α therapy failure. (66) Patients with prior treatment failure with TNF-α inhibitors were randomized in two groups either to receive secukinumab 300mg or 150mg at weeks 0 to 4 and every four weeks thereafter. (66) At week 16, both groups achieved a statistically significant PASI 75 response rate. (66) A PASI 75 response rate of 65.3% was achieved in the 300mg group and 44.3% in the 150mg group. (66) A DLQI score of 0 or 1 at week 16 was achieved by 34.7% in the 300mg group and by 30.4% in the 150mg group. (66) In the 300 mg group, 77% had a PASI 75 response rate after 72 weeks. (66) An improvement in DLQI was still seen after 72 weeks, with 54% of patients originally randomized to 300 mg achieving DLQI of 0 or 1. (66) The study demonstrated that secukinumab is effective in patients with prior treatment failure of TNF- α inhibitor therapy. (66)

In the STATURE trail participants were patients who had only a partial response to secukinumab therapy, i.e. a PASI score of ≥ 50% but < 75%. (67) These participants were divided 1:1 into two groups, one group received secukinumab 10 mg/kg intravenous at baseline and at weeks 2 and 4 and the other received 300 mg secukinumab subcutaneously at baseline and week 4. (67) IGA mod 2011 0/1 response rates were achieved by significantly more patients receiving intravenous therapy (66.7%) compared to subcutaneous injections (33.3%) at week 8. (67) PASI 75 response rates at week 8 were achieved by more participants receiving intravenous therapy (90.5%) compared to those receiving subcutaneous injections (66.7%), however this value was not statistically significantly higher. (67) The safety profiles were comparable in both groups. (67)

3.1.2 Ixekizumab

Ixekizumab is a humanized IgG4 monoclonal antibody. (68) Like secukinumab, ixekizumab binds to human IL-17A and thus leads to an inhibition of the proinflammatory effects on keratinocytes. (69)

3.1.2.1 Ixekizumab Phase III Trials

UNCOVER-1, UNCOVER-2, UNCOVER-3

In UNCOVER-1, UNCOVER-2, UNCOVER-3 patients were randomly assigned to receive ixekizumab or placebo subcutaneously. (70) The 2-week dosing group was given ixekizumab 80mg every 2 weeks and the 4-week dosing group 80mg of ixekizumab every 4 weeks. Both groups received a starting dose of 160mg ixekizumab. (70) In UNCOVER-2 and UNCOVER-3 an additional group received etanercept 50mg twice weekly. (70) At week 12 in UNCOVER-1 and UNCOVER-2 subjects with a static physician global assessment score of 0 or 1 were randomized again to placebo, ixekizumab 80mg every 4 weeks or ixekizumab 80mg every 12 weeks for another 48 weeks. (70) Patients from UNCOVER-3 received after 12 weeks 80mg ixekizumab every 4 weeks through week 60. (70)

UNCOVER-1:

At week 12 PASI 75 was achieved by 89.1% in the ixekizumab 80 mg Q2W group and by 82.6% in the ixekizumab 80 mg Q4W, this shows a significant superiority of both groups compared to the placebo group in which 3.9% achieved PASI 75. (71) sPGA, PASI 90 and PASI 100 had also higher response rates at week 12 in both dosage regimes compared to placebo. (71) Significant superiority of ixekizumab in all response rates (sPGA, PASI 75, PASI 90 and PASI 100) was observed in both groups throughout week 60. (71) More patients treated with ixekizumab had adverse events or infections at week 12 compared to placebo, the majority of which were nasopharyngitis and injection side reaction. (71)

UNCOVER-2:

Statistically significant superiority of ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W at week 12 in terms of PASI 75, PASI 90, PASI 100, DLQI and sPGA compared to placebo. (71) In comparison to etanercept ixekizumab also had

better PASI 75 and sPGA responses rates at week 12. (71) Similar to UNCOVER-1 more patients treated with ixekizumab had adverse events. (71)
UNCOVER-3:
PASI 75 and sPGA responses rates were significantly higher at week 12 compared to etanercept and placebo. (70) Throughout week 60 ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W still had significantly higher response rates in PASI 75, PASI 90, PASI 100, DLQI and sPGA compared to placebo. (70)
Patients in UNCOVER-1 and UNCOVER-2 with an sPGA score of 0 or 1 maintained after randomization at week 12 an sPGA score of 0 or 1 in 73.8% (ixekizumab 80mg every 4 weeks), 39.0% (ixekizumab 80mg every 12 weeks) and 7.0% (placebo). (70)
In terms of pharmacokinetics, efficacy and safety, UNCOVER-A has shown similarity between ixekizumab administered subcutaneously by pre-filled syringe and autoinjector. (72)

3.1.3 Brodalumab

Brodalumab is a human monoclonal antibody. (73) It binds with high affinity to IL-17RA and inhibits the downstream inflammatory activity by receptor blockade. (73)

3.1.3.1 Brodalumab Phase III Trials

AMAGINE-1, AMAGINE-2 and AMAGINE-3 were three phase III studies investigating the clinical efficacy of brodalumab. (74) (75) In all three trials, patients received brodalumab 210mg, brodalumab 140mg or placebo subcutaneously every 2 weeks and in AMAGINE-2 and AMAGINE-3 an additional group received ustekinumab. (74) (75)
AMAGINE-1:
At week 12, PASI 75, PASI 90, PASI 100 and sPGA 0 or 1 were achieved by significantly more patients treated with brodalumab in both dosing regimens compared to placebo. (74) Adverse events were reported in 59% (210mg), 58% (140mg) and 51% (placebo). (74) Serious adverse events in 1.8%, 2.7%, 1.4%. Nasopharyngitis, upper respiratory tract infections and headache were the most

common adverse effects. (74)

AMAGINE-2:

PASI 75, PASI 90, PASI 100 and sPGA 0 or 1 was achieved by significantly more patients in both brodalumab groups at week 12 compared to placebo. (75) In terms of sPGA 0 or 1, PASI 90, and PASI 100, brodalumab also achieved significantly higher response rates at week 12 compared to ustekinumab. (75)

AMAGINE-3:

At week 12, the 210mg brodalumab group achieved significantly higher PASI 75, PASI 90, PASI 100 and sPGA 0 or 1 response rates than ustekinumab. (75) In relation to placebo, both brodalumab doses achieved significantly higher values in all measures. (75)

IN AMAGINE-2 and AMAGNINE-3 adverse events appeared more frequently in patients treated with brodalumab and ustekinumab than with placebo. (75) The most frequent side effects are comparable to those of AMAGINE-1. (75)

3.1.4 Bimekizumab

IL-17F in addition to IL-17A both have an important role in the development of psoriasis. (76) Bimekizumab is a monoclonal IgG1 antibody that selectively targets both interleukins. (76)

3.1.4.1 Bimekizumab Phase III Trials

BE READY

BE READY compared bimekizumab with a placebo. (76) In the study, patients received bimekizumab 320mg or a placebo every 4 weeks. (76) After 16 weeks, those participants who achieved PASI 90 were re-randomized to receive bimekizumab 320 mg every 4 weeks, every 8 weeks or placebo until week 56. (76) PASI 90, PASI 100 and DLQI 0/1 responses were significantly higher at week 16 in bimekizumab-treated patients compared with placebo. (76) By week 16, adverse events occurred in 61% of patients in the bimekizumab group and 41% in the placebo group. (76) After week 16, 74% of patients receiving bimekizumab every 4 weeks experienced adverse events and 77% in the 8-week dosing group complained of adverse events. (76) In the placebo group, adverse events occurred

in 69%. (76)

3.2 IL-23 Inhibitors

3.2.1 Guselkumab

Guselkumab is the first human immunoglobulin G1 λ monoclonal antibody that binds to IL-23. (77) It has a high affinity and specificity for IL-23 and by binding to the p19 subunit the proinflammatory IL-23 signaling pathway is interrupted. (77)

3.2.1.1 Guselkumab Phase III Trials

VOYAGE-1 and VOYAGE-2

In VOYAGE-1 and VOYAGE-2 participants received guselkumab 100mg, adalimumab or placebo, then after 16 weeks the placebo group also switched to receive guselkumab. (78) (79) In VOYAGE-1 and VOYAGE-2, guselkumab showed significantly higher response at week 16 in terms of PASI 75, PASI 90, PASI 100, IGA 0, IGA 0/1 and DLQI compared to placebo. (78) (79) Also a significantly higher proportion of participants in the guselkumab group reached IGA 0/1, PASI75 and PASI 90 compared to adalimumab at week 16. (78) (79) The number of adverse effects and the severity of adverse effects were comparable in all groups, the most common were nasopharyngitis, upper respiratory tract infections and headache. (78) (79)

A phase III study from Ohtsuki et al. (2018) evaluated efficacy and safety of guselkumab in Japanese patients with moderate to severe plaque type psoriasis. (80) The study showed significant superiority of guselkumab (50mg and 100mg) compared to placebo at week 16 in terms of PASI 75, PASI 90, PASI 100 and IGA 0/1 and, in addition, no new safety concerns were observed. (80)

3.2.2 Tildrakizumab

Another IL-23 inhibitor is tildrakizumab. The immunopathogenesis of psoriasis is inhibited by this high-affinity, humanized, IgG1κ antibody by binding to the p19 subunit of interleukin IL-23, thereby interrupting the signaling pathway. (81) (82)

3.2.2.1 Tildrakizumab Phase III Trials

Participants in reSURFACE 1 were randomized to receive either tildrakizumab 200mg, tildrakizumab 100mg, or placebo subcutaneously. (82) In reSURFACE 2 an additional group was given etanercept 50mg. (82)
reSURFACE 1:
In part I patients received tildrakizumab or placebo at baseline and week 4. (82) In part II patients treated with tildrakizumab got another dose at week 16. (82) Those who were given placebo in part I were again randomized to receive tildrakizumab 200mg or tildrakizumab 100mg at week 12 and 16. (82)
reSURFACE 2:
In part I patients received tildrakizumab, placebo or etanercept. (82) In part II tildrakizumab was given at week 16 and etanercept once a week. (82) As in reSURFACE 1 those who were given placebo in part I were again randomized to receive tildrakizumab 200mg or tildrakizumab 100mg at week 12 and 16. (82)
In part I of reSURFACE 1 and reSURFACE 2, the tildrakizumab 100mg and 200mg groups had significantly higher PASI 75, PASI 90, PASI 100 and DLQI 0/1 response rates in week 12 compared with placebo or etanercept (for concise results see table 2). (82) In terms of safety it can be said that tildrakizumab was well tolerated during the 64-week study time. (82) Nasopharyngitis was the most common adverse event, severe adverse events were rare and comparable between all groups. (82) (83)

3.2.3 Risankizumab

Due to its affinity to the p19 subunit of IL-23, the humanized monoclonal IgG1 antibody risankizumab is capable of inhibiting psoriatic inflammation in psoriasis. (84)

3.2.3.1 Risankizumab Phase III Trials

UltIMMa-1 and UltIMMa-2
UltIMMa-1 and UltIMMa-2 were two phase III studies that aimed to assess the efficacy and safety of risankizumab in people suffering from psoriasis. (84) Participants were randomly assigned into four groups: 150 mg risankizumab, 45 mg ustekinumab, 90 mg ustekinumab or placebo. (84) Part A lasted 16 weeks and

the drugs were applicated subcutaneously at week 0, 4 and 16. Part B lasted from week 16 until week 52. The drugs were applicated at week 16, 28 and 40. (84)
In both studies, response rates of PASI 75 and PASI 90 at weeks 12 and 16 were significantly higher in the risankizumab group compared to placebo and ustekinumab (for concise results see table 2). (84) In UltIMMa-1 and UltIMMa-2, PASI 100 and DLQI 0/1 were achieved at week 16 by significantly more people receiving risankizumab than those receiving placebo or ustekinumab. (84) The frequency of adverse events in both studies was similar in all treatment groups. (84)

IMMvent

The goal of IMMvent was to compare risankizumab and adalimumab. (85) In the 16-week part A, participants were administered risankizumab 150 mg at week 0 and 4 or adalimumab 40 mg at week 0,1,3,5 and then weekly. (85) Phase B lasted from weeks 16 - 44, those patients who had an intermediate response to adalimumab were randomly assigned to continue taking adalimumab 40 mg or 150 mg risankizumab. (85) PASI 75, PASI 90, PASI 100, DLQI 0/1 and sPGA 0/1 response rates were all significantly higher in all risankizumab groups at week 16 and week 44 (for concise results see table 2). (85) In part A 56% (risankizumab) and 57% (adalimumab) had adverse events. (85) In part B, 75% of patients who switched to risankizumab and 66% of those who continued to receive adalimumab had adverse events. (85)

SustalMM

SustalMM also demonstrated the efficacy of risankizumab in Japanese patients. (86) At week 16, significantly more patients treated with risankizumab 75mg or 150mg achieved PASI 75, PASI 90, PASI 100 and DLQI 0/1 compared to placebo (for concise results see table 2). (86) No new safety findings were observed. (86)

3.2.4 Ustekinumab

Ustekinumab is a human monoclonal antibody. (87) It inhibits the inflammatory response of IL-12 and IL-23 by binding to the p 40 protein subunit of both interleukins, thereby blocking a reaction with their receptor. (87)

3.2.4.1 Ustekinumab Phase III Trials

PHOENIX 1 and PHOENIX 2

In PHOENIX 1 and PHOENIX 2, ustekinumab 45 mg or 90 mg was subcutaneously injected at weeks 0, 4 and then every 12 weeks or placebo at weeks 0 and 4. (87) (88) In PHOENIX 1 patients receiving placebo switched to ustekinumab at week 12. (87) Those who had an PASI 75 response rate at weeks 28 and 40 were again randomized at week 40 to continue ustekinumab or to quit the treatment until loss of response. (87) IN PHEONIX 2 patients with a PASI response rate ≥ 50 but <75 at week 28 were re-randomized to receive ustekinumab every 12 or every 8 weeks. (88)

In PHOENIX 1 and PHOENIX 2 PASI 75, PASI 90, PASI 100 and DLQI 0/1 at week 12 was achieved by significantly more patients that received ustekinumab 45 mg or 90 mg than those who received placebo (for concise results see table 2). (87) (88)

In PHOENIX 1 Severity and frequency of adverse events was comparable throughout the study in all groups. (87) In PHOENIX 2 adverse events occurred more frequently in patients that received treatment every 8 weeks compared to those who got it every 12 weeks. (88)

ACCEPT

ACCEPT compared the efficacy of etanercept and ustekinumab in patients with psoriasis. (89) Patients were divided into 3 groups. (89) Ustekinumab 45 or 90mg in weeks 0 and 4 or etanercept for 12 weeks in two 50mg doses per week. (89) The study showed that ustekinumab doses of 45 mg and 90 mg are superior to high dose etanercept in a 12-week period in terms of PASI 75 and PASI 90 response rates. (89)

Table 2 Efficacy of IL-17 and IL-23 inhibitors in phase 3 pivotal studies

Study	**Study drugs & dosage**	**Time point (weeks)**	**PASI 75**	**PASI 90**	**PASI 100**	**DLQI 0/1**
VOYAGE 1 (78)	Guselkumab 100mg Adalimumab Placebo	16	91.2% 73.1% 5.7%	73.3% 49.7% 2.9%	37.4% 17.1% 0.6%	56.3% 38.6% 4.2%
VOYAGE 2 (79)	Guselkumab 100mg Adalimumab Placebo	16	86.3% 68.5% 8.1%	70.0% 46.8% 2.4%	34.1% 20.6% 0.8%	51.7% 39.0% 3.3%
OHTSUKI et al (80)	Guselkumab 50mg Guselkumab 100mg Placebo	16	89.2% 84.1% 6.3%	70.8% 69.8% 0.0%	32.3% 27.0% 0.0%	64.1% 68.3% 6.6%
reSurface1 (82)	Tildrakizumab 100mg Tildrakizumab 200mg Placebo	12	64.0% 62.0% 6.0%	35.0% 35.0% 0.0%	14.0% 14.0% 1.0%	42.0% 44.0% 5.0%

reSurface2 (82)	Tildrakizumab 100mg Tildrakizumab 200mg Placebo Etanercept	12	61.0% 66.0% 6.0% 48.0%	39.0% 37.0% 1.0% 21.0%	12.0% 12.0% 0.0% 5.0%	40.0% 47.0% 8.0% 36.0%
UltIMMA-1 (84)	Risankizumab 150mg Ustekinumab Placebo	12/16	86.8% / 89.0% 70.0% / 76.0% 9.8% / 9.0%	68.0% / 75.3% 45.0% / 42.0% 3.0% / 4.9%	n.a. / 35.9% n.a. / 12.0% n.a. / 0.0%	n.a. / 65.8% n.a. / 43.0% n.a. / 7.8%
UltIMMA-2 (84)	Risankizumab 150mg Ustekinumab Placebo	12/16	88.8% / 91.0% 69.7% / 70.0% 8.2% / 6.0%	62.0% / 74.8% 47.0% / 47.5% 3.0% / 2.0%	n.a. / 50.7% n.a. / 24.2% n.a / 2.0%	n.a. / 66.7% n.a. / 46.5% n.a / 4.1%
IMMvent (85)	Risankizumab 150mg Adalimumab	16	91.0% 72.0%	72.0% 47.0%	40.0% 23.0%	66.0% 49.0%
SustalMM (86)	Risankizumab 75mg Risankizumab 150mg Placebo	16	89.7% 94.5% 8.6%	75.9% 74.5% 1.7%	22.4% 32.7% 0.0%	62.1% 58.2% 5.2%

AMAGINE -1 (74)	Brodalumab 140mg	12	60.3%	42.5%	23.3%	n.a.
	Brodulamab 210mg		83.3%	70.3%	41.9%	n.a.
	Placebo		2.7%	0.9%	0.5%	n.a.
AMAGINE -2 (75)	Brodalumab 140mg	12	66.6%	49.0%	25.7%	n.a.
	Brodulamab 210mg		86.3%	69.9%	44.4%	n.a.
	Ustekinumab		70.0%	47.0%	21.7%	n.a.
	Placebo		8.1%	1.9%	0.6%	n.a.
AMAGINE -3 (75)	Brodalumab 140mg	12	69.2%	52.0%	27.0%	n.a.
	Brodulamab 210mg		85.1%	68.9%	36.7%	n.a.
	Ustekinumab		69.3%	47.9%	18.5%	n.a.
	Placebo		6.0%	2.9%	0.3%	n.a.
UNCOVER-1 (70)	Ixekizumab 80mg Q2W	12	89.1%	70.9%	35.3%	n.a.
	Ixekizumab 80mg Q4W		82.6%	64.6%	33.6%	n.a.
	Placebo		3.9%	0.5%	0.0%	n.a.
UNCOVER-2 (70)	Ixekizumab 80mg Q2W	12	89.7%	70.7%	40.5%	64.1%
	Ixekizumab 80mg Q4W		77.5%	59.7%	30.8%	59.9%
	Etanercept		41.6%	18.7%	5.3%	33.8%

	Placebo		2.4%	0.6%	0.6%	6.0%
UNCOVER-3 (70)	Ixekizumab 80mg Q2W	12	87.3%	68.1%	37.7%	64.7%
	Ixekizumab 80mg Q4W		84.2%	65.3%	35.0%	63.7%
	Etanercept		53.4%	25.7%	7.3%	43.7%
	Placebo		7.3%	3.1%	0%	7.8%
ERASURE (62)	Secukinumab 300mg	12	81.6%	59.2%	28.6%	n.a.
	Secukinumab 150mg		71.6%	39.1%	12.8%	n.a.
	Placebo		4.5%	1.2%	0.8%	n.a.
FIXTURE (62)	Secukinumab 300mg	12	77.1%	54.2%	24.1%	n.a.
	Secukinumab 150mg		67.0%	41.9%	14.4%	n.a.
	Etanercept		44.0%	20.7%	4.3%	n.a.
	Placebo		4.9%	1.5%	0.0%	n.a.
FEATURE (63)	Secukinumab 300mg	12	75.9%	60.3%	43.1%	n.a.
	Secukinumab 150mg		69.5%	45.8%	8.5%	n.a.
	Placebo		0.0%	0.0%	0.0%	n.a.

JUNCTURE (64)	Secukinumab 300mg Secukinumab 150mg Placebo	12	86.7% 71.7% 3.3%	55.0% 40.0% 0.0%	26.7% 16.7% 0.0%	n.a. n.a. n.a.
PHOENIX 1 (87)	Ustekinumab 45mg Ustekinumab 90mg Placebo	12	67.1% 66.4% 3.1%	41.6% 36.7% 2.0%	12.5% 10.9% 0.0%	53.1% 52.4% 6.0%
PHOENIX 2 (88)	Ustekinumab 45mg Ustekinumab 90mg Placebo	12	66.7% 75.7% 3.7%	42.3% 50.9% 0.7%	18.1% 18.2% 0.0%	55.3% 56.4% 3.2%
ACCEPT (89)	Ustekinumab 45mg Ustekinumab 90mg Etanercept	12	67.5% 73.8% 56.8%	36.4% 44.7% 23.1%	n.a. n.a. n.a	n.a. n.a. n.a.
BE READY (76)	Bimekizumab 320mg Placebo	16	95.4% n.a.	90.8% 1.2	68.2% 1.2	75.6% 5.8

3.3 Efficacy of biologicals in phase 3 pivotal studies

The IL-17 inhibitors secukinumab, ixekizumab, brodalumab, bimekizumab, the IL-23 inhibitors guselkumab, tildrakizumab, risankizumab and also the IL-12/23 inhibitor ustekinumab have all been shown to be very effective, especially in comparison to placebo therapy, but also in comparison to other drugs such as adalimumab and etanercept. (62) (63) (64) (70) (74) (75) (78) (79) (80) (82) (84) (85) (86) (87) (88) (89) (76) Table 2 shows that treatment with biologics results in significantly higher PASI 75, PASI 90 and PASI 100 response rates compared to participants receiving placebo. (62) (63) (64) (70) (74) (75) (78) (79) (80) (82) (84) (85) (86) (87) (88) (89) (76)In addition, there is also a significant improvement in quality of life compared to patients who received a placebo. (62) (63) (64) (70) (74) (75) (78) (79) (80) (82) (84) (85) (86) (87) (88) (89) (76) To provide a better overview, the lowest and highest percentage values of the achieved PASI90 and PASI100 response rates were determined. In addition, the median and mean values of the PASI90 and PASI100 values of the studies in Table 2 were determined

3.3.1 PASI 90 Response rates IL-17 inhibitors

Secukinumab achieved PASI 90 response rates between 39.1% and 60.3% after 12 weeks. (62) (63) (64) A median of 50.0% and a mean of 49.4% are obtained from the PASI 90 response rate values in Table 2. (62) (63) (64)

PASI 90 response rates after 12 weeks ranged from 59.7%-70.9% for patients treated with ixekizumab. (70) The median is 66.6% while the average is 66.7%. (70)

After 12 weeks brodalumab achieved PASI 90 response rates between 42.5% and 70.3%. (74) (75) The median is 58.8% while the average is 60.5%. (74) (75)

90.8% of patients treated with bimekizumab achieved a PASI 90 response rate after 16 weeks, with a median and mean of 90.8%. (76)

3.3.2 PASI 90 Response rates IL-23 and IL-12/23 inhibitors

At week16 guselkumab achieved PASI 90 response rates between 69.8% and 73.3%. (78) (79) (80) From the PASI 90 response rate values in Table 2, the median lies at 50.0 % and the average at 49.4 %. (78) (79) (80)

PASI 90 response rates after 12 weeks ranged from 35%-39% for patients treated with tildrakizumab. (82) The median is 36.5% while the average is 36%. (82)
Risankizumab-treated patients achieved a PASI 90 at 16 weeks in 72.0% to 75.9% of cases. (84) (85) (86) The median is 74.5 %, while the average is 74.8 %. (84) (85) (86)
The IL-12/23 inhibitor ustekinumab led to a PASI 90 response rate in 36.4%-50.9% of the treated patients after 12 weeks. (87) (88) (89) This leads to a median of 50.0% and a mean of 49.4%. (87) (88) (89)

3.3.3 PASI 100 Response rates IL-17 inhibitors

Secukinumab achieved PASI100 response rates between 8.5% and 43.1% after 12 weeks. (62) (63) (64) A median of 20.4% and a mean of 21.9% are obtained from the PASI100 response rate values in Table 2. (62) (63) (64)
After 12 weeks ixekizumab achieved PASI 100 response rates between 30.8% and 40.5%. (70) The median is 35.2% while the average is 35.5%. (70)
PASI 100 response rates after 12 weeks ranged from 23.3%-44.4% for patients treated with brodalumab. (74) (75) The median is 31.9% while the average is 33.2%. (74) (75)
68.2% of patients treated with bimekizumab achieved a PASI 100 response rate after 16 weeks, with a median and mean of 68.2%. (76)

3.3.4 PASI 100 Response rates IL-23 and IL-12/23 inhibitors

At week16 guselkumab achieved PASI 100 response rates between 27% and 37.4%. (78) (79) (80) From the PASI 100 response rate values in Table 2, the median lies at 33.2% and the average at 32.7%. (78) (79) (80)
PASI 100 response rates after 12 weeks ranged from 12%-14% for patients treated with tildrakizumab. (82) The median is 13% while the average is 13%. (82)
Risankizumab-treated patients achieved a PASI100 at 16 weeks in 22.4% to 50.7% of cases. (84) (85) (86) The median is 35.9%, while the average is 36.3%. (84) (85) (86)
The IL-12/23 inhibitor ustekinumab led to a PASI100 response rate in 10.9%-18.2% of the treated patients after 12 weeks. (87) (88) (89) This leads to a median of

15.3% and a mean of 14.9%. (87) (88) (89)

3.4 Most common adverse events in pivotal phase 3 studies

3.4.1 Secukinumab

In the first 12 weeks of the ERASURE study, adverse events occurred more frequently in patients treated with secukinumab than in patients receiving placebo. (62) Infections also occurred more frequently during this period. (62) Nasopharyngitis, upper respiratory tract infections and headache were the most common adverse events. (62) In the FIXTURE study, patients treated with secukinumab or etanercept experienced similar adverse events. (62) Nasopharyngitis, headache and diarrhea were the most common in patients treated with secukinumab. (62) Injection side reactions were more common in patients treated with etanercept than with secukinumab. (62) In total, 33 patients in the FIXTURE study had a candida infection while on secukinumab therapy. (62) Of these, 22 patients (4.7%) were in the secukinumab 300mg group and 11 (2.3%) were in the secukinumab 150mg group. (62) Candida infections were more common in patients treated with secukinumab than those receiving etanercept. (62) There was one suicide in the first four weeks of the FIXTURE study. (62) The rates of serious adverse during the entire treatment period were comparable in all groups in both studies. (62) In general, the side effect profile in the FEATURE and JUNCTURE trials was similar to those reported so far. (63) (64)

3.4.2 Ixekizumab

During the first 12 weeks of the UNCOVER trails, adverse events were more common in patients receiving ixekizumab than in patients receiving placebo. (70) The most common adverse events in participants receiving ixekizumab were nasopharyngitis, upper respiratory tract infection, injection-site reaction, injection-site erythema, and headache. (70) Oral candidiasis was more common in patients treated with ixekizumab. (70) Especially in the group receiving ixekizumab every 2 weeks, candida infections were more frequent. (70) In the first 12 weeks, there was no increased risk of adverse cardiovascular events in patients treated with

ixekizumab compared to placebo. (70) Major adverse cardiovascular and cerebrovascular events occurred in 23 (0.6%) patients overall on ixekizumab therapy and in one patient in the placebo group. (70) By week 60, among all participants treated with ixekizumab, ulcerative colitis occurred in 7 patients and Crohn's disease in 7 patients. (70) No patients developed ulcerative colitis or Crohn's disease during placebo treatment. (70)

3.4.3 Brodalumab

In AMAGINE-1, patients treated with brodalumab 210mg (59%) and brodalumab 140mg (57.5%) had more adverse events than patients receiving placebo (50.9%). (74) The same is true for serious adverse events (1.8% and 2.7% vs. 1.4%). (74) Nasopharyngitis, upper respiratory tract infections and headache were the most common adverse events. (74) In all 3 groups, depression occurred in 0.5%. (74) One case of oral candidiasis occurred during treatment with brodalumab. (74)
The AMAGINE-2 study showed a similar result, with adverse events and serious adverse events being more common in patients treated with brodalumab. (75) Depression until week 12 occurred in 0.3% of patients treated with brodalumab 210mg, in 0.7% of patients treated with brodalumab 140mg and in 0.3% of patients treated with placebo. (75) Until week 12 There was one suicide attempt in a patient treated with brodalumab 210mg, until week 52 this patient had two further suicide attempts. (75) By week 52, there was one completed suicide in a patient treated with brodalumab and another completed suicide 19 days after the 52 weeks of brodalumab therapy. (75) Candida infections up to week 12 were diagnosed in 1.6% of patients receiving brodalumab 210mg, in 1.3% receiving brodalumab 140mg and 0.6% in patients receiving placebo. (75)
In AMAGINE-3, nasopharyngitis, upper respiratory tract infections and headache were the most common adverse events. (75) In this study, adverse events and serious adverse events were also slightly more common in patients treated with brodalumab. (75) By week 12, 0.3% in the brodalumab 210mg group had depression, 0.6% in the brodalumab 140mg group and 0.6% in the placebo group. (75) There had been no suicide attempts by week 52. (75) By week 12, 1.3% of those treated with brodalumab 210mg had a candida infection, 0.5% had one with

the 140mg brodalumab therapy and 0.3% in the placebo group. (75) There had been no suicide attempts by week 52. (75) By week 12, 15 out of a total of 2916 patients from all 3 trials had neutropenia. No patient who received placebo had neutropenia. (75)

3.4.4 Bimekizumab

During the first 16 weeks of the BE READY study, adverse events occurred in 61% of patients receiving bimekizumab and in 41% of patients receiving placebo. (76) During this period, serious adverse events occurred in 2% of each group. (76) Between weeks 16 and 56, 74% of patients in the group receiving bimekizumab 320mg every 4 weeks experienced an adverse event. (76) In the group receiving the same dose every 8 weeks, 77% had adverse events and in the placebo group 69%. (76) Of these, serious adverse events were 5%, 3%, and 4%, respectively. (76) The most common adverse events were nasopharyngitis, oral candidiasis and upper respiratory tract infections. (76) During the first 16 weeks, 21 patients (6%) had oral candidiasis with bimekizumab and none of the patients in the placebo group. (76) Between weeks 16-52, 9 patients (9%) treated with bimekizumab 320 mg every 8 weeks had oral candidiasis and 12 patients (11%) of those treated with bimekizumab 320 mg every 4 weeks. (76) in the bimekizumab 320 mg every 8 weeks treatment group a major adverse cardiovascular event occurred between week 16 and 52. (76) There were no new cases of active tuberculosis, inflammatory bowel disease or increased suicidality during the course of the study. (76)

3.4.5 Guselkumab

The most common adverse events that occurred during treatment with guselkumab were infections such as nasopharyngitis and upper respiratory tract infections. (78) (79) (80) The frequency and types of adverse events and serious adverse events were comparable to those patients receiving placebo but also to those receiving adalimumab. (78) (79) (80) Cases of candidiasis were low and comparable between groups, and no cases of Crohn's disease were reported. (78) (79) There was a total of 2 myocardial infarctions, one each in the guselkumab

and adalimumab groups. (79) Another MACE (cerebral infarction) occurred during guselkumab therapy in a phase 3 trial in Japan. (80) There were 2 cases of tuberculosis in patients receiving adalimumab therapy and no cases of tuberculosis in patients receiving guselkumab therapy. (79) In addition, injection side reactions occurred more frequently in patients receiving adalimumab. (78) (79)

3.4.6 Tildrakizumab

Among participants treated with tildrakizumab, the proportion of patients with serious adverse events or who discontinued treatment due to adverse events was low and comparable to those who received placebo or etanercept. (82) Nasopharyngitis was the most common adverse reaction. (82) There was an increase in injection site erythema in reSURFACE 2, but this was mainly in the etanercept group. (82) There was no significant difference in serious adverse cardiac events and candida infections. (82) No new cases of inflammatory bowel disease or exacerbations occurred. (82)

3.4.7 Risankizumab

For both UltIMMa-1 and UltIMMa-2, the proportion of patients with treatment-related adverse events was comparable between treatment groups throughout the study period. (84) Overall, infections were more common in patients receiving risankizumab or ustekinumab than in patients receiving placebo in both studies. (84) Serious adverse events up to week 16 occurred in 2.3% (UltIMMa-1) and 2% (UltIMMa-2) of patients treated with risankizumab. (84) They occurred with comparable frequency in the placebo group and the ustekinumab group. (84) During this period, upper respiratory tract infection was the most common adverse event. (84) No major adverse cardiovascular event was reported. (84) There were no events of tuberculosis, opportunistic infections or serious adverse cardiovascular events during the 16 weeks. (84) However, one death was recorded due to an unknown cause. (84)

Between week 16 and week 52 in the risankizumab treatment group of UltIMMa-2 two major adverse cardiovascular events were reported. (84) In both cases, risk

factors were known, and the events were not associated with the study drug by the investigator. (84) Between weeks 16 and 52, upper respiratory tract infection was still the most common adverse event. (84) Two cases of latent tuberculosis were observed in the risankizumab group. (84)

Another phase 3 study compared risankizumab with adalimumab. (85) Again, the frequencies of treatment-emergent adverse events, serious adverse events, and adverse events leading to study drug discontinuation were low for risankizumab. (85) In the study, there were a total of 2 cases of depression, 1 case of latent tuberculosis, 1 case of adjudicated major adverse cardiovascular event and 1 death (acute myocardial infarction not considered by the investigators to be related to the study drug) during risankizumab therapy. (85) No new cases of inflammatory bowel disease. (85)

Risankizumab was also well tolerated by the Japanese patients and, again, rates of adverse events and serious adverse events were similar for risankizumab and placebo and remained consistent over 52 weeks of treatment. (86) The safety results were consistent with the data on risankizumab reported in the previous pivotal phase 3 studies. (86)

3.4.8 Ustekinumab

Adverse events in the pivotal phase 3 studies with ustekinumab showed that the number of infections and the number of adverse events leading to treatment discontinuation were about the same in patients treated with ustekinumab compared to placebo. (87) (88) Upper respiratory tract infections and nasopharyngitis were the most common adverse events. (87) (88) There was no evidence that serious cardiovascular events or serious infections were more common with ustekinumab therapy. (87) (88) The rate of injection side effects was also low. (88) No cases of tuberculosis were reported. (87) (88)

Compared to etanercept, ustekinumab caused injection side effects less frequently. (89) Adverse events occurred more frequently in patients receiving ustekinumab 90 mg than in patients receiving ustekinumab 45 mg, but the difference was not significant. (89)

3.4 Head-to-head studies (IL-17 vs IL-23/ IL-12/23 inhibitors and IL-23 vs IL-12/23 inhibitors)

3.4.1 ECLIPSE

ECLIPSE is the first multicenter, randomized, double-blind, comparator-controlled phase 3 study comparing an IL-23p19 inhibitor to an IL-17A inhibitor. (90) 1048 patients suffering from moderate-to-severe plaque-type psoriasis were randomly assigned to either guselkumab (100 mg at weeks 0 and 4 and then every 8 weeks) or secukinumab (300 mg at weeks 0, 1, 2, 3, and 4 and then every 4 weeks). (90) At week 48, significantly more participants treated with guselkumab than patients treated with secukinumab (84% vs 70%) displayed a PASI 90 response. (90) PASI 100 response rates at week 48 were achieved by 58% in the guselkumab group and 48% in the secukiumab secukinumab group. (90) At week 12 and week 48, 85% of guselkumab-treated and 80% of secukinumab-treated participants achieved PASI-75 response rates. (90) PASI 90 at week 12 was achieved by 69% in the guselkumab group and 76% in the secukinumab group. (90)(90) The study shows that there is a faster response under therapy with secukinumab. (90) In particular, between weeks 3 and 12, more participants achieved a PASI 90 response rate with secukinumab than with guselkumab. (90) The numbers became closer between weeks 16 and 20, and from week 20 on, more participants had a higher PASI 90 response rate under guselkumab. (90) This means that there is a faster improvement under secukinumab, but under guselkumab more patients achieve better PASI values over a longer period of time (48 weeks). (90) The study did not reveal any new side effects to those previously known. (90) In both groups, the numbers of adverse events and serious events were comparable. (90) However, six non-melanoma skin cancers occurred in the guselkumab-treated participants, whereas two occurred in the secukinumab group. (90) Cases of Crohn's disease occurred in three patients on secukinumab therapy and none on guselkumab. (90)

3.4.2 IXORA-R

Ixekizumab and guselkumab were compared in IXORA-R, a head-to-head study. (91) In this randomized, double-blinded study, the main focus was on early

response. (91) The study was divided into two parts (part 1 and 2). (91) In the first part, the results were compared up to week 12. (91) 1027 patients with chronic plaque psoriasis were randomly assigned to receive ixekizumab (160mg at week 0 and then 80mg every 2 weeks until week 12) or guselkumab (100mg at weeks 0, 4 and 12). (91) In all these measurements from Table 3, ixekizumab had significantly better PASI response rates. (91) In addition, the PASI 50 response rate at week 1 was significantly higher in the ixekizumab group (28%) compared to the guselkumab group (9%). (91) More patients treated with ixekizumab also reported faster improvement of itching and quality of life. (91) By week 12, ixekizumab resulted in significantly better PASI response rates at all time points collected. (91)

The second part of the IXORA-R study relates to weeks 12 to 24. (92) Patients in the ixekizumab group received 80mg every 4 weeks and patients in the guselkumab group received 100mg at weeks 12 and 20. (92) Of the 520 patients in the ixekizumab group, 465 completed the study by week 24 and 459 of 507 in the guselkumab group. (92) At week 24, 50% of participants had achieved a PASI 100 response rate with ixekizumab and 52% with guselkumab, at week 24, no inferiority of ixekizumab compared to guselkumab was observed. (92) In addition, the second part of the study fills in missing information from the first half. (92) At week 1, significantly more people treated with ixekizumab (4.8%) achieved a PASI 75 than those treated with guselkumab (1%); this significant difference was present until week 10. (92) PASI 90 was achieved at week 2 by 5.2% in the ixekizumab group and 0.6% in the guselkumab group. (92) This value was also significantly higher and remained so until week 12. (92) The study also looked for changes in patients who had involvement of psoriasis on the fingernails. (92) In patients with nail involvement, ixekizumab resulted in complete clearance in 63% and guselkumab in 44%. (92) There was also a significant improvement in psoriatic arthritis under treatment with both drugs, but there was no significant difference between the groups. (92) Ixekizumab demonstrated a significantly faster response than guselkumab. (92) PASI 50 and PASI 75 were achieved a median of 2.0 weeks earlier with ixekizumab. (92) PASI 90 was reached 2.1 weeks

earlier and the median achievement of PASI 100 was even reached 7.5 weeks earlier. (92) The median time under ixekizumab to achieve a DLQI of 0 or 1 was 6.3 weeks and under guselkumab 12.1 weeks. (92) In terms of itch NRS of 0, participants needed 16.1 weeks vs. 20.1 weeks, respectively. (92) Patients treated with ixekizumab had significantly more days with a DLQI of 0 or, 1 PASI 100, PASI 90 and also more days without itching during the 24 weeks. (92)
Side effects and severe adverse events occurred with comparable frequency in both groups. (91) (92) 62% of the patients treated with Ixekizumab had at least one adverse event and 57% in the guselkumab group. (92) Serious adverse events occurred in 3% in both groups. (92)

3.4.3 IXORA-S, part 1

In the IXORA-S study, ixekizumab is being compared with ustekinumab. (93) 136 participants in the ixekizumab group received two 80 mg injections subcutaneously at baseline and 80 mg every 2 weeks thereafter until week 12 and then every 4 weeks. (93) In the ustekinumab group, 166 patients received the subcutaneous injections at weeks 0, 4, 16, 28, and 40. Patients weighing ≤ 100 kg received 45mg and patients weighing > 100 kg received 90 mg ustekinumab. (93) At week 12, significantly more patients achieved PASI 75, PASI 90, PASI 100, sPGA 0, sPGA (0,1) and DLQI (0,1) with ixekizumab than with ustekinumab. (93) Patients treated with ixekizumab have shown a significantly faster response. (93) PASI 75 was achieved at week 2 by 16.2% of patients receiving ixekizumab and by 1.8% in the ustekinumab group. (93) PASI 100 response rate at week 4 occurred in 6.6% in the ixekizumab group and 0% in the ustekinumab group. (93) With regard to sPGA, the results were similar. (93) Significantly more participants who had an sPGA score ≥ 3 at baseline achieved an sPGA of 0 or 1 with ixekizumab at week 2. (93) At week 4, significantly more patients also had an sPGA of 0 with ixekizumab than with ustekinumab. (93) In addition, at week 2, a DLQI of 0 or 1 was also achieved by significantly more patients with ixekizumab. (93) There was no significant difference in both groups in terms of itch NRS and skin pain VAS changes at week 12, although faster improvement occurred with ixekizumab. (93) At week 12, an improvement in itch NRS of at least 4 points from baseline (in patients with

baseline itch ≥4) was achieved in the ixekizumab group of 76.4% and in the ustekinumab group of 74.3%. (93) PASI 75, PASI 90, PASI 100, sPGA 0, sPGA (0,1) and DLQI (0 or 1) response rates were still significantly higher in the ixekizumab group from week 12-24. (93) However, changes in itch NRS and skin pain VAS remained comparable in both groups up to week 24, there was no statistical difference. (93) Except for participants with baseline itch NRS ≥ 4, significantly more patients in the ixekizumab group experienced a reduction of ≥ 4 points (85.5% vs. 72.1%). (93)
There were no significant differences in side effects in either group until week 24. (93) TEAEs occurred in 69.6% in the ixekizumab group and in 75.3% in the ustekinumab group. (93) 2.2% had Serious adverse events with ixekizumab vs. 3% with ustekinumab. (93)

3.4.4 IXORA-S, part 2

The significant superiority of ixekizumab remained after 52 weeks. (94) This applies to all clinical efficacy measures where superiority of ixekizumab was demonstrated at weeks 12 and 24. (94) Adverse events occurred in 83.7% in the ixekizumab group and 86.7% in the ustekinumab group. (94) There was no significant difference in frequency, even for severe courses, which occurred in 6.7% in the ixekizumab group and 3.6% in the ustekinumab group. (94) Nasopharyngitis was the most common side effect. (94)

3.4.5 CLEAR, part 1

CLEAR is a phase III study comparing the efficacy and safety of secukinumab and ustekinumab. (95) The 676 participants were randomly assigned to receive either secukinumab (300mg at baseline, week 1,2,3 and then every 4 weeks until week 48) or ustekinumab (weeks 0, 4, 16, 28, and 40; Patients weighing ≤ 100 kg received 45mg and patients weighing > 100 kg received 90 mg). (95)
By week 4, subjects treated with ixekizumab had higher PASI 75, PASI 90, PASI 100, IGA 0/1, and DLQI 0 or 1 responses. (95) This significant difference remained present in all areas through week 12 and up to week 16. (95) Up to week 16, there have been no significant differences in the frequency and severity of side effects.

(95) Adverse events in the secukinumab group occurred in 64.2% and in the ustekinumab group in 58.3%. (95) Serious adverse events occurred in 3% of both groups. (95)

3.4.6 CLEAR, part 2

The second part of the CLEAR study ran until week 52, with participants receiving the previously mentioned doses. (96) After 52 weeks, subjects in the secukinumab group still achieved higher scores for PASI 75, PASI 90, PASI 100, IGA 0/1 and DLQI 0 or 1. (96) During the 52 weeks adverse events and severe adverse events took place in similar frequencies in both treatment groups. (96) Nasopharyngitis and headache were the most common side effects, with comparable frequencies in both groups. (96)

3.4.7 CLARITY

Another double-blind, head-to-head, phase 3b trial that compared secukinumab and ustekinumab. (97) This 52-week study has again shown higher efficacy, faster response and improvement in DLQI in patients receiving secukinumab therapy compared to ustekinumab (for concise results see table 3). (97) Side effects were comparable in both groups and also with previous studies. (97)

3.4.8 UltIMMa-1 and UltIMMa-2

UltIMMa-1 and UltIMMa-2 were two replicated phase 3 studies comparing risankizumab and ustekinumab. (84) 506 patients in UltIMMa-1 and 491 patients in UltIMMa-2 were randomized in a 3:1:1 ratio to receive risankizumab, ustekinumab or placebo. (84) The study design of UltIMMa-1 and UltIMMa-2 has already been described above. (84)

At week 16, patients treated with risankizumab showed significantly better results in PASI 75, PASI 90, PASI 100, sPGA 0, sPGA 0/1 and DLQI 0 or 1, compared to ustekinumab and placebo. (84) At week 52, PASI 75, PASI 90, PASI 100, sPGA 0, sPGA 0/1 and DLQI 0 or 1 were still significantly better with risankizumab compared with ustekinumab and placebo (for concise results see table 3). (84) In UltIMMa-1 and UltIMMa-2, adverse events and serious adverse events occurred

with similar frequency in the risankizumab group and the ustekinumab group. (84)

3.4.9 IMMerge

IMMerge is a phase 3 study comparing risankizumab with secukinumab. (98) 164 patients in the risankizumab group received 150mg at weeks 0 and 4 and then every 12 weeks until week 40. (98) 163 patients in the secukinumab group received 300mg of secukinumab at weeks 0,1,2,3,4 and then every four weeks until week 48. (98) In terms of PASI90 response rate at week 16, there was no inferiority of risankizumab compared to secukinumab. (98) However, at week 52, significantly more patients had a higher PASI 90 response rate with risankizumab than with secukinumab. (98) PASI 75, PASI 100 and an sPGA score of 0 or 1 was also achieved by significantly more participants in the risankizumab group at week 52 (for concise results see table 3). (98) Overall, no new safety concerns were observed. (98)

3.4.10 Navigate

NAVIGATE is a randomized, double-blind phase III study comparing guselkumab and ustekinumab in terms of efficacy and safety. (99) This study selected participants who had already shown an inadequate response to ustekinumab. (99) 871 patients who had moderate to severe plaque-type psoriasis were assigned to treatment with ustekinumab at weeks 0 and 4 (45mg ≤ 100kg; 90 ≥ 100kg). (99) Those patients who had an IGA of ≥ 2 after week 16, meaning an inadequate response, were randomly assigned to either guselkumab 100mg at weeks 16, 20 and every 8 weeks afterwards until week 44, or to ustekinumab at week 16, week 28 and week 40. (99)

During the 16-week open-label run-in period, 18 people discontinued therapy. (99) Of the remainder, 268 had an IGA score ≥ 2 and were randomly assigned to guselkumab 100mg or continued ustekinumab. (99) 585 patients had an IGA score of < 2 and continued with ustekinumab. (99) The primary endpoint was observed between week 28 and 40. (99) It referred to the number of visits (with a maximum of four visits) in which the patients had an IGA score of 0 or 1 or at least a two-level improvement compared to week 16. (99)

Significantly more visits in which patients had an IGA score of 0 or 1 and at least a two-grade improvement relative to week 16 from week 28 through week 40 were within the randomized patients in the guselkumab group compared with the ustekinumab group (1.5 vs. 0.7). (99) A significantly higher number of visits in which patients reached an PASI 90 and IGA 0 was also achieved by guselkumab during this period. (99) At week 28 and week 52 significantly more patients treated with guselkumab (31.1%) reached an IGA score of 0 or 1 and at least a two-grade improvement relative to week 16 compared to ustekinumab (14.1%). (99) Significantly more patients reached an PASI 90 and PASI 100 in the guselkumab group compared to ustekinumab. (99) Patients treated with guselkumab achieved a PASI 90 in 51.1% and a PASI 100 in 20.0% at week 52, compared to 24.1% and 7.5% for ustekinumab. (99) Both scores were achieved by significantly more participants in the guselkumab group. (99) At week 52, significantly more patients treated with guselkumab (38.8%) achieved a DLQI of 0 or 1 compared to the randomized ustekinumab group (19.0%). (99) In the group receiving continuous ustekinumab, 81.1% of patients who had already achieved an IGA score of 0 or 1 at week 16 maintained this response through week 52, and 42.6% even had an IGA score of 0. (99) PASI75, PASI 90 and PASI 100 were reached by 95.7%, 69.7% and 27.2% respectively at week 16, these values were maintained until week 52. (99)

3.4.11 BE VIVID

BE VIVID was a phase 3 study comparing bimekizumab, ustekinumab and a placebo. (100) 567 patients were randomly assigned 4:2:1. (100) One group with 321 participants received bimekizumab 320mg every 4 weeks, one group with 163 participants received ustekinumab 45mg or 90mg at weeks 0,4 and then every 12 weeks and the 83 participants in the placebo group received the placebo every 4 weeks. (100) The placebo group switched to bimekizumab 320mg every 4 weeks after 16 weeks. (100) At week 16, significantly more patients in the bimekizumab group achieved a higher PASI 90, PASI 100, DLQI 0 or 1 and IGA 0 response rate compared to ustekinumab and placebo (for concise results see table 3). (100) PASI-75 response rates were significantly higher in the bimekizumab group compared to the other groups at week 4, indicating faster response compared to

ustekinumab and placebo. (100) Response rates remained significantly higher in the bimekizumab group until week 52 (for concise results see table 3). (100) In the placebo group, after switching to bimekizumab from week 16 to week 52, similar results were obtained as in the group that received bimekizumab from the beginning. (100)

3.4.12 Bimekizumab versus Secukinumab

A phase 3b study by Kristian Reich et al. compared the two IL-17 inhibitors bimekizumab and secukinumab. (101) Patients were randomized in a 1:1 ratio to receive bimekizumab 320mg every 4 weeks or secukinumab 300mg weekly until week 4 and then every 4 weeks until week 48. (101) After 16 weeks, patients in the bimekizumab group were re-randomized in a 1:2 ratio to receive the maintenance dose either every 4 weeks or every 8 weeks until week 48. (101) At week 16, 61.7% in the bimekizumab group and 48.9% in the secukinumab group had achieved a PASI 100 from baseline. (101) Bimekizumab was found to be non-inferior and superior to secukinumab. (101) However, at 48 weeks, significantly more patients in the bimekizumab group were shown to have achieved PASI100 than in the secukinumab group (67.0% vs. 46.2%). (101) In addition, there was no significant difference in terms of PASI75 and PASI90 at both week 16 and week 48 (for concise results see table 3). (101)

Table 3 Efficacy of IL-17 and IL-23 inhibitors in head-to-head studies

	PASI 75	PASI 90	PASI 100	sPGA 0/1	sPGA 0	IGA 0/1	IGA 0	DLQI 0/1
ECLIPSE (90) (guselkumab / secukinumab)								
week 12	89% / 92%	69%/76%	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.
week 48	n.a. / n.a.	84%/70%	58% / 48%	n.a. / n.a.	n.a. / n.a.	85% / 75%	62% / 50%	n.a. / n.a.
IXORA-R part1 (91) (ixekizumab / guselkumab)								
week 2	23% / 5%	5.2% / 0.6%	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.
week 4	n.a. / n.a.	21% / 8%	7% / 1%	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.	34% / 21%
week 8	n.a. / n.a.	58% / 36%	30% / 14%	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.
week 12	n.a. / n.a.	n.a. / n.a.	41% / 25%	n.a. / n.a.	42% / 25%	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.
IXORA-R part2 (92) (ixekizumab / guselkumab)								
week 24	n.a. / n.a.	n.a. / n.a.	50% / 52%	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.
IXORA-S part1 (93) (ixekizumab / ustekinumab)								
week 12	88.2% / 68.7%	72.8% / 42.2%	36% / 14.5%	83.6% / 57.2%	41.9% / 18.1%	n.a. / n.a.	n.a. / n.a.	61% / 44.6%
week 24	91.2% / 81.9%	83.1% / 59%	49.3% / 23.5%	86.6% / 69.3%	53.7% / 24.1%	n.a. / n.a.	n.a. / n.a.	66.2% / 53%

IXORA-S part2 (94) (ixekizumab / ustekinumab) week 52	88.2% / 75.9%	76.5% / 59%	52.2% / 35.5%	82.1% / 65.1%	52.9% / 36.1%	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.
CLEAR part1 (95) (secukinumab/ ustekinumab)								
week 4	50.0% / 20.6%	21% / 5.4%	4.2% / 0.9%	n.a. / n.a.	n.a. / n.a.	37.7% / 12.2%	n.a. / n.a.	34.2% / 21.2%
week 12	91.0% / 79.1%	72.8% / 53.4%	38.9% / 25.7%	n.a. / n.a.	n.a. / n.a.	80.8% / 65.1%	n.a. / n.a.	66.2% / 56.5%
week 16	93.1% / 82.7%	79.0% / 57.6%	44.3% / 28.4%	n.a. / n.a.	n.a. / n.a.	82.9% / 67.5%	n.a. / n.a.	71.9% / 57.4%
CLEAR part2 (96) (secukinumab/ ustekinumab) week 52	92.5% / 79.5%	76.2% / 60.6%	45.9% / 35.8%	n.a. / n.a.	n.a. / n.a.	80.4% / 65%	n.a. / n.a.	71.6% / 59.2%
CLARITY (102) (secukinumab / ustekinumab)								
week 4	40.2% / 16.3%	16.7% / 4.0%	5.7% / 0.7%	n.a. / n.a.	n.a. / n.a.	26.9% / 7.8%	n.a. / n.a.	33.9% / 18.0%
week 12	88.0% / 74.2%	66.5% / 47.9%	38.1% / 20.1%	n.a. / n.a.	n.a. / n.a.	72.3% / 55.4%	n.a. / n.a.	64.0% / 51.7%
week16	91.7% / 79.8%	76.6% / 54.2%	45.3% / 26.7%	n.a. / n.a.	n.a. / n.a.	78.6% / 59.1%	n.a. / n.a.	68.4% / 55.9%
CLARITY (97) (secukinumab / ustekinumab) week 52	89.0% / 82.1%	73.2% / 59.8%	48.9% / 33.5%	n.a. / n.a.	n.a. / n.a.	76.0% / 60.2%	50.3% / 33.8%	69.9% / 61.2%

UltIMMa-1 (84) (risankizumab / ustekinumab)								
week 16	n.a. / n.a.	75.3% / 42.0%	35.9% / 12.0%	87.8% / 63.0%	36.8% / 14.0%	n.a. / n.a.	n.a. / n.a.	65.8% / 43.0%
week 52	n.a. / n.a.	81.9% / 44.0%	56.3% / 21.0%	86.0% / 54.0%	57.6% / 21.0%	n.a. / n.a.	n.a. / n.a.	75.0% / 47.0%
UltIMMa-2 (84) (risankizumab / ustekinumab)								
week 16	n.a. / n.a.	74.8% / 47.5%	50.7% / 24.2%	83.7%/61.6%	51.0% / 25.3%	n.a. / n.a.	n.a. / n.a.	66.7% / 46.5%
week 52	n.a. / n.a.	80.6% / 50.5%	59.5% / 30.3%	83.0%/55.0%	59.5% / 30.3%	n.a. / n.a.	n.a. / n.a.	71.0% / 44.0%
IMMerge (98) (risankizumab / secukinumab)								
week 16	92% / 80%	74% / 66%	44% / 34%	90% / 73%	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.
week 52	90% / 70%	87% / 57%	66% / 40%	88% / 58%	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.
BE VIVID (100) (bimekizumab / ustekinumab)								
week 16	92% / 73%	85% / 50%	59% / 21%	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.	59% / 22%	67% / 42%
week 52	85% / 74%	82% / 56%	65% / 38%	n.a. / n.a.	n.a. / n.a.	n.a. / n.a.	65% / 39%	75% / 63%
Bimekizumab versus Secukinumab (101)								
week 16	93.3% / 91.1%	85.5% / 74.3%	61.7% / 48.9%	n.a. / n.a.	n.a. / n.a.	85.5% / 78.6%	n.a. / n.a.	n.a. / n.a.
week 48	88.5% / 81.4%	83.6% / 70.5%	67.0% / 46.2%	n.a. / n.a.	n.a. / n.a.	83.9% / 73.8%	n.a. / n.a.	77.7% / 70.3%

3.5 Most common adverse events in head-to-head studies

3.5.1 Eclipse

During the ECLIPSE study 78% had at least 1 adverse event in the guselkumab group; in the secukinumab group, the number was comparable at 83%. (90) Serious adverse events also occurred comparably often, 6% in the guselkumab group and 7% in the secukinumab group. (90) Nasopharyngitis and upper respiratory tract infections were the most common adverse events in both groups. (90) Six non-melanoma skin cancers were observed in the guselkumab-treated participants compared to two in the secukinumab group. (90) Candida infections occurred in 2% of guselkumab-treated patients and 6% of secukinumab-treated patients. (90) Cases of Crohn's disease were not observed in any of the guselkumab-treated patients but were observed in 3 patients receiving secukinumab. (90)

3.5.2 IXORA-R

Adverse events in IXORA-R occurred with comparable frequency in the ixekizumab group and the guselkumab group (62% vs. 57%). (92) Serious adverse events occurred in both groups in 3% each. (92) With 8% in both groups, upper respiratory tract infections were the most common side effects. (92) Six opportunistic infections occurred during the study period, of which five were in the ixekizumab group and one in the guselkumab group. (92) Three mucocutaneous candidiasis in the ixekizumab group and three herpes zoster, two of which occurred in the ixekizumab group and one in the guselkumab group. (92) Patients treated with ixekizumab showed injection side reactions more frequently than patients treated with guselkumab (13% vs. 4%). (92) None of the injection side reactions had a severe course; all had a mild to moderate course. (92) Crohn's disease occurred in a patient who had a history of IBD and was treated with ixekizumab. (92)

3.5.3 IXORA-S

83.7% of patients in the ustekinumab group from the IXORA-S study had an adverse event and 3.6% had a serious adverse event. (94) In the ixekizumab group, the number of adverse events and serious adverse events was comparable to

ustekinumab at 86.7% and 6.7%, respectively. (94) The most common side effect in both groups was nasopharyngitis. (94) Candida infections were observed in 2.2% of patients receiving ixekizumab and 1.8% of patients receiving ustekinumab. (94) In the ixekizumab group Injection site reactions were reported significantly more often (16.3% vs. 1.2%). (94) The only case of IBD during the 52 weeks was seen in the ustekinumab group. (94) No malignancies occurred. (94) Cases of depression occurred in 0.6% in the ustekinumab group and in 2.2% in the ixekizumab group. (94) There was one case of a cerebrocardiovascular event in each group. (94) Grade 3 neutropenia occurred in one participant receiving ixekizumab. (94) Grade 2 neutropenia occurred in 0.7% of those treated with ixekizumab and in 1.2% of those treated with ustekinumab. (94)

3.5.4 CLEAR

Adverse events and serious adverse events in the CLEAR study occurred with comparable frequency in the secukinumab group and the ustekinumab group. (96) Nasopharyngitis was the most common side effect in both groups. (96) Candida infections occurred in 20 patients with secukinamb and in 5 patients with ustekinumab. (96) Malignant melanoma in situ was found in two patients, only in the secukinumab group. (96) No new cases of IBD have been reported. (96) One stroke in the secukinumab group and one myocardial infarction in the ustekinumab group were observed. (96)

3.5.5 CLARITY

In CLARITY 68.5% of the patients in the secukinumab group had an adverse event and 4.9% had a serious adverse event. (97) In the ustekinumab group, the number of adverse events and serious adverse events was comparable to secukinumab at 70.7% and 3.9%, respectively. (97) Patients treated with secukinumab were more likely to have cadidiasis (2.4% vs. 0.7%). (97) In addition, more cases of IBD were observed in the secukinumab group (0.4% vs. 0%).(97)

3.5.6 UltIMMa-1 and UltIMMa-2

In the first part of the UltIMMa-1 study, 49.7% had side effects with risankizumab and 50.0% with ustekinumab. (84) Severe side effects occurred in 2.3% and 8%, respectively. (84) In the second part, side effects occurred in 61.3%(risankizumab), 66.7% (ustekinumab) and 67.0% (from placebo to risankizumab). (84) Severe adverse events occurred in 5.4%, 4.0% and 3.1%. (84) In the first part of the UltIMMa-2 study, 45.9% experienced side effects with risankizumab and 53.5% with ustekinumab. (84) Severe side effects were reported in 2.0% and 3%, respectively. (84) In the second part, side effects occurred in 55.7% (risankizumab), 74.5% (ustekinumab) and 64.9% (from placebo to risankizumab). (84) Severe adverse events were observed in 4.5%, 4.3% and 3.2%, respectively. (84) Viral upper respiratory tract infections the most common side effects in all groups. (84) Two serious adverse cardiovascular events occurred, including one patient with sudden cardiac death. (84) Both cases were in the risankizumab treatment group of UltIMMa-2. (84) Both had multiple cardiovascular risk factors. (84) One patient who was switched from placebo to risankizumab was diagnosed with breast cancer. (84) There was one case of prostate cancer in the ustekinumab treatment group. (84)

3.5.7 IMMerge

In the risankizumab group from the IMMerge study, side effects occurred in 71.3% and severe side effects in 5.5%. (98) Side effects and severe adverse events in the secukinumab group occurred with comparable frequency, 71.2% and 3.7%, respectively. (98) Nasopharyngitis, upper respiratory tract infection, headache, arthralgia, diarrhea and bronchitis were the most common adverse events in both groups. (98) Adverse events leading to study discontinuation occurred in 4.9% (secukinumab) and 1.2% (risankizumab). (98) Serious infections occurred in 1.8% (risankizumab) and 0% (secukinumab), one of which was a new-onset inflammatory bowel disease in the secukinumab group. (98) Candida infections were found in three patients treated with risankizumab and four in the secukinumab group. (98) Two MACEs (nonfatal myocardial infarctions) were found in the risankizumab group, none in the secukinumab group, both had pre-existing risk factors. (98)

3.5.8 NAVIGATE

In the NAVIGATE study, by week 16, 29.2% had at least one adverse event and 1.3% had at least one serious AE. (99) Nasopharyngitis and upper respiratory tract infections were the most common. (99) Among the serious adverse events were one pneumonia and one anal abscess and in two patients a basal cell carcinoma. (99) 64.4% had at least one adverse event in the guselkumab group from weeks 16 -60, and 55.6% in the randomized ustekinumab group. (99) Infections were the most common adverse events, accounting for 41.5% and 35.5%, respectively. (99) Musculoskeletal and connective tissue disorders were more common in the guselkumab group, occurring in 12.6% and 6.8% respectively. (99) General disorders and administration site conditions were also more common in the guselkumab group, the majority of which were injection side reactions (11.9% vs. 1.5%). (99) Serious adverse events in the guselkumab group were reported in 6.7% und 4.5% in the ustekinumab group. (99) These included one serious infection in the guselkumab group, two malignancies in the guselkumab group and three myocardial infarctions, two of which occurred with guselkumab and one with ustekinumab. (99) One patient in the guselkumab group died due to squamous cell carcinoma that developed during the study. (99) Nasopharyngitis and upper respiratory tract infections were also the most common adverse events in the group that continued the ustekinumab therapy. (99) Serious adverse events occurred in 3.4%. (99) Serious infections were found in five patients. (99) Four malignancies occurred and one myocardial infarction. (99) Out of the four cancer patients one died due to a metastatic pancreas carcinoma. (99) 0.1% of the participants had injection side reactions. (99)

3.5.9 BE VIVID

By week 16, adverse events in the BE VIVID study occurred with similar frequency in all 3 groups. (100) In 56% of participants in the bimekizumab group, 51% in the ustekinumab group and 47% in the placebo group. (100) Serious adverse events occurred in 2% (bimekizumab), 3% (ustekinumab) and 2% (placebo). (100) Overall, from the start of the study to week 52, 82% of participants in the bimekizumab

group had at least one adverse event and 80% of participants in the ustekinumab group. (100) For serious adverse events, this was true in 6% (bimekizumab) and 8% (ustekinumab). (100) Four deaths occurred during the course of the study, all of which were classified by the investigator as unrelated to the study. (100) One of these cases was a cardiac arrest within the first 16 weeks of bimekizumab therapy. (100) Nasopharyngitis, oral candidiasis and upper respiratory tract infections were the most common adverse events in the bimekizumab group. (100) 15% had oral candidiasis with bimekizumab, one case of which was severe. (100) There was only one case of oral candidiasis with ustekinumab. (100) Over the course of the study, serious infections occurred in 1% of the bimekizumab group and 3% of the ustekinumab group. (100) One patient developed a new case of IBD with bimekizumab. (100) Major adverse cardiovascular events occurred in five patients in the bimekizumab group over the course of the study. (100) No major adverse cardiovascular events occurred in the ustekinumab group. (100) Malignancies occurred in one patient each in the bimekizumab and ustekinumab groups. (100)

3.5.10 Bimekizumab versus Secukinumab

Adverse events were reported at 48 weeks in 86.1% of patients receiving bimekizumab and 81.4% of patients receiving secukinumab. (101) Serious adverse events occurred with similar frequency in both groups (3.5% bimekizumab vs. 2.7% secukinumab). (101) Adverse events leading to treatment discontinuation were also similar with 3.5% for bimekizumab and 2.7% for secukinumab. (101) Upper respiratory tract infections, oral candidiasis, and urinary tract infections were the most common adverse events that occurred during the treatment period and were reported in more than 5% of patients in either group. (101) 19.3% of patients receiving bimekizumab suffered an oral candidiasis infection, compared with only 3% in patients receiving secukinumab. (101) Ulcerative colitis occurred once in both groups. (101)

3.6 Biologics in nail psoriasis

Nail changes are common in psoriasis patients: About 41% to 56% of psoriasis patients also suffer from psoriatic nail disease. (103) (104) (105) Whereby men show a higher prevalence than women. (103) (104) In patients with psoriatic arthritis, even up to 80% suffer from nail involvement. (106) Nail psoriasis is in fact considered an independent prognostic indicator for the subsequent development of psoriatic arthritis. (107) Which is one of many reasons why an early, targeted treatment is very important. (108) Nail psoriasis leads to a reduced quality of life due to several causes. (109) On the one hand, nail psoriasis can impair manual activities such as working, typing or self-care. (109) But also sports or even walking can be made more difficult by an involvement of the nails. (109) Those affected by nail psoriasis often feel impaired in their daily lives. (109) Social problems might also be associated with nail psoriasis , especially when the fingernails are visibly affected and people often try to hide their nails. (109) In addition, the lesions can also lead to itching and pain.(109) Furthermore, studies have shown that patients with nail psoriasis have a higher disease severity and longer disease duration. (103) (104) Therefore also leading to a higher number of patients with a reduced quality of life. (104) Unfortunately, the reduction of quality of life in patients is often not considered enough in studies. (109) Comparability between studies of life quality is also often not given because different instruments are used for quantification. (109) It would be important to use consistent instruments for assessment. (109) The treatment of nail psoriasis has proven to be particularly difficult. (108) Topical preparations are often used as first line treatment when only 1-3 nails are affected. (108) However, these methods are often not sufficient. (108) In addition, side effects may also occur with local use, for example, local corticosteroids may cause atrophy or systemic uptake. (108) Local injections of corticosteroids and methotrexate can also be performed but are often painful and time-consuming and may cause atrophy and transient paresthesia. (108) Conventional oral systemic therapies such as cyclosporine, methotrexate, acitretin and leflunomide show efficacy, but these are thought to be misplaced without skin involvement. (108)

As shown in the results, new biologicals used in therapy against psoriasis, such as secukinumab, ixekizumab, brodalumab, bimekizumab, guselkumab, tildrakizumab,

Risankizumab and ustekinumab have shown efficacy against nail psoriasis. There is not enough information and comparability-studies yet, but it has been shown in some head-to-head studies that some biologics or even some groups of biologics have led to better results in the therapy of nail psoriasis than others.

TRANSFIGURE

The TRANSFIGURE trail compared the efficacy of secukinumab to placebo in patients with nail psoriasis. (110) In this double-blind, randomized, placebo-controlled, parallel-group phase 3b study, 198 patients were randomly assigned to receive secukinumab 300mg, secukinumab 150mg, or placebo. (110) After week 16, patients from the placebo group were rerandomized to secukinumab 300mg or secukinumab 150mg for up to 132 weeks. (110) The mean percent NAPSI changes from baseline were 45.6% for secukinumab 300 mg, 39.6% for secukinumab 150 mg and 10.8% for placebo at 16 weeks, both values showed significant improvement compared to placebo. (110) After 32 weeks, there was a mean NAPSI improvement of 62.6% in the 300 mg group and 59.9% in the 150 mg group. (110) The reduction from baseline was maintained up to 132 weeks, with a mean NAPSI improvement of 73.3% and 63.6% in the 300mg group and the 150mg group of secukinumab, respectively. (110) At all points in time, there was a higher percent reduction with secukinumab 300mg than with secukinumab 150mg. (110) Over time, the percentage of patients achieving a NAPSI of 0-2 also increased. (110) Overall, there was a clinically significant improvement in nail psoriasis with secukinumab, which also lasted for up to 2.5 years. (110)

UNCOVER-3

A subgroup analysis of the UNCOVER-3 study focused on the improvement of psoriasis of the fingernails in patients with moderate to severe psoriasis. (111) Of the 1346 participants in the UNCOVER-3 study, only those who had psoriasis of the fingernails at baseline were included in the subgroup analysis. (111) This would be 116 (60.1%) from the placebo group, 236 (61.8%) from the etanercept group, 228 (59.1%) from the ixekizumab Q4W group, and 229 (59.5%) from the ixekizumab Q2W group. (111)

The mean percent NAPSI improvement at week 12 was significantly higher for ixekizumab Q4W (36.7%) and Q2W (35.2%) compared with placebo (-34.3%). (111) In comparison with etanercept (20.0%) only ixekizumab Q4W was significantly better at week 12. (111) At week 60, the median percent NAPSI improvement was 81.8% in the ixekizumab Q4W-Q4W group and 83.6% in the ixekizumab Q2W-Q4W group. (111) Those participants who received placebo or etanercept at baseline and then switched to ixekizumab Q4W showed comparable improvements at week 60. (111) In addition, significantly more patients achieved a NAPSI score of 0 at week 12 in the ixekizumab Q4W group (19.7%) and ixekizumab Q2W group (17.5%) compared with the placebo group (4.3%). (111)

IXORA-S

Post-hoc data from the IXORA-S head-to-head study comparing ixekizumab and ustekinumab demonstrate the different efficacy of the two drugs in nail psoriasis. (112) In the study, 136 patients received ixekizumab and 166 patients received ustekinumab for 52 weeks. (112) 84 (61.8%) patients in the ixekizumab group and 105 (63.3%) patients in the ustekinumab group had nail psoriasis at baseline. (112) Of these, 54 (64.3%) and 63 (60.0%) had significant nail psoriasis, respectively. (112) In both groups, there was improvement with therapy. (112) However, significantly more patients treated with ixekizumab had achieved a NAPSI score of 0 compared to those patients who received ustekinumab. (112) This could be observed as early as week 16 (ixekizumab versus ustekinumab 31.0% vs. 16.2%) and this significant difference persisted through week 52 (61.9% vs. 28.6%). (112)

SPIRIT-P1

The SPIRIT-P1 study compared ixekizumab with adalimumab and placebo. (113) 298 of the 417 participants had nail psoriasis at baseline. (113) At week 24, there was a significant mean improvement in NAPSI score from baseline in the ixekizumab Q4W (-14.0), ixekizumab Q2W (-15.5), and adalimumab (-10.7) groups compared with the placebo group (-2.4). (113) In addition, complete resolution of nail psoriasis (NAPSI=0) also occurred in significantly more participants at week

24 in the ixekizumab Q2W (36.5%) and adalimumab (39.4%) groups compared with the placebo group (18.9%).(113)

IXORA-R

The head-to-head IXORA-R study compared ixekizumab with guselkumab. Moderate-to-severe nail psoriasis (PGA-F score ≥ 3) was present at baseline in 83 of 520 (16%) in the ixekizumab group and 59 of 507 (12%) in the guselkumab group. (92) Of these patients, significantly more achieved minimal nail psoriasis or even a PGA-F score of 0 at week 24 with ixekizumab compared with guselkumab (52% vs. 31%).(92)

In another head-to-head study, ixekizumab was compared with adalimumab in 368 nail psoriasis patients. (114) After 24 weeks, significantly more participants in the ixekizumab group had achieved a higher mean change in NAPSI from baseline (-15.89 in the ixekizumab group vs. -12.53 in the adalimumab group). (114)

After 52 weeks, this significant difference was still present (-17.78 vs. -15.08) A NAPSI score of 0 was achieved with similar frequency at week 24 as well as week 52 in both groups. (115)

AMAGINE-2 and AMAGINE-3

In the AMAGINE-2 and AMAGINE-3 trials the change in NAPSI in patients with nail psoriasis treated with brodalumab or ustekinumab was under investigation. (116) Brodalumab achieved significantly lower median NAPSI rates than ustekinumab from weeks 12 to 36, and at week 52 this value was numerically lower for brodalumab. (116) In both the brodalumab 210mg Q2W group and ustekinumab group, the percentage of participants who achieved a NAPSI score of 0 increased from week 12 to 52. (116) Patients treated with brodalumab were significantly more likely to achieve a NAPSI score of 0 at weeks 12 (7.9% vs. 2.2%), 36 (54.2% vs. 33.7%), and 52 (63.8% vs. 39.1%) than those receiving ustekinumab. (116)

VOYAGE-1 and VOYAGE-2

928 (50.7%) patients from the VOYAGE-1 and VOYAGE-2 studies were included in an analysis on nail psoriasis. (55) An f-PGA score of 0 or 1 was achieved by

significantly more patients in the guselkumab group (46.7%) at week 16 than in the placebo group (15.2%). (55) In addition, significantly more participants treated with guselkumab also achieved an f-PGA score of 0 compared with placebo (12.4% vs. 3.8%). (55) At week 24, comparable numbers of patients in the guselkumab group and the adalimumab group achieved an f-PGA score of 0 or 1 and an f-PGA score of 0. (55) The mean improvement in NAPSI at week 16 was significantly higher in the guselkumab group than in patients treated with placebo (37.5% vs. 0.7%). (55) A NAPSI of 0 was also achieved significantly more often at week 16 (16.0% vs. 5.4%). (55) At week 24, comparable numbers of patients in the gusalkumab group and the adalimumab group achieved a NAPSI score of 0 or 1 and a NAPSI score of 0. (55)

Further evidence for the efficacy of guselkumab in nail psoriasis comes from a study of 192 patients comparing guselkumab to placebo. (80) In this study a significantly greater improvement in mean NAPSI score in the 50mg group and in the 100mg group with guselkumab compared to placebo was observed . (80) At week 16 for the guselkumab 50 mg and 100 mg groups -1.2 and -1.5 was observed, compared with −0.2 in patients receiving placebo. (80) The improvement in NAPSI was persistent through week 52, both in patients who received guselkumb from baseline and the placebo crossover patients. (80)

Tildrakizumab

At the moment no data from clinical trials concerning the efficacy of tildrakizumab in nail psoriasis however in case reports tildrakizumab has led to improvement of nail psoriasis in 3 cases. (117) (118)

Risankizumab

In a study comparing risankizumab to ustekinumab, with a specific regard to nail psoriasis, the mean reduction in NAPSI score in the risankizumab 90mg and risankizumab 180mg groups was approximately 40% at week 12. (119) In the ustekinumab group, there was a mean 20% increase in NAPSI at week 12. (119) At week 48, there was a mean decrease of 61% and 73% in the risankizumab 90mg and risankizumab 180mg groups, respectively whereas the decrease in the

ustekinumab group a mean decrease by 18% was noted. (119)

KEEPsAKE-1

KEEPsAKE-1 described the effect of risankizumab in patients with PsA and fingernail psoriasis, following an inadequate response or intolerance of synthetic disease-modifying antirheumatic drugs compared with placebo. (120) An f-PGA score of 0 or 1 was achieved by significantly more patients treated with risankizumab at week 24, 38%, compared with 18% for placebo. (120) After 52 weeks, this value was achieved by 56% in the risankizumab group and by 45% of patients who switched from placebo to risankizumab. (120) After 24 weeks, 23.6% of risankizumab-treated patients achieved an f-PGA of 0 and 17.2% in the placebo then riankizumab group. (120) At 52 weeks, 41.3% achieved an f-PGA of 0 with riankizumab and 36.4% with placebo then risankizumab. (120)

PHOENIX 1

Part of the PHOENIX 1 study investigated whether there is improvement in nail psoriasis with ustekinumab. (121) 545 of the 766 patients had nail psoriasis. (121) At week 12, there was a significant percent improvement in NAPSI scores in the 45mg and 90mg ustekinumab groups compared to placebo (26.7 and % 24.9% vs. 11.8%). (121) At week 24, the percent improvement in NAPSI score from baseline improved to 46.5% (45 mg) and 48.7% (90 mg). (121)

3.7 Biologics in scalp psoriasis

Involvement of the scalp is very common in patients with psoriasis, with up to 80% of those affected also suffering from scalp involvement. (122) It has been shown that appropriate therapy is particularly important because up to 97% of patients report that scalp involvement affects them in their daily lives. (123) Symptoms suffered by patients include pain, itching, bleeding, embarrassment and even clothing choices may be affected. (124) Itching is one of the most bothering symptoms. (125) Women and younger patients are more likely to suffer from a reduced quality of life when the scalp is involved. (124) A further complication is hair loss. (126) This is usually reversible with treatment, but may also result in

scarring alopecia with chronic, relapsing episodes.(126) Vitamin-D analogues and corticosteroids are common topical treatment options for patients suffering from scalp psoriasis. (127) A combination therapy of vitamin D and corticosteroid has proven to be particularly effective. (128) The problem, however, is that because of the hair, it can be difficult for many to apply, and this treatment is also considered cosmetically unacceptable. (127) This could have an impact on the success of the therapy and adherence. (127) IL-17, IL-23 and IL-12/23 inhibitors have been shown to be highly effective against scalp psoriasis. The results also indicated that some inhibitors may be more effective than others.

A phase 3b study looked at the efficacy of secukinumab in scalp psoriasis. (129) 102 patients participated in the study and received either secukinumab 300mg or placebo. (129) After 12 weeks, significantly more patients receiving secukinumab achieved a PSSI 90 than those receiving placebo (52.9% vs. 2.0%). (129) At week 12, significantly more patients on secukinumab also achieved a PSSI 100 (35.3% vs. 0%). (129) At week 24, 58.8% of patients on secukinumab achieved a PSSI 90 and 47.1% achieved a PSSI 100. (129)

The UNCOVER-1, UNCOVER-2 and UNCOVER-3 studies investigated, among other things, the improvement of scalp psoriasis in patients treated with ixekizumab. (130) At week 12, significantly more patients on ixekizumab Q2W (81.7%) and ixekizumab Q4W (75.6%) achieved a PSSI90 compared to placebo (7.6%) and etanercept (55.5%). (130) At week 12, significantly more patients in the 2 ixekizumab groups also achieved a PASI 100 than placebo or etanercept (Q2W 74.6%; Q4W 68.9%; placebo 6.7%; etanercept 48.1%). (130) In the ixekizumab Q4W group, these results were maintained until week 60. (130)

Another phase 3 trail called IXORA-P investigated the continuous use of ixekizumab every 2 weeks. (131) Patients received continuous ixekizumab every 2 weeks or every 4 weeks or a dose adjustment Q4W/ Q2W. (131) Part of the study also focused on change of scalp psoriasis. (131) In the continuous ixekizumab Q2W group, significantly more participants achieved a PSSI of 0 after 52 weeks compared to the ixekizumab Q4W group (76.9% vs. 70.3%). (131) There was no significant difference compared to the Q4W/Q2W dose-matched group (72.6%). (131) (130)

In AMAGINE-1, the efficacy of brodalumab was compared to placebo in patients with scalp psoriasis. (116) During the 12-week induction period patients received either brodalumab 210 mg or placebo. (116) At 12 weeks, significantly more patients receiving brodalumab had achieved a PSSI 75 (89.0%) and a PSSI 100 (63.4%) compared with placebo (9.5% and 3.2%). (116) (131) (130)
Bimekizumab has also shown significant improvement of scalp psoriasis compared to placebo in the BE READY study. (76) After 16 weeks, 92% had a scalp IGA score of 0 or 1 with bimekizumab therapy and 7% in the placebo group. (76) In the BE VIVID study, significantly more participants who had a scalp IGA score of 2 or more at baseline and received bimekizumab (84%) showed a response after 16 weeks than those who received ustekinumab (71%). (100)
1512 (82.7%) patients from the VOYAGE-1 and VOYAGE-2 studies were included in the analysis on scalp psoriasis. (55) An ss-IGA score of 0 or 1 with an improvement of at least 2 levels from baseline was achieved by significantly more patients in the guselkumab group (81.8%) at week 16 than in the placebo group (12.4%). (55) At week 16, more patients in the guselkumab group (65.3%) also achieved an ss-IGA score of 0 than in the placebo group (8.4%). (55) At week 24, an IGA score of 0 or 1 was achieved by significantly more patients treated with guselkumab (85.0%) than those receiving adalimumab (68.5%). (55) An ss-IGA score of 0 was also achieved at 24 weeks by significantly more patients receiving guselkumab (69.9%) than adalimumab (56.3%). (55)
In a study of 192 patients comparing guselkumab to placebo, a significantly greater proportion of patients achieved an ss-IGA of 0 or 1 and ss-IGA of 0 in the guselkumab 50mg group (74.1% and 48.3%) and guselkumab 100mg group (82.8% and 63.8%) compared to the placebo group (10.5% and 3.5). (80)
A post-hoc analysis of the phase 3 reSURFACE1 trial focused on improvement in head and neck involvement in patients treated with tildrakizumab. (132) To determine the improvement of scalp psoriasis, PASI head component (PASIh) was used, this score includes neck, scalp and face. (132) At week 28, 21.5% of patients receiving tildrakizumab 100 mg had achieved complete clearance of psoriasis on the scalp, head and neck. (132)

In a comparative study between risankizumab and ustekinumab, improvement in scalp psoriasis was shown with both drugs. (119) At week 12, there was an average reduction in PSSI score of 90% in the risankizumab 90mg group and 94% in the risankizumab 180mg group. (119) In the ustekinumab group there was an improvement of 82%, but this was not maintained throughout the study compared to patients treated with risankizumab. (119)
However in a retrospective comparative study maintained improvement of scalp psoriasis with ustekinumab was observed. (133) After 48 weeks, ustekinumab resulted in a PSSI 75 in 97.5% of the participants and a PSSI 90 in 85.3%. (133) (132)

3.8 Biologics and Itch

It used to be that atopic dermatitis in particular was considered to be a disease with itch compared to psoriasis, and therefore itch was seen as a factor that could differentiate the two. (134) However, it has recently been confirmed that there is no significant difference between psoriasis and atopic dermatitis in terms of baseline itch. (134) A large proportion of patients even consider itching to be the most burdensome symptom next to intense skin flaking. (125) Itching occurs in almost all patients suffering from psoriasis and most of them suffer from itching daily. (135) (136) Certain factors such as heat, dry skin, sweat and stress furthermore have a negative effect on itching. (136) In patients suffering from psoriasis, both the healthy skin and those areas with psoriasis lesions are affected. (137) This can be a challenge because scratching the healthy skin can lead to new lesions due to Koebner's phenomena. (137) The therapy of itching in psoriasis has proven to be particularly difficult. (137) This is partly because the exact causes of psoriasis associated pruritus are not yet fully understood. (137) Furthermore, the PASI score is often not correlated with the severity of the itch. (136) In addition, other drugs used for itching also show that they have no effect on psoriasis-associated itching. (136) Antihistamines, for example, which are often used for itching show no long-term effect on itching associated with psoriasis. (136) Not all therapy options against psoriasis lesions show the same effectiveness against itching. (137) Topical corticosteroids and vitamin D analogs

have been shown to improve itching, and they also show efficacy against the particularly bothersome itching during the night. (137) Another group of drugs that have shown an effect are biologicals. But the lack of information about itch in psoriasis patients and the fact that it was recognized so late as an important symptom in psoriasis patients is reflected in the fact that it is not considered in enough studies of new drugs for therapy. (137) Itch in psoriasis patients significantly reduces the quality of life of patients, and therefore drugs that efficiently reduce itch in psoriasis are key. (137)

Secukinumab showed superior improvement in itch compared with placebo at week 12 in the ERASURE trial with both dosing regimens. (62) In the ERASURE and FIXTURE studies was seen, that 83% of patients treated with secukinumab described an improvement of itch of at least -2.2 points after 12 weeks (scale of 0 to 10, where 10 is the most severe itching and 0 is no itching). (138) 78.2% achieved a reduction of at least 2.2 points in the secukinumab 150 mg group and 16.9% in the placebo group. (138) In addition, the mean change from baseline to week 12 was significantly higher for secukinumab 300mg (-5.14) and secukinumab 150 mg (-4.9) compared to placebo (-0.4). (138)

In the head-to-head study CLEAR it was shown that patients treated with secukinumab had a significantly higher mean change from baseline in terms of itching at weeks 16 and 52. (96) At week 16, this was – 5.04 points in the secukinumab group and -4.60 points in the ustekinumab group. (96) At week 52, there was a reduction of 4.98 in the secukinumab group and 4.31 in the ustekinumab group. (96)

The UNCOVER-2 and the UNCOVER-3 trails compared ixekizumab, etanercept and placebo in patients with plaque psoriasis. (139) Patients were categorized into different groups based on the Itch Numeric Rating Scale (NRS). (139) Ixekizumab resulted in a reduction of 4 or more points in the itch NRS at week 12 in significantly more patients than etanercept or placebo, regardless of baseline itch severity. (139) At 12 weeks, the group with baseline itch NRS of 4-6 showed a reduction of 4 or more points in 70.0% of patients. (139) In the NRS group 7-8 this was true for 88.6% and in the NRS group 9-10 for 90.8%. (139) At week 12, there was a complete reduction in itching in 47.8% 42.5% and 31.9% of the groups

(Baseline itch NRS groups 4-6, 7-8, and 9-10). (139) During the 3-year treatment period of UNCOVER-3, ixekizumab has shown a lasting effect in terms of reduction of itching. (139)

In the IXORA-R head-to-head study, significantly more patients in the ixekizumab group achieved an itch NRS score of 0 after 4 weeks than in the guselkumab group (14% vs 5%). (91) After 12 weeks, significantly more patients treated with ixekizumab also reported a complete disappearance of itch symptoms. (91) This trend remained until week 16 (41% vs. 33%). (92) In addition, patients treated with ixekizumab spent significantly more days without pruritus 51.2 vs. 41.5 days. (92) The time at which complete disappearance of itch symptoms occurred was also significantly earlier compared to guselkumab. (92)

The IXORA-S study showed no significant differences between ixekizumab and ustekinumab at 12 weeks in terms of mean changes in itch NRS and reduction in itch NRS by more than 4 points. (93) Also at week 24, there was no significant difference between the two groups from baseline in itch NRS scores. (93) However, at week 24, significantly more patients who had an itch NRS ≥ 4 at baseline achieved a reduction of ≥ 4 points on the itch NRS who were treated with ixekizumab (85.5%) than those who became ustekinumab (72.1%). (93)

In the three phase 3 trials AMAGINE-1, AMAGINE-2, AMAGINE-3, brodalumab was compared to a placebo or ustkinumab. (140) At week 2, there was already a significant reduction in itching in patients treated with brodalumab 140mg or 210mg compared to placebo. (140) This difference was still present at week 12. (140) Also compared to ustekinumab, there was a significant improvement in itch after 2 weeks in both brodalumab groups. (140) At 8 weeks, the improvement in pruritus was comparable in the brodalumab 140mg group and ustekinumab. (140) However, the 210mg brodalumab group still resulted in significant improvement in pruritus compared to ustekinumab at week 8 and this remained true until week 52. (140)

The Phase 3 BE READY study showed significant improvement in itch at week 16 in patients treated with bimekizumab compared to placebo. (76) The head-to-head BE VIVID study also showed a significant improvement in itch at week 16 compared with ustekinumab and placebo. (100)

In the VOYAGE-1 trial, guselkumab (33.6%) resulted in an itch score of 0 in significantly more patients at week 16 than placebo (2.3%) and adalimumab (20.1%). (141) Guselkumab also resulted in an itch score of 0 in significantly more patients at weeks 24 (40.9%) and 48 (45.3%) than adalimumab (24.6% and 26.9%, respectively). (141) In addition, at weeks 16, 24, and 48, significantly more patients who had an itch score ≥ 4 at baseline also experienced a reduction in itch by ≥ 4 points in the guselkumab group than in the placebo group and adalimumab group. (141)

3.9 Psoriasis Arthritis

Psoriatic arthritis is a serious disease in which the IL-23/ IL-17 axis is known to play an important role, but in which the exact pathogenesis is not yet known. (142) To avoid irreversible joint damage and to avoid comorbidities that are more common in patients suffering from PsA such as inflammatory bowel disease, cardiovascular diseases, uveitis, depression, anxiety and fatty liver disease early diagnosis and therapy of PsA is crucial. (143) The diagnosis of psoriatic arthritis has proven to be particularly difficult, as unfortunately there is currently no validated molecular or imaging test.(144) The diagnosis is also complicated by the fact that psoriatic arthritis usually develops years after psoriasis.
(145) In addition, patients with rather mild psoriasis may also have severe musculoskeletal involvement as the activity and severity of psoriasis and PsA do not correlate in the same patient. (146) In a summary of the guidelines for the treatment of psoriatic arthritis, it can be said that the diagnosis and treatment decision should ideally be made on an interdisciplinary basis by a dermatologist and a rheumatologist. (147) In addition, non-steroidal anti-inflammatory drugs should be used to relieve symptoms in mild, non-erosive articular psoriatic arthritis and enthesitis. (147) In patients with potentially poor prognosis (polyarthritis, elevated inflammatory markers, erosive changes), conventional DMARDs should be used early to prevent progression of psoriatic arthritis. (147) If treatment with a conventional DMARD does not show sufficient efficacy, biologic therapy should be given. (147) This can be done either as monotherapy or in combination with the conventional DMARD.(147) Methotrexate is potentially advantageous among

conventional DMARDs because it also acts on psoriasis and could enable monotherapy of psoriasis and psoriatic arthritis. (148)

As already mentioned, almost up to one third of psoriasis patients also suffer from psoriatic arthritis. (14) Nevertheless, this progressive joint disease is still often underdiagnosed and undertreated. (149) PsA has a variable course but leads to impaired physical function and reduced quality of life in many patients. (149) Therefore, an adequate and efficient therapy is key. The efficacy of IL-17, IL-23, and IL-12/23 inhibitors in phase 3 studies in psoriatic arthritis are listed in table 4. The ACR 20 and 50 results in these studies indicate that the IL-17, IL-12/23 and IL-23 inhibitors can be considered efficient treatment options for PsA patients. In comparison with the well-established anti TNF-alpha inhibitors it could be shown that ixekizumab was more efficient than adalimumab. (114) In this study a combined primary endpoint PASI 100 and ACR50 was used, thus proving the superiority of ixekizumab versus adalimumab. (114) Using a combined endpoint responds well to the need and treatment goals of patients with PsA, as in real life the patients want to be equally free of skin and joint symptoms. The safety profile in the PsA studies was comparable to the studies performed in psoriasis patients. (113) (150) (151) (152) (153) (154) (155) (156) (157) (158) There are currently no published phase 3 studies for tildrakizumab in psoriatic arthritis, but a phase 2 study shows that tildrakizumab results in an improvement in PsA. (159) Patients were randomized to 5 groups through week 24: tildrakizumab 200 mg Q4W; tildrakizumab 200, 100, or 20 mg Q12W; or placebo Q4W. (159) At week 24, between 71.4% and 79.5% of participants treated with tildrakizumab achieved ACR20, which is significantly higher in all groups than in the placebo group with 50.6%. (159) Also, in terms of reaching ACR50 at week 24, significantly more patients in all tildrakizumab groups had reached this value compared with placebo 39.7%-52.6% vs. 24.1%. (159) ACR 70 at week 24 was achieved by significantly more patients in the tildrakizumab 200mg Q4W group (28.2%) and in the tildrakizumab 200mg Q12W group (29.1%) compared to placebo (10.1%). (159) The tildrakizumab 100mg Q12W group and the tildrakizumab 20mg Q12W group did not achieve ACR70 significantly more often than placebo. (159)

For bimekizumab, there is currently also only one phase 2 study in psoriatic arthritis published, which shows improvement in PsA patients treated with bimekizumab. (160) Participants were divided into 5 groups that received subcutaneous injections every 4 weeks for 12 weeks: bimekizumab 16mg; bimekizumab 160mg; a loading dose with bimekizumab 320mg and then bimekizumab 160mg; bimekizumab 320mg or placebo. (160) Patients in the bimekizumab 16mg and placebo groups were randomized to bimekizumab 160mg or 320mg after the 12 weeks. (160) After 12 weeks, participants in all groups treated with bimekizumab were significantly more likely to achieve ACR20 than those in the placebo group (bimekizumab 16mg (54%); bimekizumab 160mg (73%); a loading dose with bimekizumab 320mg and then bimekizumab 160mg (61%); bimekizumab 320mg (51%) vs. placebo (19%)). (160) An ACR50 was achieved by significantly more participants in the bimekizumab 16mg group (27%), in the bimekizumab 160mg group (41%), and in the loading dose group (46%) than in the placebo group (7%). (160) An ACR70 was achieved at 12 weeks only in significantly more patients compared to placebo who received a loading dose with bimekizumab 320mg and then bimekizumab 160mg (32% vs. 5%). (160)

Table 4 Treatment efficacy of IL-17 and IL-23 inhibitors in patients with psoriasis arthritis

Study	**Study drug & dosage**	**Time point (weeks)**	**ACR 20**	**ACR 50**	**ACR 70**
DISCOVER-1 (150)	Guselkumab 100mg Q4W Guselkumab 100mg Q8W Placebo	24	59% 52% 22%	36% 30% 9%	20% 12% 6%
DISCOVER-2 (151)	Guselkumab 100mg Q4W Guselkumab 100mg Q8W Placebo	24	64% 64% 33%	33% 31% 14%	13% 19% 4%
KEEPsAKE 1 (152)	Risankizumab 150mg Placebo	24	57.3% 33.5%	33.4% 11.3%	15.3% 4.7%
KEEPsAKE 2 (153)	Risankizumab 150mg Placebo	24	51.3% 26.5%	26.3% 9.3%	12.0% 5.9%
AMVISION-1 (154)	Brodalumab 140mg Q2W Brodulamab 210mg Q2W	24	52.2% 59.7%	26.8% 37.5%	11.2% 20.0%

	Placebo		18.9%	8.0%	2.5%
AMVISION-2 (154)	Brodalumab 140mg Q2W Brodulamab 210mg Q2W Placebo	24	49.5% 48.8% 27.8%	31.2% 35.4% 11.9%	15.7% 19.2% 6.1%
SPIRIT-P1 (113)	Ixekizumab 80mg Q2W Ixekizumab 80mg Q4W Placebo	24	62.1% 57.9% 30.2%	46.6% 40.2% 15.1%	34.0% 23.4% 5.7%
SPIRIT-P2 (155)	Ixekizumab 80mg Q2W Ixekizumab 80mg Q4W Placebo	24	48% 53% 19%	33% 35% 5%	12% 22% 0%
FUTURE 2 (156)	Secukinumab 300mg Secukinumab 150mg Secukinumab 75mg Placebo	24	54% 51% 29% 15%	35% 35% 18% 7%	20% 21% 6% 1%

PSUMMIT1 (157)	Ustekinumab 45mg Ustekinumab 90mg Placebo	24	42.4% 49.5% 22.8%	24.9% 27.9% 8.7%	12.2% 14.2% 2.4%
PSUMMIT 2 (158)	Ustekinumab 45mg Ustekinumab 90mg Placebo	24	43.7% 43.8% 20.2%	17.5% 22.9% 6.7%	6.8% 8.6% 2.9%

3.10 Palmoplantar plaque psoriasis and palmoplantar pustulosis

Palmoplantar plaque psoriasis and palmoplantar pustulosis are two conditions displaying similar clinicopathologic features and affecting the palms and soles. (161) Despite the small involvement of only about 5% of the body surface, palmoplantar psoriasis leads to a severe physical impairment as well as to massive impairment concerning the quality of life o affected patients. (162) Both palmoplantar psoriasis and palmoplantar pustulosis are difficult to treat forms of psoriasis. (163) Compared to chronic plaque-type psoriasis, both diseases show a poorer response to various therapies, such as local therapy, PUVA therapy, but also methotrexate and biologicals. (163) One of the reasons for this is the thicker stratum corneum of the skin and feet. (163) There are also differences in pathophysiology between palmoplantar forms and chronic plaque psoriasis, as there is a greater increase in IL-17 compared with IL-12/23. (164) (165)
Secukinumab has shown efficacy in patients with palmoplantar psoriasis in a randomized, double-blind, placebo-controlled trial called GESTURE. (166) Already after 16 weeks, patients who received secukinumab had significantly higher improvements than those who received placebo. (166) After 2.5 years, more than half of the patients still had total clearance with secukinumab. (166) In addition, a significant improvement in quality of life was described. (166) A recently published study by Galluzzo et al. has shown that also in a real life setting secukinumab shows good efficacy over 2 years in patients with palmoplantar psoriasis. (167)
Regarding palmoplantar pustular psoriasis, a phase 3 study showed that there was no significant improvement after 16 weeks compared to placebo. (168) In the study the authors discussed that possibly different entities between palmoplantar pustular psoriasis and plaque psoriasis lead to a different response of drugs like secukinumab. (168) However, it is also important to note that after 52 weeks, 41% of patients experienced a 75% reduction in the Palmoplantar Psoriasis Area and Severity Index (PPPASI) and 43% achieved a DLQI of 0 or 1 with secukinumab 300mg. (168) This suggests that affected individuals may still benefit from this treatment. (168)
Ixekizumab has also shown significantly greater efficacy in patients with palmoplantar psoriasis compared to placebo and etanercept. (169) By week 60,

more than half of the patients achieved a PPASI of 100 with ixekizumab and had no more lesions on palms and soles. (169)
The IL-17 inhibitor brodalumab was used in 4 patients with palmoplantar pustular psoriasis (PPP). (170) In three of the four patients brodalumab showed no effect and only a partial response in the fourth patient. (170) It is important to note that three patients already had insufficient therapy with secukinumab and all received several systemic drugs previously but with a therapy-refractory course. (170) Pinter et al. therefore suggest that a switch to another group is reasonable in PPP patients who have previously responded inadequately to IL-17 inhibitors. (170)
The data for ustekinumab in palmoplantar pustulosis are inconsistent. Bissonnette et al. have described that there has been unsatisfactory efficacy in patients with palmoplantar pustulosis treated with ustekinumab. (165) Hegazy et al. observed better efficacy in patients with palmoplantar pustulosis treated with ustekinumab. (171) After 16 weeks, 5 out of 9 patients had no lesions. (171) Regarding palmoplantar psoriasis, ustekinumab showed good efficacy. (172)
The IL-23 inhibitor guselkumab has shown good efficacy in palmoplantar pustulosis in 3 studies. (173) (174) (175) In the randomized clinical trial by Terui et al, at week 16 a significantly greater reduction in mean PPPASI total score from baseline was observed in the guselkumab group (-10.2 [8.07]) compared with placebo group (-6.4 [7.55]). (173) In the phase 3 study by Okubo et al, the median improvement in the guselkumab groups by week 84 from baseline was ~79% in PPPASI total scores. (174)
For tildrakizumab and risakizumab therer are only two case reports available in the literature, both have shown to be effective in palmoplantar pustulosis. (176) (177)

3.11 IL-17, IL-12/23 and IL-23 inhibitors in pediatric psoriasis

Biologics have dramatically changed the treatment of psoriasis in adults in recent years, but their use in children is not as prevalent as in adults. (178)
The S2k guidelines refer to ustekinumab being approved for the treatment of plaque psoriasis for patients 12 years of age and older. (179) In the CADMUS-Jr study, ustekinumab also demonstrated good efficacy in children aged ≥ 6 to < 12 years; beyond that, no new safety concerns were identified. (180) In this study,

84% of patients achieved a PASI 75 and 64% achieved a PASI 90 at week 12. (180) Among IL-17 inhibitors, ixekizumab was the first biologic approved for children through the IXORA-PEDS study. (181) At week 12, PASI75 was achieved in 89% of patients, and this result was maintained for 48 weeks. (181) PASI90 was achieved by 78% and PASI100 by 50% at week 12. (181)
In a recently published study, secukinumab also showed good efficacy in children. (182) Patients were randomly divided into two groups, receiving high and low doses of secukinumab according to body weight and disease severity. (182) After 12 weeks, 69.05% of patients in the low-dose group achieved a PASI90 and 59.52 achieved a PASI100, and 76.19% and 54.76% in the high-dose group. (182) By week 24, all scores continued to improve. (182) So far no data for brodalumab, bimekizumab, guselkumab, risankizumab and tildrakizumab in the treatment of pediatric psoriasis have been published (183)

3.12 Biologicals during pregnancy

Warren et al. used the Novartis global safety database to collect information on the course of pregnancies in which secukinumab was used. (184) Of the 292 pregnancies, 238 were maternal and 54 were paternal exposure cases with secukinuamb. (184) A large proportion of patients discontinued secukinumab therapy in the first trimester. (184) Only in 64.2% of the cases the outcome of the pregnancy was known. (184) Of these, 47.7% gave birth to normal full-time babies. (184) Similar to the general population, a spontaneous abortion occurred in 19.6% of the cases. (184) Treatment was not discontinued in 18 mothers. (184) Three of them proceeded with treatment during pregnancy or interrupted the treatment in the third trimester. (184) Of these 18 cases, nine were not followed up. (184) Four patients terminated the pregnancy intentionally, further there were three miscarriages, one child was born normally, and one pregnancy was ongoing. (184) The study indicates that the use of secukinumab does not affect the risk of miscarriage or malformations. (184) However, this information should be used with caution, as much of the data is not complete. (184)
Egeberg et al. searched the Eli Lilly Global Safety Database for cases with pregnancy’s who had maternal or paternal exposure to ixekizumab. (185) Of 193

cases found, 51.3% were cases with maternal exposure. (185) In clinical trials there were no congenital malformations as a result of maternal exposure. (185) In the post-marketing setting, however, there was one event, which was not causally related to ixekizumab therapy of congenital malformations. (185)
Haycraft et al. collected clinical data on tildrakizumab use during pregnancy. (186) In the nine clinical trials found, 14 pregnancies were reported. (186) After confirmation of pregnancy, tildrakizumab therapy was discontinued in all cases. (186) Of the 14 cases, eight live births occurred, with no apparent congenital anomalies. (186) There were four elective abortions, and two spontaneous abortions which is 14%, and that number is similar to the general population. (186)
A review by Gisbert et al. addressed the safety of ustekinumab during pregnancy. (187) The review of 11 studies included 21 patients with a total of 27 pregnancies. (187) The majority of patients were treated with ustekinumab for psoariasis, and 4 of the patients were treated for IBD. (187) Most studies reported uneventful pregnancies. (187) Likewise, the European League Against Rheumatism suggests that there is no increased rate of miscarriages and/or congenital malformations with ustekinumab. (188)

3.13 Quality of life and treatment with IL-17, IL-12/23 and IL-23 inhibitors

An efficient therapy for psoriasis is of great importance for the patients, as the improvement of the skin lesions also leads to an improvement of the quality of life. (91) A study from the USA showed that patients with moderate to severe plaque psoriasis want a fast response but also a long-term effect. (189) At least 90% of the participants consider clear skin for 2-3 years to be highly important. (189) However, many patients also expect a 50% improvement within 2 weeks and clear skin after about 4 weeks. (189) With the new treatment option of biologics, these desires could be achieved more often than before, as indicated, by the fact that PASI 90 and even PASI 100 can now be considered a new therapeutic target. (58)
However, a study by Wolf et al. also showed that there is still a need for improvement in the implementation of treatment goals. (190) The quality of life

and treatment goals of Austrian psoriasis patients were evaluated in a cross sectional study using a questionnaire. (190) A total of 1184 patients took part. (190) The majority of patients had a mild to moderate course. (190) Joint involvement was present in 31.7%, scalp involvement in 68.6% and nail involvement in 53.0% of the cases. (190) Systemic therapy was used in 39.7%. (190) Of these, 38% received methotrexate and 38% biologics. (190) In terms of quality of life, 48.9% reported psychological distress as moderate, somewhat severe or very severe in the last 12 months. (190) Many report a worsening due to stress. (190) In addition, many feel restricted by the disease, 38.6% avoid leisure activities in which the disease is visible and 37.7% experienced a reduction in self-esteem. (190) With regard to the burden of itching during the last 4 weeks, 82.2% of those affected reported suffering from pruritus of varying severity. (190) It was also found that many patients were not satisfied with the treatment goals. (190) Thus, 93% stated that the disappearance of all lesions was very important for them, but the therapy only achieved this goal in 47% of the cases. (190) 22.4% of the patients rated the treatment over the last years as "very good", 28.7% as "good", 30.4% as "medium", 6.19% as "insufficient" and 12.3% as "poor". (190) The vast majority of patients experience a reduction in their quality of life as a result of the disease. (190) Due to the symptoms of the disease, the external appearance but also everyday activities and partnership. (190) In addition, there are also the circumstances of a necessary therapy such as side effects, time consumption and confidence in the therapy that have to be taken into consideration. (190) These complaints lead to subjective treatment goals. (190) The study showed that 25 defined treatment goals could not be achieved by the current therapeutic measures to the extent desired by the patients. (190) Biologics achieved significantly higher patient satisfaction and could therefore be an important tool to achieve the desired goals. (190) With the IL-17, IL-12/23 and IL-23 inhibitors a significant improvement in the quality of life in psoriasis patients has been achieved. (62) (63) (64) (70) (74) (75) (78) (79) (80) (82) (84) (85) (86) (87) (88) (89) (76)

4 Discussion

Based on the pivotal phase 3 studies, as shown in the results above, it can be observed that all biologics have good efficacy in plaque psoriasis. However, it also showed that there are differences between in the various drugs.

As mentioned earlier, in the ECLIPSE study, between week 3 and week 12, PASI-90 values were higher in patients treated with the IL-17A inhibitor secukinumab than in patients treated with the IL-23p19 inhibitor guselkumab. (90) PASI-90 response rates between weeks 16 and 20 were then comparable in both groups. (90) However, guselkumab showed significantly higher PASI-90 response rates at week 48. (90) In IXORA-R, a faster response with the IL-17A inhibitor ixekizumab in terms of PASI 50 was already seen from week 1 compared to guselkumab. (92) At week 2, significantly more patients achieved PASI 75 and at week 4, significantly more patients achieved PASI 90 and PASI 100 in the ixekizumab group. (92) However, at week 24, ixekizumab was not inferior to guselkumab in terms of PASI 90. (92) Both studies showed higher PASI values at earlier time points (weeks 2-12) in patients treated with IL-17 inhibitors compared to guselkumab. (90) (92) However, the ECLIPSE study in particular showed that the IL-23 inhibitors lead to a better response in long term treatment (up to 48 weeks). (90) The IMMerge study showed similar results: at week 4, secukinumab achieved significantly higher PASI 90 scores compared to the IL-23p19 inhibitor risankizumab. (98) At week 16, risankizumab was noninferior to secukinumab in terms of PASI 90 response. (98) However, at week 52, PASI 75, PASI 90 and PASI 100 response rates were significantly higher in the risankizumab group. (98) In the CLARITY and CLEAR trials, secukinumab performed significantly better than the IL-12/23 inhibitor ustekinumab. (96) (97) In the IXORA-S trial, the IL-17A inhibitor ixekizumab also performed significantly better than the IL-23p40 inhibitor ustekinumab in PASI 75, PASI 90, PASI 100, sPGA 0, sPGA (0/1) and DLQI (0/1) at week 12. (91) This difference remained until week 52. (92) This was also the case in the BE VIVID trial, which compared the IL-17A and IL-17F inhibitor bimekizumab with ustekinumab. (100) From week 4, the bimekizumab group achieved significantly higher PASI 75 response rates and also significantly higher PASI 90, PASI 100 and DLQI 0/1 scores by week 52. (100) These studies showed better efficacy of IL-17

inhibitors compared to the IL-12/23 inhibitor ustekinumab. (91) (92) (96) (97) (100) In the UltIMMa study, the IL12/23p40 inhibitor ustekinumab was compared to the IL-23p19 inhibitor risankizumab. (84) From week 16 to 52, risankizumab achieved significantly better 75, PASI 90, PASI 100, sPGA 0, sPGA 0/1 and DLQI 0 or 1 scores than ustekinumab. (84) NAVIGATE has also showed higher efficacy of guselkumab compared to ustekinumab. (99) This results indicate that inhibiting IL-23p19 is superior to the inhibition of IL-12/23p40 in the treatment of psoriasis. (84) (99)

In the ECLIPSE study, different theories for the long-term higher efficacy of the IL-23 inhibitor are discussed. (90) On the one hand, the different doses of the drugs could be a cause. (90) Secukinumab was administered more often than guselkumab at the beginning of the study. (90) The higher concentration at the beginning could be a cause for the rapid response, and the greater intervals later on could have reduced the concentration and effect. (90) On the other hand, the inhibition of IL-23p19 could lead to a reduction in TH17 cells, as these belong to the IL-23-dependent cells. (90) This could lead to an inhibition of the formation of inflammatory cytokines. (90) In addition, one other reason for the different response could be that IL-17A and IL-17F are cytokines that are downstream of IL-23. (90) Thus, a blockade at a later point in the pathogenesis of psoriasis could lead to a faster response, but an earlier intervention to a longer duration of action. (90) The NAVIGATE study also showed successful treatment with guselkumab in patients who had an inadequate response to ustekinumab. (99) Again, the cause of the superiority is not clear, but the central role of IL-23 in the pathogenesis of psoriasis is thought to be one of the causes. (99) Other possible causes could be a more potent blockade of IL-23 with guselkumab, more frequent and higher doses of guselkumab. (99) In the UltIMMA study, variation in efficacy between 12-week dosing intervals was seen. (84) This was particularly noted in the ustekinumab group. (84) In the risankizumab group, efficacy was better maintained between doses. (84) This shows that a dosing interval of 12 weeks is appropriate for risankizumab. (84)

In summary, IL-17 inhibitors lead to a faster response. IL-23 inhibitors, on the other hand, show better efficacy in the long-term treatment. Both IL-17 inhibitors and IL-

23 inhibitors showed superiority over the IL-12 and IL-23 inhibitor ustekinumab already at the beginning of the therapy, which was also maintained over the entire period of the studies.
Sawyer et al. described in their network meta-analysis that secukinumab, ixekizumab, brodalumab, guselkumab, and risankizumab were superior to tildrakizumab and ustekinumab with respect to plaque psoriasis. (191) Brodalumab, ixekizumab, and risankizumab also showed greater efficacy than secukinumab but were not significantly more effective than guselkumab. Brodalumab, ixekizumab, guselkumab, and risankizumab showed the greatest benefit in terms of PASI 90 and PASI 100. (191)
In a meta-analysis from China, a similar outcome was observed. (192) The main criterion of the study was the achievement of PASI 90. (192) It was noted in this study that biologics are significantly more effective than placebo and that ixekizumab and bimekizumab as well as risankizumab were found to be most effective drugs. (192) Ixekizumab was found to be superior to all others in terms of efficacy. (192) However, in terms of safety the IL-23 inhibitors tildrakizumab, guselkumab, and risankizumab were found to be more favorable than the Il-17 inhibitors. (192)
In terms of drug survival, a recent multi-country and multi-center study assessed and compared the drug survival of the latest biologics used in the treatment of psoriasis. (193) The drugs evaluated in this study were ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab and risankizumab. (193) Drug survival at 12 months was higher with IL-23 inhibitors, especially in patients receiving risankizumab (96.4%) and guselkumab (93%). (193) Secukinumab, on the other hand, had the lowest drug survival at 85.5%. (193) This course remained the same even after 18 months. (193) The drug survival rate after 24 months could not be determined for risankizumab, as the drug has only been in use for a short time. (193) Therefore, guselkumab had the highest drug survival rate after 24 months, while brodalumab had the lowest. (193) Ineffectiveness was one of the most common reasons for discontinuation, especially in patients treated with ustekinumab and secukinumab. (193) On the other hand, the fewest patients who discontinued therapy due to ineffectiveness had been treated with guselkumab

and risankizumab. (193) The reasons for this are not yet completely clear. A possible reason for the lower drug survival of IL-17 inhibitors discussed in the study is that IL-17 inhibitors are approved for PsA therapy and are often selected for patients with a severe course. (193) However, it might also play a role that IL-23 inhibitors have be shown to be more effective in the long term treatment of psoriasis due to disease modification. (90) (98) (194) Another reason for the better drug survival of the IL-23 inhibitors guselkumab and risankizumab could be that they had the lowest infection rate, while secukinumab and ustekinumab had the highest. (193) The study also showed that female gender, higher BMI and earlier exposure to biologics lead to lower drug survival rates. (193)

In a similar study from Austria related to drug survival including adalimumab, etanercept, ustekinumab, secukinumab and and ixekizumab, ixekizumab was shown to result in the highest long-term improvement in PASI, followed by ustekinumab and secukinumab. (195)

Drug survival rates up to 48 months were highest in patients treated with ustekinumab. (195) However, this superiority of ustekinumab was no longer present when adjusted for biologics naivety. (195) Then ixekizumab, secukinumab and ustekinumab showed similar drug survival. (195) The risk of treatment discontinuation was higher in patients with biologic naivety and female gender, but not in patients suffering from psoriatic arthritis (195) No remission, partial remission, loss of efficacy and side- effects were the main reasons for drug discontinuation. (195)

It is also important to mention that the results from these phase 3 studies are often not applicable in real-world patients. (196) It has been shown that the effectiveness of biologicals in patients who would be not eligible for clinical trials is often much lower. (196)

Loss of efficacy and side effects (e.g. infections) are the most common reasons for switching biologics in psoriasis patients. (197) As the TNF-α inhibitors are available for quite a long time, a plethora of data exists concerning switching in this drug class. As it has been shown that switching within the anti TNF inhibitors shows less efficacy after the second or third anti-TNF-alpha inhibitor, switching to IL-17, IL-12/23 inhibitors or IL-23 inhibitors is reasonable. (198) This has also been

shown in some studies. (197) (198) Patients in which etanercept therapy or treatment with a monoclonal anti-TNF Inhibitor (e.g. adalimumab or golimumab) is no longer effective may did benefit from switching to IL-12/23 inhibitors, IL-23 and IL-17 inhibitors. (197) (198) At the moment information on switching between the newer groups of biologics (e.g. IL-17 and IL-23 inhibitors) is scarce. (198) In the NAVIGATE study patients not achieving PASI 75 at week 16 showed significantly better PASI reduction when switched to guselkumab compared to patients undergoing further treatment with ustekinumab. (99) It has also been shown that has been shown that switching from ustekinumab to brodalumab leads to favorable results. (197) Also, patients who did not respond adequately to IL-17 inhibitors can still switch to an older biologic such as TNF- α inhibitor but also ustekinumab. (197) The study by Tsai et al. also suggests that in case of loss of efficacy of TNF-α inhibitor and IL-17 inhibitor, there is still a possibility that other biologics from the same group could still be effective. (197) Switching within the IL-17 inhibitor group has also been proven to be effective. (199) However, if there is a switch due to side effects, switching to a different drug class might be recommended. (197) Tsai et al. also highlighted that it is important to perform a washout period when switching if the switch is due to side effects. (197) In contrast, this is not necessary if the switch is due to a loss of efficacy. (197) In addition, it was found that after switching, due to failure of one drug, a poorer response was observed upon switching compared with patients in which no failure was observed. (197)

Furthermore, the efficacy of the new IL-17 and IL-12/23 drugs is of great importance as 20-40% of psoriasis patients also suffer from PsA. (15) Among the biologics, TNF-α inhibitors continue to be preferred by many rheumatologists. (148) However, biologics with other mechanisms of action (IL-17, IL-23, etc.) have been shown to have similar efficacy in PsA (see table 4), but especially the IL-17 and IL-23 inhibitors have been shown to have a better efficacy in psoriasis. (148) Up to now no head-to-head studies comparing the efficacy and safety of IL-17 and IL-23 inhibitors have been performed. Psoriatic arthritis is a very heterogeneous disease, which manifests itself with different clinical phenomena and therefore the treatment is particularly difficult. (200) As with other spondyloarthropathies,

management might be problematic because uveitis and inflammatory bowel disease often coexist. (200) Due to the complex clinical picture, biologics may not be effective enough, may lose their effectiveness over time, or may cause side effects. (150) Often, the therapy must then be adapted by switching to another biologic. (150) The IL-23 inhibitor guselkumab has shown efficacy in patients who have previously received TNF inhibitors and also in patients who have had an inadequate response to TNF inhibitors. (150) A network meta-analysis also showed that due to differences in methods and clinical parameters in the individual studies, no clear differences in efficacy between the biologics could be identified. (201) The safety profile was found to be similar to that observed in previous studies in psoriasis patients, as written above. (113) (150) (151) (152) (153) (154) (155) (156) (157) (158) As previously mentioned, side effects such as inflammatory bowel disease and candida infection have been observed in patients treated with IL-17 inhibitors. (113) (155) (156) In contrast, the IL-12/23 Inhibitor ustekinumab is approved for the treatment of Crohn's disease and ulcerative colitis (202) and the IL-23 inhibitors Risankizumab and guselkumab are investigated in phase II/III studies in patients with Crohn's disease. (202)
As shown in the results, new biologics secukinumab, ixekizumab, brodalumab, bimekizumab, guselkumab, tildrakizumab, risankizumab and ustekinumab have also shown efficacy in the treatment of difficult-to-treat lesions in psoriasis patients. (55) (62) (80) (76) (91) (92) (93) (96) (100) (110) (111) (112) (113) (114) (115) (116) (117) (118) (119) (120) (121) (129) (130) (131) (132) (133) (138) (139) (140) (141) In the clinical trials on nail psoriasis the efficacy of some IL-17 inhibitors has been shown to be higher than that of the IL-12/23 inhibitor ustekinumab: ixekizumab vs. ustekinumab; (112) brodalumab vs. ustekinumab. (116) NAPSI reduction remained significantly higher up to one year. (112) (116) The IL-23 inhibitor risankizumab also showed a greater mean reduction in NAPSI score compared with ustekinumab. (119) In a recent study, risankizumab also demonstrated greater efficacy in patients with PsA and fingernail psoriasis, following inadequate response or intolerance to synthetic disease-modifying antirheumatic drugs compared to placebo. (120) The IL-17 inhibitor ixekizumab showed superior efficacy for nail psoriasis compared with the IL-23 inhibitor

guselkumab at week 24. (92) A recent network meta-analysis attempted to evaluate the efficacy of adalimumab, brodalumab, guselkumab, infliximab, ixekizumab, and ustekinumab in nail psoriasis and showed similar findings. (203) The study found that ixekizumab, followed by brodalumab, had the highest effect on complete resolution of nail psoriasis. (203) The problem is that these findings must be handled with care because the studies are hardly comparable with each other and head-to-head studies comparing IL-17 versus IL-23 inhibitors are scarce in the literature. (92) Indirect comparisons between the different drugs have to be considered difficult as these studies show a strong heterogeneity for example in outcome parameters used in the different studies. (108) In order to create a more specific guideline for the therapy of nail psoriasis in the future, uniform scoring systems would be needed to achieve comparability of the individual drugs and drug groups. (108)

Scalp psoriasis is also considered a difficult-to-treat lesion. (204) The presence of scalp psoriasis is often embarrassing for affected patients due to scaling and itch. (204) There is only one clinical trial published focusing on the efficacy of secukinumab in scalp psoriasis as primary endpoint. (129) In this study secukinumab has been proven to be highly efficient in scalp psoriasis. (129) The other data available concerning the efficacy of IL-17, IL12/23 and IL 23 inhibitors in the treatment of scalp psoriasis have been subanalyses of clinical trials. (55) (80) (76) (100) (116) (119) (131) (130) (132) (133) Unfortunately, no subanalyses regarding the efficacy of IL-23 and IL-17 have been published. (90) (91) However data comparing ustekinumab versus IL-17 inhibitors and IL-23 inhibitors have been published. (100) (119) The IL-17 inhibitor bimekizumab has shown greater efficacy than the IL-12/23 inhibitor ustekinumab at 16 weeks. (100) The effect of the IL-23 inhibitor risankizumab on scalp psoriasis lasted longer than that of ustekinumab. (119) At 12 weeks, the mean reduction in PSSI score was 90% in the risankizumab 90mg group and 94% in the risankizumab 180mg group; moreover, this persisted over a longer period of time compared with an 82% reduction in the ustekinumab group that did not persist over a longer period of time. (119) This suggests that the effect on scalp psoriasis of both IL-17 and IL-23 inhibitors is higher than that of IL-12/23 inhibitor ustekinumab. However, comparability is also lacking in scalp

psoriasis just as it is in nail psoriasis. Unfortunately, as in nail psoriasis, no uniform scoring systems have been used in the clinical trials published and there is a lack of comparative studies (55) (80) (76) (100) (116) (119) (129) (131) (130) (132) (133)

Even nowadays palmoplantar psoriasis and especially palmoplantar pustulosis are still considered to be a major therapeutic challenge. (163) The IL-17 inhibitors in particular have been shown to be very effective in palmoplantar psoriasis, but less so in palmoplantar pustulosis. (166) (167) (169) Taking into account the published data concerning guselkumab and ustekinumab results concerning the efficacy of IL12/23 and IL 23 are still conflicting. (165) (171) (172) (173) (174) (175) Head-to head studies comparing IL-17, Il 12/23 and IL-23 inhibitors are still missing. Therefore, deciding which treatment option should be chosen in patients suffering from palmoplantar pustulosis still remains a difficult task.

Itch in psoriasis patients significantly reduces the quality of life of patients, and therefore drugs that efficiently reduce itch in psoriasis are key. (137) Secukinumab, ixekizumab, brodalumab, bimekizumab, guselkumab and risankizumab and have been shown to be effective in reducing itch in psoriasis patients. (62) (76) (91) (92) (93) (96) (100) (119) (138) (139) (140) (141) Concerning the study results from the different clinical studies, IL-17 inhibitors tend to result in greater reduction in itching than compared to the reduction of itch in trials with IL-23 or IL-12/23 inhibitors. (91) (92) (93) (96) (100) (140) Unfortunately, this information is not very representative, as there are far too few head-to-head trials and most studies have used different assessment tools for itch. Furthermore, itching is a solely subjective phenomenon and therefore it is very difficult to measure and compare itch intensity. (205)

The studies with the IL-17 inhibitors secukinumab and ixekizumab have demonstrated good results in children. (181) (182) The findings are not fully comparable, but the improvements in PASI scores are comparable to those observed in the Phase 3 studies in adults. (62) (70) (181) (182) Similarly, the IL-12/23 inhibitor ustekinumab also has numerically similar results in children and adults. (87) (88) (180) A meta-analysis by Sun et al. also showed that these drugs are well effective in children. (206) For the IL-17 inhibitor brodalumab, trials are

still pending. (NCT04305327, NCT03240809) (183) Nevertheless, one concern with IL-17 inhibitors in children is the higher likelihood regarding inflammatory bowel disease. (183) Therefore, therapy with IL-23 inhibitors would be an alternative. (183) However, the clinical trials for guselkumab, tildrakizumab and risankizumab are still pending. (NCT03451851, NCT03997786, NCT04435600) (183)

As in the results shown, the use of IL-17 inhibitors such as secukinumab and ixekizumab, as well as the IL-23 inhibitor tildrakizumab and the IL-12/23 inhibitor ustekinumab, does not seem to have an adverse impact on the course of pregnancy. Similarly, a study by Martina L. Porter et al suggests that biologicals may be an option in pregnancy. (207)

In the prior reviews described in the results, the medications were predominantly taken only in the first trimester. However, IgG antibodies are not actively transported across the placental barrier via placental Fc receptors until about the 13th week of gestation. (208)

Since there is not enough data available yet, biologicals should not be used during pregnancy. (209) Therefore secukinumab, ixekizumab and ustekinumab should no longer be taken during pregnancy. The same applies for the use of guselkumab, tildrakizumab, risankizumab and brodalumab in pregnancy, as no data concerning pregnancy outcomes have been published yet. (209) (210) Due to the fact, that data on use of IL-17, Il-12/23 and IL 23 inhibitors in pregnancy are either scarce or not yet published the treatment with these drugs should be stopped when planning pregnancy or discontinued, when pregnancy is diagnosed. (209) (210) In contrast, the TNF alpha inhibitor certolizumab pegol is the only biologic confirmed to have a safety profile during pregnancy and lactation. (209) Therefore, it has been recommended to be used in pregnant women. (209) (210)As TN F-alpha inhibitors, like adalimumab, infliximab, etanercept, have been available for up to 20 years and are well researched in patients during pregnancy, they also can be considered as a treatment option in pregnant patients. (209) (210)

Focusing on adverse events, it must be noted that there have been more cases of Candida infections, IBD and injection side reaction in patients with IL-17 inhibitor therapy compared to those under treatment with IL-12/23 and IL-23 inhibitors. (62)

(63) (64) (70) (74) (75) (78) (79) (80) (82) (84) (85) (86) (87) (88) (89) (76) (90) (92) (94) (97)

IL-17 has been shown to have an important role in the defense against candida species. (211) Mice with defective IL-17 immunity were shown to have a higher susceptibility to candida infections and in humans an increased susceptibility for candida infections was observed in patients with genetic defects affecting their IL-17 immunity. (211) These observations might explain the increased number of Candida infections in patients treated with IL-17 inhibitors. In contrast, no increase in candida infections was noted in patients with IL-12/23 and IL-23 inhibitors. (62) (63) (64) (70) (74) (75) (78) (79) (80) (82) (84) (85) (86) (87) (88) (89) (76)

Patients with psoriasis are also more likely to have IBD. (212) Crohn's disease is more common in these patients than ulcerative colitis. (212) One reason for this common occurrence could be the shared use of predisposition genes, but common immunological mechanisms also play a role. (212) In patients with IBDs increased IL-17 levels were also noted. (202) These similarities led to the suggestion that blockade of IL-17 in Crohn’s disease would also lead to a clinical improvement in IBD patients. (202) However, cases of inflammatory bowel disease occurred in studies in patients treated with Il-17 inhibitors, but the frequency of IBDs in those studies were low. (213) (214) A possible reason for the occurrence of IBDs in patients under treatment with IL-17 inhibitors could be that IL-17 has been shown to have a protective function in relation to intestinal inflammation. (215) (216) It is therefore important to observe patients on IL-17 inhibitor therapy for signs of IBD. DLQI improved significantly in patients treated with IL-17, IL-12/23 and IL-23 inhibitors when compared to placebo. (62) (63) (64) (70) (74) (75) (78) (79) (80) (82) (84) (85) (86) (87) (88) (89) (76)

In conclusion, all IL-17 inhibitors (secukinumab, ixekizumab, brodalumab, bimekizumab), IL-12/23p40 inhibitors (ustekinumab) and IL-23p19 inhibitors (guselkumab, risankizumab, tildrakizumab) have shown good clinical efficacy in patients suffering from psoriasis and are thus able to improve the lesions and the quality of life of those affected.

Overall, these new drugs have a favorable side effect profile, although it can be said that the IL-23 inhibitors have shown a slightly more favorable side effect profile, as there has been an increased incidence of candida infections, IBD, and injection side reaction with the IL-17 inhibitors.
Unfortunately, regarding special locations and itching, it has been found that there are not enough studies primarily investigating the effect of IL-17 und IL-23 inhibitors in these locations and that the published studies and study subanalyses are too different, especially in regard to outcome parameters to compare and detect differences between the IL-17 and IL-23 inhibitors. Nevertheless, improvement in the treatment of difficult-to-treat locations as well as in the treatment of itch has been shown for both IL-17 and IL-23 inhibitors. To investigate the effect of the different drug classes on difficult-to-treat lesions standardization of outcome parameters in future trials is key.

5 References

1. Rendon A, Schäkel K. Psoriasis Pathogenesis and Treatment. Int J Mol Sci. 2019 Mar 23;20(6):1475.
2. Boehncke WH, Schön MP. Psoriasis. Lancet. 2015 Sep 5;386(9997):983-94.
3. Moll I. Duale Reihe Dermatologie. 8. Auflage. Stuttgart: Thieme; 2016. 375-383p.
4. Saleh D, Tanner LS. Guttate Psoriasis. 2021 Aug 3. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–.
5. Shah M, Al Aboud DM, Crane JS, Kumar S. Pustular Psoriasis. 2021 Aug 11. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–.
6. Weisenseel P, Wilsmann-Theis D, Kahl C, Reich K, Mössner R. Pustulöse Psoriasis [Pustular psoriasis]. Hautarzt. 2016 Jun;67(6):445-53.
7. Gao QQ, Xi MR, Yao Q. Impetigo Herpetiformis during pregnancy: a case report and literature review. Dermatology. 2013;226(1):35-40.
8. Sheu JS, Divito SJ, Enamandram M, Merola JF. Dapsone Therapy for Pustular Psoriasis: Case Series and Review of the Literature. Dermatology. 2016;232(1):97-101.
9. Griffiths CE, Christophers E, Barker JN, Chalmers RJ, Chimenti S, Krueger GG, et al. A classification of psoriasis vulgaris according to phenotype. Br J Dermatol. 2007 Feb;156(2):258-62.
10. Singh RK, Lee KM, Ucmak D, Brodsky M, Atanelov Z, Farahnik B, et al. Erythrodermic psoriasis: pathophysiology and current treatment perspectives. Psoriasis (Auckl). 2016;6:93-104.
11. Haneke E. Nail psoriasis: clinical features, pathogenesis, differential diagnoses, and management. Psoriasis (Auckl). 2017 Oct 16;7:51-63.
12. Melo FJ, Magina S. Clinical management of Anti-TNF-alpha-induced psoriasis or psoriasiform lesions in inflammatory bowel disease patients: a systematic review. Int J Dermatol. 2018 Dec;57(12):1521-1532.
13. Collamer AN, Battafarano DF. Psoriatic skin lesions induced by tumor necrosis factor antagonist therapy: clinical features and possible immunopathogenesis. Semin Arthritis Rheum. 2010 Dec;40(3):233-40.

14. Coates LC, Helliwell PS. Psoriatic arthritis: state of the art review. Clin Med (Lond). 2017 Feb;17(1):65-70.
15. Ocampo D V, Gladman D. Psoriatic arthritis. F1000Res. 2019 Sep 20;8:F1000 Faculty Rev-1665.
16. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic Arthritis. N Engl J Med. 2017 Mar 9;376(10):957-970.
17. Oliveira Mde F, Rocha Bde O, Duarte GV. Psoriasis: classical and emerging comorbidities. An Bras Dermatol. 2015 Jan-Feb;90(1):9-20.
18. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006 Aug;54(8):2665-73.
19. Singh S, Pradhan D, Puri P, Ramesh V, Aggarwal S, Nayek A, Jain AK. Genomic alterations driving psoriasis pathogenesis. Gene. 2019 Jan 30;683:61-71.
20. Capon F. The Genetic Basis of Psoriasis. Int J Mol Sci. 2017 Nov 25;18(12):2526.
21. Chen L, Tsai TF. HLA-Cw6 and psoriasis. Br J Dermatol. 2018 Apr;178(4):854-862.
22. Baliwag J, Barnes DH, Johnston A. Cytokines in psoriasis. Cytokine. 2015 Jun;73(2):342-50.
23. Gooderham MJ, Papp KA, Lynde CW. Shifting the focus - the primary role of IL-23 in psoriasis and other inflammatory disorders. J Eur Acad Dermatol Venereol. 2018 Jul;32(7):1111-1119.
24. Browning J. Dermatology Edited by Jean L. Bolognia, Julie V. Schaffer, Lorenzo Cerroni. Fourth edition. China: Elsevier; 2018. 138-142p
25. Monin L, Gaffen SL. Interleukin 17 Family Cytokines: Signaling Mechanisms, Biological Activities, and Therapeutic Implications. Cold Spring Harb Perspect Biol. 2018 Apr 2;10(4):a028522.
26. Kostareva OS, Gabdulkhakov AG, Kolyadenko IA, Garber MB, Tishchenko SV. Interleukin-17: Functional and Structural Features, Application as a Therapeutic Target. Biochemistry (Mosc). 2019 Jan;84(Suppl 1):S193-S205.

27. Amatya N, Garg AV, Gaffen SL. IL-17 Signaling: The Yin and the Yang. Trends Immunol. 2017 May;38(5):310-322.
28. Abusleme L, Moutsopoulos NM. IL-17: overview and role in oral immunity and microbiome. Oral Dis. 2017 Oct;23(7):854-865.
29. Gu C, Wu L, Li X. IL-17 family: cytokines, receptors and signaling. Cytokine. 2013 Nov;64(2):477-85.
30. Speeckaert R, Lambert J, Grine L, Van Gele M, De Schepper S, van Geel N. The many faces of interleukin-17 in inflammatory skin diseases. Br J Dermatol. 2016 Nov;175(5):892-901.
31. Murphy KM, Weaver C, Janeway C. Janeway Immunologie. 9. Auflage. Berlin: Springer Spektrum; 2018. 1205 p. 465-467p.
32. Vignali DA, Kuchroo VK. IL-12 family cytokines: immunological playmakers. Nat Immunol. 2012 Jul 19;13(8):722-8.
33. Langrish CL, McKenzie BS, Wilson NJ, de Waal Malefyt R, Kastelein RA, Cua DJ. IL-12 and IL-23: master regulators of innate and adaptive immunity. Immunol Rev. 2004 Dec;202:96-105.
34. Boehncke WH. Etiology and Pathogenesis of Psoriasis. Rheum Dis Clin North Am. 2015 Nov;41(4):665-75.
35. Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis. J Eur Acad Dermatol Venereol. 2017 Feb;31(2):205-212.
36. Böcker W, Denk H, Heitz PU, et al. Pathologie. 5. vollständig überarbeitete Auflage. München: Elsevier, Urban & Fischer; 2012. 834p.
37. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet. 2007 Jul 21;370(9583):263-271.
38. Schön MP, Boehncke WH. Psoriasis. N Engl J Med. 2005 May 5;352(18):1899-912.
39. Puig L. Cardiometabolic Comorbidities in Psoriasis and Psoriatic Arthritis. Int J Mol Sci. 2017 Dec 25;19(1):58.
40. Hu SC, Lan CE. Psoriasis and Cardiovascular Comorbidities: Focusing on Severe Vascular Events, Cardiovascular Risk Factors and Implications for Treatment. Int J Mol Sci. 2017 Oct 21;18(10):2211.

41. Nast A, Boehncke WH, Mrowietz U, Ockenfels HM, Philipp S, Reich K, et al. S3-Leitlinie zur Therapie der Psoriasis vulgaris Update 2011 [S3-guidelines for the treatment of psoriasis vulgaris Update 2011]. J Dtsch Dermatol Ges. 2011 Jun;9 Suppl 2:S1-104.
42. Bronckers IM, Paller AS, van Geel MJ, van de Kerkhof PC, Seyger MM. Psoriasis in Children and Adolescents: Diagnosis, Management and Comorbidities. Paediatr Drugs. 2015 Oct;17(5):373-84.
43. Nast A, Amelunxen L, Augustin M, Boehncke WH, Dressler C, Gaskins M, et al. S3 Guideline for the treatment of psoriasis vulgaris, update - Short version part 1 - Systemic treatment. J Dtsch Dermatol Ges. 2018 May;16(5):645-669.
44. Kim WB, Jerome D, Yeung J. Diagnosis and management of psoriasis. Can Fam Physician. 2017 Apr;63(4):278-285.
45. Cabrera S, Chinniah N, Lock N, Cains GD, Woods J. Inter-observer reliability of the PASI in a clinical setting. Australas J Dermatol. 2015 May;56(2):100-2.
46. Mease PJ. Measures of psoriatic arthritis: Tender and Swollen Joint Assessment, Psoriasis Area and Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI), Modified Nail Psoriasis Severity Index (mNAPSI), Mander/Newcastle Enthesitis Index (MEI), Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada (SPARCC), Maastricht Ankylosing Spondylitis Enthesis Score (MASES), Leeds Dactylitis Index (LDI), Patient Global for Psoriatic Arthritis, Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQOL), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsAJAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI). Arthritis Care Res (Hoboken). 2011 Nov;63 Suppl 11:S64-85.
47. Schmitt J, Wozel G. The psoriasis area and severity index is the adequate criterion to define severity in chronic plaque-type psoriasis. Dermatology. 2005;210(3):194-9.
48. Pathirana D, Ormerod AD, Saiag P, Smith C, Spuls PI, Nast A, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad

Dermatol Venereol. 2009 Oct;23 Suppl 2:1-70. doi: 10.1111/j.1468-3083.2009.03389.x. Erratum in: J Eur Acad Dermatol Venereol. 2010 Jan;24(1):117-8.

49. Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. Ann Rheum Dis. 2005 Mar;64 Suppl 2(Suppl 2):ii65-8; discussion ii69-73.
50. Langley RG, Feldman SR, Nyirady J, van de Kerkhof P, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. J Dermatolog Treat. 2015 Feb;26(1):23-31.
51. Kimball AB, Naegeli AN, Edson-Heredia E, Lin CY, Gaich C, Nikaï E, Wyrwich K, Yosipovitch G. Psychometric properties of the Itch Numeric Rating Scale in patients with moderate-to-severe plaque psoriasis. Br J Dermatol. 2016 Jul;175(1):157-62.
52. Rich P, Scher RK. Nail Psoriasis Severity Index: a useful tool for evaluation of nail psoriasis. J Am Acad Dermatol. 2003 Aug;49(2):206-12.
53. Hudgens S, Rich P, Geng Z, Williams D, Fleischer A, Ganguli A. Development and validation of the Physician's Global Assessment of Fingernail Psoriasis. J Eur Acad Dermatol Venereol. 2021 Nov;35(11):2324-2330.
54. Wozel G, Klein E, Mrowietz U, Reich K, Sebastian M, Streit V. Scalp psoriasis. J Dtsch Dermatol Ges. 2011 Jan;9(1):70-4.
55. Foley P, Gordon K, Griffiths CEM, Wasfi Y, Randazzo B, Song M, et al. Efficacy of Guselkumab Compared With Adalimumab and Placebo for Psoriasis in Specific Body Regions: A Secondary Analysis of 2 Randomized Clinical Trials. JAMA Dermatol. 2018 Jun 1;154(6):676-683.
56. Bronckers IMGJ, van Geel MJ, van de Kerkhof PCM, de Jong EMGJ, Seyger MMB. A cross-sectional study in young adults with psoriasis: potential determining factors in quality of life, life course and work productivity. J Dermatolog Treat. 2019 May;30(3):208-215.
57. Bai F, Li GG, Liu Q, Niu X, Li R, Ma H. Short-Term Efficacy and Safety of IL-17, IL-12/23, and IL-23 Inhibitors Brodalumab, Secukinumab, Ixekizumab, Ustekinumab, Guselkumab, Tildrakizumab, and Risankizumab for the Treatment of Moderate to Severe Plaque Psoriasis: A Systematic Review and

Network Meta-Analysis of Randomized Controlled Trials. J Immunol Res. 2019 Sep 10;2019:2546161.

58. Puig L. PASI90 response: the new standard in therapeutic efficacy for psoriasis. J Eur Acad Dermatol Venereol. 2015 Apr;29(4):645-8.
59. Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CE, Nast A, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Arch Dermatol Res. 2011 Jan;303(1):1-10.
60. Blauvelt A. Safety of secukinumab in the treatment of psoriasis. Expert Opin Drug Saf. 2016 Oct;15(10):1413-20.
61. Hueber W, Patel DD, Dryja T, Wright AM, Koroleva I, Bruin G, et al. Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. Sci Transl Med. 2010 Oct 6;2(52):52ra72.
62. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, et al.; 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.
63. Blauvelt A, Prinz JC, Gottlieb AB, Kingo K, Sofen H, Ruer-Mulard M, et al.; FEATURE Study Group. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). Br J Dermatol. 2015 Feb;172(2):484-93.
64. Paul C, Lacour JP, Tedremets L, Kreutzer K, Jazayeri S, Adams S, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). J Eur Acad Dermatol Venereol. 2015 Jun;29(6):1082–90.
65. Mrowietz U, Leonardi CL, Girolomoni G, Toth D, Morita A, Balki SA, et al.; SCULPTURE Study Group. Secukinumab retreatment-as-needed versus fixed-interval maintenance regimen for moderate to severe plaque psoriasis: A randomized, double-blind, noninferiority trial (SCULPTURE). J Am Acad Dermatol. 2015 Jul;73(1):27-36.e1.
66. Warren RB, Barker JNWB, Finlay AY, Burden AD, Kirby B, Armendariz Y, et al. Secukinumab for patients failing previous tumour necrosis factor-α inhibitor therapy: results of a randomized open-label study (SIGNATURE). Br J

Dermatol. 2020 Jul;183(1):60-70.
67. Thaçi D, Humeniuk J, Frambach Y, Bissonnette R, Goodman JJ, Shevade S, et al.; STATURE study group. Secukinumab in psoriasis: randomized, controlled phase 3 trial results assessing the potential to improve treatment response in partial responders (STATURE). Br J Dermatol. 2015 Sep;173(3):777-87.
68. Liu L, Lu J, Allan BW, Tang Y, Tetreault J, Chow CK, et al. Generation and characterization of ixekizumab, a humanized monoclonal antibody that neutralizes interleukin-17A. J Inflamm Res. 2016 Apr 19;9:39-50.
69. Syed YY. Ixekizumab: A Review in Moderate to Severe Plaque Psoriasis. Am J Clin Dermatol. 2017 Feb;18(1):147-158.
70. Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, et al.; UNCOVER-1 Study Group; UNCOVER-2 Study Group; UNCOVER-3 Study Group. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis. N Engl J Med. 2016 Jul 28;375(4):345-56.
71. Farahnik B, Beroukhim K, Zhu TH, Abrouk M, Nakamura M, Singh R, et al. Ixekizumab for the Treatment of Psoriasis: A Review of Phase III Trials. Dermatol Ther (Heidelb). 2016 Mar;6(1):25-37.
72. Callis Duffin K, Bagel J, Bukhalo M, Mercado Clement IJ, Choi SL, Zhao F, et al. Phase 3, open-label, randomized study of the pharmacokinetics, efficacy and safety of ixekizumab following subcutaneous administration using a prefilled syringe or an autoinjector in patients with moderate-to-severe plaque psoriasis (UNCOVER-A). J Eur Acad Dermatol Venereol. 2017 Jan;31(1):107-113.
73. Blair HA. Brodalumab: A Review in Moderate to Severe Plaque Psoriasis. Drugs. 2018 Mar;78(4):495-504.
74. Papp KA, Reich K, Paul C, Blauvelt A, Baran W, Bolduc C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. Br J Dermatol. 2016 Aug;175(2):273-86.
75. Lebwohl M, Strober B, Menter A, Gordon K, Weglowska J, Puig L, et al. Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis. N Engl J Med. 2015 Oct;373(14):1318-28.

76. Gordon KB, Foley P, Krueger JG, Pinter A, Reich K, Vender R, et al. Bimekizumab efficacy and safety in moderate to severe plaque psoriasis (BE READY): a multicentre, double-blind, placebo-controlled, randomised withdrawal phase 3 trial. Lancet. 2021 Feb 6;397(10273):475-486.
77. Machado Á, Torres T. Guselkumab for the Treatment of Psoriasis. BioDrugs. 2018 Apr;32(2):119-128.
78. Blauvelt A, Papp KA, Griffiths CE, Randazzo B, Wasfi Y, Shen YK, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double -blinded, placebo- and active comparator-controlled VOYAGE 1 trial. J Am Acad Dermatol. 2017 Mar;76(3):405-417.
79. Reich K, Armstrong AW, Foley P, Song M, Wasfi Y, Randazzo B, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. J Am Acad Dermatol. 2017 Mar;76(3):418-431.
80. Ohtsuki M, Kubo H, Morishima H, Goto R, Zheng R, Nakagawa H. Guselkumab, an anti-interleukin-23 monoclonal antibody, for the treatment of moderate to severe plaque-type psoriasis in Japanese patients: Efficacy and safety results from a phase 3, randomized, double-blind, placebo-controlled study. J Dermatol. 2018 Sep;45(9):1053-1062.
81. Frampton JE. Tildrakizumab: A Review in Moderate-to-Severe Plaque Psoriasis. Am J Clin Dermatol. 2019 Apr;20(2):295-306.
82. Reich K, Papp KA, Blauvelt A, Tyring SK, Sinclair R, Thaçi D, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. Lancet. 2017 Jul 15;390(10091):276-288.
83. Blauvelt A, Reich K, Papp KA, Kimball AB, Gooderham M, Tyring SK, et al. Safety of tildrakizumab for moderate-to-severe plaque psoriasis: pooled analysis of three randomized controlled trials. Br J Dermatol. 2018

Sep;179(3):615-622.

84. Gordon KB, Strober B, Lebwohl M, Augustin M, Blauvelt A, Poulin Y, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. Lancet. 2018 Aug 25;392(10148):650-661.
85. Reich K, Gooderham M, Thaçi D, Crowley JJ, Ryan C, Krueger JG, et al. Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): a randomised, double-blind, active-comparator-controlled phase 3 trial. Lancet. 2019 Aug 17;394(10198):576-586.
86. Ohtsuki M, Fujita H, Watanabe M, Suzaki K, Flack M, Huang X, et al. Efficacy and safety of risankizumab in Japanese patients with moderate to severe plaque psoriasis: Results from the SustaIMM phase 2/3 trial. J Dermatol. 2019 Aug;46(8):686-694.
87. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al.; PHOENIX 1 study investigators. 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. 2008 May 17;371(9625):1665-74.
88. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al.; PHOENIX 2 study investigators. 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. 2008 May 17;371(9625):1675-84.
89. Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, et al.; ACCEPT Study Group. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med. 2010 Jan 14;362(2):118-28.
90. Reich K, Armstrong AW, Langley RG, Flavin S, Randazzo B, Li S, et al. Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial. Lancet. 2019 Sep 7;394(10201):831-839.

91. Blauvelt A, Papp K, Gottlieb A, Jarell A, Reich K, Maari C, et al.; IXORA-R Study Group. A head-to-head comparison of ixekizumab vs. guselkumab in patients with moderate-to-severe plaque psoriasis: 12-week efficacy, safety and speed of response from a randomized, double-blinded trial. Br J Dermatol. 2020 Jun;182(6):1348-1358.
92. Blauvelt A, Leonardi C, Elewski B, Crowley JJ, Guenther LC, Gooderham M, et al.; IXORA-R Study Group. A head-to-head comparison of ixekizumab vs. guselkumab in patients with moderate-to-severe plaque psoriasis: 24-week efficacy and safety results from a randomized, double-blinded trial. Br J Dermatol. 2021 Jun;184(6):1047-1058.
93. Reich K, Pinter A, Lacour JP, Ferrandiz C, Micali G, French LE, el al.; IXORA-S investigators. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. Br J Dermatol. 2017 Oct;177(4):1014-1023.
94. Paul C, Griffiths CEM, van de Kerkhof PCM, Puig L, Dutronc Y, Henneges C, et al. Ixekizumab provides superior efficacy compared with ustekinumab over 52 weeks of treatment: Results from IXORA-S, a phase 3 study. J Am Acad Dermatol. 2019 Jan;80(1):70-79.e3.
95. Thaçi D, Blauvelt A, Reich K, Tsai TF, Vanaclocha F, Kingo K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. J Am Acad Dermatol. 2015 Sep;73(3):400-9.
96. Blauvelt A, Reich K, Tsai TF, Tyring S, Vanaclocha F, Kingo K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: Results from the CLEAR study. J Am Acad Dermatol. 2017 Jan;76(1):60-69.e9.
97. Bagel J, Blauvelt A, Nia J, Hashim P, Patekar M, de Vera A, et al. Secukinumab maintains superiority over ustekinumab in clearing skin and improving quality of life in patients with moderate to severe plaque psoriasis: 52-week results from a double-blind phase 3b trial (CLARITY). J Eur Acad Dermatol Venereol. 2021 Jan;35(1):135-142.

98. Warren RB, Blauvelt A, Poulin Y, Beeck S, Kelly M, Wu T, et al. Efficacy and safety of risankizumab vs. secukinumab in patients with moderate-to-severe plaque psoriasis (IMMerge): results from a phase III, randomized, open-label, efficacy-assessor-blinded clinical trial. Br J Dermatol. 2021 Jan;184(1):50-59.
99. Langley RG, Tsai TF, Flavin S, Song M, Randazzo B, Wasfi Y, et al. Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: results of the randomized, double-blind, phase III NAVIGATE trial. Br J Dermatol. 2018 Jan;178(1):114-123.
100. Reich K, Papp KA, Blauvelt A, Langley RG, Armstrong A, Warren RB, et al. Bimekizumab versus ustekinumab for the treatment of moderate to severe plaque psoriasis (BE VIVID): efficacy and safety from a 52-week, multicentre, double-blind, active comparator and placebo controlled phase 3 trial. Lancet. 2021 Feb 6;397(10273):487-498.
101. Reich K, Warren RB, Lebwohl M, Gooderham M, Strober B, Langley RG, et al. Bimekizumab versus Secukinumab in Plaque Psoriasis. N Engl J Med. 2021 Jul 8;385(2):142-152.
102. Bagel J, Nia J, Hashim PW, Patekar M, de Vera A, Hugot S, et al. Secukinumab is Superior to Ustekinumab in Clearing Skin in Patients with Moderate to Severe Plaque Psoriasis (16-Week CLARITY Results). Dermatol Ther (Heidelb). 2018 Dec;8(4):571-579.
103. Armesto S, Esteve A, Coto-Segura P, Drake M, Galache C, Martínez-Borra J, et al. Psoriasis ungueal: estudio en 661 pacientes con psoriasis vulgar [Nail psoriasis in individuals with psoriasis vulgaris: a study of 661 patients]. Actas Dermosifiliogr. 2011 Jun;102(5):365-72.
104. Augustin M, Reich K, Blome C, Schäfer I, Laass A, Radtke MA. Nail psoriasis in Germany: epidemiology and burden of disease. Br J Dermatol. 2010 Sep;163(3):580-5.
105. Kaur I, Handa S, Kumar B. Natural history of psoriasis: a study from the Indian subcontinent. J Dermatol. 1997 Apr;24(4):230-4.
106. Williamson L, Dalbeth N, Dockerty JL, Gee BC, Weatherall R, Wordsworth BP. Extended report: nail disease in psoriatic arthritis--clinically important, potentially treatable and often overlooked. Rheumatology (Oxford). 2004

Jun;43(6):790-4.
107. Rigopoulos D, Baran R, Chiheb S, Daniel CR 3rd, Di Chiacchio N, Gregoriou S, et al. Recommendations for the definition, evaluation, and treatment of nail psoriasis in adult patients with no or mild skin psoriasis: A dermatologist and nail expert group consensus. J Am Acad Dermatol. 2019 Jul;81(1):228-240.
108. Kaeley GS, Eder L, Aydin SZ, Rich P, Bakewell CJ. Nail Psoriasis: Diagnosis, Assessment, Treatment Options, and Unmet Clinical Needs. J Rheumatol. 2021 Aug;48(8):1208-1220.
109. Blome C, Augustin M, Klein TM. Nail Psoriasis and Quality-of-Life Measurement in Clinical Trials: Call for the Use of Nail-Specific Instruments. Am J Clin Dermatol. 2021 Nov;22(6):747-755.
110. Reich K, Sullivan J, Arenberger P, Jazayeri S, Mrowietz U, Augustin M, et al. Secukinumab shows high and sustained efficacy in nail psoriasis: 2.5-year results from the randomized placebo-controlled TRANSFIGURE study. Br J Dermatol. 2021 Mar;184(3):425-436.
111. van de Kerkhof P, Guenther L, Gottlieb AB, Sebastian M, Wu JJ, Foley P, et al. Ixekizumab treatment improves fingernail psoriasis in patients with moderate-to-severe psoriasis: results from the randomized, controlled and open-label phases of UNCOVER-3. J Eur Acad Dermatol Venereol. 2017 Mar;31(3):477-482.
112. Wasel N, Thaçi D, French LE, Conrad C, Dutronc Y, Gallo G, et al. Ixekizumab and Ustekinumab Efficacy in Nail Psoriasis in Patients with Moderate-to-Severe Psoriasis: 52-Week Results from a Phase 3, Head-to-Head Study (IXORA-S). Dermatol Ther (Heidelb). 2020 Aug;10(4):663-670.
113. Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, et al.; SPIRIT-P1 Study Group. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis. 2017 Jan;76(1):79-87.
114. Mease PJ, Smolen JS, Behrens F, Nash P, Liu Leage S, Li L, et al.; SPIRIT H2H study group. A head-to-head comparison of the efficacy and safety of

ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. Ann Rheum Dis. 2020 Jan;79(1):123-131.

115. Smolen JS, Mease P, Tahir H, Schulze-Koops H, de la Torre I, Li L, et al. Multicentre, randomised, open-label, parallel-group study evaluating the efficacy and safety of ixekizumab versus adalimumab in patients with psoriatic arthritis naïve to biological disease-modifying antirheumatic drug: final results by week 52. Ann Rheum Dis. 2020 Oct;79(10):1310-1319.
116. Elewski B, Rich P, Lain E, Soung J, Lewitt GM, Jacobson A. Efficacy of brodalumab in the treatment of scalp and nail psoriasis: results from three phase 3 trials. J Dermatolog Treat. 2022 Feb;33(1):261-265.
117. Simpson K, Low ZM, Howard A, Kern JS. Successful management of treatment resistant nail psoriasis with tildrakizumab. Australas J Dermatol. 2021 Aug;62(3):390-393.
118. Ismail FF, May J, Moi J, Sinclair R. Clinical improvement in psoriatic nail disease and psoriatic arthritis with tildrakizumab treatment. Dermatol Ther. 2020 Mar;33(2):e13216.
119. Papp KA, Blauvelt A, Bukhalo M, Gooderham M, Krueger JG, Lacour JP, et al. Risankizumab versus Ustekinumab for Moderate-to-Severe Plaque Psoriasis. N Engl J Med. 2017 Apr 20;376(16):1551-1560.
120. Kristensen LE, Soliman AM, Papp K, Merola JF, Barcomb L, Wang Z, et al. Effects of risankizumab on nail psoriasis in patients with active psoriatic arthritis: results from KEEPsAKE 1. J Eur Acad Dermatol Venereol. 2022 May;36(5):e389-e392.
121. Rich P, Bourcier M, Sofen H, Fakharzadeh S, Wasfi Y, Wang Y, et al.; PHOENIX 1 investigators. Ustekinumab improves nail disease in patients with moderate-to-severe psoriasis: results from PHOENIX 1. Br J Dermatol. 2014 Feb;170(2):398-407.
122. van de Kerkhof PC, Steegers-Theunissen RP, Kuipers MV. Evaluation of topical drug treatment in psoriasis. Dermatology. 1998;197(1):31-6.
123. Blakely K, Gooderham M. Management of scalp psoriasis: current perspectives. Psoriasis (Auckl). 2016 Mar 29;6:33-40.

124. Sampogna F, Linder D, Piaserico S, Altomare G, Bortune M, Calzavara-Pinton P, et al. Quality of life assessment of patients with scalp dermatitis using the Italian version of the Scalpdex. Acta Derm Venereol. 2014 Jul;94(4):411-4.
125. Reich A, Welz-Kubiak K, Rams L. Apprehension of the disease by patients suffering from psoriasis. Postepy Dermatol Alergol. 2014 Oct;31(5):289-93.
126. George SM, Taylor MR, Farrant PB. Psoriatic alopecia. Clin Exp Dermatol. 2015 Oct;40(7):717-21.
127. Merola JF, Qureshi A, Husni ME. Underdiagnosed and undertreated psoriasis: Nuances of treating psoriasis affecting the scalp, face, intertriginous areas, genitals, hands, feet, and nails. Dermatol Ther. 2018 May;31(3):e12589.
128. Schlager JG, Rosumeck S, Werner RN, Jacobs A, Schmitt J, Schlager C, et al. Topical treatments for scalp psoriasis. Cochrane Database Syst Rev. 2016 Feb 26;2(2):CD009687.
129. Bagel J, Duffin KC, Moore A, Ferris LK, Siu K, Steadman J, et al. The effect of secukinumab on moderate-to-severe scalp psoriasis: Results of a 24-week, randomized, double-blind, placebo-controlled phase 3b study. J Am Acad Dermatol. 2017 Oct;77(4):667-674.
130. Reich K, Leonardi C, Lebwohl M, Kerdel F, Okubo Y, Romiti R, et al. Sustained response with ixekizumab treatment of moderate-to-severe psoriasis with scalp involvement: results from three phase 3 trials (UNCOVER-1, UNCOVER-2, UNCOVER-3). J Dermatolog Treat. 2017 Jun;28(4):282-287.
131. Langley RG, Papp K, Gooderham M, Zhang L, Mallinckrodt C, Agada N, et al.; of the IXORA-P Investigators. Efficacy and safety of continuous every-2-week dosing of ixekizumab over 52 weeks in patients with moderate-to-severe plaque psoriasis in a randomized phase III trial (IXORA-P). Br J Dermatol. 2018 Jun;178(6):1315-1323.
132. Menter MA, Murakawa GJ, Glover H, Mendelsohn AM, Parno J, Rozzo SJ, Davidson D, Gupta AK. Clearance of head and neck involvement in plaque psoriasis with tildrakizumab treatment in the phase 3 reSURFACE 1 study. J Eur Acad Dermatol Venereol. 2020 Dec;34(12):e803-e805.
133. Fotiadou C, Lazaridou E, Sotiriou E, Kyrgidis A, Apalla Z, Ioannides D. Scalp psoriasis and biologic agents: a retrospective, comparative study from a

tertiary psoriasis referral centre. J Eur Acad Dermatol Venereol. 2016 Dec;30(12):2091-2096.

134. Shahwan KT, Kimball AB. Itch intensity in moderate-to-severe plaque psoriasis versus atopic dermatitis: A meta-analysis. J Am Acad Dermatol. 2017 Jun;76(6):1198-1200.e1.
135. Janowski K, Steuden S, Bogaczewicz J. Clinical and psychological characteristics of patients with psoriasis reporting various frequencies of pruritus. Int J Dermatol. 2014 Jul;53(7):820-9.
136. Yosipovitch G, Goon A, Wee J, Chan YH, Goh CL. The prevalence and clinical characteristics of pruritus among patients with extensive psoriasis. Br J Dermatol. 2000 Nov;143(5):969-73.
137. Elewski B, Alexis AF, Lebwohl M, Stein Gold L, Pariser D, Del Rosso J, et al. Itch: an under-recognized problem in psoriasis. J Eur Acad Dermatol Venereol. 2019 Aug;33(8):1465-1476.
138. Strober B, Sigurgeirsson B, Popp G, Sinclair R, Krell J, Stonkus S, et al. Secukinumab improves patient-reported psoriasis symptoms of itching, pain, and scaling: results of two phase 3, randomized, placebo-controlled clinical trials. Int J Dermatol. 2016 Apr;55(4):401-7.
139. Yosipovitch G, Reich A, Steinhoff M, Beselin A, Kent T, Dossenbach M, et al. Impact of Ixekizumab Treatment on Itch and Psoriasis Area and Severity Index in Patients with Moderate-to-Severe Plaque Psoriasis: An Integrated Analysis of Two Phase III Randomized Studies. Dermatol Ther (Heidelb). 2018 Dec;8(4):621-637.
140. Gottlieb AB, Gordon K, Hsu S, Elewski B, Eichenfield LF, Kircik L, et al. Improvement in itch and other psoriasis symptoms with brodalumab in phase 3 randomized controlled trials. J Eur Acad Dermatol Venereol. 2018 Aug;32(8):1305-1313.
141. Papp KA, Blauvelt A, Kimball AB, Han C, Randazzo B, Wasfi Y, et al. Patient-reported symptoms and signs of moderate-to-severe psoriasis treated with guselkumab or adalimumab: results from the randomized VOYAGE 1 trial. J Eur Acad Dermatol Venereol. 2018 Sep;32(9):1515-1522.

142. Blauvelt A, Chiricozzi A. The Immunologic Role of IL-17 in Psoriasis and Psoriatic Arthritis Pathogenesis. Clin Rev Allergy Immunol. 2018 Dec;55(3):379-390.
143. Gottlieb A, Merola JF. Psoriatic arthritis for dermatologists. J Dermatolog Treat. 2020 Nov;31(7):662-679.
144. Ng BCK, Jadon DR. Unmet needs in psoriatic arthritis. Best Pract Res Clin Rheumatol. 2021 Jun;35(2):101693.
145. Christophers E, Barker JN, Griffiths CE, Daudén E, Milligan G, Molta C, et al. The risk of psoriatic arthritis remains constant following initial diagnosis of psoriasis among patients seen in European dermatology clinics. J Eur Acad Dermatol Venereol. 2010 May;24(5):548-54.
146. Thaçi D, Behrens F, Greger G, Burkhardt H, Gnann H, Schopf R, et al. Association between skin and joint involvement in patients with psoriatic arthritis treated with adalimumab: analysis of data from a German non-interventional study. Dermatology. 2015;230(3):213-21.
147. Nast A, Smith C, Spuls PI, Avila Valle G, Bata-Csörgö Z, Boonen H, et al. EuroGuiDerm Guideline on the systemic treatment of Psoriasis vulgaris - Part 2: specific clinical and comorbid situations. J Eur Acad Dermatol Venereol. 2021 Feb;35(2):281-317.
148. Boehncke WH. Psoriasisarthritis: Relevantes für die dermatologische Praxis [Psoriatic arthritis: important aspects for the dermatological practice]. Hautarzt. 2021 Nov;72(11):946-952.
149. Tintle SJ, Gottlieb AB. Psoriatic arthritis for the dermatologist. Dermatol Clin. 2015 Jan;33(1):127-48.
150. Deodhar A, Helliwell PS, Boehncke WH, Kollmeier AP, Hsia EC, Subramanian RA, et al.; DISCOVER-1 Study Group. Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFα inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2020 Apr 4;395(10230):1115-1125.
151. Mease PJ, Rahman P, Gottlieb AB, Kollmeier AP, Hsia EC, Xu XL, et al.; DISCOVER-2 Study Group. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-

controlled phase 3 trial. Lancet. 2020 Apr 4;395(10230):1126-1136.
152. Kristensen LE, Keiserman M, Papp K, Mccasland L, White D, Barcomb L, et al. Efficacy and safety of Risankizumab in patients with active psoriatic arthritis after inadequate response or intolerance to DMARDs: 24-week results from the phase 3, randomized, double-blind KEEPsAKE 1 trial. Ann Rheum Dis. 2021 Jun;80:1315–1316.
153. Ostor A, Van den Bosch F, Papp K, Asnal C, Blanco R, Aelion J, et al. Efficacy and safety of Risankizumab for active psoriatic arthritis, including patients with inadequate response or intolerance to biologic therapies: 24-week results from the phase 3, randomized, double-blind, KEEPsAKE 2 trial. Ann Rheum Dis. 2021 Jun;80:138–139.
154. Mease PJ, Helliwell PS, Hjuler KF, Raymond K, McInnes I. Brodalumab in psoriatic arthritis: results from the randomised phase III AMVISION-1 and AMVISION-2 trials. Ann Rheum Dis. 2021 Feb;80(2):185-193.
155. Nash P, Kirkham B, Okada M, Rahman P, Combe B, Burmester GR, et al.; SPIRIT-P2 Study Group. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet. 2017 Jun 10;389(10086):2317-2327.
156. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al.; FUTURE 2 Study Group. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015 Sep 19;386(9999):1137-46.
157. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al.; PSUMMIT 1 Study Group. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet. 2013 Aug 31;382(9894):780-9.
158. Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al.; PSUMMIT 2 Study Group. Efficacy and safety of the anti-IL-12/23 p40 monoclonal

antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis. 2014 Jun;73(6):990-9.

159. Mease PJ, Chohan S, Fructuoso FJG, Luggen ME, Rahman P, Raychaudhuri SP, et al. Efficacy and safety of tildrakizumab in patients with active psoriatic arthritis: results of a randomised, double-blind, placebo-controlled, multiple-dose, 52-week phase IIb study. Ann Rheum Dis. 2021 Sep;80(9):1147-1157.
160. Ritchlin CT, Kavanaugh A, Merola JF, Schett G, Scher JU, Warren RB, et al. Bimekizumab in patients with active psoriatic arthritis: results from a 48-week, randomised, double-blind, placebo-controlled, dose-ranging phase 2b trial. Lancet. 2020 Feb 8;395(10222):427-440.
161. Brunasso AM, Puntoni M, Aberer W, Delfino C, Fancelli L, Massone C. Clinical and epidemiological comparison of patients affected by palmoplantar plaque psoriasis and palmoplantar pustulosis: a case series study. Br J Dermatol. 2013 Jun;168(6):1243-51.
162. Pettey AA, Balkrishnan R, Rapp SR, Fleischer AB, Feldman SR. Patients with palmoplantar psoriasis have more physical disability and discomfort than patients with other forms of psoriasis: implications for clinical practice. J Am Acad Dermatol. 2003 Aug;49(2):271-5.
163. Raposo I, Torres T. Palmoplantar Psoriasis and Palmoplantar Pustulosis: Current Treatment and Future Prospects. Am J Clin Dermatol. 2016 Aug;17(4):349-58.
164. Lee E, Zarei M, LaSenna C, Villada G, Romanelli P. Psoriasis Targeted Therapy: Characterization of Interleukin 17A Expression in Subtypes of Psoriasis. J Drugs Dermatol. 2015 Oct;14(10):1133-6.
165. Bissonnette R, Nigen S, Langley RG, Lynde CW, Tan J, Fuentes-Duculan J, et al. Increased expression of IL-17A and limited involvement of IL-23 in patients with palmo-plantar (PP) pustular psoriasis or PP pustulosis; results from a randomised controlled trial. J Eur Acad Dermatol Venereol. 2014 Oct;28(10):1298-305.

166. Gottlieb AB, Kubanov A, van Doorn M, Sullivan J, Papp KA, You R, et al. Sustained efficacy of secukinumab in patients with moderate-to-severe palmoplantar psoriasis: 2·5-year results from GESTURE, a randomized, double-blind, placebo-controlled trial. Br J Dermatol. 2020 Apr;182(4):889-899.
167. Galluzzo M, Talamonti M, Atzori L, Bardazzi F, Campanati A, Di Cesare A, et al. Secukinumab for the treatment of palmoplantar psoriasis: a 2-year, multicenter, real-life observational study. Expert Opin Biol Ther. 2022 Apr;22(4):547-554.
168. Mrowietz U, Bachelez H, Burden AD, Rissler M, Sieder C, Orsenigo R, et al. Secukinumab for moderate-to-severe palmoplantar pustular psoriasis: Results of the 2PRECISE study. J Am Acad Dermatol. 2019 May;80(5):1344-1352.
169. Menter A, Warren RB, Langley RG, Merola JF, Kerr LN, Dennehy EB, et al. Efficacy of ixekizumab compared to etanercept and placebo in patients with moderate-to-severe plaque psoriasis and non-pustular palmoplantar involvement: results from three phase 3 trials (UNCOVER-1, UNCOVER-2 and UNCOVER-3). J Eur Acad Dermatol Venereol. 2017 Oct;31(10):1686-1692.
170. Pinter A, Wilsmann-Theis D, Peitsch WK, Mössner R. Interleukin-17 receptor A blockade with brodalumab in palmoplantar pustular psoriasis: Report on four cases. J Dermatol. 2019 May;46(5):426-430.
171. Hegazy S, Konstantinou MP, Bulai Livideanu C, Tauber M, Uthurriague C, Paul C. Efficacy of ustekinumab in palmoplantar pustulosis. J Eur Acad Dermatol Venereol. 2018 May;32(5):e204-e206.
172. Bulai Livideanu C, Lahfa M, Mazereeuw-Hautier J, Paul C. Efficacy of ustekinumab in palmoplantar psoriasis. Dermatology. 2010;221(4):321-3.
173. Terui T, Kobayashi S, Okubo Y, Murakami M, Hirose K, Kubo H. Efficacy and Safety of Guselkumab, an Anti-interleukin 23 Monoclonal Antibody, for Palmoplantar Pustulosis: A Randomized Clinical Trial. JAMA Dermatol. 2018 Mar 1;154(3):309-316.
174. Okubo Y, Morishima H, Zheng R, Terui T. Sustained efficacy and safety of guselkumab in patients with palmoplantar pustulosis through 1.5 years in a

randomized phase 3 study. J Dermatol. 2021 Dec;48(12):1838-1853.
175. Duderstadt S, Raap U, Patsinakidis N. Rapid therapeutic response of palmoplantar pustulosis under biologic treatment with guselkumab. Dermatol Ther. 2021 Mar;34(2):e14792.
176. Del Campo DC. Successful Use of Tildrakizumab for Treatment of Palmoplantar Pustulosis: A Case Report. J Drugs Dermatol. 2021 Oct 1;20(10):1117-1119.
177. Alajlan AM, Qadoumi TA. Palmoplantar Psoriasis Successfully Treated With Risankizumab. Cureus. 2021 Aug 25;13(8):e17434.
178. Torrelo A. The use of biologics for childhood psoriasis. J Eur Acad Dermatol Venereol. 2019 Oct;33(10):1816.
179. Eisert L, Augustin M, Bach S, Dittmann M, Eiler R, Fölster-Holst R, et al. S2k guidelines for the treatment of psoriasis in children and adolescents - Short version part 2. J Dtsch Dermatol Ges. 2019 Sep;17(9):959-973.
180. P Philipp S, Menter A, Nikkels AF, Barber K, Landells I, Eichenfield LF, et al. Ustekinumab for the treatment of moderate-to-severe plaque psoriasis in paediatric patients (≥ 6 to < 12 years of age): efficacy, safety, pharmacokinetic and biomarker results from the open-label CADMUS Jr study. Br J Dermatol. 2020 Oct;183(4):664-672.
181. Paller AS, Seyger MMB, Alejandro Magariños G, Bagel J, Pinter A, Cather J, et al.; IXORA-PEDS study group. Efficacy and safety of ixekizumab in a phase III, randomized, double-blind, placebo-controlled study in paediatric patients with moderate-to-severe plaque psoriasis (IXORA-PEDS). Br J Dermatol. 2020 Aug;183(2):231-241.
182. Magnolo N, Kingo K, Laquer V, Browning J, Reich A, Szepietowski JC, et al. A phase 3 open-label, randomized multicenter study to evaluate efficacy and safety of secukinumab in pediatric patients with moderate to severe plaque psoriasis: 24-week results. J Am Acad Dermatol. 2022 Jan;86(1):122-130.
183. Scott JB, Paller AS. Biologics in pediatric psoriasis and atopic dermatitis: revolutionizing the treatment landscape. Cutis. 2020 Nov;106(5):224-226;E1;E2.

184. Warren RB, Reich K, Langley RG, Strober B, Gladman D, Deodhar A, et al. Secukinumab in pregnancy: outcomes in psoriasis, psoriatic arthritis and ankylosing spondylitis from the global safety database. Br J Dermatol. 2018 Nov;179(5):1205-1207.
185. Egeberg A, Iversen L, Kimball AB, Kelly S, Grace E, Patel H, et al. Pregnancy outcomes in patients with psoriasis, psoriatic arthritis, or axial spondyloarthritis receiving ixekizumab. J Dermatolog Treat. 2021 Sep 21:1-7.
186. Haycraft K, DiRuggiero D, Rozzo SJ, Mendelsohn AM, Bhutani T. Outcomes of pregnancies from the tildrakizumab phase I-III clinical development programme. Br J Dermatol. 2020 Jul;183(1):184-186.
187. Gisbert JP, Chaparro M. Safety of New Biologics (Vedolizumab and Ustekinumab) and Small Molecules (Tofacitinib) During Pregnancy: A Review. Drugs. 2020 Jul;80(11):1085-1100.
188. Götestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016 May;75(5):795-810.
189. Gorelick J, Shrom D, Sikand K, Renda L, Burge R, Dworkin C, et al. Understanding Treatment Preferences in Patients with Moderate to Severe Plaque Psoriasis in the USA: Results from a Cross-Sectional Patient Survey. Dermatol Ther (Heidelb). 2019 Dec;9(4):785-797.
190. Wolf P, Weger W, Legat F, Painsi C, Saxinger W, Müllegger R, et al. Lebensqualität und Behandlungsziele bei Psoriasis aus Patientensicht: Ergebnisse eines österreichweiten Querschnitt-Survey. J Dtsch Dermatol Ges. 2018 Aug;16(8):981-991.
191. Sawyer LM, Malottki K, Sabry-Grant C, Yasmeen N, Wright E, Sohrt A, et al. Assessing the relative efficacy of interleukin-17 and interleukin-23 targeted treatments for moderate-to-severe plaque psoriasis: A systematic review and network meta-analysis of PASI response. PLoS One. 2019 Aug 14;14(8):e0220868.
192. Xu S, Gao X, Deng J, Yang J, Pan F. Vergleich der Wirksamkeit und Sicherheit von Biologika bei mittelstark bis stark ausgeprägter Plaque-Psoriasis:

Metaanalyse multipler Therapien. J Dtsch Dermatol Ges. 2021 Jan;19(1):47-57.

193. Torres T, Puig L, Vender R, Lynde C, Piaserico S, Carrascosa JM, et al. Drug Survival of IL-12/23, IL-17 and IL-23 Inhibitors for Psoriasis Treatment: A Retrospective Multi-Country, Multicentric Cohort Study. Am J Clin Dermatol. 2021 Jul;22(4):567-579.
194. Eyerich K, Weisenseel P, Pinter A, Schäkel K, Asadullah K, Wegner S, et al. IL-23 blockade with guselkumab potentially modifies psoriasis pathogenesis: rationale and study protocol of a phase 3b, randomised, double-blind, multicentre study in participants with moderate-to-severe plaque-type psoriasis (GUIDE). BMJ Open. 2021 Sep 13;11(9):e049822.
195. Graier T, Salmhofer W, Jonak C, Weger W, Kölli C, Gruber B, et al. Biologic drug survival rates in the era of anti-interleukin-17 antibodies: a time-period-adjusted registry analysis. Br J Dermatol. 2021 Jun;184(6):1094-1105.
196. Mason KJ, Barker JNWN, Smith CH, Hampton PJ, Lunt M, McElhone K, et al; BADBIR Study Group. Comparison of Drug Discontinuation, Effectiveness, and Safety Between Clinical Trial Eligible and Ineligible Patients in BADBIR. JAMA Dermatol. 2018 May 1;154(5):581-588.
197. Tsai YC, Tsai TF. Switching biologics in psoriasis - practical guidance and evidence to support. Expert Rev Clin Pharmacol. 2020 May;13(5):493-503.
198. Wang TS, Tsai TF. Biologics switch in psoriasis. Immunotherapy. 2019 Apr;11(6):531-541.
199. Gasslitter I, Kirsten N, Augustin M, Torz K, Mrowietz U, Eyerich K, et al. Successful intra-class switching among IL-17 antagonists: a multicentre, multinational, retrospective study. Arch Dermatol Res. 2019 Jul;311(5):421-424.
200. Tahir H, Grewal S. Current unmet needs and emerging novel pharmacotherapies in psoriatic arthritis. Expert Opin Pharmacother. 2022 Mar;23(4):417-420.
201. Migliore A, Gigliucci G, Birra D, Saporito R, Cicerchia L, Massafra U, et al. Biologics for psoriatic arthritis: network meta-analysis in review. Eur Rev Med Pharmacol Sci. 2021 Sep;25(18):5755-5765.

202. Moschen AR, Tilg H, Raine T. IL-12, IL-23 and IL-17 in IBD: immunobiology and therapeutic targeting. Nat Rev Gastroenterol Hepatol. 2019 Mar;16(3):185-196.
203. Reich K, Conrad C, Kristensen LE, Smith SD, Puig L, Rich P, et al. Network meta-analysis comparing the efficacy of biologic treatments for achieving complete resolution of nail psoriasis. J Dermatolog Treat. 2021 Mar 1:1-9.
204. Camela E, Ocampo-Garza SS, Cinelli E, Villani A, Fabbrocini G, Megna M. Therapeutic update of biologics and small molecules for scalp psoriasis: a systematic review. Dermatol Ther. 2021 Mar;34(2):e14857.
205. Reich A, Mędrek K, Szepietowski JC. Interplay of Itch and Psyche in Psoriasis: An Update. Acta Derm Venereol. 2016 Aug 23;96(217):55-7.
206. Sun HY, Phan K, Paller AS, Sebaratnam DF. Biologics for pediatric psoriasis: A systematic review and meta-analysis. Pediatr Dermatol. 2022 Jan;39(1):42-48.
207. Porter ML, Lockwood SJ, Kimball AB. Update on biologic safety for patients with psoriasis during pregnancy. Int J Womens Dermatol. 2017 Feb 4;3(1):21-25.
208. Palmeira P, Quinello C, Silveira-Lessa AL, Zago CA, Carneiro-Sampaio M. IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol. 2012;2012:985646.
209. Owczarek W, Walecka I, Lesiak A, Czajkowski R, Reich A, Zerda I, et al. The use of biological drugs in psoriasis patients prior to pregnancy, during pregnancy and lactation: a review of current clinical guidelines. Postepy Dermatol Alergol. 2020 Dec;37(6):821-830.
210. Johansen CB, Jimenez-Solem E, Haerskjold A, Sand FL, Thomsen SF. The Use and Safety of TNF Inhibitors during Pregnancy in Women with Psoriasis: A Review. Int J Mol Sci. 2018 May 3;19(5):1349.
211. Ling Y, Puel A. IL-17 and infections. Actas Dermosifiliogr. 2014 Oct;105 Suppl 1:34-40.
212. Cottone M, Sapienza C, Macaluso FS, Cannizzaro M. Psoriasis and Inflammatory Bowel Disease. Dig Dis. 2019;37(6):451-457.

213. Schreiber S, Colombel JF, Feagan BG, Reich K, Deodhar AA, McInnes IB, et al. Incidence rates of inflammatory bowel disease in patients with psoriasis, psoriatic arthritis and ankylosing spondylitis treated with secukinumab: a retrospective analysis of pooled data from 21 clinical trials. Ann Rheum Dis. 2019 Apr;78(4):473-479.
214. Reich K, Leonardi C, Langley RG, Warren RB, Bachelez H, Romiti R, et al. Inflammatory bowel disease among patients with psoriasis treated with ixekizumab: A presentation of adjudicated data from an integrated database of 7 randomized controlled and uncontrolled trials. J Am Acad Dermatol. 2017 Mar;76(3):441-448.e2.
215. O'Connor W Jr, Kamanaka M, Booth CJ, Town T, Nakae S, Iwakura Y, et al. A protective function for interleukin 17A in T cell-mediated intestinal inflammation. Nat Immunol. 2009 Jun;10(6):603-9.
216. Awasthi A, Kuchroo VK. IL-17A directly inhibits TH1 cells and thereby suppresses development of intestinal inflammation. Nat Immunol. 2009 Jun;10(6):568-70.