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)

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ABSTRACT

Background Guselkumab is an interleukin (IL)-23 pathway blocker with proven efficacy in patients with moderate-to-severe plaque psoriasis. Early intervention with guselkumab may result in changes to the clinical disease course versus later intervention.

Methods and analysis Here we present the rationale and design of a phase 3b, randomised, double-blind, multicentre study (GUIDE), comparing treatment effects of guselkumab in patients with short (<2 years) or longer (>2 years) duration of plaque-type psoriasis, measured from first appearance of psoriatic plaques. Participants achieving skin clearance (Psoriasis Area and Severity Index (PASI)=0) by week 20 and maintaining complete clearance at week 28 visit (‘super-responders’ (SRe)) will be randomised to continue approved maintenance dosing every 8 weeks (q8w) versus an investigative maintenance dosing interval of 16 weeks (q16w) until week 68. Primary endpoint: proportion of participants withdrawing from guselkumab treatment for up to 48 weeks. Participants not achieving SRe criteria (non-SRe) will remain in the study with q8w guselkumab dosing through week 68. Additional to serum samples obtained from all patients, skin biopsies and whole blood samples will be taken from SRe and non-SRe participants at various time points in optional substudies. Analyses include: genetics; immunophenotyping (fluorescence-activated cell sorting); gene and protein expression profiling; immunohistology. By merging clinical endpoints with mechanistic findings, this study aims to elucidate how IL-23 blockade with guselkumab may modify the disease course by altering molecular and cellular drivers that cause relapse after treatment withdrawal, particularly among SRe.

Trials registration number Registered at ClinicalTrials.gov (NCT03818035). All primary endpoint results (prespecified analyses) will be submitted to peer-reviewed, international journals within 18 months after primary completion date.

INTRODUCTION

Plaque psoriasis is a common, chronic immune-mediated inflammatory disease characterised by plaques of red, dry, itchy and scaly skin that can manifest in all skin areas and vary in size from a few millimetres in diameter to covering large parts of the body surface. Psoriasis is associated with multiple comorbidities including cardiovascular disease, hypertension, metabolic syndrome, chronic kidney disease and...
psoriatic arthritis.1 Thus, plaque psoriasis patients carry a high burden of disease that extends beyond the visible signs in the skin. Peak disease onset is in early adulthood and the disease course is chronic; therefore, the need for treatment is lifelong.2–4 Currently, patients with moderate-to-severe plaque psoriasis are usually treated for several years with a combination of topicals, UV-light or conventional systemic immunosuppressive drugs. Commonly, patients switch to biological therapy several years after diagnosis, and most often when a satisfactory response has not been achieved, contraindications exist, or an adverse event forces a switch.5–7

The immunopathogenesis of psoriasis is based on a complex interplay between genetic susceptibility, environmental triggers and components of innate and adaptive immunity. At its core, psoriasis is a T-cell-mediated disease, in which dysregulation of the immune system in the skin promotes inflammatory responses and results in abnormal proliferation of keratinocytes and extensive infiltration of inflammatory cells.8,9 With the recognition that the interleukin (IL)-23/IL-17A/F immune axis is central to the pathogenesis of psoriasis, and that therapeutics targeting IL-23, IL-17A, IL-17A/F represent the most advanced and effective treatment options for patients, IL-23 has emerged as a ‘master regulator’ in psoriasis.2

IL-23 promotes terminal differentiation, expansion and maintenance of IL-17 producing cells (T17), expressing CD4+ (T helper 17 (Th17)) or CD8+ (Tc17) T cells.5–7,9–11 IL-23 has also been reported to impair the function of regulatory T cells (Treg) and to promote the differentiation of Treg into Th17-like cells in psoriatic patients, thereby dampening anti-inflammatory Treg responses.12–15 Further, IL-23 appears to be involved in the differentiation and survival of pathogenic tissue-resident memory T cells (TRM),16 which are thought to be responsible for recurrence of psoriatic skin lesions in previously affected sites.17 The physiological role of IL-23 in the human immune system is not well established. Observations of reduced antigen-specific immunoglobulins of all isotypes and a diminished delayed type hypersensitivity in IL-23p19-deficient mice point towards a defect at the level of T cells. However, the safety profile of guselkumab in clinical trials in psoriasis patients is not consistent with a generalised memory T cell defect.18–20

By targeting pathogenic T cells, in particular TRM in affected tissue, inhibition of IL-23 may have a profound effect on the pathophysiology of psoriasis that might extend beyond clearance of psoriasis plaques while on treatment. Guselkumab, an antibody that binds to the p19 subunit of IL-23, was the first approved selective inhibitor of IL-23 for the treatment of chronic plaque psoriasis.

Here, we discuss the concept of modifying the disease course towards long-term remission as a potential novel treatment goal for psoriasis. Also, we discuss the recently commenced Phase 3b, Randomised, Double-blind, Active-controlled, Multicentre Study to Evaluate Further Therapeutic Strategies with Guselkumab in Subjects with Moderate-to-Severe Plaque Psoriasis (GUIDE) study, which seeks to test the hypothesis that in psoriasis, early intervention with an IL-23 inhibitor could lead to better clinical responses and more durable maintenance of response after drug withdrawal.

The pathogenesis of psoriasis
IL-23 is a ‘master regulator’ cytokine in psoriasis
IL-23 has emerged as a ‘master regulator’ cytokine in many chronic inflammatory diseases, particularly in psoriasis.2–3,8–11,21–24 IL-23 bridges the innate and adaptive immune systems, as it acts on T cells as well as innate immune cells (eg, natural killer cells, macrophages, dendritic cells and innate lymphoid cells). IL-23 normally confers immunity against bacterial and fungal infections. However, dysregulated production of IL-23 promotes the development of chronic inflammation. It signals through the IL-23 receptor, which is believed to be expressed on several types of immune cells, including T cells, natural killer cells, neutrophils, mast cells, innate lymphoid cells and macrophages.25–27

Binding of IL-23 to its receptor primarily activates signal transducer and activator of transcription (STAT3), which has critical functions in Th17 and Tc17 cell activation, differentiation, proliferation and survival. STAT3 directly regulates the genes encoding IL-17A, IL-17F and IL-23R and indirectly controls expression of the retinoic acid receptor-related orphan receptor (ROR)γt transcription factor, a regulator of Th17 differentiation.29

Skin resident memory T cells provide rapid local immune responses
Tissue-resident memory T cells are a recently identified subset of non-circulating memory T cells that persist long-term in peripheral tissues. In both mice and humans, these cells express CD69, and subsets also express CD103 and CD49a.17,30 CD69 appears to be involved in retention of TRM in peripheral tissues. CD103 is a known ligand of E-cadherin, a homotypic adhesion molecule expressed by epithelial cells in barrier tissues.31 Under healthy conditions, TRM differentiate and accumulate in tissues following infections or vaccinations to provide rapid local immune responses on re-exposure to pathogens. However, TRM may also develop after sensitisation to self-antigens, and thus be involved in the pathogenesis of autoimmune disorders such as psoriasis.31–34

One of the main challenges in the treatment of psoriasis is recurrence of psoriatic skin lesions, usually at the same locations on the body. The persistent localised presence of pathogenic TRM derived from clonally expanded autoreactive T cells may explain this phenomenon.17,32–34 The first hint for the involvement of TRM in psoriasis was provided by the unexpected observation that blockade of E-selectin, which inhibits T cell migration from the blood into the skin, was ineffective in the treatment of psoriasis.35 Skin transplant experiments in mice demonstrated that non-lesional, presporiatic human skin grafts developed into psoriasis lesions after transplantation onto immunodeficient mice.36–37 These lesions emerged
through activation and proliferation of resident T cells transferred with non-lesional skin grafts.

Transcriptomic analysis of skin biopsies from human patients revealed that a subset of disease-related genes remained abnormally expressed in healed lesional skin responding to antitumour necrosis factor α treatment.36 These included T cell-associated genes, as well as genes associated with ‘structural’ cell types, such as keratinocytes, which collectively represent a ‘molecular scar’ in resolved psoriatic lesions (figure 1A). Additional histological studies verified the presence of residual dermal CD8+ T cells in resolved psoriatic skin. IL-17A+ CD8+ T RM and IL-22+ CD4+ T RM cells were found to persist in the epidermis, possibly representing a form of disease memory in clinically healed regions of psoriasis.16 39 40 In particular, a distinct population of epidermal CD8+ T cells coexpressing CD103, CCR6 and IL-23R was highly enriched in resolved lesions.16 These findings point towards a possible scenario, in which CD8+ T RM drive inflammation and recruitment of circulating leucocytes into the tissue through IL-23-dependent IL-17A production, while CD4+ T RM promote keratinocyte activation and development of acanthosis through production of IL-22. CD49a was recently identified as a phenotypic marker for the differentiation of CD8+ CD103+ T RM on a functional basis.36 39 CD49a+ T RM produced IL-17, preferentially expressed IL-23R, and were enriched in psoriatic lesions, whereas CD49a+ T_reg produced interferon-γ and were enriched in the skin of vitiligo patients. Another recent study detected IL-17-producing αβ T cell clones with psoriasis-specific antigen receptors in residual T cell populations of clinically resolved psoriatic skin.41 These cells were postulated to represent lesion-initiating pathogenic T cells in psoriasis.41 Increasing evidence indicates that the majority of CD8+ T cells in psoriasis plaques are present as T RM,42 implying a predominant role for CD8+ T RM in psoriasis recurrence. In biopsies obtained from psoriatic lesions, the majority of IL-17A-producing CD8+ T cells were T RM whereas the majority of IL-17A-producing CD4+ T cells were non-T RM (defined as CD3+/CD4+/CD103-/CD49a+ T cells).43 T_reg display functional deficits in psoriasis T_reg, which account for 5%–10% of skin resident T cells, sustain immune homeostasis and maintenance of self-tolerance by suppressing inflammation, and specifically effector T cells.44 T_reg are characterised by high expression of Foxp3, a key transcription factor essential for their function, and IL-25, the IL-2 receptor alpha chain. T_reg proliferate under conditions similar to those found in inflamed skin.12 33 45 46 T_reg and T17 cells share naïve T cells as their common precursor, and their differentiation programmes are reciprocally interconnected (figure 1B). T_reg exert anti-inflammatory effects by suppressing the activity of other skin-resident T cells, such as T17 cells.35 The balance between proinflammatory T17 cells and immunosuppressive T_reg plays a critical role in the pathogenesis of several autoimmune diseases.9 45 46 Studies finding elevated T17/T_reg ratios in patients with rheumatoid arthritis (RA), psoriasis, multiple sclerosis, non-alcoholic fatty liver disease and inflammatory bowel disease support this notion.45 48 In psoriasis, dysfunction of T_reg has been suggested as a potential mechanism behind the imbalance of T_reg and pathogenic T cells.14 49 50 Psoriatic T_reg demonstrate proliferative and functional deficits that may permit hyperproliferation of pathogenic T cells.50 Recently, STAT3-phosphorylation induced by IL-23, IL-6 and IL-21 was revealed to impair T_reg function.15 Lineage plasticity and interconversion between T_reg and T17 cells could represent another mechanism of T_reg dysfunction.3 45 Since Foxp3 and RORc are lineage-determining transcription factors for T_reg and T17 cells, respectively, their balance regulates the fate of T_reg thereby affecting the T17/T_reg ratio.35 For example, instability of Foxp3 in T_reg was reported to lead to the generation of potentially autoreactive effector T cells.46 Another pathogenic mechanism may be the phenotypic conversion of T_reg into Th17 cells.12 44 45 Peripheral blood derived T_reg from patients with severe psoriasis have an enhanced propensity to convert into IL-17A-expressing cells, which is associated with progressive loss of Foxp3 and increased expression of RORγt. This shift from T_reg to a Th17-related phenotype is promoted by IL-23.12 The finding that IL-17A+Foxp3+CD4+ positive cells are present in psoriasis plaques suggests that conversion of T_reg into IL-17A-producing cells may also occur in vivo.42 45 A more recent study confirmed that IL-23 drives plasticity of T_reg by inducing Foxp3−RORγt+IL-17A cells, and that this process is regulated by RORγt signalling.13

Expanding the concept of modifying disease memory in psoriasis Overall, current knowledge suggests that epidermal T_RM generated by immune challenges in peripheral tissues persist in previously lesional psoriatic skin after healing. In response to triggers that may induce recurrence of disease, T_RM can mount rapid, localised immune responses featuring the production of cytokines with critical roles in the pathogenesis of psoriasis. Recent findings suggest that IL-23 is involved in the differentiation and survival of pathogenic T_RMs.12 Given that investigations of the pathogenic role of T_RMs in psoriasis are still at an early stage, many questions still need to be addressed in this field. This study will explore the question, if the reduction or even eradication of T_RMs through IL-23 inhibition by a monoclonal antibody such as guselkumab can be achieved and leads to improvement of clinical disease beyond the period of treatment. Explorative analysis of this study will link underlying cellular changes (ie, the frequencies of T_RM and T_reg) to the clinical course of disease recurrence during the withdrawal period (week 68–week 116). By comparing subjects starting the drug withdrawal period with complete skin clearance (absolute Psoriasis Area and Severity Index (PASI) score of 0) with those with some remaining plaques (absolute PASI score >0 and <3) we aim to gain insights into the correlation between speed of disease recurrence and changes of T cell frequencies. Biopsies will therefore be taken at week 68 and at the timepoint of loss of disease control (PASI >5). This immunological understanding of long-term drug-free remission would be a step towards...
Figure 1  Current pathogenic model of psoriasis.\(^{2,12,14,41,65}\) (A) T cell subsets in psoriasis, their differentiation, function and phenotype. High TGF-β concentration promotes IL-10 and IL-17 producing \(T_{reg}\) differentiation, while the presence of IL-6, TGF-β, IL-1-β and IL-21 promote dominant Th17 cell differentiation expressing an IL-17/IFN-γ cytokine signature. (B) In early psoriasis, environmental stimuli in combination with a loss of tolerance activate the innate immune system, leading to the production of IL-23 by dermal DCs and macrophages. IL-23 then drives activation and expansion of T17 cells which subsequently generate a cytokine milieu that promotes a feedforward inflammatory cascade in epidermal keratinocytes, leading to parakeratosis and psoriatic lesions. IL-17 autoamplifies its signal by triggering the production of chemokines by activated keratinocytes, which subsequently recruits more T17 cells and other immune cells (eg, neutrophils, DCs and macrophages). Persistent high levels of IL-23 in psoriatic skin sustain IL-17 production, thus fuelling the self-amplifying inflammatory process. As psoriasis progresses to a more chronic state, sustained high levels of IL-23 in combination with low concentrations of TGF-β promote \(T_{RM}\) expression, favouring T17 cell differentiation and suppressing \(T_{reg}\) differentiation. \(T_{RM}\) are a subset of non-circulating memory T cells that persist long-term in peripheral tissues and are characterised by the markers CD69 and CD103. (C) Inhibition of the regulatory cytokine IL-23 is hypothesised to lead to long-lasting therapeutic effects by restoring a ‘physiological’ \(T_{reg}/T_{RM}\) balance. This is in contrast to the blockade of an effector cytokine, which leads to reduction of inflammatory cells but has less effect on the relative numbers of proinflammatory and anti-inflammatory T cells. Ahr, aryl hydrocarbon receptor; CCR, chemokine receptor; CD, cluster of differentiation; CXCR, CXC chemokine receptor; DC, dendritic cell; IFN, interferon; IL, interleukin; RORγt, retinoic acid receptor-related orphan receptor transcription factor; T17, IL-17 producing T cells; T-bet, T box protein expressed in T cells; TGF, transforming growth factor; Th17, T helper 17; \(T_{reg}\) regulatory T cell; \(T_{RM}\) tissue-resident memory T cell.
disease modification, a principle that has been described for treatment of other autoimmune diseases (eg, RA and Crohn’s disease) with biological agents, but this is not yet clearly defined for psoriasis.

**Early intervention with IL-23 inhibitors may lead to long-lasting and disease-modifying effects**

Psoriasis predominantly presents as a skin disease and affects patients’ quality of life physically, emotionally and socially. Treatment should aim to improve overall prognosis by reducing the severity of disease and preventing relapse, with the ultimate goal of modifying the course of disease. However, it is well known that initial approaches to treatment of even moderate-to-severe psoriasis are based on topical therapy, which is typically not highly effective. The current German guideline proposes the use of biologics when failure of conventional first-line therapeutics in plaque psoriasis can be anticipated. Thus, therapy with biologics is often not started until other systemic options have failed, which could be several years after the onset of disease. According to the Dutch registry BioCAPTURE, between 2005 and 2015 the median disease duration at the start of first-line conventional systemic therapy in patients with severe psoriasis was 11.0 years and the median disease duration at start of treatment with biologics was 18.9 years.

In other immune-mediated inflammatory diseases such as RA, early intervention with biologics has been shown to increase remission rates, improve symptoms and halt joint damage. In addition, patients with RA with recent onset disease (<2 years) exhibited better treatment responses than those with long-standing disease. It can be hypothesised that, in the treatment of psoriasis, a ‘hit hard and early’ approach might also result in high response rates with long-lasting remission after treatment stop, provided that the ‘hard hit’ aims at the right target. In particular, early intervention with selective and direct IL-23 inhibitors which specifically interfere with the major disease-driving pathway in psoriasis could prove beneficial. Early intervention with IL-23 inhibitors may have the potential of restoring a ‘healthy’ Th17/Treg balance and controlling Treg levels, thus promoting a long-lasting and possibly disease-modifying therapeutic effect (figure 1C).

In clinical studies, direct IL-23 inhibition has been shown to successfully induce remission in psoriasis with clearance rates that exceed those achieved by other non-biological and biological systemic psoriasis treatments. Approximately 44% of patients achieved complete clearance (PASI score=0) and about 70% of patients achieved nearly complete clearance (PASI score ≤1) after 24 weeks of treatment with guselkumab. Recently presented long-term data for guselkumab demonstrated that efficacy for treatment of moderate-to-severe psoriasis was maintained through 5 years. Interestingly, some patients, who had achieved a 90% improvement from their baseline PASI score (PASI 90 response) with guselkumab, sustained their clinical response for several months after withdrawal of treatment, after complete washout of the drug (five half-lives; mean T½: 15–18 days). Maintenance of PASI 90 response after drug withdrawal was associated with continued suppression of IL-17A, IL-17F and IL-22. In exploratory analyses, participants with shorter disease duration (<2 years) seemed to have a higher maintenance of response rate after drug withdrawal than participants with a longer history of disease (ie >10 years). Furthermore, achieving an absolute PASI score of 0 at week 28 was associated with long-term maintenance of PASI 90 response: long-term maintenance of PASI 90 response was achieved by 45.8% of participants who achieved an absolute PASI score of 0 at week 28 compared with 24% of participants who did not (OR of 2.66; p<0.005, Fisher’s exact test). These results imply that a distinct subset of patients with short disease duration (<2 years) and striking clinical response to guselkumab treatment (absolute PASI score of 0 at week 28) may more readily achieve long-term, drug-free disease control. Overall, preliminary clinical data suggest that early intervention with selective IL-23 inhibitors may have the potential to wield a profound effect in psoriasis that extends beyond short-term clearance of psoriatic skin lesions, and could instead lead to a long-term, sustained clinical response in certain patients.

**MATERIALS AND METHODS**

**Evaluating disease modification in clinical trials: the GUIDE study**

Currently, therapeutic intervention is individualised depending on the patient’s measurable severity of disease, which is traditionally assessed by the PASI and Investigator Global Assessment tools. Since it is difficult to predict which biological treatment may induce an adequate clinical response in a given patient, the choice of an optimal therapeutic agent remains a challenge, and therapies are often characterised by cycles of medication trial and error. Biomarker-based assessment of clinical response to treatment and corresponding precision dosing may become an attractive approach towards a more individually tailored therapy in psoriasis.

GUIDE (NCT03818035) is a phase 3b randomised, double-blind, parallel-group, multicentre trial, including >850 adult participants with moderate-to-severe plaque type psoriasis, of whom approximately 40% will have disease duration of ≤2 years. In part 1 of the study, all participants receive guselkumab at week 0 (baseline), and weeks 4, 12, 20 and 28 (figure 2) following the standard guselkumab treatment regimen. It is assumed that about 280 participants will qualify to be categorised as super-responders (SRe), defined as those with an absolute PASI score of 0 at both week 20 and week 28. SRe are then randomly assigned to either of two treatment groups: Group 2a receives guselkumab 100mg by subcutaneous injection every 8 weeks (q8w) and group 2b receives the same dose every 16 weeks (q16w). In addition, participants with disease duration ≤2 years are equally distributed to...
both groups. Participants with a PASI score ≥0 at weeks 20 and/or 28 continue to receive guselkumab 100 mg q8w until week 60 (defined as study group 2c). Participants in groups 2a and 2b with a PASI score <3 at week 68 will enter part 3 of the study and be withdrawn from study medication and followed through week 116. Participants with more substantial loss of response, defined as having PASI score >5 at any visit during part 2 or 3 of the study, enter the retreatment arms (groups 2d or 3c) and receive guselkumab 100 mg at weeks 0, 8, and 16 calculated from the date of loss of disease control (study part 3). Groups 3a: SRe randomised to GUS 100 mg q8w in study part 2 with withdrawal of GUS at week 68 (study part 3). Group 3b: SRe with fluctuating disease (PASI score 3–5) at week 68 or loss of disease control (PASI score >5) at any other visit after week 68, who will enter the retreatment arm and receive GUS 100 mg at R0, R8, and R16 calculated from the date of loss of disease control (study part 3). GUS, guselkumab; PASI, Psoriasis Area and Severity Index score; q8w, every 8 weeks; q16w, every 16 weeks; R, retreatment week; SRe, super-responder; W, week.

**Figure 2** Study setup and design. SRe are defined as participants who receive on-label GUS treatment until W20 and respond with a score of PASI=0 at W20 and W28. "Blinded treatment. Group 1: All participants who are enrolled and scheduled to receive GUS 100 mg at W0, W4, then q8w until W28 (study part 1). Group 2a: SRe (PASI score=0 at W20 and W28) randomised to GUS 100 mg q8w at W28–W60 (study part 2). Group 2b: SRe randomised to GUS 100 mg q16w at W28–W60 (study part 2). Group 2c: non-SRe with a PASI score ≥0 at W20 and/or W28 who will receive GUS 100 mg q8w at W28–W60 (study part 2). Group 2d: SRe with loss of disease control between W28 and W68, who will enter the retreatment arm and receive GUS 100 mg at R0, R8, and R16 calculated from the date of loss of disease control (study part 2). Group 3a: SRe randomised to GUS 100 mg in study part 2 with withdrawal of GUS at W68 (study part 3). Group 3b: SRe with fluctuating disease (PASI score 3–5) at W68 or loss of disease control (PASI score >5) at any other visit after W68, who will enter the retreatment arm and receive GUS 100 mg at R0, R8, and R16 calculated from the date of loss of disease control (study part 3). GUS, guselkumab; PASI, Psoriasis Area and Severity Index score; q8w, every 8 weeks; q16w, every 16 weeks; R, retreatment week; SRe, super-responder; W, week.

**Hypothesis and study evaluations**

Guselkumab treatment may have greater modifying effects on immunopathological mechanisms of disease in participants who are SRe than in those who do not achieve SRe criteria (non-SRe). The hypothesis of this study is that among SRe participants, guselkumab dosed q16w is non-inferior to guselkumab dosed q8w as assessed by the proportion of participants with an absolute PASI score <3 at week 68 (box 1). The study is also designed to investigate whether dosing guselkumab at these different intervals in SRe may affect maintenance of drug-free control of disease from week 68 through week 116.

Further, the study will investigate whether participants with short disease duration (≤2 years) show faster and higher guselkumab responses compared with participants with longer disease duration, and whether participants with shorter disease duration are able to maintain longer drug-free control of disease after guselkumab is withdrawn in study part 3 (box 1).

**Statistical analysis**

Statistical analyses in this study will be performed separately for each part of the study and will focus on the comparison of the two randomised treatment groups (ie, group 2a: SRe receiving guselkumab 100 mg q8w vs group 2b: SRe receiving guselkumab 100 mg q16w) in study part 2. The analyses will be confirmatory for the primary endpoint, and exploratory for the major and all other secondary endpoints. The study is designed to demonstrate that guselkumab 100 mg q16w treatment is non-inferior to guselkumab 100 mg q8w treatment in SRe, as assessed by the proportion of participants with an absolute PASI score <3 at week 68. A non-inferiority margin of 10% was chosen based on a minimally clinically
Primary objective
► To demonstrate that ‘super-responders’ (SRe; defined as psoriasis patients who receive on-label guselkumab treatment until week 20 and respond with a Psoriasis Area and Severity Index (PASI) score=0 at both week 20 and week 28) maintain control of disease until week 68 with a prolonged guselkumab dosing interval of 16 weeks (100 mg q16w). To be demonstrated in study part 2 (see figure 2 for study design).

Secondary objectives
► To determine
  — Whether participants with short disease duration (<2 years) show more rapid and more pronounced guselkumab responses compared with participants with longer disease duration, and whether participants with shorter disease duration are able to maintain longer drug-free control of disease after guselkumab withdrawal. To be evaluated in study parts 1, 2 and 3.
  — Whether guselkumab dosing at different treatment intervals (q8w vs q16w) in SRe from week 28 to week 60 may affect maintenance of drug-free control of disease after 68 weeks of guselkumab treatment. To be evaluated in study part 3.
  — The safety and tolerability of guselkumab in participants with moderate-to-severe plaque-type psoriasis.

Exploratory objectives
► To characterise:
  — Immune cellular features at baseline (week 0) and changes (quantitative and qualitative characterisation) in lesional skin of participants during treatment with guselkumab as determined by fluorescence activated cell sorting (FACS)-based analysis. To be explored in substudy 1.
  — Immune cellular features in the blood of participants at baseline (week 0), and changes (quantitative and qualitative characterisation) during and after treatment with guselkumab as determined by FACS-based analysis. To be explored in substudy 1.
  — Molecular (gene expression) changes in the skin of participants treated with guselkumab as determined by RNA sequencing (RNAseq) and quantitative PCR. To be explored in substudy 2.
  — Tissue immunopathological changes in the skin of participants during and after treatment with guselkumab as determined by immunohistochemistry/immunofluorescence/in situ hybridisation. To be explored in substudy 2.
  — Effects of guselkumab treatment on serum biomarkers as determined by immunoassays. To be explored in substudy 3.
  — The association between changes in the various exploratory biomarker endpoints and (1) efficacy of guselkumab, (2) duration of psoriasis, (3) maintenance of response after stopping guselkumab treatment and (4) ability to achieve a PASI 100 response at weeks 20 and 28 (super responder status). To be explored in all substudies.

Various pharmacological/clinical response relationships allowing assessment of interindividual variability in clinical outcomes and possible identification of subject population groups that may show particularly differentiating responses to guselkumab. The substudies also aim to further understand the mechanism of action (MoA) of guselkumab at the molecular and cellular levels during and after treatment. Changes in gene expression as well as quantitative and qualitative changes in different types of immune cells are evaluated in skin biopsies and blood (Box 2).

In substudy 1 (cellular MoA substudy), 6 mm skin biopsy samples are collected from non-lesional skin at baseline (week 0) and lesional skin at weeks 0, 4, 28 and 68 from approximately 60 participants. In addition, if participants lose control of disease (having a PASI >5) in study parts 2 or 3 and go into retreatment, an additional biopsy is taken from an active lesional plaque. Biopsies will be dissociated into single-cell suspension and subjected to fluorescence-activated cell sorting (FACS)-based immunophenotyping analysis of T cells, macrophages and dendritic cells. Further, whole blood samples for the isolation of peripheral blood mononuclear cells are collected from consenting participants for subsequent immunophenotyping analyses by FACS. In substudy 2 (gene expression substudy), 6 mm skin biopsies are collected in a subset of participants (target n=100) at selected sites to evaluate gene expression profiles and cellular content by surface protein staining. Immune staining techniques include H&E stain, immunohistochemistry and...
immunofluorescence analyses. For substudy 3 (serum analysis), serum samples are collected from all participants at weeks 0, 4, 28, 68 and 80 to assess pharmacodynamic effects on blood protein analytes associated with the response to guselkumab as well as markers related to psoriasis. Measurements include, but are not limited to, serum IL-17A, IL-17F, IL-22 and beta defensin-2 (BD-2) levels. Genetic variation can be an important contributing factor to interindividual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Substudy 4 (genetic analyses) may help to identify subpopulations that respond differently to a drug. The goal of the genetic (DNA) analysis is to identify genetic factors that may influence responses to guselkumab in the populations of psoriasis patients studied.

Together, these substudies will relate immunopathological mechanisms to clinical course and characteristics of plaque psoriasis and may thus provide insights into individualised guselkumab treatment algorithms. This could include identification of predictors of optimal responses to guselkumab.

Together with the underlying mechanistic biomarker substudies, GUIDE evaluates whether selective IL-23 blockade exerts significant modifying effects on disease pathophysiology by studying and correlating clinical (eg, duration of disease), serological (eg, drug serum concentration) and immunopathophysiological (eg, balance of Treg and T RM ) disease parameters in patients treated with guselkumab for a year followed by withdrawal of treatment, and evaluates whether these effects are more pronounced in patients with shorter disease duration.

ETHICS AND DISSEMINATION

The GUIDE study was designed and will be conducted and reported in accordance with the International Confer-
ence on Harmonisation Harmonised Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, and in accordance with the Declaration of Helsinki. A positive opinion has been obtained from the ethics committee Medical Council Hamburg (PVN5925).

All patients are required to provide written informed consent. A separate consent form will be signed by patients taking part in the optional mechanistic substudies 1 and 2 and the optional pharmacogenetic testing (substudy 4).

All study results will be published. Data for the primary endpoint analysis at week 68 are expected to be available in 2022; final results are expected to be published in 2024.

Status and perspective
GUIDE started enrolment in February 2019 in Germany and in December 2019 in France. Full enrolment was achieved in November 2020. Final database lock is expected in 2023.

Patient and public involvement
Patients or the public will not be involved in the design, or conduct, or reporting, or dissemination plans of this research.

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