Secukinumab treatment in new-onset psoriasis: aiming to understand the potential for disease modification – rationale and design of the randomized, multicenter STEPIIn study

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Abstract

Background To date, biological treatments have been assessed in subjects with a long-term history of psoriasis and previous failures to systemic and topical therapies. In rheumatoid arthritis and other immune-mediated inflammatory diseases, early intensive systemic treatment prolongs treatment-free remission. We hypothesize that, by treating patients with psoriasis early with an effective systemic therapy, we may be able to alter the clinical outcome and the natural course of the disease. The STEPIIn study (NCT03020199) investigates early intervention with secukinumab versus narrow-band ultraviolet B (nb-UVB) phototherapy in subjects with new-onset psoriasis.

Objective To determine whether early intervention with either nb-UVB treatment or secukinumab in subjects with new-onset plaque psoriasis might modify the natural course of the disease.

Methods One hundred and sixty subjects aged 18–50 years with new-onset (≤12 months) moderate-to-severe plaque psoriasis and naïve to systemic treatment and phototherapy will be randomized to secukinumab 300 mg or nb-UVB. The Main Study has two treatment arms: Arm A1, subcutaneous secukinumab 300 mg at baseline, Weeks 1, 2, 3 and 4, and every 4 weeks thereafter until and including Week 52; Arm B1, one/two cycles of nb-UVB for 12 weeks each (maximum 28-week break between cycles). After treatment discontinuation, patients will be followed up and monitored for disease activity up to Week 208. A Mechanistic Sub-study will assess immunological changes and pathogenic tissue-resident memory T cells in skin biopsies.

Conclusions STEPIIn is the first study to investigate whether early intensive treatment in new-onset psoriasis can modify the long-term natural course of the disease and thus become a novel treatment strategy for patients with psoriasis.

Conflict of interest

L Iversen has been a paid speaker for MSD, Pfizer, AbbVie, Almirall, Janssen Cilag, Eli Lilly, Novartis and LEO Pharma and has been a consultant or served on Advisory Boards with Pfizer, AbbVie, Almirall, BMS, Janssen Cilag, Novartis, Eli Lilly, LEO Pharma and MSD. He has served as an investigator for MSD, Pfizer, AbbVie, Janssen Cilag, Eli Lilly, Novartis, Amgen and LEO Pharma and received research and educational grant from Pfizer, AbbVie, Novartis, MSD and Leo Pharma. L Eidsmo has received consultancy fees from Galderma, Leo...
Psoriasis is a common condition with an estimated prevalence of 2–4% in Western countries.1 It has a substantial impact on the physical and psychological quality of life.2,3 Psoriasis is considered an immune-mediated inflammatory disease (IMID) in which both innate and adaptive immune responses are involved in the pathogenesis.

Treatment approaches to psoriasis range from conventional to systemic interventions that target the immune system at different stages. The induction of apoptosis in several different cell types residing in the skin (e.g. keratinocytes and T lymphocytes) and the shift of the immune response away from the Th1/Th17 axis and towards the counter-regulatory Th2 axis is known to be driven by nb-UVB irradiation of impaired skin.4 Alefacept has also been known to induce the apoptosis of activated memory T cells and to target the activation and proliferation of T cells.5 Therapies have advanced over time to targeting specific immune cytokines such as TNF, a key regulator of immune cells and its effectors, through intervention with TNF-targeting antibodies. Downstream, more psoriasis specific modulators are IL-12/23, or recently IL-17A, and their associated signalling pathways.

The induction of the IL-23/IL-17A pathway in various immune cells, including T cells, neutrophils and dendritic cells (DCs), plays a crucial role in the pathogenesis of psoriasis.6,7 IL-17A, a proinflammatory cytokine downstream of IL-23, is secreted by T cells in psoriatic lesions.6–10 IL-17A activates epidermal keratinocytes to secrete chemokines and other proinflammatory mediators, which recruit inflammatory cells, including neutrophils, IL-17A+ effector T cells, DCs and innate lymphoid cells to the affected skin site.8,11,12 Drs that selectively neutralize IL-17A (such as secukinumab) lead to significant clinical improvement of moderate-to-severe psoriasis. Recent studies have shown that IL-17A inhibitors have superior efficacy compared to other, more upstream biologic treatments such as etanercept and ustekinumab.13–15

Subclinical inflammation in resolved psoriatic plaques
Psoriasis can be effectively treated with biologic systemic agents.1,3,14,16,17–22 However, a relapse to pre-treatment psoriasis severity occurs following treatment cessation in the majority of patients.20–22 The psoriatic skin lesions often recur, but not always, at previously affected locations, as discussed in Clark et al., Suarez-Farinas et al. and Park et al.23–25 This phenomenon of a ‘molecular scar’ is reinforced by a difference in the gene expression patterns of healed psoriatic skin lesions versus that of the unaffected, clinically normal skin.24 Tian et al. examined five microarray data sets to identify 20 genes that best discriminated between lesional and adjacent non-lesional skin...
using the Meta-analysis derived (MAD) transcriptome, and the Meta Threshold Gradient Directed Regularization (MTGDR) method. Of those 20 genes, alterations in expression of six genes were correlated with differential methylation patterns between psoriatic skin lesions and normal skin. Moreover, four of the 20 genes were identified as part of a residual disease genomic profile, commonly known as a molecular scar, following treatment with tumour necrosis factor (TNF) inhibitors.

Gene expression patterns in skin that appear to be fully resolved from psoriasis after treatment show that subclinical inflammation continues and inflammatory cytokines and chemokines persist. Although the number of inflammatory DCs decreases in resolved lesions, Langerhans cells retain the increased gene expression of IL-23, thereby contributing to localized disease memories in resolved skin. Skin epithelial stem cells have also been mentioned to serve as memory cells in autoimmune skin disorders. The molecular scar may involve several aspects of the pathogenesis of psoriasis. Tissue-resident T cells may provide an important insight into the persistence of the lesion, while genomic imprinting may represent a molecular explanation; targeting the clues to the persistence of the lesion may open a new approach for true disease modification in psoriasis.

**Tissue-resident memory T cells**

Tissue-resident memory T (TRM) cells develop in peripheral tissues in response to infections or inflammation and provide a rapid immunity barrier to recurring infections for years following the primary pathogen encounter. TRM cells reside in previously infected peripheral tissues, such as the skin, and are capable of initiating in situ inflammation when exposed to antigens presented by local DCs. Increased numbers of IL-17A-producing TRM cells are present in the epidermis and dermis of psoriatic lesions in patients with plaque-type psoriasis and persist even after full resolution of psoriasis plaques. These cells may be important in both chronicity and site-specific recurrence of psoriasis in resolved lesions following discontinuation of treatment. It is not fully understood what antigen polyclonal TRM cells recognize in psoriasis or whether TRM cells can leave peripheral tissues and migrate to other sites in the body where the cognate antigen is present. Such migration out of the peripheral tissues could potentially contribute to an increase in the spread of psoriatic plaques at other locations in the skin.

A key mechanism by which TRM cells challenge infections in peripheral tissues is the recruitment of additional immune cells from the circulation. It is likely that a similar scenario occurs during the establishment and perpetuation of chronic inflammatory diseases such as psoriasis.

In psoriasis, there is an increased recruitment of IL-17A-producing cells to inflamed tissues (Fig. 1). IL-17A induces, among other inflammatory mediators, the expression of CCL20, a chemokine that binds to CCR6. CCR6 is expressed on IL-17A-producing cell types such as IL-17A effector and memory T cells, γδ T cells, and ILC3 cells. Thus, IL-17A drives a feed-forward loop that employs the CCL20-CCR6 axis and may therefore play a crucial role at early stages during the establishment of psoriasis.

Moreover, IL-17A signalling activates keratinocytes to produce IL-23, IL-6, and IL-1β, which promote the de novo differentiation of IL-17A-producing T cells in secondary lymphoid organs. Hence, in addition to the accumulation of already established IL-17A-producing cells, IL-17A signalling may indirectly instruct additional T cells to commit to the inflammatory type-17 programme.

We hypothesize that, in the early stages of psoriasis, only few effector/memory IL-17+ T cells have invaded the inflamed skin. In the absence of treatment, these cells may accumulate and establish a continuously expanding pool of IL-17+ TRM cells that will ultimately lead to chronic disease. Secukinumab-treated psoriasis patients exhibit a very fast clinical response that is associated with the downregulation of inflammatory mediators in the skin, including CCL20 and IL-1β. Therefore, secukinumab treatment in early-stage psoriasis may interrupt the recruitment of IL-17A-producing cells to inflamed tissues and thus potentially modify the disease. As far as the authors are aware, no previous studies have examined the effect of early intervention in new-onset psoriasis on skin biomarkers, and in particular, TRM cells.

By treating psoriasis patients early and intensively with therapies targeting the main disease pathways, such as the IL-17A-neutralizing antibody secukinumab, we hypothesize that the clinical outcome and the natural course of the disease can be altered. This could mean longer periods of treatment-free remission, limited spread of psoriatic lesions to new anatomical locations or, ultimately, complete resolution of the psoriatic disease.

**Evidence from other IMIDs**

Current hypotheses suggest that early intensive treatment of an autoimmune disease with biologic drugs can dampen the immune mechanisms that lead to a chronic inflammation. Experience from other chronic IMIDs such as rheumatoid arthritis (RA), Crohn’s disease and multiple sclerosis (MS) has shown that early intensive treatment can significantly improve long-term outcomes in disease activity.

Patients treated within 2 years of RA onset showed significant improvements in function following treatment versus patients treated 2 years after onset. Initiation of treatment before 3 months versus before 12 months in patients with RA also makes a difference in long-term outcomes, indicating a ‘window of opportunity’ for better treatment outcomes early in the course of the disease. Significant short- and long-term improvements are observed when systemic biologic treatment is administered early in the course of the disease. In the Behandel Stratageen (BeSt) study, at 2 years after treatment, more RA patients who had been treated early with infliximab versus
delayed infliximab could discontinue therapy owing to a good response (56% versus 29%). A review highlighted that active treatment administered within a year of RA onset provided a response rate in 53% of patients; however, the response rate progressively diminished over time for patients with a longer disease duration.61

Short- and long-term studies have shown that patients who receive treatment with interferon-β for early onset of MS can benefit greatly through prevention or delay of disease activity, as evidenced by clinical and magnetic resonance imaging outcomes.55,56 In a recent study on Psoriasis Randomised Etabencept Study in Patients with Psoriatic Arthritis (PRESTA), patients with concomitant psoriatic arthritis and moderate-to-severe psoriasis responded well to etanercept 50 mg treatment once weekly, irrespective of disease duration. However, patients with psoriatic arthritis with ≤2 years of disease had greater improvements than those with ≥2 years of disease.62

**STEPIn Study – the concept of intensive, early intervention in the treatment and disease modification of psoriasis**

Treatment of psoriasis during the first few years after disease onset is often conservative and mainly involves topical agents

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**Figure 1** IL-17A: the key cytokine in the progression to chronic active psoriasis. In early-onset psoriasis, IL-17A is the key cytokine that orchestrates the expansion of IL-17+ T cells in the skin via two mechanisms. IL-17A induces keratinocytes to express the chemokine CCL20 that binds to CCR6 and thereby recruits IL-17A+ effector cells from the periphery into the skin. In addition, IL-17A induces the expression of IL-6 and IL-1β which in turn trigger the differentiation of new IL17+ effector cells in secondary lymphoid organs. This feedforward-loop shifts the balance of the skin-resident T-cell population, increasing the pool of IL-17+ effector and IL-17+ TRM cells in the skin which then drive chronic and relapsing psoriasis.12,33,50-54,56,57,59
but rarely results in complete clearance of psoriatic lesions and many patients experience an exacerbation.60 The current European S3-Guidelines on the systemic treatment of psoriasis vulgaris recommend a treatment algorithm for psoriasis starting with topical therapy, with the addition of, or followed by, narrow-band ultraviolet B (nb-UVB) phototherapy plus a non-biological therapy (first-line therapy), followed by biological therapy (second-line therapy).63 Because the use of systemic agents is a second-line option, treatment with these agents is normally begun only when first-line therapies fail to provide adequate results,64 which could be several years after disease onset.65–67 Accumulating evidence and experience from other IMIDs have led us to hypothesize that early intensive biological systemic treatment in subjects with new-onset psoriasis may prolong symptom-free periods, prevent reactivation of old lesions or hinder occurrence of new lesions and prevent chronicity of the disease before extensive systemic inflammation is established. This concept was supported in a subanalysis of two secukinumab extension studies (ERASURE and FIXTURE) where a substantial portion of patients with a PASI 75 response after 1 year of 300 mg secukinumab treatment and who discontinued therapy did not relapse for at least 1 or 2 years following discontinuation. The time to relapse showed a correlation with the mean duration of disease at baseline; patients with a longer relapse-free period had a shorter disease duration. To provide further clinical evidence for the potential of disease modification, the STEPiN study will be the first to investigate the outcomes of early intensive intervention in subjects with new-onset psoriasis (NCT 03020199; EUDRACT 2015-002423-26).

Materials and methods

Study aims and objectives

The aims of the study are to compare the clinical outcomes of early treatment with secukinumab versus nb-UVB in subjects with new-onset (within the last 12 months) moderate-to-severe plaque psoriasis who are naïve to phototherapy and systemic treatment. The ultimate outcome is to demonstrate that early treatment with secukinumab can achieve total or almost total clearance of psoriasis, impact disease chronicity and modify the disease course compared with current standard of nb-UVB treatment.

In order to investigate clinical remission following early intervention, the key specific objectives of this study are to compare the efficacy of secukinumab 300 mg subcutaneously (s.c.) versus nb-UVB in terms of (1) the proportion of subjects achieving ≥90% improvement in Psoriasis Area and Severity Index (PASI) 90 responders at Week 52 and (2) the proportion of all subjects who achieve at least PASI 90 at Week 104 following cessation of treatment at Week 52. The primary and secondary objectives of STEPiN are summarized in Table 1.

Table 1 STEPiN study objectives

| Primary objective |
|-------------------|
| To explore the effects of early treatment with secukinumab (Arm A1) versus nb-UVB (Arm B1) based on the proportion of all randomized subjects who achieve at least PASI 90 at Week 104 |
| To evaluate the superiority of early treatment with subcutaneous (s.c.) secukinumab 300 mg (Arm A1) versus standard-of-care treatment with narrow-band ultraviolet B (nb-UVB) (Arm B1) in subjects with new-onset moderate-to-severe plaque psoriasis in terms of ≥90% improvement (reduction) in Psoriasis Area and Severity Index (PASI) 90 response at Week 52 |

Secondary objectives

- To explore the effects of early treatment with secukinumab (Arm A1) versus nb-UVB (Arm B1) based on the proportion of all randomized patients who achieve at least Investigator’s Global Assessment (IGA mod 2011) of 0 or 1 at Week 52
- To evaluate whether early treatment with nb-UVB (Arm B1) based on the proportion of all randomized subjects who achieve at least PASI 90 at Week 104

Study design

STEPiN is a Phase IV, randomized, multicenter study involving 196 adult subjects. Two sets of subjects, those with new-onset psoriasis and those with chronic psoriasis are involved and are allocated to three main treatment arms as follows: Arm A, subjects with new-onset plaque psoriasis randomized to treatment with s.c. secukinumab, composed of Arm A1 (A1a and A1b) and Arm A2; Arm B1, subjects with new-onset plaque psoriasis randomized to treatment with nb-UVB, composed of Arm B1a and Arm B1b; Arm C, subjects with chronic plaque psoriasis, with appearance of first symptoms 5 years ago or longer, treated with s.c. secukinumab, composed of Arm C1 and Arm C2 (Fig. 2).

Blinding cannot be applied in this study given the nature of the treatments.

The study consists of a Main Study and a Mechanistic Sub-study. The Main Study includes two treatment arms: Arm A1, s.c. injections of secukinumab 300 mg at baseline, Weeks 1, 2, 3 and 4, and every 4 weeks thereafter until and including Week 52; Arm B1, one or two cycles of nb-UVB of 12 weeks each with a maximum break of 28 weeks between cycles. The Mechanistic Sub-study includes five treatment arms, in which additional skin biopsies are performed at baseline and at Weeks 16, 52, 104 and 208 to assess the immunopathology of the skin, including the number of inflammatory T_R BM cells.

Overall, safety monitoring of each treatment arm will include adverse events (AEs) and serious AEs, discontinuation and laboratory abnormalities.

Study interventions

Secukinumab 300 mg will be administered as two open-label s.c. injections of 150 mg each. Narrow-band-UVB will be applied in one or two cycles; each cycle will be of 12 weeks, with 2–3 treatment sessions per week totalling 24–36 sessions per cycle, and will be performed according to the investigational site’s
Figure 2. Study design. BL, baseline; KSE, key secondary endpoint; PASI, Psoriasis Area and Severity Index; s.c, subcutaneous; PE, primary endpoint; nb-UVB, narrow-band ultraviolet B.
protocol. Subjects in Arm B may use topical treatment of calcipotriol 50 μg/g and betamethasone 0.5 mg/g applied once daily in addition to nb-UVB during the first 4 weeks of each cycle (nb-UVB and topical treatments are commonly used in combination to optimize psoriasis treatment).68 Bland emollients and topical glucocorticosteroids of mild-to-moderate potency can be used on the face, scalp and/or genitoanal area in all treatment arms, both during the treatment and follow-up periods.

Study population
A total of 196 male and female subjects aged 18–50 years will be included. In Arms A and B, patients with new-onset moderate-to-severe plaque psoriasis (within the last 12 months) who are naive to phototherapy and systemic treatment can be included. In Arm C, patients with chronic plaque psoriasis (appearance of first symptoms 5 years or longer) can be included, with no restriction on previous exposure to phototherapy and systemic (including biologic) treatment. In the Main Study, a total of 160 subjects will be randomized to Arms A1 (n = 80; A1a [n = 68] + A1b [n = 12]) and B1 (n = 80; B1a [n = 68] + B1b [n = 12]). The Mechanistic Sub-study will include a total of 60 subjects, 12 subjects each randomized to Arms A1b, B1b, A2, C1 and C2 (with an overlap of arms A1b and B1b in both the Main Study and the Mechanistic Sub-study). Key inclusion and exclusion criteria are summarized in Table 2.

Randomization
At baseline, the subjects will be randomized using an interactive response technology system to the study arms A1, A2 or B1 (new-onset subjects) and C1 or C2 (subjects with chronic disease). Randomization of subjects to the study treatment arms will be stratified by treatment status: naïve or non-naïve. Thirty-six treatment-naïve patients will be randomized in a 1:1:1 ratio to Arm A1b, A2 or B1b, whereas another 136 treatment-naïve patients will be randomized in 1:1 ratio to Arm A1a or B1a. Twenty-four non-naïve patients will be randomized in a 1:1 ratio to Arm C1 or C2.

Subject follow-up procedures

Main study At the end of the 52-week treatment period, subjects who fail to achieve a PASI 50 response will be discontinued from the study. All subjects with a ≥PASI 50 response in Arms A1 and B1 will enter a follow-up period. Upon relapse, defined as a ≥50% loss in maximum PASI improvement from baseline, subjects will be discontinued from the study. Subjects will not receive study treatment during the follow-up but will be observed maximally until Week 208. If no relapse occurs, subjects achieving <PASI 90 at Week 52 will be followed up until Week 104, and subjects achieving ≥PASI 90 at Week 52 will be followed up until Week 208.

Mechanistic sub-study At the end of the treatment period, subjects who do not achieve a PASI 50 response will be discontinued from the study. All subjects in Arms A1b and B1b with ≥PASI 50 responses will enter the follow-up period. Subjects in Arms A1b and B1b will not receive study treatment during the follow-up period but will be observed maximally until Week 208; if a 50% loss of maximum PASI improvement is experienced, subjects will be discontinued from the study. If no relapse occurs in Arms A1b and B1b, subjects achieving <PASI 90 at Week 52 will be followed up until Week 104 and those achieving ≥PASI 90 at Week 52 will be followed up until Week 208. For Arm A2, subjects achieving <PASI 90 at Week 104 will have their end-of-study visit and stop study participation. Subjects achieving ≥PASI 90 will be followed up until Week 208. There will be no follow-up for subjects in Arms C1 and C2.

Primary and key outcome measures
The primary and key secondary outcomes are based on PASI and Investigator’s Global Assessment (IGA) 0/1 improvement.

Table 2 Key inclusion and exclusion criteria for the STEPIn study

| Inclusion criteria | Exclusion criteria |
|--------------------|-------------------|
| • New-onset plaque psoriasis with appearance of the first psoriasis plaque within the last 12 months before randomization and naïve to any systemic treatment and phototherapy (Arms A1, A2 and Arm B1) | • Forms of psoriasis other than plaque type |
| • Chronic plaque psoriasis with appearance of the first psoriasis symptoms 5 years or longer and intolerance or inadequate response to phototherapy or any systemic treatment including biologics, except for interleukin (IL)-17A inhibitors (Arm C1 and Arm C2) | • Ongoing use of prohibited treatments |
| • Moderate-to-severe plaque psoriasis defined at screening and baseline by all of the following: o Psoriasis Area and Severity Index (PASI) ≥10 | • Previous treatment with phototherapy or any systemic treatment |
| o Body surface area (BSA) ≥10% | • (Arms A1, A2 and B1) |
| o Investigator’s Global Assessment (IGA) mod 2011 ≥ 3 | • Pregnant or nursing (lactating) women |
| | • Women of childbearing potential |
achieved after 52 weeks of treatment and post-treatment follow-up assessment at Week 104, respectively. The analysed variables are the proportion of subjects who achieve PASI 90 and the proportion of subjects who achieve an IGA (mod 2011) of at least 0 or 1. Other efficacy variables to be measured include the subject’s assessment of pain, itching and scaling and the Subject’s Global Assessment (SGA) of psoriatic disease. Whenever possible, the same assessor will perform the assessments at all visits.

**Statistical analysis**

The primary efficacy variable is the proportion of PASI 90 responders at Week 52; subjects who do not achieve PASI 90 at Week 52 will be considered non-responders. The following two-sided hypothesis will be tested for the primary analysis: \( H_0: P_{\text{sec}} = P_{\text{nbUVB}} \) versus \( H_A: P_{\text{sec}} \neq P_{\text{nbUVB}} \), where \( P_{\text{sec}} \) and \( P_{\text{nbUVB}} \) are the proportion of PASI 90 responders in the secukinumab (Arm A1) and nb-UVB (Arm B1) groups, respectively, at Week 52. The primary analysis will be based on the full analysis set comprising all subjects randomized to the study and performed using an exact logistic regression model. Multiple imputations will be the primary method of handling missing data at Week 52.

Similar to the primary analysis, the key secondary analysis for all randomized subjects achieving a PASI 90 response at Week 104 will be performed after cessation of treatment at Week 52 (irrespective of their responses over the past visits). To adjust for multiplicity, a hierarchical testing procedure will be used, which will first test the primary hypothesis at a two-sided 5% level of significance.

IGA 0 or 1 response at Week 52 will be examined using an exact logistic regression model similar to the primary analysis, with treatment as an explanatory variable and baseline IGA score as a covariate. The estimated adjusted odds ratio will be calculated along with the associated 95% confidence interval.

The involved sample size of 80 subjects per arm in Arms A1 and B1 is calculated to ensure a 90% power for the key secondary analysis. Further, this sample would result in obtaining a power of 99% for the primary analysis. The Mechanistic Sub-study will not involve any formal testing of the hypothesis; the sample size is obtained in an illustrative manner. In addition, safety, immunological modifications (mechanistic study) and quality of life will be evaluated.

**Ethics**

The study was designed and will be conducted and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, and in accordance with the Declaration of Helsinki.

**Conclusions**

To our knowledge, the STEPIn study is the first study to investigate a novel concept in psoriasis, that is, whether early intensive treatment in subjects with new-onset psoriasis can modify the natural course of the disease. In clinical practice, biologic agents are often prescribed to patients with moderate-to-severe psoriasis after inadequate response to topical or conventional systemic agents. This also implies that biologic intervention usually occurs at a late stage of the disease, often >10 years after the initial onset of symptoms. At this disease state, the homing of T\(_{\text{RM}}\) cells to the skin leading to chronicity of the disease has already likely developed. The results of the STEPIn study will contribute to further understanding of T\(_{\text{RM}}\) cell dynamics and could potentially contribute to changing the treatment paradigm for patients with psoriasis by identifying a new treatment strategy in patients with new-onset psoriasis. In addition, the Mechanistic Sub-study will provide insight into the effect of nb-UVB or early and late interventions with secukinumab on skin biomarkers, particularly on the T\(_{\text{RM}}\) cells. This treatment approach could potentially alter the disease burden on patients and their need for treatment.

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**Authorship**

LI is the principal investigator of the trial. LE, JA, MR, AO, LS, TT, IB, PK, MS, RB, JO, AF and JF participated in the study design/implementation/conduct of the STEPIn study. All authors contributed to the review of the protocol and approved the final manuscript.

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