NOVARTIS

Global Medical Affairs - General Medicine

Secukinumab (AIN457)

Clinical Trial Protocol CAIN457A2322 / NCT03020199

A randomized, multicenter STudy to evaluate the Effect of secukinumab 300 mg s.c. administered during 52 weeks to patients suffering from new-onset moderate to severe plaque Psoriasis as early Intervention compared to standard treatment with narrow-band UVB (STEPIn study)

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List of abbreviations

AE	Adverse event
[redacted]	[redacted]
BSA	Body surface area
CRO	Contract research organization
[redacted]	[redacted]
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of study
FAS	Full analysis set
GCP	Good clinical practice
[redacted]	[redacted]
IEC	Independent ethics committee
IGA	Investigator's global assessment
IMID	Immune-mediated inflammatory disease
IL	Interleukin
IRB	Institutional review board
IRT	Interactive response technology
LLN	Lower limit of normal
MCMC	Markov Chain Monte Carlo
MedDRA	Medical dictionary for regulatory activities
nb-UVB	Narrow-band ultraviolet light B
PASI	Psoriasis area and severity index
[redacted]	[redacted]
SAE	Serious adverse event
[redacted]	[redacted]
[redacted]	[redacted]
TB	Tuberculosis
[redacted]	[redacted]
ULN	Upper limit of normal
[redacted]	[redacted]

[redacted]

Glossary of terms

Dosage	Dose of the study treatment given to the patient in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g., prior to starting any of the procedures described in the protocol)
Epoch	A part of the study which serves a specific purpose. Typical epochs are: screening, treatment, and follow-up
Medication number	A unique identifier on the label of each investigational drug package
Patient number	A unique number assigned to each patient upon signing the informed consent
Personal data	Patient information collected by the investigator that is transferred to Novartis for the purpose of the clinical study. This data include patient identifier information, study information, and biological samples
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug(s), placebo/comparator active drug run-ins or background therapy
Study treatment discontinuation	Point/time when the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer, and does not allow any further collection of personal data

[redacted]

Protocol amendments

Protocol Amendment 02 of 26-Sep-2019

Amendment rationale

Amendment 02 was implemented to provide additional details for the statistical analysis and increase the patient recruitment rate by loosening one inclusion criterion.

The study is currently ongoing. The changes were made mainly to improve the understanding and execution of the protocol and will not have an impact either on the patients' safety or on the objectives of the study.

Changes to the protocol

Changes to specific sections are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The following modifications were made to the protocol:

- The glossary of terms was updated with new definitions of personal data and withdrawal of consent
- Clarification was added that subjects who discontinue the study during the Follow-up Epoch will have all assessments of end of study (EOS) performed
- Inclusion criterion 3 was modified by allowing earlier episodes of mild psoriasis resolved spontaneously within 6 months. The reason for this change was that some subjects did not proceed into screening because they could have had symptoms of psoriasis previously, but without a proper diagnosis. In consensus with medical experts, subjects with such a history would not change the scientific value of the study, nor the study population, and hence this inclusion criterion was slightly loosened to improve study recruitment
- Withdrawal of consent language was modified to align with the requirements of the General Data Protection Regulation
- [redacted] Additionally, clarification was provided that physical examination at Week 104 has to be recorded in the source documents at the site
- Table 6-3 was updated with the definition of EOS
- The hypothesis testing for the efficacy analyses was modified to 1-sided tests at 2.5% significance level instead of 2-sided at 5% significance level
- Age and body mass index were included as covariates for the analyses

[redacted]

- The Wald test was replaced by the Fisher's exact test, which is mainly used when the sample size is small or the proportions are extreme. This study is of adequate size and the Wald test was proposed. However, responses for the key secondary endpoint are expected to be low; therefore, it was decided that the Fisher's exact test is more appropriate
- Clarification was added that missing data for the primary endpoint and the key secondary endpoint will be imputed with modified multiple imputation method
- The power of the key secondary endpoint was re-assessed after considering dropout rates
- The assumptions for the sample size calculations were modified. The power calculations for the primary endpoint are now based on the asymptotic Wald test instead of on the Fisher's exact test, as the accuracy of the Wald test increase in larger sample sizes and adequate response rates (which are expected for the primary endpoint). The software for the calculation was modified from nQuery Advisor® 7.0 to PASS 11

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are substantial and require IRB/IEC approval prior to implementation.

The changes herein affect the study-specific model ICF and the sub-study ICF.

Protocol Amendment 01 of 11-Apr-2017

Amendment rationale

The purpose of the amendment was to address requests from health authorities and to include modifications for improvement of the clarity of the protocol.

In addition, the upper limit of the age range was changed to better reflect the patient population and improve study recruitment.

Changes to the protocol

Changes to specific sections are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The following modifications were made to the protocol:

- The investigator's global assessment mod 2011 was included as additional secondary and exploratory objectives
- [redacted]
- The upper limit of the age range for inclusion of patients in the study was changed from 40 years to 50 years

[redacted]

- The risks-benefit section was updated with information on risks for secukinumab, biopsies and others
- The exclusion criterion involving barrier methods of contraception was modified to include applicable countries beyond the UK
- The optional use of calcipotriol 50 μg/g and betamethasone 0.5 mg/g with nb-UVB was further clarified
- The number of patients per group in the Mechanistic Sub-study was reduced from 15 to 12
- The number of biopsies to be taken from lesional or resolved skin and from never-lesional skin was corrected

[redacted]

Protocol summary

Protocol number	CAIN457A2322
Title	A randomized, multicenter STudy to evaluate the Effect of secukinumab 300 mg s.c. administered during 52 weeks to patients suffering from new-onset moderate to severe plaque Psoriasis as early Intervention compared to standard treatment with narrow-band UVB (STEPIn study)
Brief title	Study of the efficacy of early intervention with secukinumab 300 mg s.c. compared to narrow-band UVB in patients with new-onset moderate to severe plaque psoriasis
Sponsor and clinical phase	Novartis Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine whether early intervention with subcutaneous (s.c.) secukinumab 300 mg in patients with new-onset moderate to severe plaque psoriasis may lead to prolonged symptom-free periods by preventing reactivation of old lesions or ultimately totally hindering the occurrence of new lesions, i.e., changing the natural course of the disease (Main Study).
Primary objective	To demonstrate that early treatment with secukinumab 300 mg s.c. (Arm A1) is superior to standard of care treatment with nb-UVB (Arm B1) in patients with new-onset moderate to severe plaque psoriasis with respect to patients achieving ≥ 90% improvement (reduction) in psoriasis area and severity index (PASI 90) response at Week 52.
Secondary objectives	***Key secondary objective*** To evaluate the superiority of early treatment with secukinumab (Arm A1) versus nb-UVB (Arm B1) based on the proportion of all randomized patients who achieve at least PASI 90 at Week 104. ***Additional secondary objective*** To evaluate the effects of early treatment with secukinumab (Arm A1) compared with nb-UVB (Arm B1) based on the proportion of all randomized patients who achieve at least investigator's global assessment (IGA mod 2011) 0/1 response at Week 52.
Study design	The design consists of the Main Study involving all patients in Arms A1 (A1a and A1b) and B1 (B1a and B1b) and a Mechanistic Sub-study, which comprises 5 treatment arms (A1b, A2, B1b, C1, and C2). The Main Study will be multicenter, randomized, 2-treatment-arm (secukinumab and nb-UVB), parallel-group and open-label.

Population	The overall study population (Main Study and Mechanistic Sub-study) will consist of a total of 196 male and female patients aged between 18 and 50 years inclusive. ***Main Study*** The Main Study will be conducted in patients with new-onset moderate to severe plaque psoriasis not previously treated with any systemic treatment or phototherapy. A total of 160 patients will be randomized to Arm A1 or Arm B1 in approximately 75 sites worldwide. Since a maximum screening failure rate of 20% is expected, approximately 245 patients will be screened. ***Mechanistic Sub-study*** Any patient who consents can participate in the Mechanistic Sub-study. Patients with new-onset plaque psoriasis will be randomized to Arm A1b, Arm A2, or Arm B1b, those with chronic plaque psoriasis will be randomized to Arm C1 and Arm C2 (12 patients each). For Arm A1b or Arm B1b, the first 12 patients will be included on a first come first serve basis.
Key inclusion criteria	Patients eligible for inclusion in this study must fulfill all of the following criteria: 1. Able to understand and communicate with the investigator, willing and capable to comply with all study procedures, and provide written signed and dated informed consent (personally or by a witness) before any assessment is performed 2. Aged 18 to 50 years inclusive 3. New-onset plaque psoriasis with appearance of the first psoriasis plaques within the last 12 months before randomization and naïve to any systemic treatment and phototherapy (Arm A1, Arm A2, and Arm B1). Episodes of mild psoriasis, which occurred at least 3 years before screening and resolved spontaneously within 6 months will be accepted 4. 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 biologicals, except for IL-17A inhibitors (Arm C1 and Arm C2) 5. Moderate to severe plaque psoriasis defined at screening and baseline by PASI ≥ 10, and body surface area (BSA) ≥ 10%, and IGA mod 2011 ≥ 3
Key exclusion criteria	Patients fulfilling any of the following criteria will not be eligible for inclusion in this study: 1. Forms of psoriasis other than plaque-type (e.g., pustular, erythrodermic, guttate, light sensitive, and drug induced) 2. Ongoing use of prohibited treatments 3. Previous treatment with phototherapy or any systemic treatment 4. Pregnant or nursing (lactating) women 5. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the Treatment Epoch or longer if required by locally-approved prescribing information (e.g., 20 weeks in the EU and countries where applicable for secukinumab)

[redacted]

Study treatment	Secukinumab (AIN457) 300 mg Narrow-band UVB
Efficacy assessments	• Body surface area and psoriasis area severity index • Investigator's global assessment mod 2011 [redacted]
Safety assessments	• Physical examination • Vital signs • Height and body weight • Laboratory evaluations (hematology, clinical chemistry, high-sensitivity C-reactive protein) • Electrocardiogram (ECG) • Pregnancy • Adverse events
[redacted]	
Data analysis	The primary efficacy variable is the proportion of patients who achieve PASI 90 at Week 52. The analysis for the primary objective will be based on the full analysis set (FAS). For the primary analysis, the following hypothesis testing will be performed: H_{01}: $p_{sec} = p_{nbUVB}$ versus H_{A1}: $p_{sec} > p_{nbUVB}$ The primary analysis method for PASI 90 response at Week 52 will use a logistic regression model with treatment as an explanatory variable and significant covariates among baseline PASI score, age, and body mass index. The best subset of the significant covariates will be selected using a forward selection method. Interaction terms will also be considered, if significant, among the best subset of selected covariates and the treatment term. The key secondary variable is the proportion of all randomized patients who achieve PASI 90 at Week 104. In order to reduce selection bias, all patients who do not achieve PASI 90 at Week 52 will also be included in the analysis at Week 104 using the PASI improvement obtained at Week 104 only. For the key secondary analysis, the following hypothesis testing will be performed: H_{02}: $p^*_{sec} = p^*_{nbUVB}$ versus H_{A2}: $p^*_{sec} > p^*_{nbUVB}$
Keywords	Psoriasis, IL-17A, secukinumab, narrow-band UVB, PASI

[redacted]

1 Introduction

1.1 Background

Psoriasis is an immune-mediated inflammatory disease (IMID) which may have a major impact on a patient's life, especially when its intensity is moderate or severe. There is evidence that treatment of psoriasis during the first years is conservative and frequently based on topical agents which rarely clear lesions completely. Treatment with biologic systemic agents is often initiated only when topical agents, phototherapy and conventional systemic treatment have proved to be inadequate, even in patients with moderate to severe disease (Maza et al 2012).

Psoriatic skin lesions are a "riot" of disorder, featuring dense inflammatory cell infiltrates, massive proliferation, impaired differentiation of the epidermis, formation of new blood vessels, and alterations in lymphatic structures. With effective therapy, psoriatic lesions resolve without scarring, which is remarkable, given the number of neutrophils in psoriatic skin lesions and the scarring observed in other neutrophil-mediated disorders, including pyoderma gangrenosum. Successful treatment of psoriasis leads to resolution of epidermal thickness, reduction in the number of inflammatory cells, and return of previously affected skin to a clinically normal state.

Once therapy is discontinued, psoriatic skin lesions tend to recur, usually at the same sites that were previously affected. Understanding and repairing the residual lesion in treated psoriatic skin may mean the difference between treating psoriasis and curing it.

There is evidence in other IMIDs (e.g., rheumatoid arthritis and Crohn's disease) that targeted systemic treatment, including biologics given early in the treatment pathway, may improve short- and long-term patient outcomes.

Both short- and long-term outcomes of early and intensive intervention in rheumatoid arthritis have clearly demonstrated benefits (Quinn et al 2005, Quinn et al 2012, van der Kooij et al 2009). In the BeSt study, 48% of the patients with initial intensive treatment with tumor necrosis factor alpha (TNFα) inhibitors and methotrexate could even stop the biologic treatment and remain in remission at year 4 of the study.

A patient-centered therapeutic approach, undertaken early in the psoriasis treatment pathway (early intervention) with the goal of complete clearance, may improve control of cutaneous symptoms and may also modify the course of the disease and the associated burden.

There is also evidence that – despite clinical clearance of psoriatic lesions – a subclinical inflammation may continue in the skin that may become clinical once treatment is stopped e.g., during or after a "drug holiday". A possible explanation for this phenomenon can be found in the identification of a T-cell subset called tissue resident memory T cells (T_{rm}) that has been proven to contribute to a tissue-localized immunological memory to viral infections of the skin (e.g., infections with herpes simplex virus).

This subtype of T cell has also been suggested to be a key player for generating chronicity of immune-mediated inflammatory or auto-reactive disorders like psoriasis (Clark 2015).

A newly published study identifies accumulation of IL-17 producing T_{rm} cells in the lesional or resolved skin of patients with psoriasis, which remain in the skin after resolution of lesions during treatment with biologic therapy, indicating the importance of this subset also in psoriasis

[redacted]

(Cheuk et al 2014). The presence of these cells in the skin may explain the chronicity of the disease and the reoccurrence of relapses to the same anatomic locations.

Cheuk et al (2014) also showed that T_{rm} cells in the psoriatic plaques produce interleukin (IL)-17A and IL-22 upon activation, supporting the notion of T_{rm} cells in psoriasis as Th17 cells with IL-17A as a key effector cytokine. In addition to the direct pathogenic effect of IL-17A from T cells on keratinocytes, IL-17A is also released by granulocytes and mast cells and plays an important role in early attracting more immune cells to the target organ.

Based on the increasing knowledge of the altered balance of T_{rm} cell subsets in psoriasis, inhibition of IL-17A early after disease onset may be a novel and important therapeutic approach interfering with the immune system before the establishment of extensive and chronic inflammation. This effect would be achieved in part by early blocking the recruitment of inflammatory cells, including Th17, and partly by blocking the key effector functions of T_{rm} cells.

Secukinumab is the first IL-17A inhibitor approved for the treatment of moderate to severe plaque psoriasis. It is hypothesized that early treatment with secukinumab in new-onset moderate to severe plaque psoriasis may both block recruitment of inflammatory cells and antagonize the effect of the key cytokine IL-17A produced by a subset of T cells.

1.2 Purpose

The purpose of this study is to determine whether early intervention with subcutaneous (s.c.) secukinumab 300 mg in patients with new-onset moderate to severe plaque psoriasis may lead to prolonged symptom-free periods by preventing reactivation of old lesions or ultimately totally hindering the occurrence of new lesions, i.e., changing the natural course of the disease (Main Study). New-onset psoriasis here is defined as psoriasis diagnosed within the last 12 months and not yet treated with systemic drugs or narrow-band ultraviolet light B (nb-UVB).

For the purpose of this study, early intervention with secukinumab will be compared with early intervention with nb-UVB.

In addition, a sub-study will be included, which aims to mechanistically understand the impact of early and late short- or long-term intervention with secukinumab on skin biomarkers (Mechanistic Sub-study).

[redacted]

2 Study objectives and endpoints

2.1 Primary objective

To demonstrate that early treatment with secukinumab 300 mg s.c. (Arm A1) is superior to standard of care treatment with nb-UVB (Arm B1) in patients with new-onset moderate to severe plaque psoriasis with respect to patients achieving ≥ 90% improvement (reduction) in psoriasis area and severity index (PASI 90) response at Week 52.

2.2 Secondary objectives

2.2.1 Key secondary objective

To evaluate the superiority of early treatment with secukinumab (Arm A1) versus nb-UVB (Arm B1) based on the proportion of all randomized patients who achieve at least PASI 90 at Week 104.

2.2.2 Additional secondary objective

To evaluate the effects of early treatment with secukinumab (Arm A1) compared with nb-UVB (Arm B1) based on the proportion of all randomized patients who achieve at least investigator's global assessment (IGA mod 2011) 0/1 response at Week 52.

2.3 Exploratory objectives

[redacted]

4. To explore the effects of treatment with secukinumab compared with nb-UVB based on the proportion of patients who achieve at least investigator's global assessment (IGA mod 2011) 0/1 response at Week 104

[redacted]

[redacted]

8. To explore in biopsies from lesional (or resolved) and never-lesional skin of patients the following immunological modifications:
   - Mean changes in the total number of T_{rm} in dermis and epidermis
   - Mean changes in the number of different subsets of T cells in resolved skin compared to lesional psoriasis Changes from baseline in the number of dermal lymphoid dendritic cells-T cell aggregates in the skin
   - Changes from baseline in inflammatory gene expression response in never-lesional and lesional or resolved skin
   - Changes from baseline in inflammatory gene expression profiles in biopsies where tissue resident T cells have been ex-vivo activated by CD3-ligation
   - Systemic effect of secukinumab on biomarkers associated with moderate to severe plaque psoriasis and response to secukinumab
9. To explore the effects of treatment with secukinumab (Arms A1 and A2) compared with late secukinumab intervention (Arm C1 and Arm C2) with regard to:
   - Immuno-pathological changes in the involved skin locations
   - Epigenetic profiling of the skin
   - Disease activity (measured by PASI, SAPIS and SGA)
   - Safety

3 Investigational plan

3.1 Study design

Patients will be allocated to 3 main treatment arms:

- Arm A (patients with new-onset plaque psoriasis to be treated with secukinumab): composed of Arm A1 (A1a and A1b) and Arm A2
- Arm B1 (patients with new-onset plaque psoriasis to be treated with nb-UVB): composed of Arm B1a and Arm B1b
- Arm C (patients with chronic plaque psoriasis to be treated with secukinumab): composed of Arm C1 and Arm C2

An overview of the treatment arms is summarized in Table 3-1.

Table 3-1 Summary information for study arms

Arm	Psoriasis duration	Study part	Treatment	Treatment duration
A1a	new-onset	Main	Secukinumab	52 weeks
A1b	new-onset	Main and mechanistic	Secukinumab	52 weeks
A2	new-onset	Mechanistic	Secukinumab	104 weeks
B1a	new-onset	Main	nb-UVB	52 weeks
B1b	new-onset	Main and mechanistic	nb-UVB	52 weeks
C1	chronic	Mechanistic	Secukinumab	52 weeks
C2	chronic	Mechanistic	Secukinumab	104 weeks

[redacted]

The design consists of a Main Study and a Mechanistic Sub-study.

The Main Study will be multicenter, randomized, 2-treatment-arm (secukinumab and nb-UVB), parallel-group and open-label. It will include 3 clinical epochs (Screening Epoch, Treatment Epoch, and Follow-up Epoch) involving all patients in Arms A1 (A1a and A1b) and B1 (B1a and B1b).

The Mechanistic Sub-study will be open-label and comprise 5 treatment arms (A1b, A2, B1b, C1, and C2). It will include 2 epochs (Screening Epoch and Treatment Epoch) for patients in Arms C1 and C2. Patients from Arms A1b, A2, and B1b will undergo the 3 clinical epochs of the Main Study.

Details of the Main Study and the Mechanistic Sub-study with the number of patients and treatment regimen for each arm are provided in the following sub-sections. The randomization to the treatment arms is outlined in Section 5.3.

Screening Epoch

Patient's eligibility for the study will be assessed at the screening visit (Day -28 to Day -1 before baseline) and at the baseline visit (see Table 6-1).

Main Study

Treatment Epoch

At the baseline visit, eligible patients will be randomized to one of the following treatment arms (see Figure 3-1):

- **Arm A1**: patients with new-onset plaque psoriasis will receive 300-mg secukinumab by s.c. injection at baseline, Weeks 1, 2, 3, 4 and then every 4 weeks until Week 48 inclusive
- **Arm B1**: patients with new-onset plaque psoriasis will receive 1 or 2 cycles of nb-UVB of 12 weeks each with a maximum break of 28 weeks between cycles (patients with PASI 90 at Week 40 will not receive a second treatment cycle). Only during the first 4 weeks of each cycle, nb-UVB treatment may be given in combination with topical calcipotriol 50 µg/g and betamethasone 0.5 mg/g

Follow-up Epoch

At the end of the Treatment Epoch at Week 52, all patients with ≥ PASI 50 response from Arm A1 and Arm B1 will enter the Follow-up Epoch. Patients who do not achieve a PASI 50 response, will have all assessments of EOS and be discontinued from the study.

During the Follow-up Epoch, patients will not receive study treatment; they will be observed maximally until Week 208, and compared regarding the proportion of them who achieve PASI 90 scores at Week 104.

Patients who relapse (those who experience a loss of 50% of the maximum improvement in PASI score achieved during the Treatment Epoch) will have all assessments of EOS and be discontinued from the study.

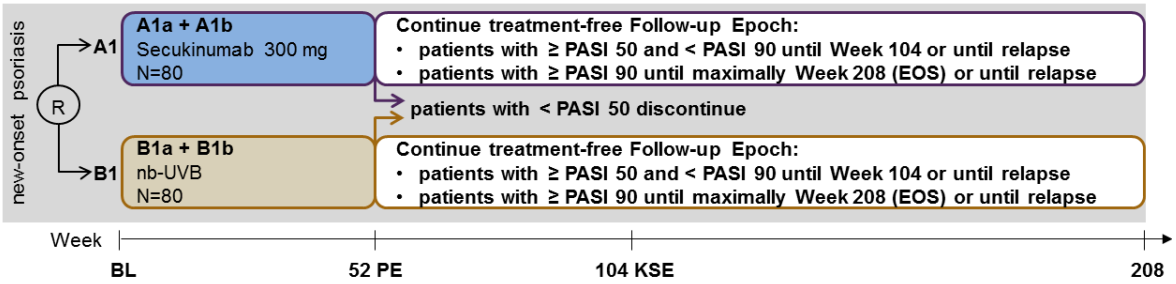
If no relapse occurs, patients who achieve < PASI 90 at Week 52 in Arms A1 (A1a and A1b) and B1 (B1a and B1b) will be followed (according to the visit schedule outlined in Table 6-3)

[redacted]

until Week 104, while patients who achieve ≥ PASI 90 at Week 52 will be followed until Week 208.

The investigator should provide ongoing adequate care for patients who relapse. If the investigator decides to continue treating the patients with secukinumab, a new loading dose of commercially available secukinumab could be considered. The treatment with secukinumab after relapse will be out of scope of the study.

Figure 3-1 Study design – Main Study



BL = baseline, EOS = end of study, KSE = key secondary endpoint, nb-UVB=narrow-band ultraviolet B, PASI = psoriasis area and severity index, PE = primary endpoint, R = randomization.

Mechanistic Sub-study

A separate informed consent will be obtained from study patients who agree on having skin biopsies taken and therefore become eligible for this Mechanistic Sub-study. Besides the biopsies, patients will undergo the same assessments as in the Main Study.

Treatment Epoch

At the baseline visit, eligible patients will be allocated to one of the treatment arms of the Mechanistic Sub-study (see Figure 3-1 and Section 5.3):

- Arm A1b: secukinumab 300 mg s.c. administered at baseline, once weekly at Weeks 1, 2, 3 and 4; and thereafter every 4 weeks until Week 48 inclusive (last dose administered at Week 48)
- Arm A2: secukinumab 300 mg s.c. administered at baseline, once weekly at Weeks 1, 2, 3 and 4; and thereafter every 4 weeks until Week 100 inclusive (last dose administered at Week 100)
- Arm B1b: 1 or 2 cycles of nb-UVB of 12 weeks each with a maximum break of 28 weeks between cycles
- Arm C1: secukinumab 300 mg s.c. administered at baseline, once weekly at Weeks 1, 2, 3 and 4; and thereafter every 4 weeks until Week 48 inclusive (last dose administered at Week 48)
- Arm C2: secukinumab 300 mg s.c. administered at baseline, once weekly at Weeks 1, 2, 3 and 4; and thereafter every 4 weeks until Week 100 inclusive (last dose administered at Week 100)

Arm C1 and Arm C2 with patients having chronic psoriasis, will serve as control groups in the Mechanistic Sub-study.

Skin biopsies will be taken from all patients who participate as described in Section 6.6.4.

[redacted]

Follow-up Epoch

At the end of the Treatment Epoch, all patients with ≥ PASI 50 response from Arm A1b and Arm B1b will enter the Follow-up Epoch. Patients who do not achieve a PASI 50 response, will have all assessments of EOS and be discontinued from the study.

During the Follow-up Epoch, patients will not receive study treatment; they will be observed maximally until Week 208, and compared regarding the proportion of them who achieve PASI 90 scores at Week 104.

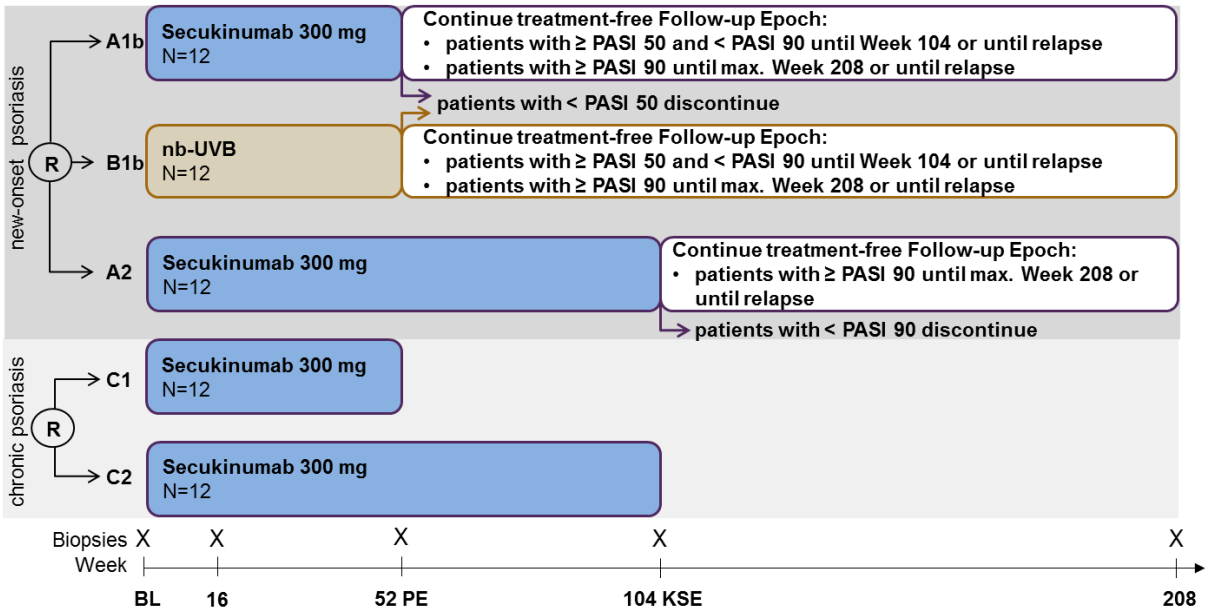
Patients who relapse (those who experience a loss of 50% of the maximum improvement in PASI score achieved during the Treatment Epoch) will have all assessments of EOS and be discontinued from the study.

If no relapse occurs, patients who achieve < PASI 90 at Week 52 in Arms A1b and B1b will be followed (according to the visit schedule outlined in Table 6-3) until Week 104, while patients who achieve ≥ PASI 90 at Week 52 will be followed until Week 208.

For Arm A2, patients who achieve < PASI 90 at Week 104 will have their EOS assessment and stop participating in the study, while those who achieve ≥ PASI 90 will be followed (according to the visit schedule outlined in Table 6-3) until Week 208.

Arms C1 and C2 will not be followed up.

Figure 3-2 Study design – Mechanistic Sub-study



BL = baseline, EOS = end of study, KSE = key secondary endpoint, nb-UVB=narrow-band ultraviolet B, PASI = psoriasis area and severity index, PE = primary endpoint, R = randomization.

[redacted]

3.2 Rationale for study design

The rationale for an early intensive intervention in psoriasis is based on several years of experience of successful early intensive interventions in other chronic IMIDs, especially rheumatoid arthritis (Quinn et al 2005, Quinn et al 2012, van der Kooij et al 2009). The current hypothesis is that early intensive intervention with biologicals in the autoimmune process dampens the immune mechanism that leads to a chronic inflammatory disease. In rheumatoid arthritis it has been shown that early intervention can modify disease activity (in particular bone erosion) and severity outcomes. The effect of early intervention on disease severity has also been seen in Crohn's disease and early intervention is a developing hypothesis in other IMIDs like multiple sclerosis and psoriatic arthritis.

Based on the increasing knowledge about the role of T_{rm} cells in psoriasis, inhibition of IL-17A early after the onset of the disease may be a novel and important therapeutic approach interfering with the immune system before the establishment of extensive and chronic inflammation occurs. This effect would in part be through an early blockade of recruitment of inflammatory cells, including Th17 cells, and partly by blocking the key effector functions of T_{rm} cells. The expected clinical outcome would be to change the natural course of the disease to a milder state by hindering spreading of psoriasis (T_{rm} cells) to new anatomical locations or ultimately totally hindering reoccurrence of new lesions, i.e., inducing minimal disease activity.

Besides the Main Study, a Mechanistic Sub-study (on skin biopsies) will be performed to investigate the effects of secukinumab and nb-UVB [redacted]

Due to the nature of the treatments given, the study will be open label.

In order to reduce selection bias, all randomized patients will be involved in the analysis at Week 104 using the PASI improvements obtained at Week 52.

The patient population will be described in more detail in the Section 4.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

Secukinumab 300 mg s.c. and dose regimen with an initial weekly induction at baseline, Weeks 1, 2, 3 and 4, followed by s.c. administration every 4 weeks up to Week 48 inclusive for Arms A1 and C1, and until Week 100 inclusive for Arms A2 and C2 is based on the Phase III registration program. Secukinumab will be given to patients with new-onset moderate to severe plaque psoriasis. This is an earlier intervention with biologic therapy than current standard clinical practice. However, the aim of the study is to demonstrate the benefit of early, intensive treatment with secukinumab and with the ultimate goal of altering the natural course with a reduced disease burden and need for treatment.

3.4 Rationale for choice of comparator

The comparator treatment is nb-UVB, which may be combined with topical treatment (calcipotriol 50 µg/g and betamethasone 0.5 mg/g) during the first 4 weeks of each cycle, which is considered in many hospitals/investigational sites as the first treatment for patients with

[redacted]

moderate to severe plaque psoriasis. However, the literature states that reappearance of symptoms may occur as early as one month after the last session, suggesting that the effect of nb-UVB on the underlying inflammation in the skin is minimal or not long-lasting, though some reports mention relapse-free periods of up to 35 months (Ryu et al 2014).

In contrast to broadband UVB lamps, which emit light in a broad range over the UVB spectrum, including both the therapeutic wavelengths specific to the treatment of skin diseases, plus the shorter wavelengths responsible for sunburning (erythema), conventional nb-UVB lamps, emit light over a very short range of wavelengths (311 ± 2 nm;) concentrated in the therapeutic range, and minimally in the sunburning range. Nb-UVB is therefore theoretically safer and more effective than broadband UVB and has become the phototherapy treatment of choice for psoriasis, vitiligo, atopic dermatitis (eczema) and other photo-responsive skin disorders (Ryu et al 2014).

In most countries, nb-UVB is indicated in moderate to severe psoriasis after the failure of topical treatment. The intensity of radiation and the interval between sessions may vary per country or even per site. Typically, one cycle of nb-UVB may comprise a period of 12 weeks with 2 to 3 treatment sessions per week totaling 24 to 36 sessions per cycle. It is common practice to apply a second cycle within 1 year depending on the effect of the first one. As deep remission has proven to be a key factor for the successful maintenance of low disease activity after discontinuation of treatment in other IMIDs, a more aggressive treatment strategy will be implemented in this study.

3.5 Purpose and timing of interim analyses/design adaptations

See Section 9.7 for details of interim analyses of the study.

3.6 Risks and benefits

Risks

The potential risks for patients participating in this study are listed below.

Risks associated with the administration of secukinumab

At least 9642 patients with psoriasis, psoriasis arthritis, ankylosing spondylitis or rheumatoid arthritis, and healthy volunteers have received secukinumab treatment in Novartis-sponsored investigational clinical studies.

Four placebo-controlled Phase III studies in plaque psoriasis were pooled to evaluate the safety of secukinumab in comparison to placebo up to 12 weeks after the initiation of treatment. In total, 2076 patients were evaluated (692 on 150 mg, 690 on 300 mg and 694 on placebo).

Fewer injection site reactions were reported with secukinumab 1-mL pre-filled syringe (containing 150 mg secukinumab) than with etanercept, while the active treatment groups showed higher frequencies than placebo.

The safety data from the completed and ongoing studies including AEs and serious adverse events (SAEs), laboratory parameters and immunogenicity demonstrate a favorable safety profile. Observed risks included infections, in particular of the upper respiratory tract, neutropenia and hypersensitivity reactions that can be seen with the administration of foreign proteins. Most of the infections were non-serious, mild to moderate in severity, clinically easy

[redacted]

to manage and did not lead to treatment discontinuation. Cases of neutropenia were uncommon, generally mild to moderate and transient, and did not lead to treatment discontinuation, and only a few cases were temporally associated with non-serious infections.

Subjects with pre-existing malignancies within the past 5 years are generally excluded from studies with secukinumab, although there is no scientific basis to suggest that secukinumab would increase the risk for malignancies. Indeed, the majority of the preclinical data available in the literature suggest that blocking IL-17A may actually prevent tumor growth.

Risks associated with nb-UVB

The main risk derived from the treatment with nb-UVB is the occurrence of "sun burn" leading to itching, irritation, redness of the skin, and tanning. These symptoms can mostly be avoided or moderated by adapting the radiation dose and the intervals between sessions. Calcipotriol (component of the combination product calcipotriol 50 μg/g and betamethasone 0.5 mg/g), which may be given for the first 4 weeks of each cycle of nb-UVB, may also cause redness and itching. The risk of skin cancer is considered minimal.

The risk to study patients will be minimized by complying with the eligibility criteria and study procedures and close clinical monitoring.

Risks associated with the skin biopsy procedure

A skin biopsy is a routine procedure as part of the diagnostic practice in all dermatology clinics, which may cause bleeding and infections. Patients may have bruising, swelling, or pain in the area, and also develop scarring later on and might experience fainting caused by a drop in blood pressure. They may also have an allergic response from the anesthetic agent used for the procedure. Patients who are smokers or take steroids are at higher risk of having problems healing after the procedure.

Other risks

Problems or side effects that are not currently known could also occur.

The procedures done at each visit are standard medical procedures. Blood samples will be taken. The risks of taking blood may include fainting, pain and/or bruising. Rarely, there may be a small blood clot or infection where the needle punctures the skin. The blood pressure cuff may also cause discomfort or bruising of the upper arm.

Benefits

The potential benefits of an intervention with secukinumab may result in quick clearance of psoriatic plaques and prolong relapse-free periods or even complete prevention of relapses as hypothesized in this study for patients with new-onset psoriasis. Patients may benefit from 1 or 2 years of treatment that has been proven to be safe and effective.

Patients randomized to treatment with nb-UVB may also benefit from a reduction in psoriasis severity.

All quality, non-clinical pharmacology and toxicology data, as well as the available clinical efficacy and safety data, are considered sufficient to expect a positive benefit/risk ratio for the treatment of the study patients.

[redacted]

4 Population

The overall study population (Main Study and Mechanistic Sub-study) will consist of a total of 196 male and female patients aged between 18 and 50 years inclusive.

Main Study

The Main Study will be conducted in patients with new-onset moderate to severe plaque psoriasis not previously treated with any systemic treatment or phototherapy.

A total of 160 patients will be randomized to Arm A1 or Arm B1 in approximately 75 sites worldwide. Since a maximum screening failure rate of 20% is expected, approximately 245 patients will be screened.

Mechanistic Sub-study

Patients who consent to the additional biopsies will be able to participate in the Mechanistic Sub-study. Patients with new-onset plaque psoriasis will be randomized in 1:1:1 ratio to Arm A1b, Arm A2, or Arm B1b, those with chronic plaque psoriasis will be randomized in a 1:1 ratio to Arm C1 and Arm C2 (12 patients each).

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Able to understand and communicate with the investigator, willing and capable to comply with all study procedures, and provide written signed and dated informed consent (personally or by a witness) before any assessment is performed
2. Aged 18 to 50 years inclusive
3. New-onset plaque psoriasis with appearance of the first psoriasis plaques within the last 12 months before randomization and naïve to any systemic treatment and phototherapy (Arm A1, Arm A2, and Arm B1). Episodes of mild psoriasis, which occurred at least 3 years before screening and resolved spontaneously within 6 months will be accepted
4. 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 biologicals, except for IL-17A inhibitors (Arm C1 and Arm C2)
5. Moderate to severe plaque psoriasis defined at screening and baseline by PASI $\geq$ 10, and BSA $\geq$ 10%, and IGA mod 2011 $\geq$ 3

4.2 Exclusion criteria

Patients fulfilling any of the following criteria will not be eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population is representative of all eligible patients.

1. Forms of psoriasis other than plaque-type (e.g., pustular, erythrodermic, guttate, light sensitive, and drug induced)
2. Ongoing use of prohibited treatments (see Section 5.5.8)
3. Previous treatment with phototherapy or any systemic treatment (Arm A1, Arm A2 and Arm B1)

[redacted]

4. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test (> 5 mIU/mL)
5. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the Treatment Epoch or longer if required by locally-approved prescribing information (e.g., 20 weeks in the EU and countries where applicable for secukinumab). Effective contraception methods include:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
   - Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
   - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps). For countries where applicable, the use of spermicidal foam/gel/film/cream/ vaginal suppository will be allowed
   - Use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception

   In case of use of oral contraception, women should have been stable on the same pill for a minimum of 12 weeks before taking study treatment.

   Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
6. Active ongoing inflammatory diseases other than psoriasis or psoriatic arthritis that might confound the evaluation of the benefit of secukinumab therapy
7. Underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions) which in the opinion of the investigator significantly immunocompromises the patient and/or places the patient at unacceptable risk for receiving an immunomodulatory therapy
8. Significant medical problems, including but not limited to the following: uncontrolled hypertension (systolic: ≥ 160 mm Hg and/or diastolic blood pressure ≥ 95mmHg), congestive heart failure [New York Heart Association status Class III or IV]
9. Serum creatinine concentration exceeding 176.8 μmol/L (2.0 mg/dL) at screening

[redacted]

10. Screening total white blood cell count < 2 500/μL, or platelets < 100 000/μL, or neutrophils < 1 500/μL, or hemoglobin < 8.5 g/dL
11. Active systemic infections during the last 2 weeks (exception: common cold) prior to randomization
12. Past medical history record of infection with human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C prior to screening
13. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratosis or carcinoma *in situ* [Bowen's disease] that have been treated with no evidence of recurrence in the past 3 months; carcinoma *in situ* of the cervix or non-invasive malignant colon polyps that have been removed)
14. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis (TB) infection as defined by a positive QuantiFERON® TB-Gold In-Tube assay at Screening. Patients with a positive or indeterminate QuantiFERON® TB-Gold In-Tube assay may participate in the study if full TB workup (according to local practice/guidelines) completed within 12 weeks prior to Day1 (baseline) establishes conclusively that the patient has no evidence of active TB. If the presence of latent TB is established, then treatment must have been initiated and maintained according to local country guidelines prior to Day1 (baseline).
15. Any medical or psychiatric condition which, in the investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol.
16. History or evidence of ongoing alcohol or drug abuse, within the last 6 months before randomization
17. Plans for administration of live vaccines during the study period or within 6 weeks prior to randomization. Use of any other investigational treatment within 30 days prior to baseline or within a period of 5 half-lives of the study treatment, whichever is longer
18. History of hypersensitivity to the study treatment or its excipients or to drugs of similar chemical classes including latex hypersensitivity
19. Patients with photosensitive disorders

5 Treatment

5.1 Study treatment

5.1.1 Study and control drugs

Study treatment

Secukinumab (AIN457) 300 mg will be administered in an open-label fashion according to label as 2 s.c. injections of secukinumab 150 mg (1-mL liquid formulation in a pre-filled syringe). Each 300-mg dose will be provided as 2 pre-filled syringes of 150-mg secukinumab in a single box. Each syringe is labeled as AIN457 150 mg/1 mL.

[redacted]

Reference treatment

Narrow-band UVB applied in 1 or 2 cycles, each comprising a period of 12 weeks with 2 to 3 treatment sessions per week totaling 24 to 36 sessions per cycle. The application will be performed according to the investigational site's protocol, taking into account the patient's skin type (Section 14.5). A maximum dose of 3 J/cm^2 on the body and 1 J/cm^2 on the face is recommended (Mehta and Lim 2016).

5.1.2 Additional treatment

The patients in Arm B will be allowed to use topical treatment with calcipotriol 50 µg/g and betamethasone 0.5 mg/g applied once daily (50 grams will be the maximum amount that can be applied per week) in addition to nb-UVB only during the first 4 weeks of each cycle.

The topical cream will be used as per the sites' standard procedure and as per the expert opinion of the principal investigator.

5.2 Treatment arms

Main Study

Patients will be randomly assigned to one of the following 2 treatment arms (see Figure 3-1 and Section 5.3).

Arm A1: 80 patients (68 in Arm A1a and 12 in Arm A1b) with new-onset psoriasis will receive 300 mg secukinumab by s.c. injection at baseline, Weeks 1, 2, 3, 4 and then every 4 weeks until Week 48 inclusive.

Arm B1: 80 patients (68 in Arm B1a and 12 in Arm B1b) with new-onset psoriasis will receive 1 or 2 cycles of nb-UVB of 12 weeks each with a maximum break of 28 weeks between cycles (patients with PASI 90 at Week 40 will not receive a second treatment cycle). Only during the first 4 weeks of each cycle, nb-UVB treatment should be applied in combination with topical calcipotriol 50 µg/g and betamethasone 0.5 mg/g.

Mechanistic Sub-study

The Mechanistic Sub-study includes patients qualifying for the Main Study who provide additional consent for the collection of biopsies (Arms A1b, B1b), as well as patients who will only participate in the sub-study (Arms A2, C1, and C2):

- Twelve patients randomized to Arm A1b treated for 52 weeks with secukinumab 300 mg s.c.
- Twelve patients with new-onset psoriasis in Arm A2 treated for 104 weeks with secukinumab 300 mg s.c.
- Twelve patients randomized to Arm B1b treated with 1 or 2 cycles of nb-UVB of 12 weeks each with a maximum break of 28 weeks between cycles
- Twelve patients with chronic psoriasis (> 5 years) randomized to Arm C1 treated for 52 weeks with secukinumab 300 mg s.c.
- Twelve patients with chronic psoriasis (> 5 years) randomized to Arm C2 treated for 104 weeks with secukinumab 300 mg s.c.

[redacted]

The randomization ratios for the treatment arms in the Main Study and the Mechanistic Sub-study are outlined in Section 5.3.

5.3 Treatment assignment and randomization

At the baseline visit, all eligible patients will be randomized via the interactive response technology (IRT) system to Arm A1, or Arm B1 for the Main Study or to Arm A1b, Arm A2, Arm B1b, Arm C1, and Arm C2 for the Mechanistic Sub-study. Qualified site personnel will contact the IRT provider after the investigator has confirmed that the patient fulfills all the inclusion/exclusion criteria. The IRT system will assign a randomization number to the patient, which will be used to link the patient to a treatment arm, and will specify a unique medication number for the first package of study treatment to be dispensed to the patients.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. A study patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Randomization of patients to the study treatment arms will be stratified by treatment status, i.e., naïve to any systemic treatment including phototherapy or non-naïve.

Stratum 1: Naïve patients

A total of 172 naïve patients will be randomized.

Thirty-six patients will be randomized in a 1:1:1 ratio to Arm A1b (12 patients), Arm A2 (12 patients) and Arm B1b (12 patients).

One hundred thirty-six patients will be randomized in a 1:1 ratio to Arm A1a (68 patients) and Arm B1a (68 patients).

Stratum 2: Non-naïve patients

Twenty-four non-naïve patients will be randomized in a 1:1 ratio to Arm C1 (12 patients) and Arm C2 (12 patients).

5.4 Treatment blinding

Given the nature of the treatments, blinding cannot be applied in this study. Patients receiving nb-UVB treatment will mostly experience redness, itching and tanning due to the radiation. This can be minimized by adjusting the radiation dose or intervals, but effective radiation will always result in at least some redness of the skin, hence blinding is deemed impossible.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on study related medical questions or problems.

[redacted]

5.5.1 Patient numbering

Each patient is uniquely identified by a Patient Number which is composed by the 4-digit site number assigned by Novartis and a 3-digit sequential number assigned by the investigator (e.g., Patient [redacted] at Site [redacted] will be assigned Patient Number [redacted]). Once assigned to a patient, the Patient Number will not be reused.

Upon signing the informed consent form, the investigator will assign the patient the next sequential number. The investigator or his/her staff will contact the IRT and provide the requested identifying information to register the patient into the IRT. The site must select the electronic Case Report Form (eCRF) book with a matching Patient Number from the Electronic Data Capture system to enter data.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the Screening Epoch Disposition eCRF page.

5.5.2 Dispensing the study treatment

Each study site will be supplied with study treatment. The secukinumab treatment packaging has a 2-part label. A unique medication number is printed on each part of this label.

At all visits where secukinumab is dispensed, the IRT system will allocate a medication number. Immediately before administration of the study treatment, the investigator or other qualified site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that unique patient number. These documents will be kept in a secured location to which only site personnel will have access. The first dose of study treatment will be administered by a suitably qualified individual (nurse, physician, or other qualified site personnel).

Once the home administration of study treatment applies, the investigator will dispense, supported by the IRT system, an appropriate number of investigational treatment packages for home administrations and detach the outer part of the label from the packaging as indicated above.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by designated site personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only qualified site personnel has access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Pharma Organization Quality Assurance.

The study treatment, i.e., secukinumab pre-filled syringes must be stored in a locked refrigerator at 2-8°C (36-46°F), and must be carefully controlled in accordance with regulations governing investigational medicinal products and local regulations.

[redacted]

Study treatment should not be frozen. Medication labels will be written in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment, but no information about the patient.

Qualified site personnel must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log which will be kept in the Pharmacy File in a secure location to which only qualified site staff will have access to. Monitoring of drug accountability will be performed by a field monitor. At the conclusion of the study, and as appropriate during its course, the investigator will return all unused study treatment, packaging and drug labels to an approved local or central depot for destruction as per local laws. The investigator will keep documentation evidence of destruction only in case the destruction happens at the site and a copy of the completed drug accountability log to the Novartis assigned monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

Calcipotriol 50 µg/g and betamethasone 0.5 mg/g (given during the first 4 weeks of each cycle of nb-UVB treatment) should be stored at temperatures below 25°C.

5.5.4 Instructions for prescribing and taking study treatment

Secukinumab 300 mg s.c.

Secukinumab will be administered subcutaneously throughout the study. The first dose(s) of secukinumab will be administered under supervision at the study site. Self-administration by study patients at home will be allowed from the second dose or when the patient, after being instructed and trained, is qualified to self-inject at the discretion of the investigator. After Week 4 (the last weekly administration of secukinumab), the patients will be contacted by the investigator or staff and be reminded to start the self-administration of secukinumab every 4 weeks instead of every week.

Secukinumab must be injected s.c. in never-lesional areas of the skin to one of the following body regions: front of thighs, or lower abdomen (but not the area 2 centimeters around the navel). Investigator/qualified site staff can also inject secukinumab s.c. in the outer upper arms. Study treatment should not be injected into areas where the skin is tender, bruised, red, scaly or hard, and areas with scars or stretch marks should be avoided. As far as possible, the injection site should be changed from administration to administration throughout the study.

Detailed instructions on the self-administration of the study treatment will be described in the instructions for use and provided to each patient.

Patients will be provided with a patient diary. The investigator should indicate in the patient diary the dates of the self-administration of secukinumab injections at home and instruct the patient on how to complete it and to annotate any AEs and concomitant medication in the comments section. Patients will also be asked to return all used and unused medication and packaging at each scheduled study visit. The diary will be checked by the investigator or study nurse at the following site visit, the information has to be transferred to the eCRF and AEs have to be reported. At the end of the study, the site personnel should collect the paper diaries from the patients.

[redacted]

Narrow-band ultraviolet light B

Nb-UVB will be applied by experienced personnel according to the investigational site's protocol. In general, it is aimed that one cycle consists of 2 to 3 sessions per week during 12 weeks. Patients need to wear goggles during the procedure and men are asked to wear genital protection.

The patients could use topical treatment with calcipotriol 50 µg/g and betamethasone 0.5 mg/g applied once daily (50 grams will be the maximum amount that can be applied per week) in addition to nb-UVB during the first 4 weeks of each cycle to reflect the site's standard procedure.

During visits at the clinical sites, study assessments should be conducted before treatment administration. The first study treatment administration will occur at baseline, after all study scheduled assessments have been performed and only after the scheduled blood samples have been drawn (see Section 5.2, Table 6-1 and Table 6-2 for the details on secukinumab injections).

At study visits when pre-dose blood samples or biopsies have to be taken, the study treatment will be administered only after the collection. [redacted]

All dates and times of injections administered during the study must be recorded on the Dosage Administration Record eCRF page. The date and exposure of nb-UVB will be recorded on the Dosage Administration Record eCRF page, whereas the potential use of additional topical treatment will be documented on the Concomitant Medication eCRF page. All kits of study treatment assigned by the IRT will be recorded/data based in the IRT.

The investigator should promote compliance by instructing the patient, so the study treatment is administered exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to attend a study visit as scheduled, or if the patient is unable to take the study treatment as instructed.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Interruptions or treatment dose adjustments will not be permitted for secukinumab. Any adaptation of the nb-UVB regimen that the site would normally do will be permitted, for example in case of excessive skin irritation with nb-UVB, and then the dose of radiation may be adapted, depending on investigator's clinical judgement.

A maximum of 1 dose of secukinumab may be missed during a period of 52 weeks but not during the first 4 weeks of the Treatment Epoch.

During an nb-UVB cycle, a period of maximally 2 weeks may be inserted between consecutive sessions e.g., if a patient is ill or if a patient is on vacation.

If a dose is not administered to a patient, this deviation event must be recorded on the Dosage Administration Record eCRF page.

5.5.6 Rescue medication

Rescue treatment will not be allowed during the first 52 weeks. Mild to moderate potency glucocorticosteroids will be permitted during the Follow-up Epoch.

[redacted]

5.5.7 Concomitant medication

All treatments administered during the 6 months prior to start of study treatment (including any treatments started during the Screening Epoch) for any reason NOT including psoriasis will be entered in the Concomitant Medications eCRF page or the Procedures and Significant Non-drug Therapies eCRF page. Start date, end date, dose, unit, frequency, route and reason for administration or change are to be recorded in the concomitant medications/significant non-drug therapies eCRF. The investigator/qualified site staff must instruct the patient to notify the study site about any new medications that he/she takes after being enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts study treatment must be recorded.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the monitor before randomizing a patient or allowing a new medication to be started.

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-1 and Table 5-2 is NOT allowed after baseline.

No other treatments for psoriasis than the study treatments and the additional use of calcipotriol 50 μg/g and betamethasone 0.5 mg/g during the first 4 weeks in Arm B1 will be allowed during the Treatment Epoch. Bland emollients and topical glucocorticosteroid treatments of mild to moderate potency on the face, scalp, and/or genitoanal area for Arm A1, Arm A2, Arm B1, Arm C1, and Arm C2 are an exception. Exposure to UV light (e.g., sunbathing and/or the use of tanning devices) other than nb-UVB within the study, from enrollment to Week 104 of the study should be limited. Mild to moderate potency topical glucocorticosteroids will be allowed during the Follow-up Epoch.

[redacted]

Table 5-1 Prohibited treatment (Arm A1, Arm A2 and Arm B1)

Prohibited treatments [a, b]	Washout period (before baseline)
Secukinumab	No prior use allowed
Any biologic drug directly targeting IL-17A or the IL-17 receptor (other than secukinumab, e.g., brodalumab, ixekizumab)	No prior use allowed
Alefacept, briakinumab, efalizumab	No prior use allowed
Biological immunomodulatory agents other than the above listed (e.g., adalimumab, etanercept, infliximab)	No prior use allowed
Other systemic immunomodulatory treatments [c] (e.g., methotrexate, cyclosporine A, glucocorticosteroids [oral, i.v., intramuscular, s.c., intra-articular, transdermal], cyclophosphamide) and any treatment for psoriatic arthritis, except for NSAIDs	No prior use allowed
Any biologic drug directly targeting IL-12/IL-23 other than ustekinumab or IL-23 (e.g., guselkumab, tildrakizumab)	No prior use allowed
Other systemic psoriasis treatments (e.g., retinoids, fumarates, apremilast)	No prior use allowed
Photo-chemotherapy (e.g., psoralen plus UVA [PUVA]) or phototherapy [d]	No prior use allowed
Topical treatment that is likely to impact signs and symptoms of psoriasis (e.g., vitamin D analogues, pimecrolimus, retinoids, Salicyl-Vaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids) [e]	2 weeks
Live virus vaccinations	6 weeks
Any investigational treatment or participation in any interventional study	4 weeks or 5 half-lives (whichever is longer)

NSAID = nonsteroidal anti-inflammatory drug, UVA = ultraviolet light A

a) If the prohibited treatment is used during the study for any indication, patients must discontinue its use if they wish to continue in the study

b) In case of undue safety risk for the patients, they should discontinue study treatment at the discretion of the investigator/qualified site staff. If patients treated with secukinumab receive a live virus vaccination during the study, they must discontinue study treatment

c) Inhalational glucocorticosteroids with only a topical effect (e.g., to treat asthma) are not considered systemic immunomodulatory treatments and are therefore acceptable

d) Phototherapy or photo-chemotherapy will not be allowed, except for nb-UVB in Arm B1

e) Topical treatment should be tapered-off during the Screening Epoch and stopped 12 hours prior to randomization; only mild to moderate topical glucocorticosteroids on the face, scalp, and/or genitoanal area will be allowed. During the Treatment Epoch, bland emollients or topical glucocorticosteroid treatments of mild or moderate potency on the face, scalp, and/or genitoanal area will be allowed. Mild to moderate-potency topical glucocorticosteroids and bland emollients will be allowed during the Follow-up Epoch

[redacted]

Table 5-2 Prohibited treatment (Arm C1 and Arm C2)

Prohibited treatments [a]	Washout period (before baseline) [b]
Any biologic drug directly targeting IL-17A or IL-17 receptor (e.g., secukinumab, brodalumab, ixekizumab)	No prior use allowed
Alefacept, briakinumab, efalizumab	6 months
Biological immunomodulatory agents other than the above listed (e.g., adalimumab, etanercept, infliximab)	3 months
Other systemic immunomodulatory treatments [c] (e.g., methotrexate, cyclosporine A, glucocorticosteroids, cyclophosphamide) and any treatment for psoriatic arthritis, except for NSAIDs	4 weeks
Any biologic drug directly targeting IL-12/IL-23 other than ustekinumab or IL-23 (e.g., guselkumab, tildrakizumab)	6 months
Other systemic psoriasis treatments (e.g. retinoids, fumarates, apremilast)	4 weeks
Photo-chemotherapy (e.g., psoralen plus UVA [PUVA])	4 weeks
Phototherapy (e.g., UVA, UVB)	2 weeks
Topical treatment that is likely to impact signs and symptoms of psoriasis (e.g., vitamin D analogues, pimecrolimus, retinoids, Salicyl-Vaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids) [d]	2 weeks
Live virus vaccinations	6 weeks
Any investigational treatment or participation in any interventional study	4 weeks or 5 half-lives (whichever is longer)

a) If the prohibited treatment is used during the study for any indication, patients must discontinue its use if they wish to continue in the study

b) In case of undue safety risk for the patients, they should discontinue study treatment at the discretion of the investigator/qualified site staff. If patients treated with secukinumab receive a live virus vaccination during the study, they must discontinue study treatment

c) Inhalational glucocorticosteroids with only a topical effect (e.g., to treat asthma) are not considered systemic immunomodulatory treatments and are therefore acceptable

d) Topical treatment should be tapered-off during the Screening Epoch and stopped 12 hours prior to randomization; only mild to moderate topical glucocorticosteroids on the face, scalp, and/or genitoanal area will be allowed. During the Treatment Epoch, bland emollients or topical glucocorticosteroid treatments of mild or moderate potency on the face, scalp, and/or genitoanal area will be allowed.

NSAID = nonsteroidal anti-inflammatory drug, UVA = ultraviolet light A, UVB = ultraviolet light B

5.5.9 Emergency breaking of assigned treatment code

Not applicable.

[redacted]

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when he or she has completed the last visit planned in the protocol.

Patients who have been screened and have a screening visit recorded in the IRT system at the time that the planned enrolment number is met will be allowed to enter the study and be randomized if they are eligible.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

For all patients a safety follow-up visit should be conducted (e.g., by telephone) 30 days after the last study visit or 12 weeks after the last dose of study treatment, whichever is later. The information to be collected at this follow-up visit includes concomitant medications, AEs, and survival status.

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study treatment is stopped earlier than planned in the protocol, and can be initiated by either the patient or the investigator.

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Pregnancy (see Section 6.5.6 and Section 7.6)
- Use of prohibited treatment (see Table 5-1)
- Any other protocol deviation that results in a significant risk to the patient's safety
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study
- The investigator believes that patient's continuation in the study would negatively impact the risk/benefit balance of study participation

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Table 6-1, Table 6-2, and Table 6-3, undergo an EOS visit, and then be discontinued from the study. If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail or letter) should be made to contact them as specified in Section 5.6.3.

The investigator must also contact the IRT to register the patient's discontinuation from treatment.

5.6.3 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient:

- Does not want to participate in the study anymore and
- Does not allow further collection of personal data

[redacted]

In this situation, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in Table 6-1, Table 6-2, and Table 6-3.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a patient's samples until their time of withdrawal) according to applicable law.

All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

Patients who withdraw their consent to participate in the Mechanistic Sub-study, will still be able to participate in the Main Study provided they keep their consent to this part of the study.

5.6.4 Loss to follow up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents the steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow up until his/her scheduled EOS visit has occurred.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit-risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the IRBs/IECs of the early termination of the study.

5.6.6 Discontinuation during the Follow-up Epoch

During the Follow-up Epoch, patients must be discontinued from the study under the following circumstances:

- Patient wish
- Pregnancy (see Section 6.5.6)
- Use of prohibited treatment
- Any other protocol deviation that results in a significant risk to the patient's safety

[redacted]

- Occurrence of relapse

6 Visit schedule and assessments

Table 6-1, Table 6-2, and Table 6-3 list all of the assessments and indicates with an "X" the visits when they will be performed. An "S" indicates that the data for that assessment are to be recorded in the source documents at the site.

Patients should be seen for all visits on the designated day or as closely as possible to the originally planned visit. Missed or rescheduled visits should not lead to automatic discontinuation and will be discussed on an individual basis. The investigator and the patient can also request an unscheduled visit whenever necessary, especially during the treatment-free Follow-up Epoch where a worsening of symptoms and quality of life could occur, the investigator should remind the patient of this option.

Patients who prematurely discontinue the study for any reason should be scheduled for an EOS visit as soon as possible, at which time all of the assessments listed for the final visit (EOS) will be performed before any new treatment is initiated. All dispensed investigational product should be reconciled and the AEs and concomitant medications reconciled on the CRF.

At a minimum, patients will be contacted for safety evaluations during the 30 days following the last study visit or following the last administration of study treatment (see Section 5.6.1). Attempts to contact the patient should be recorded in the source documentation.

[redacted]

Table 6-1 Assessment schedule: Screening Epoch and Treatment Epoch (all arms)

	SE	Treatment Epoch																	
Visit number	**SC[a]**	**1**							**2**		**3**			**4**				**5[b]**	
Time (weeks)		**B**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**U**
Secukinumab administration at the site		X							X		X			X					
Secukinumab administration at home			X	X	X	X	X	X		X		X	X		X	X	X		
nb-UVB (Arm B1)		One or 2 cycles (of 12-week duration each)																	
Informed consent	X																		
Provide patient diary		S																	
Inclusion/exclusion criteria	X	X																	
Randomization		X																	
Demographics	X																		
Medical history	X	X																	
Vital signs	X	X							X		X			X				X	X
Weight		X																X	
Physical examination	S	S							S		S			S				S	S
Laboratory [c]	X								X		X			X				X	X
BSA determination	X	X																	
PASI assessment	X	X							X		X			X				X	X
[redacted]																			
IGA mod 2011	X	X							X		X			X				X	
[redacted]																			
QuantiFERON	X																		
hs-CRP	X								X		X			X				X	
Serum β-hCG	X																		
Urine β-hCG		X							X		X			X				X	X
ECG		X																	

[redacted]

	SE	Treatment Epoch																	
Visit number	**SC[a]**	**1**							**2**		**3**			**4**				**5[b]**	
Time (weeks)		**B**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**U**
[redacted]																			
Skin biopsies (Arm A1b, B1b, A2, C1, C2)		Baseline, Week 16 and Week 52																	
Prior/concomitant medication	X	X																	X
AEs/SAEs		X																	X

a) The screening visit will take place from Day -28 to Day -1 before baseline

b) For Arms A1, B1 and C1

c) Laboratory evaluations will include hematology and clinical chemistry

The first dose of secukinumab will be administered under supervision at the study site and self-administration by study patients at home will be allowed from the second dose on, or when the investigator considers the patient is qualified to self-inject after being instructed and trained

[redacted]

Table 6-2 Assessment schedule: Continued Treatment Epoch, Weeks 52-104 (Arms A2 and C2)

	Treatment Epoch (continued for Arms A2 and C2)														
Visit number	**5**			**6** [a]	**7**		**8** [a]		**9**	**10** [a]			**11**	**12**	
Time (weeks)	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**U**
Secukinumab administration at the site	X				X				X				X		
Secukinumab administration at home		X	X	X		X	X	X		X	X	X			
Vital signs	X				X				X				X	X	X
Weight	X													X	
Physical examination	S				S								S	S	S
Laboratory [b]	X				X									X	X
PASI assessment	X				X				X				X	X	X
[redacted]															
IGA mod 2011	X				X				X				X	X	
[redacted]															
hs-CRP	X				X									X	
Urine β-hCG	X				X									X	X
[redacted]															
Skin biopsies	X													X	
Prior/concomitant medication	X														
AEs/SAEs	X														

The assessments for Week 52 are those shown in Table 6-1 and should be performed only once.

a) For Arms A2 and C2, Visits 6, 8, and 10 are home visits and not scheduled investigational site visits

b) Laboratory evaluations will include hematology and clinical chemistry.

[redacted]

Table 6-3 Assessment schedule: Follow-up Epoch

	Follow-up Epoch (Arm A1, B1, A2 [a])														
Visit number	**6**	**8**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	
Time (weeks)	**64**	**76**	**88**	**100**	**104**	**116**	**128**	**140**	**152**	**164**	**176**	**188**	**200**	**EOS[c] 208**	**U**
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight					X									X	
Physical examination		S			S				S					S	S
Laboratory [b]		X			X				X					X	X
PASI assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]															
IGA mod 2011	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
hs-CRP		X			X				X					X	
[redacted]															
Urine β-hCG		X			X				X					X	
[redacted]															
Skin biopsies					X									X	
Prior/concomitant medication	X														X
AEs/SAEs	X														X

a) Arm A2 from Week 105 on.

b) Laboratory evaluations will include hematology and clinical chemistry.

c) EOS is defined as the last visit for a patient independently of whether the discontinuation or completion is planned as per protocol (Week 52, 104, or 208 or due to relapse) or an early discontinuation.

[redacted]

6.1 Information to be collected on screening failures

All patients who sign the informed consent, but discontinue prior to the first administration of study treatment are considered screening failures. The screening visit date, the Demography eCRF page, the Informed Consent eCRF page, the Inclusion/Exclusion eCRF page, and the Rescreening eCRF page must be completed for those patients who fail to enter the Treatment Epoch. Reporting of SAEs during the Screening Epoch should be followed as described in Section 7.2. The Adverse Events eCRF page should be completed for any SAEs that occurred during the Screening Epoch. Potential AEs and hospitalizations that are not SAEs which may have occurred from the time of signing the informed consent until the time of screening failure will be followed by the investigator and collected only in the source data.

If a patient discontinues prior to randomization, the IRT provider should be notified, and the reason for the patient not being randomized will be entered on the Screening Epoch Disposition eCRF page. The screening visit date, the Demography eCRF page, the Informed Consent eCRF page, and the Inclusion/Exclusion eCRF page must be completed.

Patients who fail screening for any reason may be rescreened. There will be no restriction on the number of times a potential patient may be rescreened or on how much time must pass from the date of screen failure and the date of rescreening. If a patient rescreens for the study, then the patient must sign a new informed consent form and be issued a new patient number prior to performing any study–related assessment or collecting any data for the screening visit for the patient under the new screening patient number. For all patients, the investigator/qualified site staff will record if the patient was rescreened on the Rescreening eCRF page and any applicable screening numbers the patient was issued prior to the current screening number. The date of the new informed consent signature must be entered on the Informed Consent eCRF page to correspond to the new screening patient number.

The Withdrawal of Consent eCRF page must be completed if consent was withdrawn during the Screening Epoch before the patient was randomized.

For all patients who sign the informed consent and enter into the next period of the study, all AEs occurring after the informed consent is signed will be recorded on the Adverse Events eCRF page.

Investigators will have the discretion to record abnormal test findings on the Medical History eCRF page whenever, in their judgment, the test abnormality occurred prior to the informed consent signature.

6.2 Patient demographics/other baseline characteristics

All baseline assessments should be performed prior to the first study treatment administration. Depending on the assessment, these may be completed at the screening visit (e.g., demographics) or at baseline [redacted]

Patient demographics and baseline characteristics will be collected at the screening visit. Data to be collected on all patients include: date of birth, age, sex, race, ethnicity, height, weight, and skin type (Section 14.5).

The history of plaque psoriasis will be collected at the screening visit. The information to be collected includes the following:

[redacted]

- Date of first diagnosis of plaque psoriasis by a physician
- Presence of psoriatic arthritis (including questions on signs and symptoms captured in the eCRF) and the date of the first diagnosis by a physician
- Use of psoriasis treatments, e.g., patients who used prescription treatments of family members suffering from psoriasis without having consulted a physician

6.2.1 Smoking history

The current and/or previous use of tobacco products will be recorded, as well as the estimated number of pack-years based on the approximate consumption per year. Non-smokers will be advised to not start smoking during the study.

6.2.2 Relevant medical history/current medical conditions

Relevant medical history and current medical conditions, not including psoriasis or psoriatic arthritis, prior to signing of the informed consent will be recorded in the Medical History eCRF page. Whenever possible, diagnoses and not symptoms will be recorded.

Patients with Crohn's disease will be eligible for the study but should be closely followed when randomized to secukinumab.

Significant findings that are observed after the patient has signed the informed consent form and that meet the definition of an AE must be recorded in the Adverse Event eCRF page.

6.2.2.1 Psoriasis medical history/previous psoriasis therapies

Disease history will be collected at the screening visit. The information to be collected and entered in the Psoriasis History eCRF and Prior Psoriasis Therapies eCRF will include the following:

- Date of first diagnosis (by a physician) of plaque psoriasis
- Previous treatments of psoriasis (including previous use of biologic therapies, as well as phototherapy and/or photo-chemotherapy) and the reason for discontinuation of each therapy
- Presence of psoriatic arthritis and the date of first diagnosis (by a physician)

6.2.3 Prior and concomitant medications

Concomitant medications and prior medications taken within the 6 months preceding study enrollment will be captured at the screening visit, and updated at baseline.

6.2.4 Determination of tuberculosis status

Determination of TB status will be required before administration of study treatment and should be performed as defined by local guidelines. Tuberculosis status must be determined by medical history, signs, symptoms, and TB testing (QuantiFERON® TB-Gold In-Tube assay).

Any significant findings will be recorded in the Tuberculosis Assessment eCRF page and the Medical History eCRF page, as necessary.

[redacted]

QuantiFERON TB-Gold In-Tube assay

This test (Figure 6-1) will only be used to screen the patient population for latent TB infection (Doherty et al 2008) and determine patient's eligibility for the study.

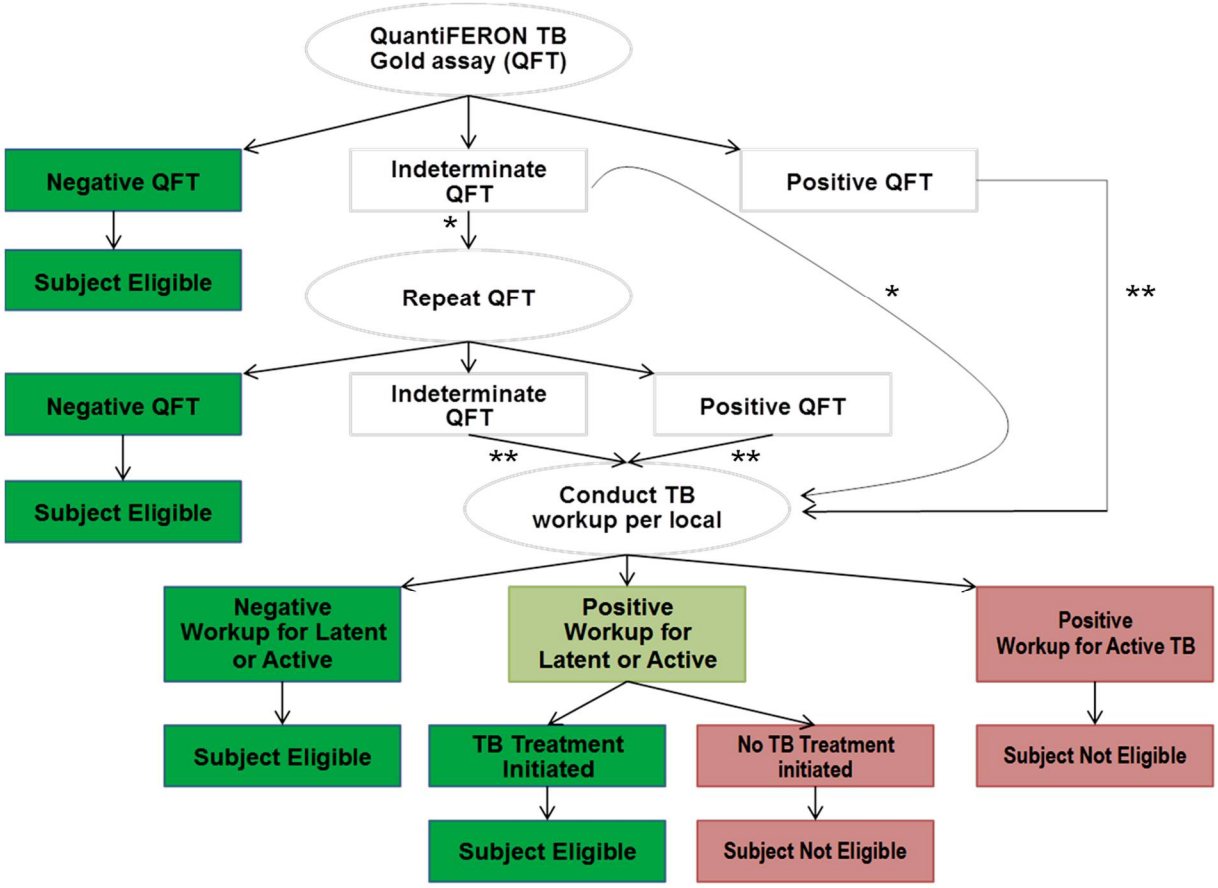
This blood-based assay is specific for Mycobacterium tuberculosis and is not influenced by previous bacillus Calmette-Guerin vaccination or exposure to other Mycobacteria species. In contrast to the purified protein derivative skin test, it is also insensitive to a booster effect, since the patient is not exposed to the vaccine. The assay measures the production of interferon-gamma and presents it relative to negative and positive control samples (Manuel and Kumar 2008).

The QuantiFERON®-TB Gold In-Tube assay will be supplied by the central laboratory. Details on the collection, shipment of samples and reporting of results by the central laboratory will be provided to investigators in the laboratory manual.

- If the test result is negative, the patient may be randomized
- If the test result is positive, the investigator should perform workup for the test result as per local procedures:
  - Patients who are **positive** for latent TB per workup may be randomized to the study if sufficient treatment has been initiated according to local routine clinical practice and will be maintained for the prescribed duration
  - Patients who are **positive** for active TB per workup are not eligible for the study
  - Patients who are **negative** for TB (no signs of latent or active TB) per workup may be randomized to the study
- If the test result is **indeterminate**, it is **recommended to repeat it once**. The investigator may decide to skip the repetition of the test and proceed directly to the workup (this is however not recommended). If a TB workup was conducted within 12 weeks prior to randomization, the results can be used to assess eligibility
  - If the second test is **negative**, the patient may be randomized
  - If the second test is **positive or indeterminate**, the investigator should perform workup as per local guidelines. The patient will not be eligible for randomization if "active or latent TB are present" and will be untreated as per local guidelines

[redacted]

Figure 6-1 Tuberculosis screening flowchart



The patient will not be eligible for randomization if active or latent TB are present and is untreated as per local guidelines.

* If the result of the first QuantiFERON®-TB Gold In-Tube assay is indeterminate, the investigator may choose to repeat the assay or refer the patient for TB workup as per local guidelines.

** If the result of any assay is positive, or the result of 2 sequential assays is indeterminate, the investigator must refer the patient for TB workup as per local guidelines (if no workup of the 12 weeks prior to randomization is available).

6.2.5 Other baseline characteristics

Baseline characteristic data to be collected on all patients include (see also Table 6-1): 12-lead ECG, vital signs, hematology, clinical chemistry (all laboratory assessments will be performed in a central laboratory except where indicated), physical examination, height, weight, medical history, [redacted], as well as assessments of PASI, BSA and IGA mod 2011. A serum pregnancy test will be performed to women of childbearing potential.

6.3 Treatment exposure and compliance

All doses of study treatment administered will be recorded on the appropriate Dosage Administration Record eCRF page. Patient compliance to the study treatment should be assessed by qualified site personnel at each study visit using the study kits and documentation regarding study treatment dispensation and administration.

[redacted]

Compliance will also be assessed continuously during the conduct of the study by Novartis study personnel using medication kits and the corresponding documentation. Study treatment doses and the corresponding dates of self-administration at home should be documented in a self-administration log. Patients will be required to return the self-administration log as well as all dispensed study treatment at every visit to the investigational site for a compliance check.

6.4 Efficacy

All efficacy assessments should be performed prior to the administration of study treatment.

6.4.1 Assessment of body surface area and psoriasis area severity index

The investigator or trained qualified designee will complete the PASI assessment as indicated in Table 6-1, Table 6-2, and Table 6-3. Whenever possible, the same evaluator should perform this assessment at all visits.

The total BSA affected by plaque psoriasis will be estimated from the percentages of the affected areas, including head, trunk, upper limbs and lower limbs.

The following calculations will be done: each reported percentage will be multiplied by the factor that corresponds to the respective body region (head = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4). The resulting 4 percentages will be added up to estimate the total BSA affected by plaque psoriasis.

A PASI score (Fredriksson and Pettersson 1978, Gottlieb et al 2005) will be derived as indicated in Table 6-4. The head, trunk, upper limbs and lower limbs will be assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the 4 body regions will be assigned a score of 0-4. The area covered by lesions on each body region will be estimated as a percentage of the total area of that particular body region. Further practical details to help with the assessment are provided below:

1. The neck is assessed as part of the head
2. The axillae and groin are assessed as part of the trunk
3. The buttocks are assessed as part of the lower limbs
4. When scoring the severity of erythema, scales should not be removed

Because the head and neck, upper limbs, trunk and lower limbs correspond to approximately 10%, 20%, 30% and 40% of the BSA, respectively, the PASI score is calculated using the formula:

$$PASI = 0.1(E_H+I_H+D_H)A_H + 0.2(E_U+I_U+D_U)A_U + 0.3(E_T+I_T+D_T)A_T + 0.4(E_L+I_L+D_L)A_L$$

The keys for the letters are provided in Table 6-4.

PASI scores can range from a lower value of 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.0.

The baseline value for the analysis of the PASI will be collected at baseline.

Patients require a total BSA of 10% or more affected by plaque psoriasis and a PASI score of 10 or more at screening and baseline to be eligible for this study.

[redacted]

Table 6-4 Psoriasis area severity index scoring system

Body region	Erythema (E)	Thickening (plaque elevation, induration, I)	Scaling (desquamation, D)	Area score (based on true area %, A) [a]
Head (H) [b]	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = no involvement 1 ≥ 0 to < 10% 2 = 10 to < 30% 3 = 30 to < 50% 4 = 50 to < 70% 5 = 70 to < 90% 6 = 90-100%
Trunk (T) [c]	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = no involvement 1 ≥ 0 to < 10% 2 = 10 to < 30% 3 = 30 to < 50% 4 = 50 to < 70% 5 = 70 to < 90% 6 = 90 -100%
Upper limbs (U)	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = no involvement 1 ≥ 0 to < 10% 2 = 10 to < 30% 3 = 30 to < 50% 4 = 50 to < 70% 5 = 70 to < 90% 6 = 90 -100%
Lower limbs (L) [d]	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = no involvement 1 ≥ 0 to < 10% 2 = 10 to < 30% 3 = 30 to < 50% 4 = 50 to < 70% 5 = 70 to < 90% 6 = 90 - 100%

a) Percentage (not score) of body region (not whole body) affected will be entered in the eCRF.
b) Neck is assessed as part of the Head (H) body region.
c) Axillae and groin are assessed as part of the Trunk (T) body region.
d) Buttocks are assessed as part of the Lower limbs (L) body region.

[redacted]

Definitions of efficacy variables based on the psoriasis area severity index

The following definitions will be used in this study based on the CHMP guidelines for psoriasis (CHMP/EWP/2454/02):

- **PASI 50-89 response**: patients who achieve ≥ PASI 50, but < PASI 90 improvement (reduction) compared with baseline
- **PASI 90 response**: patients achieving ≥ 90% improvement (reduction) in PASI score compared to baseline are defined as PASI 90 responders
- **PASI 100 response/remission**: PASI = 0, complete clearance
- **Relapse:** when the achieved maximal PASI improvement from baseline is reduced by ≥ 50% (CHMP/EWP/2454/02)

[redacted]

6.4.4 Investigator's global assessment mod 2011

The impact of study treatment on psoriatic disease will be assessed by the IGA mod 2011 (Langley et al 2015) at the times indicated in Table 6-1, Table 6-2 and Table 6-3.

Patients require an IGA mod 2011 score at screening of ≥ 3 in order to participate in the study and the score will be recorded in the eCRF.

The rating scale for overall psoriatic disease is shown in Table 6-5.

The IGA mod 2011 used in this study is static, i.e., it refers exclusively to the patient's disease state at the time of the assessments, and does not attempt a comparison with any of the patient's previous disease states, whether at baseline or at a previous visit.

[redacted]

Table 6-5 Investigator's global assessment mod 2011 rating scale

Score	Short description	Detailed description
0	Clear	No signs of psoriasis. Post-inflammatory hyperpigmentation may be present
1	Almost clear	Normal to pink coloration of lesions; no thickening; no to minimal focal scaling
2	Mild	Pink to light red coloration; just detectable to mild thickening; predominantly fine scaling
3	Moderate	Dull bright red, clearly distinguishable erythema; clearly distinguishable to moderate thickening; moderate scaling
4	Severe	Bright to deep dark red coloration; severe thickening with hard edges; severe/coarse scaling covering almost all or all lesions

Note: involvement of nails is not part of the assessment

Based on this scale, patients will be considered as responders if they achieve a score of 0/1 and improve by at least 2 points compared with baseline.

6.4.5 Appropriateness of efficacy assessments

Psoriasis area severity index scores outcome measures, the assessment of the severity of the psoriasis symptoms and the extent to which the patient's body area is affected by the disease, is mandated by the European Medicines Agency (EMA) for the clinical investigation of medicinal products for the treatment of psoriasis (CHMP/EWP/2454/02).

As indicated in Section 6.4.4, the IGA mod 2011 scale has been developed by Novartis in collaboration with health authorities, in particular the FDA. It is based on the previous version of the scale, which was used in Phase II secukinumab studies. In the modified scale, the categories "very severe" and "severe" have been condensed into a single category "severe" and the explanations/descriptions of the points on the scale have been improved to ensure appropriate differentiation between them.

6.5 Safety

From baseline, all blood draws and safety assessments must be performed prior to study treatment administration. Appropriate safety assessments (e.g., evaluation of AEs and SAEs) should be repeated after dosing with study treatment.

6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities, and the vascular and neurological systems. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be examined.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to signing the informed consent must be included in the Medical History eCRF page. Significant findings made after the first administration of investigational drug which meet the definition of an AE must be recorded on the Adverse Event section of the eCRF.

[redacted]

6.5.2 Vital signs

Vital signs include blood pressure and pulse measurements. After the patient has been sitting for 5 minutes, with the back supported and both feet placed on the floor, systolic and diastolic blood pressures will be measured 3 times using an automated validated device, e.g., OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1-2 minute intervals and the mean of the 3 measurements will be used. If the available cuff sizes are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

If possible, assessments should be performed by the same study site staff member throughout the study.

Normal blood pressure will be defined as a systolic pressure of 90 to < 120 mm Hg, and a diastolic blood pressure of 60 to < 80 mm Hg under the measurement conditions outlined above. Notable blood pressure findings will be hypertension (systolic blood pressure of ≥ 140 mm Hg and/or diastolic blood pressure of ≥ 90 mm Hg) or hypotension (systolic blood pressure of < 90 mm Hg and/or a diastolic blood pressure of < 60 mm Hg). A blood pressure indicative of prehypertension (systolic blood pressure of 120 to < 140 mm Hg and/or diastolic blood pressure of 80 to < 90 mm Hg) will not be regarded as notable (Chobanian et al 2003).

A normal pulse rate will be defined as a rate of 60 to 100 beats per minute (bpm) under the measurement conditions outlined above. Notable pulse rate will be a rate below 60 bpm (bradycardia) or above 100 bpm (tachycardia).

Whether action needs to be taken to address notable vital signs will be decided by the investigator, taking into account the overall status of the patient. No specific action is foreseen as part of the study protocol.

6.5.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

6.5.4 Laboratory evaluations

A central laboratory will be used for the analysis of blood and urine collected (with the exception of pregnancy tests). Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. For the identification of notable values, the laboratory manual should be consulted. Whether action needs to be taken to address notable laboratory values will be decided by the investigator taking into account the overall status of the patient. No specific action is foreseen as part of the study protocol.

For clinically notable thresholds please refer to Appendix 1 or to the laboratory manual.

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils including bands, lymphocytes, monocytes, eosinophils, basophils), and platelet count will be measured.

[redacted]

6.5.4.2 Clinical chemistry

Blood urea, creatinine, total bilirubin, alkaline phosphatase, international normalized ratio, sodium, potassium, chloride, calcium, phosphorous, total protein, albumin, uric acid, and lipid panel will be measured.

For a local analysis of urine, dipsticks will be provided by the central laboratory to the sites for the assessment. Sites should record the results in the source documentation and report these in the eCRF for each patient.

6.5.4.3 High-sensitivity C-reactive protein

This marker will be assessed at the visits when clinical chemistry is performed (see Table 6-1, Table 6-2, and Table 6-3).

6.5.5 Electrocardiogram

For the baseline visit an ECG must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection at baseline is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Only clinically significant abnormalities should be reported in the eCRF Adverse Event page. If the ECG findings are clinically relevant and would prevent the patient from participating in the study (taking into account the patient's overall status and the medication profile), the patient should be recorded as a screen failure, should not be enrolled and should not receive treatment.

Single 12-lead ECGs will be collected. The original ECGs, appropriately signed, should be collected and archived at the study site.

Each ECG tracing must be labelled with study number, patient initials, patient number, date and time, and filed in the study site source documents. Clinically significant ECG findings at baseline must be discussed with the sponsor before administration of study treatment.

6.5.6 Pregnancy

A serum or urine β-hCG test will be performed in all pre-menopausal women as shown in Table 6-1, Table 6-2, and Table 6-3.

All pre-menopausal women who are not sterile at screening will also have a urine pregnancy test performed locally. Any woman with a confirmed positive pregnancy test (hCG > 5 mIU/mL) during screening will not be eligible for randomization.

Women of childbearing potential should use an effective method of contraception while on treatment, or longer if required by locally-approved prescribing information (e.g., 20 weeks after the last dose in the EU and countries where applicable for secukinumab). A positive urine pregnancy test during the Treatment Epoch of the study requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If the serum β-hCG test is positive, study treatment must be definitively discontinued, as described in Section 5.6.2.

If a β-hCG test is positive during the Follow-up Epoch, the patient will be discontinued from the study.

[redacted]

6.5.7 Appropriateness of safety measurements

The safety assessments selected in this study are reliable and standard measures for a biologic immunomodulatory agent in adult patients with psoriasis.

6.6 Other assessments

6.6.1 Clinical outcome assessments

6.6.1.1 Clinician-reported outcomes

6.6.1.1.1 Evaluation of psoriasis arthritis symptoms

Questions about signs and symptoms of psoriatic arthritis including pain, swelling and stiffness of the joints, neck, back, fingers, toes, and enthesis will be addressed and captured in the eCRF.

[redacted]

[redacted]

[redacted]

6.6.2 Resource utilization

Not applicable.

6.6.3 Pharmacokinetics

Not applicable.

6.6.4 Immunological analysis of skin biopsies

This study includes an optional biopsy collection which requires a separate informed consent if the patient agrees to participate in the Mechanistic Sub-study.

Skin biopsies will be taken from patients in Arm A1b, Arm A2, Arm B1b, Arm C1, and Arm C2 to assess the total number of T_{rm} cells and subsets of these cells, especially those capable of producing IL-17A and IL-22 inflammatory mediators considered to be vital to maintain subclinical inflammation. [redacted]

Punch biopsies from lesional or resolved skin (2 biopsies, 4 millimeters in diameter) and never-lesional skin (1 biopsy, 3 millimeters in diameter) will be taken according to the schedule shown in Table 6-6. After collection, biopsies need to be transported on ice or dry ice within 24 hours to the laboratory (Karolinska Institute, Stockholm, Sweden) for further processing using a Novartis delegated service provider.

[redacted]

Table 6-6 Schedule for the collection of skin biopsies

	Collection time				
Arm	**Baseline**	**Week 16**	**Week 52**	**Week 104**	**Week 208**
A1b	X	X	X	X [a]	X [a]
A2	X	X	X	X	X [a]
B1b	X	X	X	X [a]	X [a]
C1	X	X	X		
C2	X	X	X	X	

a) Only patients eligible for the Follow-up Epoch will have biopsies taken at the marked time points

Laboratory manuals will be provided with detailed information on sample collection, handling, and shipment. The sample collection date and exact time must be entered on the Sample Collection eCRF page.

[redacted]

7 Safety monitoring

7.1 Adverse events

An AE is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study until the EOS visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an AE irrespective if a clinical event has occurred. The occurrence of AEs must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from

[redacted]

baseline (randomization) or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying AEs. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded in the Adverse Event eCRF page under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade:
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment
  - no relationship to study treatment or other investigational treatment or
  - relationship to study treatment or
  - relationship to other investigational treatment or
  - relationship to both study treatment and other investigational treatment or indistinguishable
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported
- whether it constitutes a SAE (see Section 7.2 for definition of SAE) and which seriousness criteria have been met
- action taken regarding the investigational treatment

All AEs must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g., further observation only)
- investigational treatment dosage increased/reduced
- investigational treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Worsening of psoriasis in this study is evaluated via the use of PASI, IGA mod 2011 [redacted] assessments and is not expected to be captured as an AE in the eCRF. Exceptions include cases when a) a new type of psoriasis is diagnosed (e.g. guttate psoriasis), and b) the worsening of psoriasis is so severe that a qualitatively different status is reached.

Information about common side effects already known about the study treatment can be found in the Investigator Brochure. This information will be included in the patient informed consent

[redacted]

and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between Investigator Brochure's updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

The investigator should also instruct each patient to report any new AE (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must also be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of serious adverse event

An SAE is defined as any AE (appearance of [or worsening of any pre-existing] undesirable sign[s], symptom[s] or medical conditions[s]) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g., defined as an event that jeopardizes the patient or may require medical or surgical intervention. All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (see ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see ICH-E2D Guideline).

[redacted]

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

7.2.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 12 weeks following the last administration of study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 12-week period following the last administration of study treatment should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to each specific component of the study treatment (if the study treatment consists of several components) complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

Not applicable.

7.4 Renal safety monitoring

Not applicable.

[redacted]

7.5 Reporting of study treatment errors including misuse/abuse

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient (EMA/762563/2014).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Treatment error type	Document in DAR eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/abuse	Yes	Yes	Yes, even if not associated with a SAE

DAR = dose administration record

7.6 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE Report Form.

Pregnancy outcomes should be collected for the female partner of any male who take study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

7.7 Prospective suicidality assessment

Not applicable.

[redacted]

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and eCRF with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRF, the adherence to the protocol and to Good Clinical Practice (GCP) and the progress of enrollment. Key study personnel must be available to assist the field monitors during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRF are performed according to the study-specific monitoring plan. No information in source documents about the identity of the study patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff (or designated Contract Research Organization [CRO] staff) review the data entered into the eCRFs by investigator/qualified site staff for completeness and accuracy and instruct the investigator/qualified site staff to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Investigator/qualified site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Investigator/qualified site staff will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator/qualified site staff site.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Patient-reported outcomes data will be collected from all patients. These data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO) or transferred by investigator/qualified site staff into the eCRF, respectively.

Randomization codes, data about study treatments dispensed to the patient, all IRT recorded dosage changes, and some efficacy data will be tracked using IRT. The system will be supplied by a vendor that will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

8.4 Data Monitoring Committee

The implementation of a Data Monitoring Committee to review the safety data of this study is not planned. However, a Scientific Steering Committee is formed. The task of the Committee is to safeguard proper execution of the study and monitor the progress.

8.5 Adjudication Committee

Not required.

9 Data analysis

9.1 Analysis sets

The following analysis sets will be used:

- **Full analysis set**: The FAS will be comprised of all patients who were randomized to the study. Following the intent-to-treat principle, patients will be analyzed according to the treatment assigned at baseline
- **Safety set (SAF)**: The safety set includes all patients who took at least one dose of study treatment during the Treatment Epoch, whether or not they were randomized. Patients will be analyzed according to the treatment received

The treatment arms (see Section 5.2) for the analyses of data will include:

Main Study

- Sixty-eight patients from Arm A1a and 12 from Arm A1b
- Sixty-eight patients from Arm B1a and 12 from Arm B1b

[redacted]

Mechanistic Sub-study

- Twelve patients from Arm A1b
- Twelve patients from Arm A2
- Twelve patients from Arm B1b
- Twelve patients from Arm C1
- Twelve patients from Arm C2

9.2 Patient demographics and other baseline characteristics

Demographics and baseline characteristics

Summary statistics will be presented for continuous demographic and baseline characteristic variables for each treatment arm and for all patients in the FAS. The number and percentage of patients in each category will be presented for categorical variables for each treatment arm and for all patients.

Medical history

Any condition entered as medical history or current medical conditions at baseline will be coded using the MedDRA dictionary. Medical history will be summarized for all patients in the FAS by system organ class and preferred term in the MedDRA dictionary. Summaries for psoriasis-specific medical history will be provided.

Cardiovascular medical history assessed prior to randomization will also be summarized.

9.3 Treatments

The analysis of study treatment data will be based on the SAF. The duration of exposure to study treatment will also be summarized by treatment arm.

Prior and concomitant treatments

Prior and concomitant treatments will be summarized by treatment arm in separate tables for the SAF and for the treatment epochs separately.

Prior treatments are defined as treatments taken and stopped prior to the first dose of study treatment. Any treatment given at least once between the day of first dose of randomized study treatment (baseline) and the last study visit will be a concomitant treatment, including those which were started pre-baseline and continued into the Treatment Epoch.

Treatments will be presented in alphabetical order, by ATC codes and main groups. Tables will also show the overall number and percentage of patients receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

In addition, medical procedures and significant non-drug therapies as coded in MedDRA will be summarized.

[redacted]

9.4 Analysis of the primary variable

The primary objective of this study is to demonstrate the superior efficacy of secukinumab 300 mg s.c. compared to nb-UVB in patients with new-onset moderate to severe plaque psoriasis with respect to patients achieving PASI 90 response at Week 52.

9.4.1 Primary variable

The primary efficacy variable is the proportion of patients who achieve PASI 90 at Week 52. The analysis for the primary objective will be based on the FAS.

9.4.2 Statistical model, hypothesis, and method of analysis

For the primary analysis, the following hypothesis testing will be performed:

$$H_{01}: p_{sec} = p_{nbUVB} \; versus \; H_{A1}: p_{sec} > p_{nbUVB}$$

where p_{sec} and p_{nbUVB} are the proportion of PASI 90 responders in the secukinumab 300 mg s.c. (Arm A1) and nb-UVB (Arm B1) groups, respectively.

The primary analysis method for PASI 90 response at Week 52 will use a logistic regression model with treatment as an explanatory variable and significant covariates among baseline PASI score, age, and body mass index. The best subset of the significant covariates will be selected using a forward selection method based on the likelihood ratio test. Interaction terms will also be considered, if significant, among the best subset of selected covariates and the treatment term.

Statistical significance will be evaluated at a 1-sided alpha level of 0.025. The estimated adjusted odds ratio for Arm A1 versus Arm B1 will be displayed along with the associated 2-sided 95% confidence interval (equivalent to the 1-sided 97.5% confidence interval) and p-value.

If there are issues related to the convergence of the logistic regression model, the above hypothesis will be tested using a Wald test.

The primary analysis is not expected to be influenced by the use of topical treatment within the first 4 weeks since, any effect will be worn off by Week 52.

9.4.3 Handling of missing values/censoring/discontinuations

Missing data will be handled with a modified multiple imputation method. Patients who discontinued the study before Week 52 because of lack of efficacy or AEs will be considered non-responders. Missing values for other reasons will be inserted by means of the multiple imputation method.

The multiple imputation method is a simulation-based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets, which can then be analyzed using standard methods. Rubin (1987) presented rules how to combine the multiple sets of estimates to produce overall estimates and confidence intervals that adequately incorporate missing data uncertainty.

[redacted]

Missing values for the "change from baseline PASI score" will be imputed simultaneously based on an underlying normal distribution and using the data augmentation procedure of Markov Chain Monte Carlo (MCMC) method. The change from baseline in PASI score appears to follow closer to a normal distribution than the actual PASI score. The imputations will be done separately for each treatment group. Further details will be provided in the statistical analysis plan.

9.4.4 Supportive analyses

A non-responder imputation will be used as supportive analysis, i.e., a missing value of PASI 90 response at Week 52 will be imputed with non-response regardless of the reason for missing data (e.g., premature study discontinuation, missed visit, administrative issues).

9.5 Analysis of secondary variables

9.5.1 Key secondary variable

The key secondary variable is the proportion of all randomized patients who achieve PASI 90 at Week 104. In order to reduce selection bias, all patients who do not achieve PASI 90 at Week 52 will also be included in the analysis at Week 104 using the PASI improvement obtained at Week 104 only.

A patient who fails to achieve PASI 90 response at Week 104, irrespective of the responses over the past visits will be considered non-responder. Similarly, patients who achieved PASI 90 response at Week 104, but not at any of the past visits will be considered responder.

This would mean that if a patient achieves PASI 85 (85% improvement in PASI score compared to baseline) at Week 52, and the improvement in PASI increases to 90% at Week 104, the patient will be considered responder in the analysis at Week 104.

For the key secondary analysis, the following hypothesis testing will be performed:

$$H_{02}: p^*_{sec} = p^*_{nbUVB} \; versus \; H_{A2}: p^*_{sec} > p^*_{nbUVB}$$

where p^*_{sec} and p^*_{nbUVB} are the proportion of patients who achieve PASI 90 response at Week 104 in the secukinumab 300 mg s.c. (Arm A1) and nb-UVB (Arm B1) groups respectively. This testing will be performed using an exact logistic regression analysis similar to the primary analysis, with the strategy below under consideration.

Missing data will be handled similarly as for the primary endpoint analysis. Patients who relapse will be considered non-responders in addition to those who discontinue the study before Week 104 because of lack of efficacy or AEs.

In addition, the proportion of all randomized patients who achieve PASI 90 at 52 weeks after cessation of treatment will be analyzed as an exploratory supportive analysis using an exact logistic regression analysis similar to the key secondary analysis.

Testing strategy

Since the primary and the key secondary hypotheses are not mutually independent, an adjustment for multiplicity is considered here to control the alpha level (Type I error) i.e., familywise error rate.

[redacted]

This adjustment will be made using a hierarchical testing procedure, which states that first H_{01} will be tested at 1-sided $\alpha = 2.5\%$ level of significance. The obtained p-value from the fitted logistic regression model will be divided by 2 and this resultant p-value needs to be considered. If the resultant p-value is smaller than 0.025, H_{01} is rejected at 2.5% significance level, concluding that there is strong evidence to consider that secukinumab is performing better than nb-UVB at Week 52. However, if this resultant p-value is greater than 0.025, H_{01} is not rejected at 2.5% significance level, concluding that the evidence obtained from the observed sample is not strong enough to say that any one of the treatment arms is performing better than the other.

The testing sequence will continue to test H_{02} at α=2.5% (1-sided), only if H_{01} is rejected.

9.5.2 Investigator's global assessment mod 2011

The secondary efficacy variable is the proportion of all randomized patients who achieve at least IGA 0/1 response at Week 52. Patients will be considered responders if they achieve a score of 0/1 and improve by at least 2 points compared with baseline.

This analysis will be based on the FAS.

The method for IGA 0/1 response at Week 52 will use a logistic regression model similar to the primary analysis, with treatment as an explanatory variable and the significant variables among baseline IGA score, age, and body mass index, and their interactions with treatment. Forward selection procedure based on the likelihood ratio test would be used to select the best subset of covariates. The estimated adjusted odds ratio for Arm A1 versus Arm B1 will be displayed along with the associated 95% confidence interval.

If there were issues related to the convergence of the logistic regression model, the above hypothesis will be tested using a 1-sided Wald test.

Missing IGA 0/1 response values will be imputed with non-response regardless of the reason for the missing data (e.g., premature study discontinuation, missed visit, or administrative issue).

9.5.3 Safety variables

All safety evaluations will be performed on the SAF.

For the Main Study, the safety of secukinumab compared with nb-UVB will be evaluated. For the Mechanistic Sub-study, similar safety evaluations will be performed by treatment and study epoch.

Adverse events

Treatment emergent AEs (events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized. Only primary paths within MedDRA will be considered for AE reporting.

Adverse events will be summarized by presenting, for each treatment arm, the number and percentage of patients having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a patient reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a patient reported

[redacted]

more than one AE within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

Separate summaries will be provided for psoriatic arthritis, death, SAEs, other significant AEs leading to discontinuation from the study, and AEs leading to study treatment discontinuation. In addition, exposure adjusted summaries including 95% confidence intervals for the occurrence rate of AEs in 100 patient years will be provided by treatment.

Laboratory data

The summary of laboratory evaluations will be presented for 2 groups of laboratory tests (hematology and clinical chemistry). Descriptive summary statistics for the changes from baseline to each study visit will be presented by test group, laboratory test, and treatment arm. Changes from baseline will only be summarized for patients with both baseline and post-baseline data.

For each parameter, the maximum change from baseline within each study epoch will be analyzed analogously.

In addition, shift tables will be provided for all parameters based on Common Toxicity Grade Criteria (CTC). The normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high. These summaries will be presented by laboratory test and treatment arm. Shifts will be presented for most extreme post-baseline values.

Vital signs

Vital sign measurements will be analyzed using summary statistics for the change from baseline for each post-baseline visit and presented by vital sign and treatment arm. Changes from baseline will only be summarized for patients with both baseline and post-baseline values.

9.5.4 Resource utilization

Not applicable.

9.5.5 Pharmacokinetics

Not applicable.

9.5.6 DNA

Not applicable.

[redacted]

9.5.8 PK/PD

Not applicable.

[redacted]

[redacted]

9.6 Analysis of exploratory variables

This section describes the analyses for exploratory endpoints.

[redacted]

[redacted]

9.6.3 Investigator's global assessment mod 2011 score and response over time

Treatment Arm A1 will be compared with Arm B1 based on IGA mod 2011 0/1 responses at Week 104 using a similar logistic regression model as described in Section 9.5.2.

Further, IGA mod 2011 0/1 responses at each visit will be analyzed by means of a logistic regression model similar to the secondary analysis with treatment as a predictor variable and the significant variables among baseline IGA mod 2011 score, age, and body mass index, and their interactions with treatment. Forward selection procedure based on the likelihood ratio test would be used to select the best subset of covariates. The estimated adjusted odds ratio will be displayed along with the associated 95% confidence interval.

Missing IGA 0/1 response values will be imputed with non-response regardless of the reason for the missing data (e.g., premature study discontinuation, missed visit, or administrative issue).

IGA mod 2011 score will be summarized descriptively, using number and percentages by visits.

For the treatment arms in the Mechanistic Sub-study, the above-stated analyses will also be repeated over the 52 weeks of the Treatment Epoch (i.e., until Week 52 for Arms A1b, B1b, and C1, and until Week 104 for Arms A2 and C2).

[redacted]

[redacted]

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9.7 Interim analyses

A primary endpoint analysis is planned after all patients complete the visit at which the primary endpoint is assessed (Week 52). A key secondary endpoint analysis is planned if all patients have reached Week 104.

An interim analysis for the Mechanistic Sub-Study will be performed at Week 16. As this analysis at Week 16 will not involve any formal hypothesis testing, no adjustment for multiplicity will be required.

Additional interim analyses might be conducted as regarded appropriate (e.g., to provide additional data for regulatory or publication purposes).

9.8 Sample size calculation

The sample size calculation is performed for the primary endpoint (proportion of PASI 90 responders at Week 52) and the key secondary endpoint (proportion of all randomized patients

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who achieve PASI 90 response at Week 104, see Section 9.9). The selected total sample size is 160 patients, such that 80 patients are randomized in each arm.

The sample size calculation based on the proportion of PASI 90 responders at Week 104 was performed using PASS 11.

The power calculations for the primary endpoint are based on the asymptotic Wald test to compare secukinumab 300 mg s.c. versus nb-UVB using the hierarchical method to adjust for multiplicity. Based on data (unpublished) and experiences from recent studies, it is assumed that the proportion of PASI 90 responders at Week 52 will be around 70% after early treatment with secukinumab 300 mg s.c. (Arm A1) and around 35% after 1 or 2 cycles of nb-UVB treatment (Arm B1). With assumed approximate 0% dropout rate in Arm A1, and 20% in Arm B1 until Week 52 due to lack of efficacy or AEs (considered non-responders), the response rate would change to 70% and 28%, respectively. Assuming an absolute difference of 42% in the proportion of patients achieving PASI 90 at Week 52, the sample size of 80 patients in each arm would provide 99.9% power at the 1-sided significance level of 0.025 using asymptotic Wald test for equality of proportions (using PASS 11).

For the Mechanistic Sub-study, additional 12 randomized patients will be treated for 104 weeks with secukinumab 300 mg s.c. (Arm A2), along with 12 patients each from Arm A1b and Arm B1b, and will serve as active groups. Further, 12 patients identified with chronic plaque psoriasis will be allocated to secukinumab 300 mg s.c. for 52 weeks (Arm C1) and another 12 patients with chronic plaque psoriasis will be treated during 104 weeks with secukinumab 300 mg s.c. (Arm C2), both serving as control groups for the Mechanistic Sub-study. As the Mechanistic Sub-study will not involve any formal testing of hypothesis, the sample size for it is obtained in an illustrative manner.

9.9 Power for analysis of secondary variables

Sample size calculation is based on the assumptions for the key secondary efficacy endpoint with adequate power.

The absolute difference in the proportion of PASI 90 responders at Week 104 is considered to be 18% (23% of responders in Arm A1, and 5% in Arm B1). With assumed approximate 7% dropout rate in Arm A1 and 16% in Arm B1 (considered non-responders) before Week 104 due to lack of efficacy, AEs or relapse, the response rates would decrease to 21% and 4%, respectively. Using Fisher's exact test at 1-sided significance level of 0.025 with a power of around 89%, the sample size required is 80 patients in each treatment arm.

This sample size of 80 patients per treatment arm would provide a power of around 99.9% for the secondary efficacy endpoint, using the asymptotic Wald test at 1-sided significance level of 0.025, and assuming an absolute difference of 35% in the proportion of IGA 0/1 responders at Week 52 (considering 80% responders in Arm A1 and 45% in Arm B1). With assumed approximate 0% dropout rate in Arm A1 and 20% in Arm B1 before Week 52 (considered non-responders), the response rates would change to 80% and 36%, respectively.

[redacted]

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a study, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the study protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

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10.5 Quality control and quality assurance Novartis maintains a robust Quality Management system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance, a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal standard operating procedures, and are performed according to written Novartis processes.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol amendments

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC, where required, prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 must be followed.

12 References

References are available upon request.

Regulatory guidelines

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13 Appendix 1: Clinically notable laboratory values and vital signs

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests. Notable values for blood pressure and pulse are presented in Section 6.5.2.

Liver function and related variables

Total bilirubin:	> 2 x ULN
Alkaline phosphatase:	> 2.5 x ULN

Renal function and electrolyte variables

Creatinine (serum):	> 1.5 x ULN
Potassium:	> 6 mmol/L or < 3 mmol/L
Sodium:	> 160 mmol/L or < 115 mmol/L

Urinalysis variable

Protein urine dipstick:	2+ (100 mg/dL)

Hematology variables

Hemoglobin:	≥ 20 g/L decrease from baseline
Platelet count:	< lower limit of normal (LLN)
White blood cell count:	< 0.8 x LLN
Neutrophils:	< 0.9 x LLN
Eosinophils:	> 1.1 x ULN
Lymphocytes:	> 1.1 x ULN

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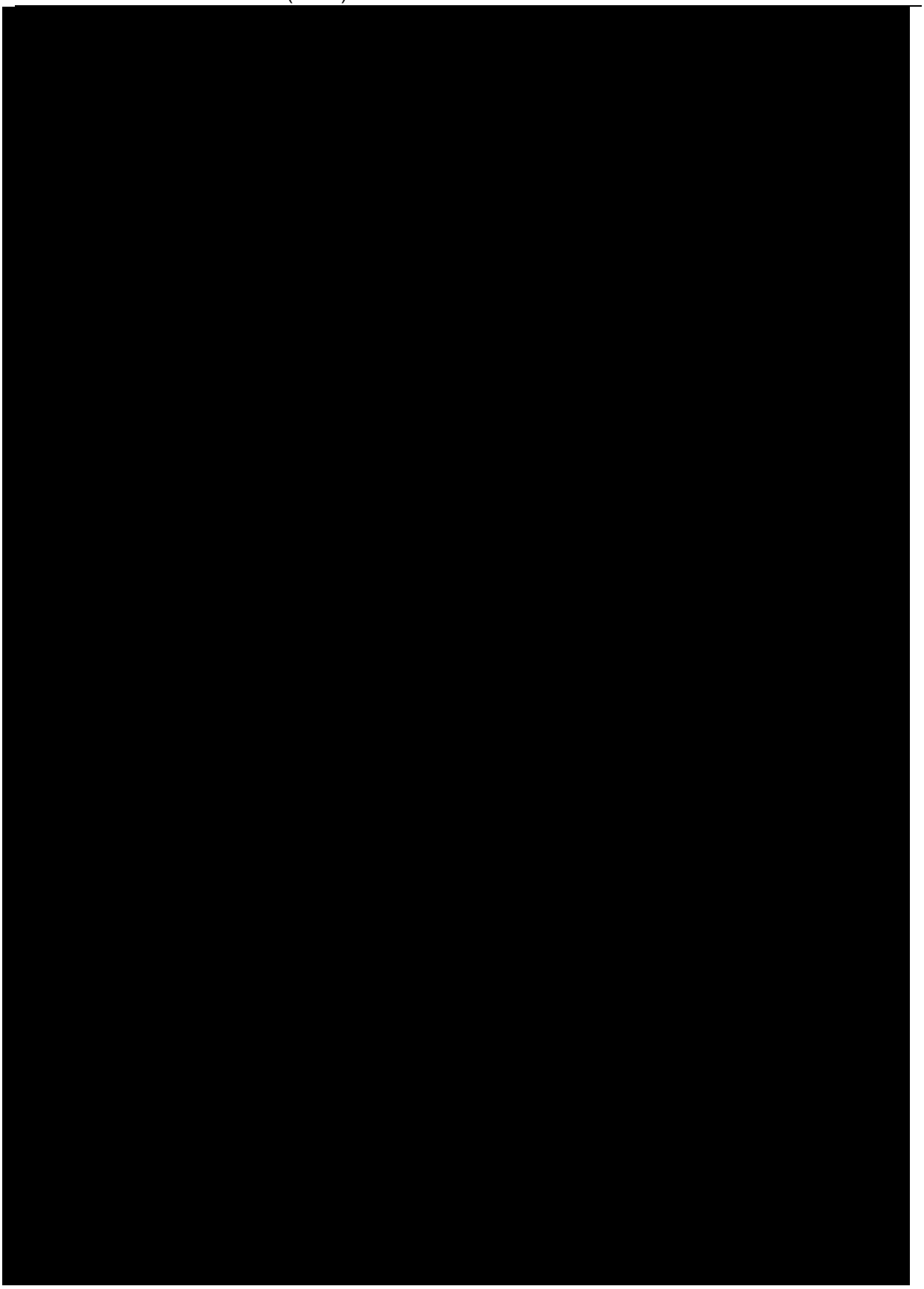

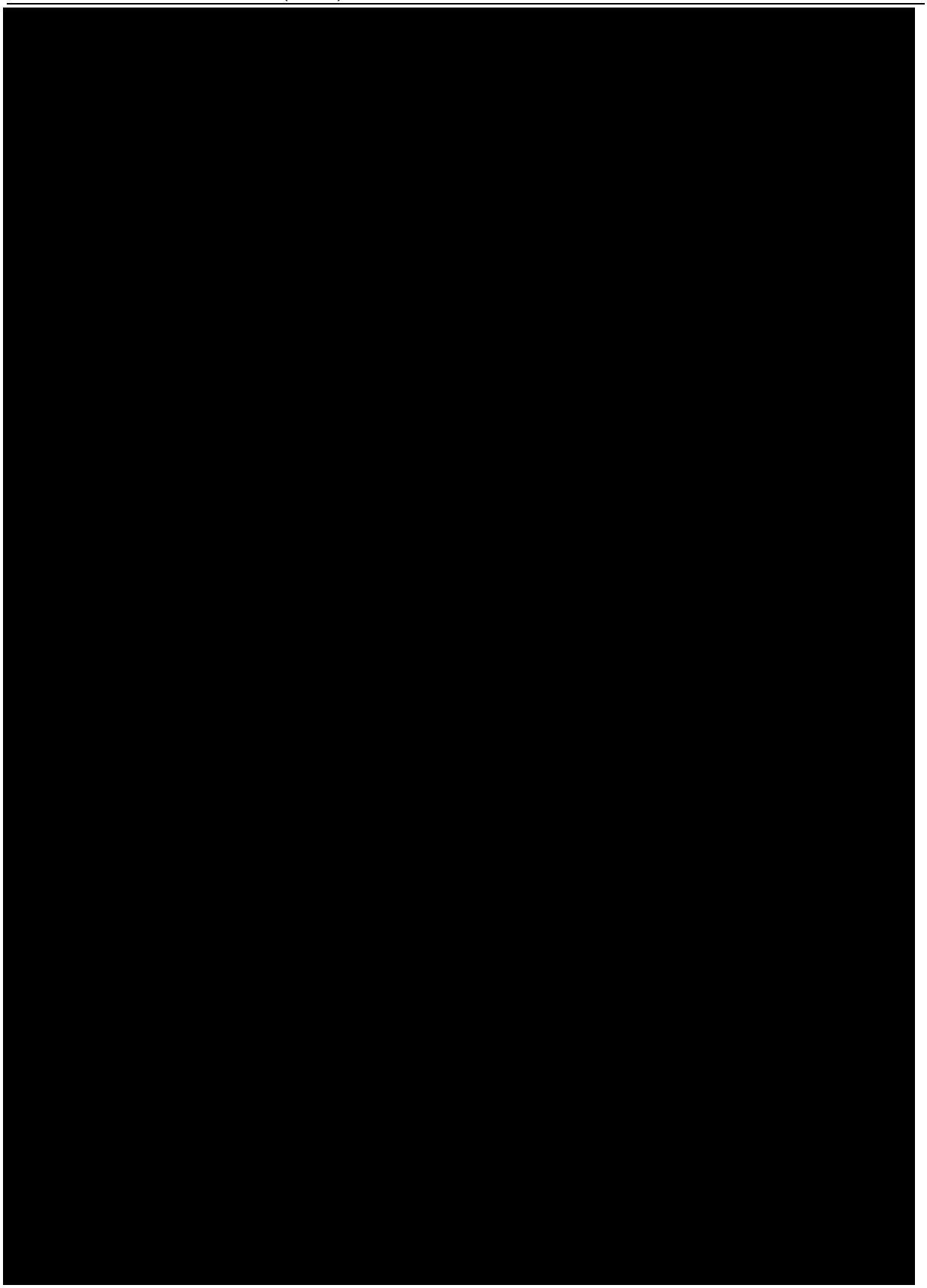

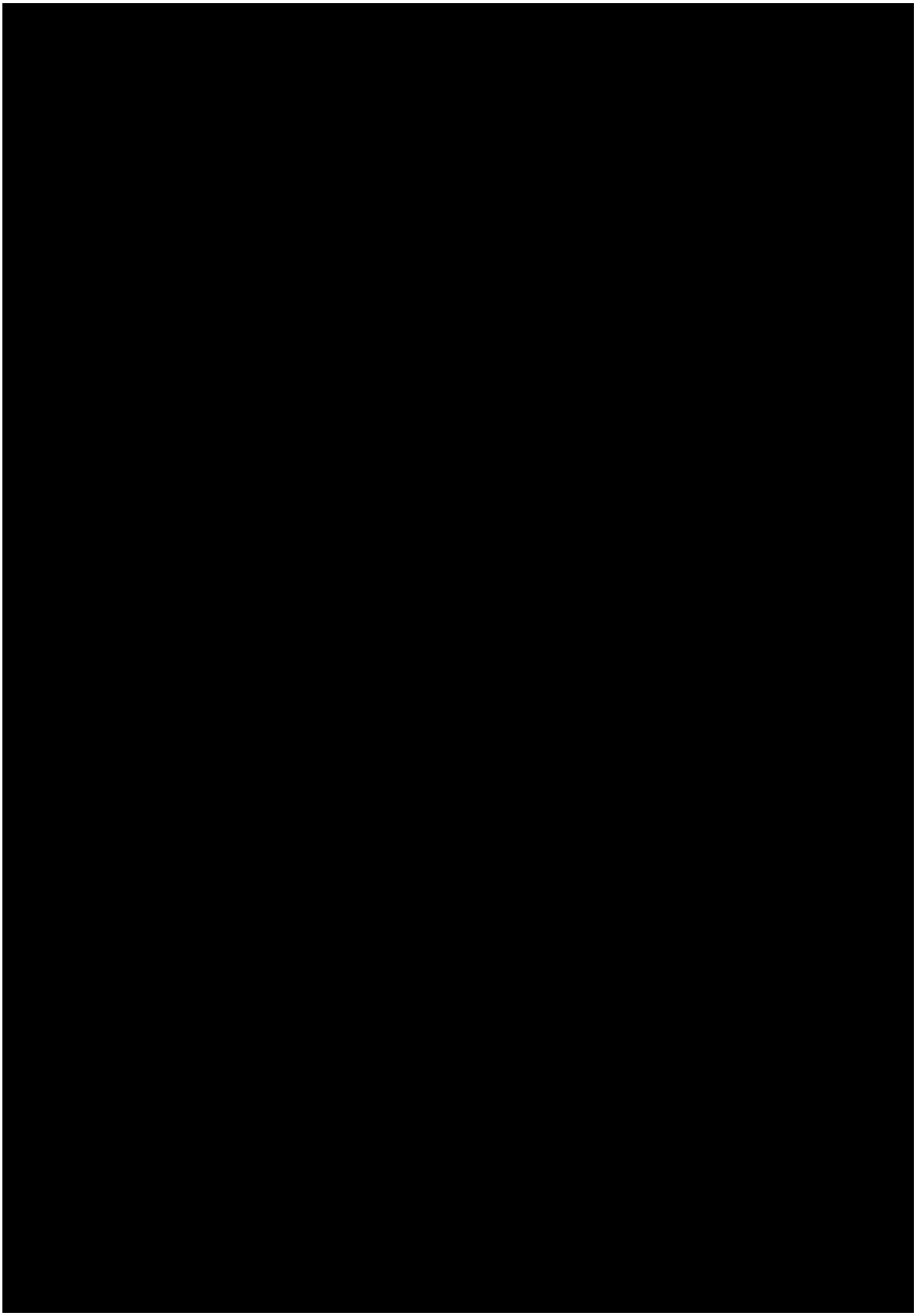

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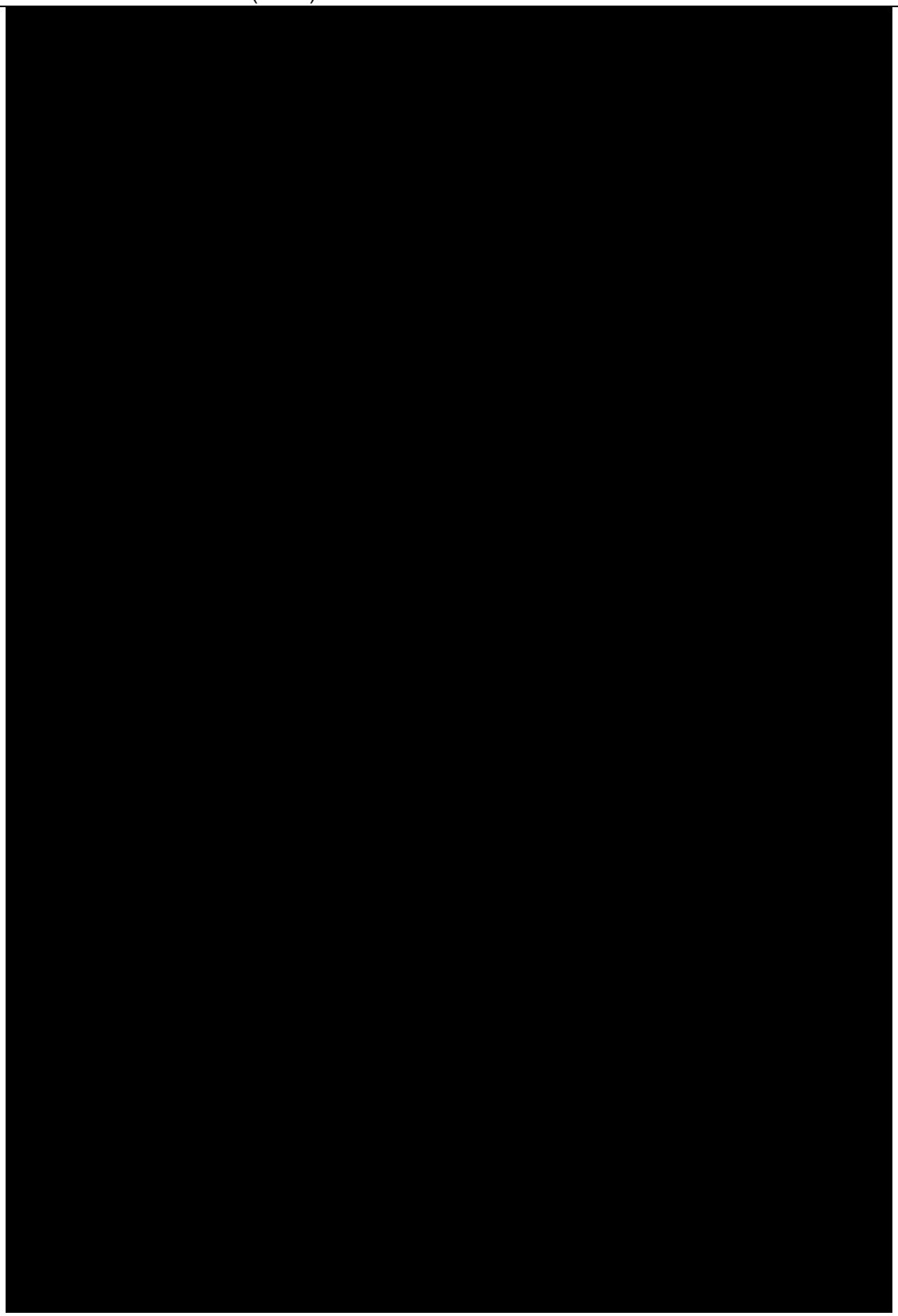

14.5 Skin type classification scale

Fitzpatrick Classification Scale

Skin Type	Skin Color	Characteristics	Score
I	White; very fair; red or blond hair; blue eyes; freckles	Always burns, never tans	(scores 0–6)
II	White; fair; red or blond hair; blue, hazel, or green eyes	Usually burns, tans with difficulty	(scores 7–13)
III	Cream white; fair with any eye or hair color; very common	Sometimes mild burn, gradually tans	(scores 14–20)
IV	Brown; typical Mediterranean caucasian skin	Rarely burns, tans with ease	(scores 21–27)
V	Dark Brown; mid-eastern skin types	very rarely burns, tans very easily	(scores 28–34)
VI	Black	Never burns, tans very easily	(scores 35–36)

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