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Clinical Research Germany, Therapeutic Area Dermatology, Allergology, Rheumatology

Cosentyx / Secukinumab (AIN457)

Non-Interventional Study Final Report

PROSPECT: Observational, descriptive study of **PR**ior and c**O**ncomitant p**S**oriasis treatments in **P**atients receiving S**EC**ukinumab in the routine **T**reatment of moderate to severe plaque-type psoriasis

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PASS information

Title

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Version identifier of the final study report

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Active substance

Secukinumab (AIN457), pharmacotherapeutic group: immunosuppressants, interleukin inhibitors, ATC code: L04AC10

Medicinal product

Name of the medicinal product	**Marketing authorization number (centrally authorized medicinal product)**
Cosentyx 150 mg solution for injection in pre-filled syringe	
• 2 pre-filled syringes	EU/1/14/980/003
• 6 (3 x 2) pre-filled syringes (multipack)	EU/1/14/980/006
Cosentyx 150 mg solution for injection in pre-filled pen	
• 2 pre-filled pens	EU/1/14/980/005
• 6 (3 x 2) pre-filled pens (multipack)	EU/1/14/980/007

Procedure number

EMEA/H/C/3729

Marketing authorization holder

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Joint PASS	No
Research question and objectives	The objective of this descriptive study was to assess prior and concomitant psoriasis treatments in patients receiving secukinumab in the routine treatment of moderate to severe plaque-type psoriasis, focusing on duration of transition periods from prior treatments to secukinumab and on the use of concomitant treatments. Furthermore, effectiveness as assessed in clinical routine as well as safety is described here.
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Table of contents

Table of contents 4
List of tables 6
List of figures 7
1 Abstract 8
2 List of abbreviations 9
3 Investigators 11
4 Other responsible parties 11
5 Milestones 11
6 Rationale and background 11
7 Research question and objectives 12
7.1 Primary endpoint 13
7.2 Secondary endpoints 13
[redacted] 15
8 Amendments and updates to the protocol 15
9 Research methods 16
9.1 Study design 16
9.2 Setting 17
9.2.1 Study time frames 17
9.2.2 Source and method of primary data collection 18
9.3 Subjects 18
9.3.1 Inclusion criteria 18
9.3.2 Exclusion criteria 18
9.4 Variables 19
9.4.1 Patient demographics 19
9.4.2 Psoriasis and other medical history 19
9.4.3 Prior and concomitant treatments 19
9.4.4 PASI 19
9.4.5 Routine effectiveness and quality of life assessments 21
9.4.6 Safety 22
9.5 Data sources and measurement 22
9.6 Bias 29
9.7 Study size 29
9.8 Data transformation 29
9.9 Statistical methods 30
9.9.1 Main summary measures 30

9.9.2 Main statistical methods 30
9.9.3 Safety analysis 34
9.9.4 Missing values 34
9.9.5 Interim analyses 37
9.9.6 Amendments to the statistical analysis plan 37
9.10 Quality control 38
9.10.1 Program layout and location 38
9.10.2 Statistical software 38
10 Results 39
10.1 Participants 39
10.2 Descriptive data 40
10.2.1 Demographic data 40
10.2.2 Psoriasis anamnesis 41
10.2.3 Non-psoriasis medical history 44
10.2.4 Prior non-psoriasis treatment 45
10.2.5 Concomitant non-psoriasis treatment 46
10.3 Outcome data 46
10.3.1 Analysis sets used 46
10.3.2 Prior psoriasis treatment 46
10.3.3 Concomitant psoriasis treatment 50
10.3.4 Secukinumab treatment and deviation from standard secukinumab treatment 53
10.4 Main results 55
10.4.1 Primary endpoint 55
10.4.2 Secondary endpoints 59
[redacted] 71
10.6 Adverse events/adverse reactions 71
10.6.1 Summary on patients with AEs 71
10.6.2 Analysis and description of AEs 73
10.6.3 Analysis and description of SAEs 77
10.6.4 Deaths 81
10.6.5 Adverse events leading to any action with secukinumab 83
11 Discussion 84
11.1 Key results 84
11.1.1 Baseline, demographic and treatment data 84
11.1.2 Primary endpoint 85

11.1.3 Secondary endpoints 86
11.1.4 Adverse events 87
11.2 Limitations 88
11.3 Interpretation 88
11.4 Generalizability 89
12 Other information 89
13 Conclusion 89
14 References 91
Appendices 92
Annex 1 – List of stand-alone documents 92
Annex 2 – Additional information 92

List of tables

Table 5-1 Study milestones 11
Table 6-1 Psoriasis treatment categories and groups in Germany 12
Table 9-1 The PASI scoring system 21
Table 9-2 Data collection 23
Table 10-1 Patient disposition – Analysis set (all patients) 39
Table 10-2 Study and treatment completion (analysis set) 40
Table 10-3 Baseline demography 41
[redacted] [redacted] 42
Table 10-5 Non-psoriasis disorders occurring in >1% of all patients 44
Table 10-6 Frequency of prior psoriasis treatments by category (all patients) 47
Table 10-7 Psoriasis treatment history by treatment categories (all patients) 48
Table 10-8 Duration of prior psoriasis treatments – treatment categories (all patients) 49
Table 10-9 Reasons for discontinuation of prior treatments (all patients) 50
Table 10-10 Frequency of concomitant treatments – categories (all patients) 51
Table 10-11 Duration of concomitant psoriasis treatments (all patients) 52
Table 10-12 Reasons for discontinuation of concomitant treatments (all patients) 52
Table 10-13 Secukinumab treatment (all patients) 53
Table 10-14 Mean duration of transition periods [days] for treatment categories (all patients) 55
[redacted] [redacted] 58

Table 10-16 Duration of transition periods compared to treatment intervals (all patients) 59
Table 10-17 Duration of transition periods compared to systemic terminal half-life (all patients) 60
[redacted] [redacted] 61
Table 10-19 Number of patients with documented measures at regular visits (all patients) 63
Table 10-20 PASI scores per regular study visits (all patients) 63
Table 10-21 PASI score during the study (all patients) 64
Table 10-22 PASI response rates for patients with PASI > 10 at baseline 66
Table 10-23 Course of BSA and reduction of BSA from baseline [%] during study 68
Table 10-24 IGA 0/1 response rates per visit (all patients) 69
Table 10-25 PGA scores per regular study visits (all patients) 69
Table 10-26 Course of DLQI and reduction (%) from baseline during study 70
Table 10-28 Overview of patients with AEs investigator's and sponsor's assessment (all patients) 72
Table 10-29 Patients with adverse events in total by PSOC and occurring in ≥ 1% of patients on PT level 73
Table 10-30 Patients with AEs assessed as related to secukinumab on PSOC level for all patients and on PT level occurring in ≥ 1% of patients (investigator's assessment) 76
Table 10-31 Summary of patients with adverse events with MedDRA Preferred Term "Psoriasis" 77
Table 10-32 Patients with SAEs by PSOC, occurring in >1 patient on PT level (investigator's assessments) 78
Table 10-33 Intensity of SAEs investigator's and sponsor's assessment 80
Table 10-34 SAEs with outcome death 81
Table 10-35 Summary of patients with AEs (unrelated and related) leading to any action with secukinumab 83

List of figures

Figure 9-1 Study design 17
Figure 10-1 Duration of transition periods (in days) – treatment categories 56
Figure 10-2 Duration of transition periods (in days) – selected conventional and systemic treatments 57
Figure 10-3 Mean PASI per visit (all patients) 65
Figure 10-4 PASI response rates per visit for patients with PASI > 0 (all patients) 67

1 Abstract

The abstract is provided separately.

2 List of abbreviations

ACE	Angiotensin-converting-enzyme
ADR	Adverse drug reaction
AE	Adverse event
ATC	Anatomical therapeutic chemical
bid	Twice a day (bis in die)
BSA	Body surface area
CI	Confidence interval
CRO	Contract research organization
DLQI	Dermatology life quality index
eCRF	Electronic case report form
EMA	European medicines agency
ENCePP	European network of centres for pharmacoepidemiology and pharmacovigilance
EU	European Union
FDA	Food & Drug administration
GPP	Good pharmacoepidemiology practices
GVP	Good pharmacovigilance practices
HA	Health authority
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A reductase
ICD-9-CM	The international classification of diseases, 9th revision, clinical modification
ICF	Informed consent form
ICH	International conference on harmonization
ICMJE	International committee of medical journal editors
IEC	Independent ethics committee
IGA	Investigator's global assessment
IQR	Inter-quartile range
IRB	Institutional review board
ISPE	International society for pharmacoepidemiology
MAH	Marketing authorization holder
MedDRA	Medical dictionary for regulatory activities
MTX	Methotrexate
NAPSI	Nail psoriasis severity index
NIS	Non-interventional study
Novartis PS	Novartis patient safety
NVS	Novartis
PAS	Post-authorization study
PASI	Psoriasis area and severity index
PASS	Post-authorization safety study
PGA	Physician's global assessment
prn	As needed (pro re nata)
PSOC	Primary system organ class
PSSI	Psoriasis scalp severity index
PT	Preferred term
qd	Every day (quaque die)
qid	Four times a day (quarter in die)
SAE	Serious adverse event
SAP	Statistical analysis plan

SDV	Source data verification
SmPC	Summary of product characteristics
SOC	System organ class
SOP	Standard operating procedure
tid	Three times a day (ter in die)
WHO	World health organization
WHO-DD	WHO drug dictionary

3 Investigators

Principal investigator (PI)	The study's principal investigators constitute a steering committee. The steering committee chair is: Prof. Dr. [redacted] [redacted], Germany Phone: [redacted] Fax: [redacted]

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Study Statistician	[redacted], [redacted] Germany
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5 Milestones

Table 5-1 Study milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	01 September 2015	27 August 2015	
End of data collection (Last date of data collection)	31 March 2018	16 May 2018	
Registration in the EU PAS register	01 September 2015	21 August 2015	
Interim Analysis Study Report	31 December 2016	13 December 2016	
Final report of study results	30 September 2018	30 January 2019	

6 Rationale and background

In Germany, treatment of moderate to severe psoriasis usually involves the following treatment categories and treatment groups, some of which include more than one individual treatment type:

Table 6-1 Psoriasis treatment categories and groups in Germany

Treatment Categories	Topical treatments	Conventional systemic treatments (and phototherapy):	Biologic treatments:
Treatment Groups (one or with one or more types per group)	- Topical steroids - Vitamin D3 analogues - Calcineurin inhibitors - all other topical treatments (e.g. dithranol, tar, laser)	- Fumaric acid esters - Methotrexate - Photo- and Photochemotherapy - Ciclosporin - Acitretin - Apremilast - all other systemic treatments (e.g. systemic steroids)	- Ustekinumab - Adalimumab - Etanercept - Infliximab - Secukinumab

The German treatment guidelines for psoriasis recommend combinations of some of these treatments for selected patients and purposes. Therefore, especially topical treatments are often combined with both conventional systemic treatments and biologics, and conventional systemic treatments are sometimes combined with biologics [1]. Moreover, an international consensus group recently recommended switching psoriasis treatments with minimal transition periods if switching is done due to lack of efficacy [2]. As a consequence some patients experience short term and low dose exposure to two biologics after the transition from a failing to a new biologic. This is a result of the potentially long elimination half-life of the respective failing biologic.

Cosentyx (secukinumab) was approved in Europe for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Extensive phase III study data have shown that secukinumab is an effective and safe treatment in this indication [3-7]. However, in these studies patients were required to have washed out all conventional systemic, biologic and topical treatments during long transition periods and only bland emollients were allowed as concomitant psoriasis treatments. Therefore, there is a lack of data on the effect of shorter transition periods and concomitant psoriasis treatment with other pharmacologically active substances on the effectiveness and safety of secukinumab.

It was, however, expected that in routine treatment of psoriasis, due to the current recommendations and medical practice, transition periods before administration of secukinumab are short, and some concomitant treatments with pharmacologically active substances are given in parallel, tapered or stopped only after the effectiveness of secukinumab in the individual patient becomes evident, despite lack of precedent.

The goal of this short-term, descriptive, observational study was to determine the transition periods of prior treatments and the use of concomitant treatments of patients who receive secukinumab in routine treatment of psoriasis.

7 Research question and objectives

The objective of this descriptive study - without any formal a priori hypothesis - was to assess prior and concomitant psoriasis treatments in patients receiving secukinumab during the routine treatment of moderate to severe plaque-type psoriasis, focusing on duration of transition periods from prior treatments to secukinumab and on the use of concomitant treatments. Furthermore, effectiveness as assessed in clinical routine as well as safety is described. [redacted]

7.1 Primary endpoint

The descriptive primary endpoint of the study was the assessment of the duration of the transition periods from prior treatments to secukinumab with adequate precision for the following prior treatment categories and groups:

- All topical treatments
- All conventional systemic treatments (and phototherapy)
- All biologic treatments
- Fumaric acid esters
- Methotrexate
- Ciclosporin

The study was powered to determine the duration of the transition period of the methotrexate treatment group with a precision of 7 days (see section 9.7).

7.2 Secondary endpoints

The following secondary endpoints were assessed:

- The duration of the transition periods from prior treatments to secukinumab per prior treatment group with adequate precision for the following prior treatment groups:
  - Topical steroids
  - Vitamin D3 analogues
  - Calcineurin inhibitors
  - All other topical treatments (e.g. dithranol, tar, laser)
  - Photo- and Photochemotherapy
  - Acitretin (instead of “retinoids” due to changed eCRF wording)
  - Apremilast
  - Ustekinumab
  - Adalimumab
  - Etanercept
  - Infliximab

- The proportion of patients with a transition period of ≤ 1 treatment interval, > 1 and ≤ 3 treatment intervals, > 3 and ≤ 5 treatment intervals, and > 5 treatment intervals per treatment group. This endpoint was not calculated for phototherapy (deviating from the observational plan) as this analysis was not feasible.

- The proportion of patients with a transition period of ≤ 1 systemic terminal half-life, > 1 and ≤ 3 systemic terminal half-lives, > 3 and ≤ 5 systemic terminal half-lives and > 5 systemic terminal half-lives for the following treatment groups:
  - Fumaric acid esters
  - Methotrexate
  - Ciclosporin
  - Acitretin
  - Apremilast
  - Ustekinumab
  - Adalimumab
  - Etanercept
  - Infliximab
- Discontinuation of concomitant treatments per treatment group (as per SAP v3.0, dated 12 October 2018)

  This endpoint has been modified, as analysis of the original definition of this endpoint given in the observational plan ("relative dose tapering of concomitant treatments") was not feasible due to low data amount.
- Dose of concomitant treatments per treatment group (as per SAP v3.0, dated 12 October 2018)[1],
- Clinical effectiveness of secukinumab as assessed by Psoriasis Area and Severity Index (PASI):
  - Raw PASI and the number of patients with a PASI of 0, and a PASI below 1, 2, 3, 5, and 10 were assessed over time.
  - For patients who had a PASI > 10 at the first visit, PASI 50, 75, 90, and 100 response rates were assessed, which correspond to the number of patients achieving at least a 50, 75, 90 or 100% reduction in PASI.
- Clinical effectiveness of secukinumab, as assessed in routine treatment [e.g. Investigator's Global Assessment (IGA), Physician's Global Assessment (PGA), Dermatology Life Quality Index (DLQI),Psoriasis Scalp Severity Index (PSSI), Nail Psoriasis Severity Index (NAPSI)].
- Clinical safety as assessed in routine treatment [(adverse events (AEs) and serious adverse events (SAEs)].

[1] According to SAP v3.0, dated 12 October 2018: "per individual treatment type" was replaced by "per treatment group" due to low data amount.

[redacted]

8 Amendments and updates to the protocol

The original protocol was amended once to increase sample size and site number, and prolong the recruitment period based on the predefined interim analysis. Moreover, reconciliation of AE data with the national registry PsoBest was removed after clarification of the collaboration with PsoBest.

Number	Date	Section of study protocol	Reason
1	13 May 2016	Section 7.5 sample size	As the standard deviation of the duration of the transition period in methotrexate pre-treated patients was much higher in interim analysis data than expected during the planning of the study, sample size was increased to 2504 patients to obtain an acceptable precision
		Sections 4, 7.2.4 and 7.5	Recruitment period was extended until 30 Sep 2017 to be able to recruit 2504 patients. Accordingly, the end of data collection had to be shifted to 31 Mar 2018, and the date of final study report had to be moved to 30 Sep 2018.
		Section 7.2.1	The number of sites was increased to 300-400 in order to be able to recruit 2,504 patients.
		Section 7.1 and 7.2.2	[redacted]

[2] According to SAP v3.0, dated 12 October 2018: Deviation from the observational plan: "…did not receive secukinumab in a clinical trial" was replaced by "…did not participate in a clinical trial with secukinumab" due to the changed wording in the eCRF.

		Section 8.6	A further interim analysis of baseline data was planned to be conducted after recruitment of 2,000 patients to reassess the precision for all groups of previous treatments, given the high variability of data obtained in the first interim analysis.
		Section 7.2.2	Reconciliation of AE data with the national registry PsoBest was removed as the collaboration with PsoBest was clarified and reconciliation of safety events between PROSPECT and PsoBest was no longer required. Consequently, the prerequisite for patients from PsoBest to provide informed consent for reconciliation of adverse event reports with PsoBest was removed.

9 Research methods

9.1 Study design

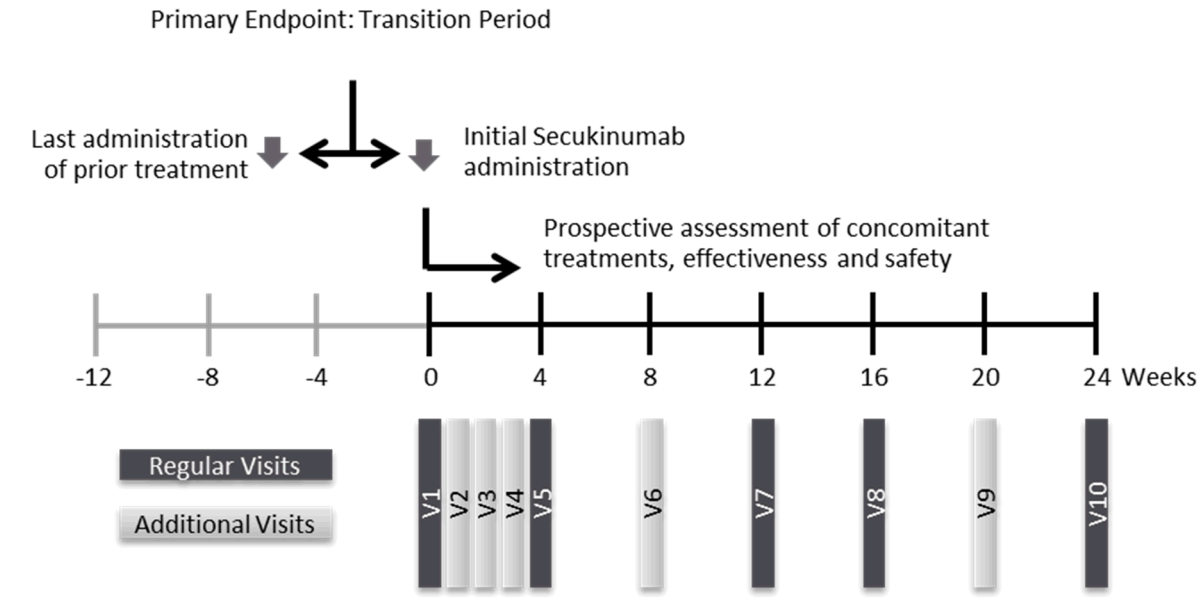
This was a single-cohort, non-interventional study (NIS) with a study duration of 24 weeks, recruiting patients for whom the decision for treatment with secukinumab for plaque-psoriasis had been made before inclusion. The study collected data from patients during routine secukinumab treatment and was thought to be representative for the prior and concomitant treatment categories and groups used in Germany. This study was a voluntary post authorization safety study (PASS).

The descriptive primary endpoint of the study was the assessment of the transition periods from prior treatments to secukinumab per treatment group with adequate precision. This endpoint was assessed retrospectively, due to the inclusion of patients at the initiation of routine secukinumab treatment. Furthermore, the relative dose of concomitant treatments per treatment group and the absolute dose of concomitant treatments per individual treatment type was assessed prospectively.

PASI is part of the guideline definition of both, treatment severity and treatment goals, for patients with plaque psoriasis. Therefore it was expected that PASI was assessed for all patients as part of the clinical routine. In order to describe the effectiveness and safety of secukinumab in routine clinical treatment and in the context of routine transition periods and concomitant medication, PASI was documented. Moreover, IGA-, PGA- and DLQI-results and other results of measures of clinical effectiveness, if used by the treating physician during routine clinical practice, as well as AEs, were documented prospectively. [redacted]

[redacted]

Figure 9-1 Study design



9.2 Setting

The study population consisted of a representative group of adults with moderate to severe plaque type psoriasis who were candidates for systemic therapy and for whom routine treatment with secukinumab was planned. A total of 2,505 patients were enrolled at 335 sites in Germany.

The study was scheduled to recruit patients between 01 September 2015 and 30 September 2017. Study completion of the last patient was planned to be no later than 31 March 2018. This study period covered the initial period of routine clinical use of secukinumab in Germany (available as marketed drug since 01 June 2015).

9.2.1 Study time frames

The study data relate to two study time frames:

1. The prospective time frame consisted of 24 weeks starting with the baseline visit (week 0) and ending with the end of study visit (week 24). Data from the prospective time frame were captured at baseline and during the regular and additional study visits.
2. The retrospective time frame consisted of the time prior to the baseline visit (week 0). Data from the retrospective time frame were captured at baseline. It was intended to cover all of the patient's psoriasis history and prior psoriasis treatment as well as detailed information about disease severity and treatment types and doses during the

6 months preceding the baseline visit if possible. Importantly the day of the last treatment with the last prior psoriasis therapy had to be documented as precisely as possible.

9.2.2 Source and method of primary data collection

The treating physicians and site staff were responsible for primary data collection by capturing the data in electronic case report forms (eCRF). The primary data captured in the eCRF had to be based on written site files and documents, i.e. source data.

9.3 Subjects

9.3.1 Inclusion criteria

Patients eligible for inclusion in this study had to fulfill all of the following criteria at baseline (Visit 1, week 0):

1. Patients had to give a written, signed and dated informed consent before documentation in the study commenced.
2. Men or women had to be at least 18 years of age.
3. Diagnosis of clinically moderate to severe plaque-psoriasis. Other forms of psoriasis could be present if moderate to severe plaque-psoriasis was the reason for secukinumab treatment.
4. Candidates for systemic therapy.
5. Documented decision for treatment with marketed secukinumab in compliance with the prescribing information and the summary of product characteristics (SmPC).
6. Initial treatment with marketed secukinumab planned for the day of the baseline visit.

9.3.2 Exclusion criteria

Patients fulfilling any of the following criteria at baseline (Visit 1, week 0) were not eligible for inclusion in this study. Conditional exclusion criteria were activated during the course of the study as soon as predefined recruitment criteria had been met without the need for a protocol amendment. No additional exclusion criteria could be applied by the treating physician, in order to ensure that the study population was representative for all eligible patients.

1. Initial treatment with marketed secukinumab prior to the day of informed consent.
2. Parallel enrollment in any interventional clinical trial.
3. Parallel enrollment in a NIS sponsored by Novartis or one of her divisions or affiliates.
4. After 300 patients who had participated in a clinical trial with secukinumab prior to inclusion in this NIS had been recruited, no further patients who had participated in a clinical trial with secukinumab were included.

9.4 Variables

9.4.1 Patient demographics

Patient demographic and baseline characteristic data collected of all patients included: year of birth, sex, race, body height, and body weight.

9.4.2 Psoriasis and other medical history

The psoriasis disease history was recorded for all patients including: date of first psoriasis symptoms, date of first psoriasis diagnosis, signs of higher disease severity or disease impact (severe psoriasis, symptoms of psoriasis in one of the following areas: scalp, face, palms, soles, nails, genitals, signs and symptoms of psoriatic arthritic including but not limited to joint pain, joint swelling, joint redness, enthesitis, and dactylitis).

Significant non-psoriasis medical history being active and or treated during the last up to 6 months prior to inclusion were recorded in a free text-field. Moreover, all non-psoriasis medical history related to recorded prior and concomitant treatments was recorded.

9.4.3 Prior and concomitant treatments

Prior treatments were defined as treatments taken and stopped prior to first dose of secukinumab during this study. Any treatment given at least once between the day of first dose of secukinumab during this study and the last day of study visit was planned to be documented as concomitant treatment. Treatments which had been started pre-baseline and continued into the treatment period were analysed as prior and concomitant treatment.

The primary outcome variable was the duration of the transition period (in days) between the last dose of a prior psoriasis treatment and the first dose of secukinumab.

Prior and concomitant psoriasis treatments were documented including start date, end date, dose and reason for discontinuation (with a distinction between at least failure to respond, contraindication or intolerance). Administration and dose of secukinumab were captured by individual administration records. Other significant prior and concomitant treatments were documented up to 6 month before the baseline visit.

9.4.4 PASI

PASI is part of the guideline definition of both, treatment severity and treatment goals, for patients with plaque psoriasis. Therefore, it was expected that PASI was assessed for all patients as part of the clinical routine.

The total body surface area (BSA) affected by plaque-type psoriasis was estimated from the percentages of areas affected, including head, trunk, upper limbs and lower limbs (see below for full details of the PASI assessment). The following calculations were done: Each reported percentage was multiplied by its respective body region corresponding factor (head = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4). The resulting four percentages were added up to estimate the total BSA affected by plaque-type psoriasis.

A PASI score was derived as indicated in Table 6-3 of the protocol. The head, trunk, upper limbs and lower limbs were assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation).

The average degree of severity of each sign in each of the four body regions was assigned a score of 0-4. The area covered by lesions on each body region was 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 was assessed as part of the head
2. The axillae and groin were assessed as part of the trunk
3. The buttocks were 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 body surface area, respectively, the PASI score is calculated using the formula:

PASI = 0.1(EH+IH+DH)AH + 0.2(EU+IU+DU)AU + 0.3(ET+IT+DT)AT + 0.4(EL+IL+DL)AL

The keys for the letters are provided in Table 9-1.

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 analysis of the PASI is collected at the baseline visit.

Table 9-1 The PASI 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-<10% 2=10-<30% 3=30-<50% 4=50-<70% 5=70-<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-<10% 2=10-<30% 3=30-<50% 4=50-<70% 5=70-<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-<10% 2=10-<30% 3=30-<50% 4=50-<70% 5=70-<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-<10% 2=10-<30% 3=30-<50% 4=50-<70% 5=70-<90% 6=90-100%

a Percentage (not score) of body region (not whole body) affected was enterend in the eCRF
b Neck was assessed as part of theHead (H) body reagion
c Axillae and groin were assessed as part of the Trunk (T) body region
d Buttocks were assessed as part of the Lower limbs (L) body region

9.4.5 Routine effectiveness and quality of life assessments

If in addition to PASI, other measures of effectiveness and quality of life such as IGA, PGA, and/or DLQI were used during clinical routine, the resulting scores were documented in the eCRF. If available from the medical history, assessments conducted up to 6 months before informed consent should also be recorded in eCRFs.

IGA modified 2011 (IGA mod 2011) is a 5 point scale which measures overall psoriatic disease. It provides a global rating of psoriasis severity in a single numeric score as determined by the study investigator. Unlike PASI score, it is static in that it refers exclusively to the subject's

disease state at the time of the assessment and does not attempt a comparison with any of the subject's previous disease states (at baseline or previous visits). The IGA mod 2011 scale has been developed in collaboration with health authorities, in particular the FDA. The scale has been condensed from a 6-point scale into a 5-point scale by merging the two highest points on the 6-point scale ('very severe' and 'severe') into a single point ('severe'). Explanations and descriptions of the points on the scale have been improved from the previous version to ensure appropriate differentiation between the points.

While achieving a score of 0/1 on the prior 6 point Physician/Investigator Global Assessment (PGA/IGA) scales correlated well with a PASI 75 response, the same score on the IGA mod 2011 correlates best with a greater PASI 90 response rate.

The Psoriasis Scalp Severity Index (PSSI) assesses severity of scalp disease along the parameters of erythema, induration, and desquamation. The PSSI uses a 5-point scale to grade the three aforementioned clinical parameters. The parameters scores are summed and multiplied by an integer (0-6) that represents the area of affected scalp. The PSSI score ranges from zero to 72.

Dermatology life quality index (DLQI) is an important score to evaluate the QoL of patients. A total of 10 questions in 6 domains with a score of 0-3/question sum up to a possible total score of 30 points. It ranges from 0-1 (no effect at all on patient's life) to 21-30 (extremely large effect on patient's life) [10,11].

9.4.6 Safety

Information about AEs and SAEs were collected as described in chapter 9.5 and assessed and treated as in routine clinical practice.

9.5 Data sources and measurement

This study involved a primary data collection. Therefore the data sources were the treating physicians and the patients. Records from routine clinical documentation were used for source data verification (SDV). These included electronical and paper-based patient's charts, hospital discharge files, prescription drug files and doctor's letters.

Medical history/current medical conditions and AEs were coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Safety data were transferred to Novartis at a frequency as defined in section 10 of the study protocol (CAIN457ADE07 Non-interventional study protocol v01). Clinical data were transferred to Novartis on an ongoing basis.

Data collection schedule

This was a NIS and that did not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Patients were treated according to the local prescribing information, and routine medical practice in terms of visit frequency and types of assessments performed and only these data were collected as part of the study. The treating physician was asked to complete the appropriate CRF at every patient visit if possible.

However, in Table 9-2 is the recommended data collection schedule that most likely mirrors the patterns of routine clinical care of most patients being treated with secukinumab. It was expected that most patients were likely to be seen at the regular visits, but some patients may also be seen at some of the additional visits. A visit window was not applied. If a visit occurred in between the predefined visit time points it could be recorded as the next visit that was closest, unless another visit up to that point in time was already scheduled. The date of the visit should be documented accurately.

Table 9-2 Data collection

Type of visit	Baseline	Regular visits	Additional visits	Regular end of study visit
Time of visit (week)	**0**	**4, 12, 16**	**1, 2, 3, 8, 20**	**24**
Informed consent	X			
Inclusion/Exclusion criteria	X			
Baseline characteristics	X			
Psoriasis disease history	X			
Prior psoriasis treatments (duration of treatment, last dose and day of discontinuation)	X			
Prior results of assessments (e.g. PASI, IGA, PGA)	X			
Prior results of questionnaires (e.g. DLQI)	X			
Documentation of secukinumab treatment	X	X	X	X
Documentation of concomitant treatments	X	X	X	X
PASI assessment	X	X	X	X
Results of other routine assessments (e.g. IGA, PGA)	X	X	X	X
Results of routine questionnaires (e.g. DLQI)	X	X	X	X
Adverse Events	X	X	X	X

DLQI = dermatology life quality index, IGA = investigator's global assessment, PGA = physician's global assessment, PASI = psoriasis area and severity index

For patients who discontinued prematurely, the reason for discontinuation should be determined.

Safety related measurements

All AEs – including SAEs and safety endpoints (where relevant) – had to be collected and recorded in the study database, irrespective of causal association. All AEs, including SAEs occurring in association with exposure to the Novartis drug of interest, also had to be recorded in the Novartis safety database.

Adverse Drug Reactions (ADRs) occurring in association with exposure to a Novartis drug other than the Novartis drug of interest, had to be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting and Novartis Drug Safety & Epidemiology (DS&E) as a spontaneous report.

All adverse reactions identified for non-Novartis products should have been reported to the local Health Authority in accordance with national regulatory requirements for individual case

safety reporting or the Marketing Authorization Holder as these were not recorded in the Novartis safety database.

Adverse event reporting

An AE was any untoward medical occurrence in a patient administered secukinumab that did not necessarily have a causal relationship with the treatment.

An AE could therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug of interest, whether or not related to the medicinal product(s).

Drug of interest included the drug under evaluation and the comparator drug(s) if specified as part of the research objective, given at any time during the study. The drug of interest of this study was Cosentyx®/secukinumab.

If a patient started with the drug of interest during the study, medical conditions/diseases present before starting the drug of interest were considered AEs only if they worsened after first intake of the drug of interest. If a patient had already started therapy with the drug of interest before he had signed informed consent, medical conditions/diseases that worsened after signing informed consent were considered an AE. The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. AEs might have also been detected when they were volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All AEs had to be recorded on the AE page of the eCRF with the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the drug(s) of interest (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a SAE

As the drug under evaluation was a biological drug (monoclonal antibody) the documentation of the batch number of the drug which was used at the time of the occurrence of the (S)AE was necessary, in addition to the before mentioned information.

In addition, all reports of the following special scenarios were also considered an AE irrespective if a clinical event had occurred:

- Drug-drug or drug-food interaction
- Drug exposure during pregnancy
- Drug use during breast-feeding
- Lack of effectiveness

Reports of lack of effectiveness without an associated clinical event had to be recorded on the AE page of the eCRF even if lack of efficacy parameters were collected and recorded elsewhere within the study database.

- Overdose
- Drug abuse and misuse

- Drug maladministration or accidental exposure
- Dispensing errors / Medication errors

Reports of overdose, drug abuse and misuse, drug maladministration or accidental exposure and dispensing errors/medication errors without an associated clinical event had to be recorded on the AE page of the eCRF irrespective of whether or not the information was recorded elsewhere within the study database.

- Withdrawal or rebound symptoms

Any treatment of any AE should have been recorded on the AE page of the eCRF. Some examples of treatment to be recorded were: no action taken (i.e., further observation only); drug of interest dosage adjusted/temporarily interrupted; drug of interest permanently discontinued due to this adverse event; treatment medication introduced or adjusted; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged.

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

Information about common AEs already known about the medicinal product could be found in the locally available labelling document for the approved indication under evaluation in this study. This information was included in the patient informed consent and should have been discussed with the patient prior to study start and during the study as needed.

Non-serious AEs associated with the Novartis drug of interest also had to be recorded in the safety database:

Serious adverse event reporting

An SAE was defined as an event which:

- was fatal or life-threatening

  Life-threatening was an event which constituted a fatal risk for the patient at the time of the event and which not only may have become fatal by hypothetical worsening or further complications.

- Resulted in persistent or significant disability/incapacity
- Constituted a congenital anomaly/birth defect
- Required inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization was for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (not applicable for psoriasis)
  - Elective or pre-planned treatment for a pre-existing condition that was unrelated to the indication under study and had not worsened since the start of the drug of interest (secukinumab)

- Social reasons and respite care in the absence of any deterioration in the patient's general condition

- Was medically significant, i.e., defined as an event that jeopardized the patient or may require medical or surgical intervention to prevent one of the outcomes listed above e.g. may have required treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission

Note: Transmission of infectious agent via medicinal product was considered to be a serious adverse reaction and should have been reported and assessed as medically significant in the absence of other seriousness criteria.

The assessment whether an AE constituted an SAE was only dependent on the presence of one of the above mentioned formal criteria and independent from the assessment whether a causal relationship between the drug and the occurrence of the SAE had been suspected.

Causality assessment

For the assessment of causality between the drug and the event there existed the options "no causal relationship" and "causal relationship suspected". A medical causality assessment was absolutely necessary and had to be documented in any case. It should have been taken into account that many different aspects should be considered for causality assessment. These aspects could concern the individual patient, the underlying disease, comorbidities, concomitant medication (if applicable) or also non-medicinal factors.

No causal relationship: there existed no reasonable possibility of a causal relationship between drug and AE.

Causal relationship suspected: there existed a reasonable possibility of a causal relationship between drug and AE.

Disease progression

A progression of the underlying disease during treatment with the drug under evaluation (secukinumab) only had to be documented as AE if a causal relationship with the drug under evaluation had been suspected or if as a result of the disease progression one or more of the formal criteria for an SAE applied.

Abnormal laboratory values and test results

Abnormal laboratory values or test results only should have been documented as AE if they

- Constituted a change in terms of a worsening of the respective parameter in comparison to the baseline value (baseline visit). This term became invalid if there was no baseline value

AND

- the changed laboratory parameters
  - were assessed as clinically relevant OR
  - were accompanied by clinical signs or symptoms OR

- required therapeutic intervention OR
- led to a dosage reduction and/or temporary interruption or permanent discontinuation of the drug under evaluation.

In these cases, they had to be documented on the AE page.

Changes of quantifiable parameters had to be documented as SAEs if formal criteria for an SAE applied (see SAE definition).

Notification timelines for SAE

To ensure patient safety, every SAE, regardless of causality assessment, occurring after the patient had provided informed consent (applicable to patients who already took secukinumab before start of the study) or had started therapy with secukinumab (applicable to patients who started secukinumab therapy during this study) and until 30 days after the patient had stopped study participation (defined as time of last dose of the Novartis drug of interest taken or last visit whichever was later) had to be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 day period should only have been reported to Novartis if the treating physician or other involved health care professional suspected a causal relationship to the Novartis drug of interest.

Recurrent episodes, complications, or progression of the initial SAE had to be reported as follow-up to the original episode, regardless of when the event occurs. This report had to be submitted within 24 hours by the treating physician or other involved health care professional after receiving the follow-up information. An SAE that was considered completely unrelated to a previously reported one should have been reported separately as a new event.

Information about all (S)AEs was collected and recorded on the SAE page in the eCRF. The treating physician or other involved health care professional had to assess the relationship to the Novartis drug of interest, complete the (S)AE page and save the completed page in the eCRF within 24 hours. Follow-up information was reported in the same manner as the initial report. The follow-up information should have described whether the event had resolved or continued, if and how it has been treated. When a patient withdrew from study participation, the 'End of Observation'-Page had to be completed in the eCRF.

If the SAE was not previously documented in the SmPC a local DS&E Department associate might have urgently required further information from the treating physician or other involved health care professional for Health Authority reporting.

Reporting of SAEs and AEs

Information on any AE (non-serious, serious) was documented in the individual eCRF of the respective patient in the study database. The study center documented every SAE within 24 hours after becoming aware of it, every non-serious AE within 10 days. The information on SAEs was forwarded to Novartis and the CRO automatically via eCRF system/e-mail (PDF format) after saving of the data by the study center. Information on non-serious AEs was transferred from the study database to Novartis DS&E by CRO on a periodic basis, but not less frequently than every week.

Exception: if documentation of an SAE in the eCRF was not possible for technical or other reasons, the SAE could be documented on paper and faxed directly to the CRO:

[redacted]

Fax: [redacted]

The original report form had to be dated with the fax date and was stored in the study documentation until forwarding to the CRO. The original of the SAE form and the fax confirmation had to be stored at the study center, together with the CRF documentation.

In case that documentation of an nsAE in the eCRF was not possible for technical or other reasons, the AE could be documented on paper and faxed directly to the CRO.

If information about an AE was of preliminary nature, information had to be completed as soon as possible and sent as follow-up to Novartis. The follow-up report had to be sent in the same manner as the initial report and should have been clearly stated as follow-up report and contain the date of the initial report. If known, the missing information of the initial report should have been completed and newly received information (e.g. if and which treatment was given, outcome (recovered/continuing) or further study participation of the patient (further participation/discontinuation of study)) should have been reported.

If information was incomplete or queries were necessary for other reasons, Novartis DS&E or the contracted CRO contacted the treating physician or other involved health care professional. In special cases, e.g. if an SAE was not listed in the summary of product characteristics, urgent response to the query by the physician could be necessary to fulfil legal reporting obligations to the authorities. In these cases, the physician participating at this NIS or other involved health care professional was obliged to appropriate cooperation so that reporting obligations could be fulfilled.

Hospital reports and other findings or laboratory results in context of AEs should have been sent to Novartis **only upon request**.

Pregnancies

To ensure patients' safety, any occurrence of a pregnancy in a patient treated with the Novartis drug of interest had to be reported to the local Novartis DS&E Department within 24 hours. The pregnancy should have been 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 new-born complications.

Pregnancy should have been recorded on a Pharmacovigilance Pregnancy Form and reported by the treating physician or other involved health care professional to Novartis. In case of any congenital abnormality, birth defect or maternal and new-born complications, the possible relationship to the Novartis drug of interest should have been reported.

This had to be documented on the pregnancy form with the initial report or as follow-up report if pregnancy had already been reported. The pregnancy form had to be filled in completely with the recent information, including information about birth and child, and the completed and

signed form had to be forwarded to the local Novartis DS&E Department via fax. Additionally, any SAE experienced during pregnancy had to be reported on the SAE Report Form.

Pregnancy outcomes had to be collected for the female partners of any males who took the Novartis drug of interest in this study. Consent to report information regarding these pregnancy outcomes should have been obtained from the mother.

9.6 Bias

Site specific preferences might have biased towards misrepresentation of prior and concomitant treatment types and transition periods and concomitant treatments if the site selection process or the recruitment was imbalanced. To limit this bias, a balanced selection of sites and a balanced recruitment was sought. Specifically, it was intended to include a significant proportion of study sites that have not been involved in secukinumab clinical trials. Furthermore, the retrospective documentation of transition periods was an inherent limitation of this study design.

9.7 Study size

The duration of the transition period should be estimated with sufficient precision for all groups of previous treatments, especially for methotrexate due to its international significance as a first-line treatment. Data from the PsoBest registry (online on http://www.psobest.de/einschlusszahlen/, retrieved 04-April-2015) suggested that about 20% of systemic treatments in Germany were methotrexate. Thereof at least 50% (i.e., 10% of the included patients) were expected to stop prior to treatment with methotrexate before starting treatment with secukinumab. Therefore, a total of 1,200 patients would have resulted in 120 patients who previously had undergone transition from methotrexate to secukinumab. With 120 patients in this group the mean duration of the transition period could be estimated with an adequate precision [95% CI] of about 4 days assuming a standard deviation of 3 weeks (21 days).

The pre-defined interim analysis of baseline data after enrolment of 800 patients suggested that the proportion of patients transitioning from methotrexate to secukinumab is slightly higher than expected (11.3% instead of 10.0%). However, based on the interim analysis data, we had to expect a much higher standard deviation for the duration of the transition period in those patients than estimated during the planning of the study (60 days instead of 21 days). To obtain a precision [95% CI] of +/- 4 days for the mean duration of the transition period with this high standard deviation, a total of 7,655 patients would have been required. Targeting a precision [95% CI] of +/- 7 days - which reflects the dosing interval of methotrexate - instead of +/-4 days, this would lead to 283 patients who previously had undergone transition from methotrexate to secukinumab and an overall sample size of 2,504 patients. Please refer to section 10 of this report.

9.8 Data transformation

See detailed statistical methods below.

9.9 Statistical methods

This study involved a primary data collection. Therefore the sources of data were the treating physicians and the patients. Records from routine clinical documentation were used for SDV. These included electronical and paper-based patient's charts, hospital discharge files, prescription drug files and doctor's letters.

The treating physicians and site staff was responsible for primary data collection by capturing the data in electronic case report forms (eCRF).

9.9.1 Main summary measures

Parameters which were at least interval scaled were tabulated by the following sample statistics: Number of non-missing data, mean, standard deviation, minimum, median and maximum.

Parameters which were nominally or ordinally scaled were tabulated by absolute and relative frequencies. In general, missing values were not considered for calculation of percentages (i.e., adjusted percentages are calculated) if not otherwise specified.

9.9.2 Main statistical methods

All data were analysed descriptively. [redacted]

Analysis population

The analysis set (AS) comprised all patients who fulfilled all inclusion criteria, did not fulfill any exclusion criterion and have received at least one dose of secukinumab during the study. Patients that have been locked in the eCRF were not regarded as "enrolled" and therefore excluded from the analysis set.

[redacted]

[redacted]

9.9.2.1 Assessment windows, baseline and post baseline definitions

The study data related to two study time frames:

1. The prospective time frame consisted of 24 weeks starting with the baseline visit (week 0) and ending with the end of study visit (week 24). Data from the prospective time frame were captured at baseline and during the regular and additional study visits.
2. The retrospective time frame consisted of the time prior to the baseline visit (week 0). Data from the retrospective time frame were captured at baseline. It was intended to cover all of the patients' psoriasis history and prior psoriasis treatment as well as detailed information about disease severity and treatment types and doses during the 6 months preceding the baseline visit if possible. Importantly the day of the last treatment with the last prior psoriasis therapy had to be documented as precisely as possible.

Baseline was defined as start of treatment with secukinumab during the study. Post-baseline visits were all visits after the baseline visit.

Visits were labelled as follows:

- Visit 1 = baseline
- Visit 2 = week 1
- Visit 3 = week 2
- Visit 4 = week 3
- Visit 5 = week 4
- Visit 6 = week 8
- Visit 7 = week 12
- Visit 8 = week 16
- Visit 9 = week 20
- Visit 10 = week 24

9.9.2.2 Patient disposition, background and demographic characteristics

The patient disposition was displayed by number of patients enrolled, received at least one dose of secukinumab during the study and completed the study. [redacted]

[redacted]

Demographic parameters, psoriasis anamnesis, other relevant medical history, PASI at baseline and other measures of effectiveness/quality of life at baseline were analysed using sample statistics and frequency tables. Each visit was analysed regarding the number of patients for whom the respective visit had been documented or could have been documented.

[redacted]

9.9.2.3 Analysis of primary endpoint

The duration of transition periods from prior treatments to secukinumab was analysed by sample statistics (including inter-quartile range (IQR)) and 95% confidence intervals (CIs) for prior treatment categories and groups (as defined in section 7.1). In addition, histograms and box-and-whiskers-plots were generated.

The duration of transition periods was also analyzed by reason for discontinuation of the respective prior treatment using sample statistics presented separately for each treatment category.

All analyses (without figures) were also performed for treatment category “topical treatments” with restriction on topical monotherapies with a maximum transition period of 3 months, according to changes in SAP version 2.0 (dated 02 August 2017).

9.9.2.4 Analysis of secondary endpoints

The duration of transition periods from prior treatments to secukinumab was analysed by sample statistics (including IQR) and 95% CIs for prior treatment groups. In addition, histograms and box-and-whiskers-plots were generated. According to changes in SAP version 2.0 (dated 02 August 2017), the same analyses (without figures) were also performed for treatment category “topical treatments” with restriction on topical monotherapies with a maximum transition period of 3 months.

Proportions of patients within certain categories of transition were calculated with 95 % CIs and displayed by stacked bar plots for prior treatment groups.

Discontinuation of concomitant psoriasis treatments was analyzed by frequency tables.

Dose and treatment interval of concomitant psoriasis treatments were analysed per treatment group using sample statistics and frequency tables. The following variables were analysed: dose and treatment interval for conventional systemic and biologic treatments, treatment interval for topical treatments and number of cycles for phototherapy.

PASI was analysed numerically and in categories (categories: PASI = 0, PASI < 1, PASI < 2, PASI < 3, PASI < 5, PASI < 10, PASI ≥ 10, PASI > 20). Numerical analysis: Sample statistics per visit was calculated for raw values and reduction from baseline. Difference to baseline was analysed using paired t-tests. [redacted] Categorical

analysis: categories were presented by frequency tables per visit and by shift tables from baseline to week 4, 12, 16 and 24. [redacted]

Mean PASI per visit was visualized using time course plots. Distribution of PASI per visit was displayed using box-and-whiskers-plots.

PASI 50, 75, 90, and 100 response rates were presented as frequency tables and displayed using time course plots.

BSA (in %), DLQI, PSSI, and NAPSI were analysed in the same way as the PASI, numerically.

PSSI/NASPI 50, 75, 90 and 100 response rates were presented as frequency tables.

IGA mod 2011, IGA mod 2009, and PGA were analysed using frequency tables per visit and shift tables from baseline to last assessment. Difference to baseline was analysed by Bowker's test of symmetry. [redacted]

DLQI 0/1 response rates and IGA mod 2011 0/1 response rates were presented as frequency tables and displayed using time course plots.

Assessment of PASI, BSA, IGA mod 2011, IGA mod 2009, PGA, DLQI, PSSI, and NAPSI per visit was analysed using frequency tables.

[redacted]

9.9.2.5 Secukinumab

The mean dose, mean treatment interval, number of secukinumab administrations and duration of exposure to secukinumab were analysed by sample statistics and frequency tables. Deviations from standard secukinumab treatment were analysed using frequency tables. A listing of secukinumab treatment of patients with deviations from the standard secukinumab dose (300 mg) was also provided.

9.9.2.6 Prior and concomitant treatments

The frequency of prior and concomitant psoriasis treatment categories, groups and individual types was summarized (for this analysis, prior treatments continuing into the study period are counted both as prior and concomitant treatments). The dosages of prior psoriasis treatments were presented by the average dose (maintenance dose) and last dose before baseline. In addition, treatment durations were summarized. Reasons for discontinuation of prior and concomitant psoriasis treatments were tabulated. Analysis of the last prior psoriasis treatment of a patient

was performed using frequency tables. A listing of prior psoriasis treatments of patients with conventional systemic treatment/phototherapy as last prior psoriasis treatment and prior biologic treatments was provided. Psoriasis treatment history was summarized using frequency tables.

Graphical analysis of prior psoriasis treatments were performed using bar charts and pie charts.

Prior and concomitant medications were coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system.

Prior non-psoriasis treatments with last administration no more than 6 months prior to first dose of secukinumab during the study and concomitant non-psoriasis treatments were presented in alphabetical order, by ATC codes and grouped by anatomical main group. Tables also showed the overall number and percentages of subjects receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

9.9.3 Safety analysis

AEs were analysed using frequency tables presenting the number and percentage of subjects having any AE, having an AE in each primary system organ class (PSOC), and having each individual AE (preferred term (PT)). This analysis was also conducted for AEs by severity and for AEs related to secukinumab therapy. If a subject reported more than one AE with the same PT, the AE with the greatest severity was presented. If a subject reported more than one AE within the same primary SOC, the subject was counted only once with the greatest severity at the SOC level, where applicable.

In addition, AEs and SAEs were summarized by presenting the total number of events in each primary SOC and in each PT.

Separate summaries were provided for deaths, SAEs, other significant AEs leading to any action with secukinumab, secukinumab discontinuation, secukinumab dose increase and secukinumab dose reduction.

Exposure adjusted incidence rates were reported overall and by SOC and PT.

According to changes in SAP version 2.0 (dated 02 August 2017), a frequency table for Lowest Level Terms was provided for AEs with PT “Psoriasis”.

9.9.4 Missing values

In general, missing values were not replaced. Exceptions:

- For the calculation of time periods with incomplete dates, the day of incomplete dates was replaced by 15 and the month of incomplete dates was replaced by 6. If this resulted in a negative time period and the period was calculated as end date - start date, the time period was set to 0. If this resulted in a time period < 1 day and the period was calculated as end date - start date + 1 day, the time period was set to 1 day. This rule concerned the duration of transition periods and the treatment duration of prior and concomitant psoriasis treatments.

- If the eCRF page "End of observation" was missing, missing values were replaced as follows (added according to SAP version 3.0, dated 12 October 2018):
    - Premature study discontinuation: Set to "No", if visit 10 was documented. Set to "Yes", otherwise.
    - Date of last observation: Set to date of last visit.
    - Premature discontinuation of secukinumab treatment:
        - If "Premature study discontinuation" = "No": Set to "No", if number of secukinumab administrations ≥ 10 or date of last documented secukinumab administration ≥ Date of last observation. Set to "Yes", otherwise.
        - If "Premature study discontinuation" = "Yes": Set to "No", if date of last documented secukinumab administration > Date of last observation. Set to "Yes", otherwise.
    - Date of last secukinumab treatment during the study: Date of last secukinumab administration ≤ date of last observation + 3 days

Values remaining implausible after finalization of data management procedures were adjusted when creating analysis datasets. The documentation of adjustments was part of the description of analysis datasets. The following adjustments were performed (to be extended during analysis):

- Assessments of measures of clinical effectiveness and quality of life before and at baseline were assigned to "before baseline" and "baseline" according to the date of assessment, not according to the location of documentation in the CRF.
- Visits were assigned to visit numbers according to the visit date in case of Implausibilities between visit date and visit number.
- If the question for any signs of higher disease severity or disease impact has been answered by "No" but at least one sign of higher disease severity or disease impact has been ticked, each sign of higher disease severity of disease impact was set to "unticked".
- If a specification of other symptoms of psoriatic arthritis has been given but the item "other symptoms of psoriatic arthritis" had not been ticked, the specification was set to missing.
- If another ethnicity has been specified but the item "other ethnicity" has not been ticked, the specification was set to missing.
- If at least one reason for premature study/treatment discontinuation has been ticked but neither the question for premature study discontinuation nor the question for premature treatment discontinuation has been answered by "Yes", the ticked reason(s) was set to "unticked" (added according to SAP version 2.0, dated 02 August 2017).
- If the question regarding the end of a prior psoriasis treatment has been answered by "up to 6 months ago", "6 months up to 1 years ago", or "continuing during the study" but the treatment duration in months has been entered, the treatment duration in months was set to missing.

- If the question for the end of a prior psoriasis treatment has not been answered by "continuing during the study" but the end date of the treatment during the study has been entered or "still continuing" has been ticked, the end date of the treatment during the study and "still continuing" was set to missing.
- If the question for the end of a prior psoriasis treatment has been answered by "continuing during the study" but the end date of the treatment was before baseline, the end date of the treatment was set to missing.
- If the question for the end of a prior psoriasis treatment has been answered by "continuing during the study", "still continuing" has been ticked, and both the end date of the treatment and the end date of the treatment during the study were missing but at least one reason for end of treatment has been ticked, each reason for end of treatment was set to "unticked".
- If "still continuing" was ticked for a concomitant psoriasis treatment and the end date of the treatment was missing but at least one reason for end of treatment has been ticked, each reason for end of treatment was set to "unticked".
- If another route of administration has been specified for a prior/concomitant psoriasis treatment but the item "route of administration" has not been answered by "other", the specification was set to missing.
- If another dose unit has been specified for a prior/concomitant psoriasis treatment but the item "dose unit" has not been answered by "other", the specification was set to missing.
- If another dose interval has been specified for a prior/concomitant psoriasis treatment but the item "dose interval" has not been answered by "other", the specification was set to missing.
- If another classification of phototherapy has been specified for a prior/concomitant psoriasis treatment but the item "classification of phototherapy" has not been answered by "other", the specification was set to missing.
- If the question for the end of a prior psoriasis treatment has not been answered by "continuing during the study" and the end date of treatment was after the first secukinumab administration during the study, the question for end of treatment was set to "continuing during the study" (added according to SAP version 2.0, dated 02 August 2017).
- If the start date of a prior psoriasis treatment was not before baseline or the first secukinumab administration during the study, the respective treatment was not considered a prior psoriasis treatment during analysis (added according to SAP version 2.0, dated 02 August 2017).
- If the start date or end date of a concomitant psoriasis treatment was before the first secukinumab administration during the study, the respective treatment was not considered a concomitant psoriasis treatment during analysis (added according to SAP version 3.0, dated 12 October 2018).

- If the start date of a concomitant psoriasis treatment was after the date of the last administration of secukinumab during the study, the respective concomitant psoriasis treatment has not been considered a concomitant treatment during analysis.
- If the MedDRA Preferred Term of an AE was PREGNANCY, the respective event was not considered for safety analysis (added according to SAP version 2.0, dated 02 August 2017).
- Secukinumab administrations with date of administration >3 days after end of observation will be excluded from analyses (added according to SAP version 3.0, dated 12 October 2018).
- If the date of assessment is before date of informed consent for a post-baseline value of any measure of effectiveness/quality of life (PASI, BSA, DLQI, PSSI, NAPSI, IGA mod 2011, IGA mod 2009, PGA), the assessment will be excluded from analysis (added according to SAP version 3.0, dated 12 October 2018).
- If weight = 0, weight will be set to missing. If height = 0, height will be set to missing (added according to SAP version 3.0, dated 12 October 2018).
- Secukinumab administrations with missing date of administration and missing dose will be excluded from analyses (added according to SAP version 3.0, dated 12 October 2018).
- If end of observation is at least 365 days after date of last visit, end of observation will be set to date of last visit (added according to SAP version 3.0, dated 12 October *2018).*

9.9.5 Interim analyses

After 800 patients had been recruited, an interim analysis of the baseline data determined, whether sufficient precision for all groups of previous treatments was likely to be achieved. It was necessary to adjust the study sample size via a protocol amendment to obtain adequate and representative coverage of all previous treatment groups. Additionally, secondary endpoints, secukinumab treatment and prior/concomitant treatments were analyzed. Data recorded per visit were only analyzed up to visit 8 (week 16).

Paragraph added according to changes in SAP (version 2.0, dated 02 August 2017). After the increase of sample size via protocol amendment 1 based on the first interim analysis, a further interim analysis was conducted after 2,000 patients had been enrolled to reassess the precision for all groups of previous treatments. In this second interim analysis, safety data were also analyzed and data recorded per visit were analyzed up to end of study. Safety data were taken from a snapshot of the eCRF database drawn after reconciliation of AEs. From this snapshot, only those AEs were analyzed which were also present in the data snapshot taken shortly after the 2000th patient had been enrolled (these events were identified via event ID).

9.9.6 Amendments to the statistical analysis plan

The interim analysis performed after inclusion of the first 800 patients resulted in an increase of the sample size. The SAP was adapted accordingly, as described in the respective sections.

In SAP version 2.0 dated 02 August 2017 the following changes were implemented:

- [redacted]

- Further adjustments for missing/implausible values added,
- Second interim analysis with safety analyses added,
- Minor corrections were implemented.

In SAP version 3.0 dated 12 October 2018, the following changes were implemented:

- Analysis population “Analysis set and no previous clinical trial” was added,
- Definition and analysis of dose changes/discontinuation of prior and concomitant psoriasis treatments were modified,
- [redacted]
- Exposure adjusted incidence rate was added to statistical methods and safety analysis,
- Further adjustments for missing/implausible values were added,
- Parameter definitions for response parameters was updated,
- Parameter definitions “serious adverse event” and “Suspected relationship to secukinumab” were added,
- Sample size determination was adapted to protocol amendment,
- Modifications/corrections were made in list of analysis tables and figures,
- Minor corrections were implemented.

In SAP version 3.1 dated 25 January 2019, parameter definitions of "serious adverse event" and "suspected relationship to secukinumab" (sections 5.8, 5.13.18, 5.13.19) were refined in order to clarify safety analyses conducted (“investigator’s assessment”, consistent with the second interim analysis based on SAP version 2.0, reflecting the objective of the study as pre-defined in protocol “Clinical safety as assessed in routine treatment AEs and SAEs”) and “sponsor’s assessment”, using the maximum outcome of assessment of pharmacovigilance department (sponsor) and investigator’s assessment, which can be considered a more conservative approach.

9.10 Quality control

9.10.1 Program layout and location

SAS programming was performed according to [redacted] SOP 0210 “Evaluation of Clinical data”, Version 1.0 and SAS Programming instructions, Version 3.0.

9.10.2 Statistical software

SAS (for Unix) Version 9.2 was used for all analyses. Tables, lists and figures were produced by the SAS Output delivery system (ODS) as rtf document which was transferred into docx-Format to reduce size.

10 Results

Reported are the results of the final analysis dated 24 October 2018.

First patient first visit was 27 August 2015, last patient last visit was 12 April 2018.

10.1 Participants

Patients fulfilling the criteria laid out in section 9.3 were eligible for inclusion in the study. Patients were excluded from the study if they had received marketed secukinumab prior to the day of informed consent (prior secukinumab in clinical trials was allowed), were enrolled in any interventional study, or were enrolled in any other Novartis non-interventional study.

The number of patients included in the analysis is described in Table 10-1. A total of 2,505 patients were enrolled, 2,503 of them have received at least one dose of secukinumab (99.9%). A total of 3 patients were excluded from the analysis set (AS) resulting in 2,502 patients (99.9%).

Overall, 2,230 patients (89.1%) had completed the study, 272 patients discontinued the study prematurely (10.9%) and/or 238 patients discontinued secukinumab treatment prematurely (9.5%). Most frequently reported reasons for premature study / treatment discontinuation were AEs (72 patients, 2.9%), insufficient response (58 patients, 2.3%), and lost to follow-up (52 patients, 2.1%). A summary is provided in Table 10-2.

Table 10-1 Patient disposition – Analysis set (all patients)

Variable	All patients (N=2505)
Number of patients, n (%)	
enrolled	2505 (100.0)
received at least one dose of secukinumab	2503 (99.9)
Included in AS	2502 (99.9)
Reason for exclusion from AS – multiple answers possible, n (%)	
Did not receive any dose of secukinumab	2 (0.1)
Initial treatment with marketed secukinumab not planned for the day of the baseline visit	1 (0.0)
Initial treatment with marketed secukinumab prior to the day of informed consent	1 (0.0)

AS = analysis set
Source: PT-Table 1.1

Table 10-2 Study and treatment completion (analysis set)

Variable	All patients (N=2505)
Number of patients, n (%)	
Completed the study	2230 (89.1)
Discontinued the study prematurely	272 (10.9)
Discontinued secukinumab prematurely	238 (9.5)
Reasons for premature study/treatment discontinuation, n (%)	
any reason	258 (10.3)
adverse event	72 (2.9)
insufficient response	58 (2.3)
lost to follow-up	52 (2.1)
non-compliance	30 (1.2)
loss of efficacy	27 (1.1)
improvement of disease	14 (0.6)
death	3 (0.1)
contraindication	1 (0.0)
other	33 (1.3)

AS = analysis set
Source: PT-Table 1.2

[redacted]

The total study duration was 950 days, cumulative exposure was 1086.0 patient-years (PT-Table 1.5).

A visit overview is provided in PT-Table 1.11. Baseline visits were documented for 2501 patients.

10.2 Descriptive data

10.2.1 Demographic data

Baseline demographic data for all patients are described in Table 10-3. Overall, 1545 patients (61.8%) were male. Patients' mean age ± SD was 48.0 ± 14.0 years.

Baseline demographic data for the 3 subgroups are provided in PT-Tables 1.6a, 1.6b and 1.6c.

[redacted]

Table 10-3 Baseline demography

Variable	All patients (N=2502)
Gender, n (%)	
male	1545 (61.8)
female	956 (38.2)
missing	1
Ethnicity, n (%)	
caucasian	2308 (95.5)
black	5 (0.2)
asian	17 (0.7)
other	86 (3.6)
missing	86
Age (years)	
n (%)	2501 (100)
Mean ± SD	48.0 ± 14.0
Median (range)	49.0 (18.0-89.0)
Weight at baseline (kg)	
n (%)	2393 (95.6)
Mean ± SD	87.1 ± 20.3
Median (range)	85.0 (40.0-250.0)
Height at baseline (cm)	
n (%)	2388 (95.4)
Mean ± SD	174.2 ± 9.6
Median (range)	175.0 (143.0-204.0)
BMI (kg/m^2)	
n (%)	2385 (95.3)
Mean ± SD	28.6 ± 6.0
Median (range)	27.6 (17.4-67.8)

BMI = body mass index, SD = standard deviation
Source: PT-Table 1.6

10.2.2 Psoriasis anamnesis

Since first psoriasis symptoms a mean of 19.4 ± 13.4 years (median 17.0, range: 0.0-81.0) had passed. Since first diagnosis of plaque psoriasis a mean of 17.9 ± 13.2 years (median 16.0, range: 0.0-81.0) had passed (PT-Table 1.7).

A higher disease severity or impact was observed in 2,336 patients (93.4%). The following signs of a higher disease severity or impact were documented most frequently. Number of patients with concomitant treatment are displayed as [n]:

- Severe psoriasis (1,739 patients, 69.5%), [678]
- Scalp affected (1,596 patients, 63.8%) [646]
- Nails affected (999 patients, 39.9%) [427].

In 1,002 patients (40.0%) [454], 4 or more of these signs were observed.

Symptoms of psoriatic arthritis were observed in 714 patients (28.5%) [314]. [redacted]

Some differences between subgroups can be seen regarding time since first psoriasis treatment and first diagnosis of plaque psoriasis: while less time has passed in patients with no prior systemic treatment, this was more time in patients who were included in a previous clinical trial (PT-Table 1.7b and c).

Clinical effectiveness and QoL before baseline are provided in PT-Tables 1.8.

Measures at baseline are provided in PT-Tables 1.9 and 1.9a, 1.9b and 1.9c and summarized in Table 10-4 for all patients and subgroups.

Baseline PASI score was available for 2294 patients (91.7%) and was in the mean 18.0 ± 12.3 (median 15.7, range: 0-72). Comparing the subgroups, a higher mean (± SD) PASI score was observed in patients who have not taken part in a previous secukinumab clinical trial (19.8 ± 11.7, median 17.0, range: 0-72).

Mean DLQI for all patients was 13.7 ± 7.9 points. Patients who did not take part in a previous secukinumab clinical trial, mean DLQI was 15.1 ± 7.1 points.

Patients who did not take part in previous clinical trials, had more assessments with 3 and 4 points at IGA (mod 2011) scoring.

Mean (± SD) values for BSA, PPSI and NAPSI were comparable for all patients and for patients with higher disease severity / impact and prior systemic treatment, while they were higher in patients who didn't take part in a previous clinical trial. For details refer to Table 10-4.

Table 10-4 Measures of clinical effectiveness and QoL at baseline [redacted] for all patients

	Analysis set	
	[redacted]	All patients
Variable		**(N=2502)**
PASI		
n (%)		2294 (91.69)
Mean ± SD		18.0 ± 12.29
Median (range)		15.7 (0-72)
PASI, n (%)		(n=2294)
PASI = 0		67 (2.9)
PASI < 1		129 (5.6)
PASI < 2		183 (8.0)
PASI < 3		216 (9.4)
PASI < 5		289 (12.6)
PASI < 10		558 (24.3)
PASI ≥10		1736 (75.7)
PASI > 20		811 (35.4)
IGA mod 2011 [a], n (%)		(n=172)

Table 10-4 Measures of clinical effectiveness and QoL at baseline [redacted] for all patients

	Analysis set	
	[redacted]	All patients
Variable		**(N=2502)**
0		27 (15.7)
1		45 (26.2)
2		21 (12.2)
3		58 (33.7)
4		20 (11.6)
5		1 (0.6)
		(n=107)
PGA, n (%)		
0		25 (23.4)
1		7 (6.5)
2		8 (7.5)
3		28 (26.2)
4		20 (18.7)
5		19 (17.8)
BSA (%)		
n (%)		410 (16.39)
Mean ± SD		19.2 ± 18.13
Median (range)		14.0 (0-100)
DLQI		
n (%)		941 (37.61)
Mean ± SD		13.7 ± 7.92
Median (range)		14.0 (0-30)
PSSI		
n (%)		73 (2.92)
Mean ± SD		3.0 ± 6.03
Median (range)		0.0 (0-25)
NAPSI		
n (%)		92 (3.68)
Mean ± SD		16.7 ± 18.53
Median (range)		10.0 (0-80)

BSA = body surface area, DLQI = dermatology life quality index (ranging from 0-1 =no effect at all to 21-30=extremely large effect on patient's life), IGA = investigator's global assessment (ranging from 0=clear to 4=severe), mod. 2011 = modified 2011, NAPSI = nail psoriasis severity index (score ranging from 0-4 with 0=none and 4 = present symptoms including nail bed and mail matrix), PASI = psoriasis area and severity index (0= no symptoms to 4=very severe symptoms), PGA = physician's global assessment, PSSI = psoriasis scalp severity index (ranging from 0 to 72)

a IGA mod 2009 was not included in this table due to low patient numbers

For details of PASI refer to Table 9-1; for other scores refer to section 9.4.5.

Source: PT-Tables 1.9, 1.9a, 1.9b, 1.9c

10.2.3 Non-psoriasis medical history

A total of 1,414 (56.5%) patients had any medical history not related to psoriasis (PT-Table 1.10).

The most common diseases reported on MedDRA PSOC and MedDRA PT were:

- Vascular disorders in 622 patients (24.9%) mainly with hypertension (585 patients 23.4%) and essential hypertension (14 patients, 0.6%),
- Metabolism and nutrition disorders in 499 patients (19.9%) with diabetes mellitus and type 2 diabetes mellitus (119 patients, 4.8% and 98 patients, 3.9%, respectively), hypercholesterolaemia (116 patients, 4.6%) and obesity (113 patients, 4.5%),
- Musculoskeletal and connective tissue disorders in 350 patients (14.0%) with psoriatic arthropathy (144 patients, 5.8%), osteoarthritis (37 patients 1.5%), arthralgia (28 patients, 1.1%), and osteoporosis (28 patients, 1.1%),
- Psychiatric disorders in 266 patients (10.6%) mainly with depression (158 patients, 6.3%).

Non-psoriasis disorders occurring in >1% of the patients are summarized in Table 10-5.

Table 10-5 Non-psoriasis disorders occurring in >1% of all patients

MedDRA PSOC MedDRA PT	All patients (N=2502) n (%)
Patients with any disease	**1414 (56.5)**
Vascular disorders	**622 (24.9)**
Hypertension	585 (23.4)
Metabolism and nutrition disorders	**499 (19.9)**
Diabetes mellitus	119 (4.8)
Hypercholesterolaemia	116 (4.6)
Obesity	113 (4.5)
Type 2 diabetes mellitus	98 (3.9)
Hyperuricaemia	52 (2.1)
Hyperlipidaemia	43 (1.7)
Musculoskeletal and connective tissue disorders	**350 (14.0)**
Psoriatic arthropathy	144 (5.8)
Osteoarthritis	37 (1.5)
Arthralgia	28 (1.1)
Osteoporosis	28 (1.1)
Psychiatric disorders	**266 (10.6)**
Depression	158 (6.3)
Endocrine disorders	**198 (7.9)**
Hypothyroidism	129 (5.2)
Respiratory, thoracic and mediastinal disorders	**146 (5.8)**
Asthma	54 (2.2)
Chronic obstructive pulmonary disease	35 (1.4)

Table 10-5 Non-psoriasis disorders occurring in >1% of all patients

MedDRA PSOC MedDRA PT	All patients (N=2502) n (%)
Skin and subcutaneous tissue disorders	**143 (5.7)**
Cardiac disorders	**139 (5.6)**
Coronary artery disease	45 (1.8)
Gastrointestinal disorders	**137 (5.5)**
Gastrooesophageal reflux disease	43 (1.7)
Infections and infestations	**119 (4.8)**
Nervous system disorders	**120 (4.8)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**82 (3.3)**
Immune system disorders	**71 (2.8)**
Seasonal allergy	30 (1.2)
Eye disorders	**54 (2.2)**
Hepatobiliary disorders	**54 (2.2)**
Hepatic steatosis	31 (1.2)
Surgical and medical procedures	**52 (2.1)**
Investigations	**48 (1.9)**
Renal and urinary disorders	**47 (1.9)**
General disorders and administration site conditions	**41 (1.6)**
Reproductive system and breast disorders	**36 (1.4)**
Blood and lymphatic system disorders	**27 (1.1)**

MedDRA = Medical dictionary for regulatory activities (version 21.0), PSOC = primary system organ class, PT = preferred term
Source: PT-Table 1.10

10.2.4 Prior non-psoriasis treatment

Nine-hundred and sixty-one (961) of all 2,502 patients (38.4%) received any prior non-psoriasis treatment, details by World health organization drug dictionary anatomical therapeutic chemical (WHO-DD ATC) system are provided in PT-Table 3.10.

The most commonly documented treatments on WHO-DD ATC 1st and 5th level were related to[3]:

- Cardiovascular system (575 patients, 23.0%) with mainly angiotensin-converting-enzyme (ACE) inhibitors (plain) (184 patients, 7.4%), angiotensin II antagonists (plain) (155 patients, 6.3%) and 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG CoA reductase) inhibitors (alone) (128 patients, 5.1%);
- Alimentary tract and metabolism (409 patients, 16.3%) with other agents for local oral treatment (143 patients, 5.7%), proton pump inhibitors (141 patients, 5.6%), and biguanides (107 patients, 4.3%);

[3] Numbers were calculated by the author

- Nervous system (314 patients, 12.5%) with mainly salicylic acid and derivatives (111 patients, 4.4%), selective serotonin reuptake inhibitors (62 patients, 2.5%), and other antimigraine preparations (50 patients, 2.0%).

10.2.5 Concomitant non-psoriasis treatment

A total of 1188 patients (47.5%) received and concomitant non-psoriasis treatment, details by WHO-DD ATC system are provided in PT-Table 3.11.

The most commonly documented treatments on WHO-DD ATC 1st and 5th level were related to[4]:

- Cardiovascular system (629 patients, 27.7%) with mainly ACE inhibitors (plain) (205 patients, 8.2%), angiotensin II antagonists (plain) (178 patients, 7.1%), and HMG COA reductase inhibitors (alone) (142 patients, 5.7%);
- Alimentary tract and metabolism (541 patients, 21.6%) with other agents for local oral treatment (171 patients, 6.8%), proton pump inhibitors (164 patients, 6.6%) and biguanides (119 patients, 4.8%), and;
- Nervous system (387 patients, 15.5%) with mainly salicylic acid and derivatives (134 patients, 5.4%), selective serotonin reuptake inhibitors (66 patients, 2.6%), and other antimigraine preparations (52 patients, 2.1%).

10.3 Outcome data

10.3.1 Analysis sets used

For description of primary and secondary analyses, the AS (n=2502 patients) was used.

10.3.2 Prior psoriasis treatment

Frequency of prior psoriasis treatments

Frequency of prior psoriasis treatments are provided in PT-Tables 3.3 (treatment end).

Topical and conventional systemic treatments (including phototherapy) ended in about 1/3 of treatments (1,611/5,296 treatments, 30.4% and 1,648/4718 treatments, 34.9%, respectively) no more than one year ago, while biologic treatments ended in 62.1% of the treatments (819/1,318 treatments, 62.1%) no more than one year ago. Details are provided in Table 10-6.

[4] Numbers were calculated by the author

Table 10-6 Frequency of prior psoriasis treatments by category (all patients)

Treatment category End	All patients (N=2502)
Topical treatments	Treatments (n=5296)
ended more than 10 years ago	381 (7.2)
ended 5 to 10 years ago	560 (10.6)
ended 2 to 5 years ago	847 (16.0)
ended 1 to 2 years ago	639 (12.1)
ended not more than 1 year ago	1611 (30.4)
continuing during the study	1256 (23.7)
no information about end of treatment/continuation during the study	2 (0.0)
Conventional systemic treatments (and phototherapy)	(n=4718)
ended more than 10 years ago	479 (10.2)
ended 5 to 10 years ago	816 (17.3)
ended 2 to 5 years ago	984 (20.9)
ended 1 to 2 years ago	688 (14.6)
ended not more than 1 year ago	1648 (34.9)
continuing during the study	103 (2.2)
no information about end of treatment/continuation during the study	0 (0.0)
Biologic treatments	(n=1318)
ended more than 10 years ago	15 (1.1)
ended 5 to 10 years ago	141 (10.7)
ended 2 to 5 years ago	202 (15.3)
ended 1 to 2 years ago	140 (10.6)
ended not more than 1 year ago	819 (62.1)
continuing during the study	1 (0.1)
no information about end of treatment/continuation during the study	0 (0.0)

Note: Percentages are related to the total number of prior psoriasis treatments within the respective Treatment category.
Source: PT-Table 3.3.1

Details on end of treatment of prior topical treatments, topical steroid, Vitamin D3 analogues, topical steroids in combination with vitamin D3 analogues, calcineurin inhibitors, and other topical treatments are provided in PT-Tables 3.3.2, 3.3.2.1, 3.3.2.2, 3.3.2.3, 3.3.2.4, 3.3.2.5.

Details on end of treatment of prior conventional systemic treatment (including phototherapy) are provided in PT-Table 3.3.3.

Methotrexate treatments ended no more than 1 year ago in 565 of 1275 treatments (44.3%).

Details on end of treatment of prior biologic treatments are provided in PT-Table 3.3.4.

Last prior psoriasis treatments were mostly conventional systemic treatments (including phototherapy) (712/2502 patients, 28.5%), followed by biologic treatments (excluding secukinumab) (335/2502 patients, 13.4%), topical treatments (312/2502 patients, 12.5%), and topical & conventional systemic treatments (including phototherapy) given in parallel (278/2502 patients, 11.1%). Details are given in PT-Table 3.3.5.

Overall, 1,029 patients had received conventional systemic treatments (including phototherapy) (either alone or in combination with other treatments) as last prior psoriasis treatment, the majority of them had received 1 treatment (368, 35.8%), 2 (289, 29.0%) or 3 treatments (206, 20.0%) (PT-Table 3.3.6).

A total of 669 patients had a biologic treatment as last prior psoriasis treatment, the majority of them had 1 treatment (462, 69.1%) or 2 treatments (142, 21.2%) (PT-Table 3.3.7).

A by-patient listing of prior psoriasis treatments of patients with conventional systemic treatment/phototherapy as last prior psoriasis treatment and prior biologic treatments is provided in PT-Table 3.3.8.

Table 10-7 summarizes psoriasis treatment history by treatment categories for all patients (several answers were possible per treatment).

Table 10-7 Psoriasis treatment history by treatment categories (all patients)

Treatment category	All patients (N=2502)
Topical treatments, n (%)	
no prior treatment	600 (24.0)
prior treatment but not last treatment before baseline	567 (22.7)
last treatment before baseline and washed out	666 (26.6)
last treatment before baseline and not washed out	856 (34.2)
started at baseline	27 (1.1)
started after baseline	59 (2.4)
Conventional systemic treatments (and phototherapy), n (%)	
no prior treatment	396 (15.8)
prior treatment but not last treatment before baseline	1013 (40.5)
last treatment before baseline and washed out	1029 (41.1)
last treatment before baseline and not washed out	93 (3.7)
started at baseline	0 (0.0)
started after baseline	18 (0.7)
Biologic treatments, n (%)	
no prior treatment	1600 (63.9)
prior treatment but not last treatment before baseline	232 (9.3)
last treatment before baseline and washed out	669 (26.7)
last treatment before baseline and not washed out	1 (0.0)
started at baseline	0 (0.0)
started after baseline	0 (0.0)

Source: PT-Table 3.3.9

History and doses of prior psoriasis treatments

Details on psoriasis history of topical treatments, conventional systemic treatments (including phototherapy) and biologic treatments are provided in PT-Tables 3.3.10, 3.3.11 and 3.3.12.

Details on doses of prior psoriasis treatments are provided in PT-Tables 3.5.1 (conventional systemic treatments incl. phototherapy) and PT-Table 3.5.2 (biologic treatments).

Duration of prior psoriasis treatments

The duration of prior psoriasis treatments by category is summarized in Table 10-8. Details of duration of the different categories are provided in PT-Tables 3.6.2 (topical treatments), 3.6.3 (conventional systemic treatments incl. phototherapy) and 3.6.4 (biologic treatments).

Table 10-8 Duration of prior psoriasis treatments – treatment categories (all patients)

Variable	All patients (N=2502)
Duration of prior psoriasis treatments (days)	
Topical treatments	
n	3959
Mean ± SD	686.2 ± 1396.0
Median (range)	150.0 (1.0-15766.0)
Conventional systemic treatments (and phototherapy)	
n	4473
Mean ± SD	481.7 ± 938.9
Median (range)	150.0 (1.0-16560.0)
Biologic treatments	
n	1296
Mean ± SD	621.9 ± 723.1
Median (range)	330.0 (1.0-5876.0)

SD = standard deviation
Source: PT-Table 3.6.1

Reasons for discontinuation of prior treatments

For the analysis set (N=2,502), a total of 4,078 discontinued prior therapies were recorded within 12 months prior to baseline. Overall, insufficient response (2,252/4,078, 55.2%) and loss of efficacy (646/4078, 15.8%) were the most common reasons to discontinue prior psoriasis treatments. Discontinuation of prior treatment owing to adverse events was higher for conventional systemic treatment (321/1648, 19.5%) than for biologic treatment (20/819, 2.4%) or topical treatment (6/1611, 0.4%). Results are summarized in Table 10-9.

Table 10-9 Reasons for discontinuation of prior treatments (all patients)

	Treatment categories		
Reason for discontinuation, n (%)	**Topical treatments (n=1611)**	**Conventional systemic treatments incl. phototherapy (n=1648)**	**Biologic treatments (n=819)**
Insufficient response	949 (58.9)	978 (59.3)	325 (39.7)
Loss of efficacy	159 (9.9)	267 (16.2)	220 (26.9)
Adverse event	6 (0.4)	321 (19.5)	20 (2.4)
Contraindication	5 (0.3)	32 (1.9)	3 (0.4)
Lack of compliance	16 (1.0)	16 (1.0)	4 (0.5)
Improvement of disease	157 (9.7)	47 (2.9)	39 (4.8)
Other reason	303 (18.8)	212 (12.9)	275 (33.6)
Unknown	125 (7.8)	70 (4.2)	22 (2.7)
missing	0 (0.0)	0 (0.0)	0 (0.0)

Note: Reason for treatment discontinuation was recorded only for treatments that ended no more than 1 year before baseline.
Source: PT-Table 3.8.1

Details on the different treatment categories and reasons for discontinuation are provided in PT-Tables 3.8.2 (topical treatments), 3.8.3 (Conventional systemic treatments including phototherapy) and 3.8.4 (biologic treatments).

10.3.3 Concomitant psoriasis treatment

Frequency of concomitant psoriasis treatments

Frequency of concomitant psoriasis treatments are provided in PT-Tables 3.4.

A total of 929 patients received 1,415 topical treatments, which mostly had started before baseline (856 patients, 92.1%).

Overall, 111 patients received concomitantly 122 conventional systemic treatments (including phototherapy), which also mostly had started before baseline (93 patients (83.8%).

Only 1 patient received 1 biologic treatment concomitantly, which had started before baseline.

Details are provided in Table 10-10.

Table 10-10 Frequency of concomitant treatments – categories (all patients)

Treatment category Start	All patients (N=2502) Treatments / Patients n(%)
Topical treatments	1415 / 929
started before baseline	1256 (88.8) / 856 (92.1)
started at baseline	36 (2.5) / 28 (3.0)
started after baseline	123 (8.7) / 98 (10.5)
Conventional systemic treatments (and phototherapy)	122 / 111
started before baseline	103 (84.4) / 93 (83.8)
started at baseline	0 (0.0) / 0 (0.0)
started after baseline	19 (15.6) / 19 (17.1)
Biologic treatments	1 / 1
started before baseline	1 (100.0) / 1 (100.0)
started at baseline	0 (0.0) / 0 (0.0)
started after baseline	0 (0.0) / 0 (0.0)

Note: Percentages are related to the total number of concomitant psoriasis treatments/patients within the respective treatment category.
Source: PT-Table 3.4.1

Details on frequency of concomitant treatment with topical treatments, topical steroid, Vitamin D3 analogues, topical steroids in combination with vitamin D3, calcineurin inhibitors, and other topical treatments are provided in PT-Tables 3.4.2, 3.4.2.1, 3.4.2,2, 3.4.2.3, 3.4.2.4, 3.4.2.5.

Details on frequency of concomitant treatment with conventional systemic treatment (including phototherapy) are provided in PT-Table 3.4.3. Twenty-five methotrexate treatments that were given to 25 patients have started mainly (23 patients/treatments, 92.0%) before baseline.

Details on frequency of biologic treatments are provided in PT-Table 3.4.4. The only biologic treatment given concomitantly was Ustekinumab in 1 patients, and was started before baseline.

Details on dose of concomitant treatments are provided in section 10.4.2 (secondary endpoints).

Duration of concomitant psoriasis treatments

Duration of concomitant psoriasis treatments by treatment categories are provided in PT-Tables 3.7 and is summarized in Table 10-11. Details of duration of the different categories are provided in PT-Tables 3.7.2 (topical treatments), 3.7.3 (conventional systemic treatments incl. phototherapy) and 3.7.4 (biologic treatments).

Mean (± SD) duration of topical treatments was 136.5 ± 65.9 days, mean (± SD) duration of conventional systemic treatments (including phototherapy) was 104.1 ± 74.4 days.

Table 10-11 Duration of concomitant psoriasis treatments (all patients)

Treatment category	All patients (N=2502)
Duration of concomitant psoriasis treatments (days)	
Topical treatments	
n	1414
Mean ± SD	136.5 ± 65.9
Median (range)	169.0 (1.0-267.0)
Conventional systemic treatments (including phototherapy)	
n	122
Mean ± SD	104.1 ± 74.4
Median (range)	110.5 (1.0-263.0)
Biologic treatments	
n	1
Mean ± SD	129.0 ± -
Median (range)	129.0 (n.a.)

n.a. = not applicable, SD = standard deviation
Source: PT-Table 3.7.1

Mean (± SD) duration of concomitant Methotrexate was 132.9 ± 60.8 days (PT-Table 3.7.3).

Reasons for discontinuation of concomitant treatments

For the analysis set (N=2,502), a total of 1,041 patients discontinued concomitant therapies during this NIS. Overall, improvement of disease (198 patients, 21.3% under topical treatment, 19 patients, 17.1% under conventional systemic treatments) was the main reason to discontinue concomitant treatment, followed by other reasons (75 patients, 8.1% and 19 patients, 17.1%) and insufficient response (40 patients, 4.3% and 12 patients, 10.8%). Results are summarized in Table 10-12.

Table 10-12 Reasons for discontinuation of concomitant treatments (all patients)

	Treatment categories		
Reason for discontinuation, n (%)	**Topical treatments (n=929)**	**Conventional systemic treatments incl. photo-therapy (n=111)**	**Biologic treatments (n=1)**
Insufficient response	40 (4.3)	12 (10.8)	1 (100.0)
Loss of efficacy	1 (0.1)	3 (2.7)	1 (100.0)
Adverse event	2 (0.2)	1 (0.9)	-
Contraindication	-	1 (0.9)	-
Lack of compliance	-	3 (2.7)	-
Improvement of disease	198 (21.3)	19 (17.1)	-
Other reason	75 (8.1)	19 (17.1)	-
Unknown	-	-	-

Percentages are related to the number of patients with at least one concomitant psoriasis treatment within the respective treatment category.
Source: PT-Table 3.9.1

Details on the different treatment categories and reasons for discontinuation are provided in PT-Tables 3.9.2 (topical treatments), 3.9.3 (Conventional systemic treatments including phototherapy) and 3.9.4 (biologic treatments).

10.3.4 Secukinumab treatment and deviation from standard secukinumab treatment

In this NIS, patients received a mean (± SD) secukinumab dose of 299.1 ± 9.7 mg by a mean (± SD) number of 9.0 ± 1.8 administrations. More than half of the patients (1,321 patients, 52.8%) received 10 administrations of secukinumab per patient, 639 patients (25.5%) received >7 and ≤9 administrations, 337 patients (52.8%) received >5 and ≤7 administrations, 120 patients (4.8%) received ≤5 administrations, and 85 patients (3.4%) received >10 administrations.

The mean (± SD) treatment interval during the initial phase was 9.5 ± 6.8 days, with the majority of patients (2133 of 2502 patients, 86.2%) having an interval of 5 to 9 days.

The mean (± SD) treatment interval during the maintenance phase was 29.6 ± 4.7 days, with the majority of patients (2298 of 2502, 94.8%) having an interval of 25 to 35 days.

The duration of exposure was in the mean (± SD) 158.4 ± 38.4 days (PT-Table 3.1).

Table 10-13 summarizes secukinumab treatment during this NIS.

Table 10-13 Secukinumab treatment (all patients)

Variable	All patients (N=2502)
Mean dose (mg)/administration	
n (%)	2502 (100)
Mean ± SD	299.1 ± 9.7
Median (range)	300.0 (150.0-330.0)
Mean treatment interval during the initial phase, n (%)	
< 5 days	-
5 to 9 days	2133 (86.2)
10 to 20 days	89 (3.6)
> 20 days	253 (10.2)
Mean treatment interval during the initial phase (days)	
n (%)	2475 (98.9)
Mean ± SD	9.5 ± 6.8
Median (range)	7.0 (5.6-42.0)
Mean treatment interval during the maintenance phase, n (%)	
< 25 days	31 (1.3)
25 to 35 days	2298 (94.8)
> 35 days	94 (3.9)

Table 10-13 Secukinumab treatment (all patients)

Variable	All patients (N=2502)
Mean treatment interval during the maintenance phase (days)	
n (%)	2423 (96.8)
Mean ± SD	29.6 ± 4.7
Median (range)	28.4 (10.1-169.0)
Number of secukinumab administrations per patient	
n (%)	2502 (100)
Mean ± SD	9.0 ± 1.8
Median (range)	10.0 (1.0-15.0)
Number of secukinumab administrations per patient, n (%)	
<= 5	120 (4.8)
> 5 and <= 7	337 (13.5)
> 7 and <= 9	639 (25.5)
10	1321 (52.8)
> 10	85 (3.4)
Duration of exposure (days)	
n (%)	2502 (100)
Mean ± SD	158.4 ± 38.4
Median (range)	169.0 (1.0-322.0)

SD = standard deviation
Source: PT-Table 3.1

The frequency of deviations from standard secukinumab treatment is provided in PT-Table 3.2.1:

- 1 patient (0.04%) had a dose increase due to insufficient response.
- 43 patients (1.7%) had a dose reduction due to improvement of disease (14 patients, 32.6%), an AE (9 patients, 20.9%), lack of compliance (4 patients, 9.3%), a contraindication (1 patient, 2.3%), or other reasons (23 patients, 53.5%).
- In 593 patients (23.7%) the interval between administrations was extended. As reasons, lack of compliance (106 patients, 17.9%), AEs (88 patients, 14.8%), improvement of disease (25 patients, 4.2%), insufficient response (25 patients, 4.2%), contraindication or loss of efficacy (1 patient, 0.2%), or other reasons (419 patients, 70.7%) were reported.
- 365 patients (14.6%) had an interval reduction due to lack of compliance (48 patients, 13.2%), insufficient response (20 patients, 5.5%), AEs (11 patients, 3.0%), loss of efficacy (9 patients, 2.5%), improvement of disease (5 patients, 1.4%), or other reasons (293 patients, 80.3%).

A line-listing of patients with deviations from standard secukinumab dose with reasons is provided in PT-Table 3.2.2. Patients with premature discontinuation of secukinumab treatment and patients with premature discontinuation of secukinumab treatment due to AEs are listed in PT-Tables 3.2.3 and 3.2.4.

10.4 Main results

10.4.1 Primary endpoint

The descriptive primary endpoint of the study was the assessment of the duration of the transition periods from prior treatments to secukinumab with adequate precision for the following prior treatment categories and groups (topical, conventional systemic, biologic treatments, fumaric acid esters, methotrexate, and ciclosporin).

There was some variation between the transition periods associated with different types of prior treatment. Variations were most obviously between the median transition periods, while mean (± SD) values did not vary that much (PT-Table 2.1.1). Details are provided in Table 10-14.

Topical monotherapies restricted to a maximum transition period of 3 months (n=220) due to short half-lives of topical therapies had a mean transition period of 25.9 ± 25.7 days (median 15.0, range:1-90) (PT-Table 2.1.1m).

Regarding the prior treatment groups fumaric acid ester, methotrexate and ciclosporin, the shortest mean (± SD) transition period was reported in patients with prior methotrexate treatment (55.7 ± 65.8 days) (PT-Table 2.1.3).

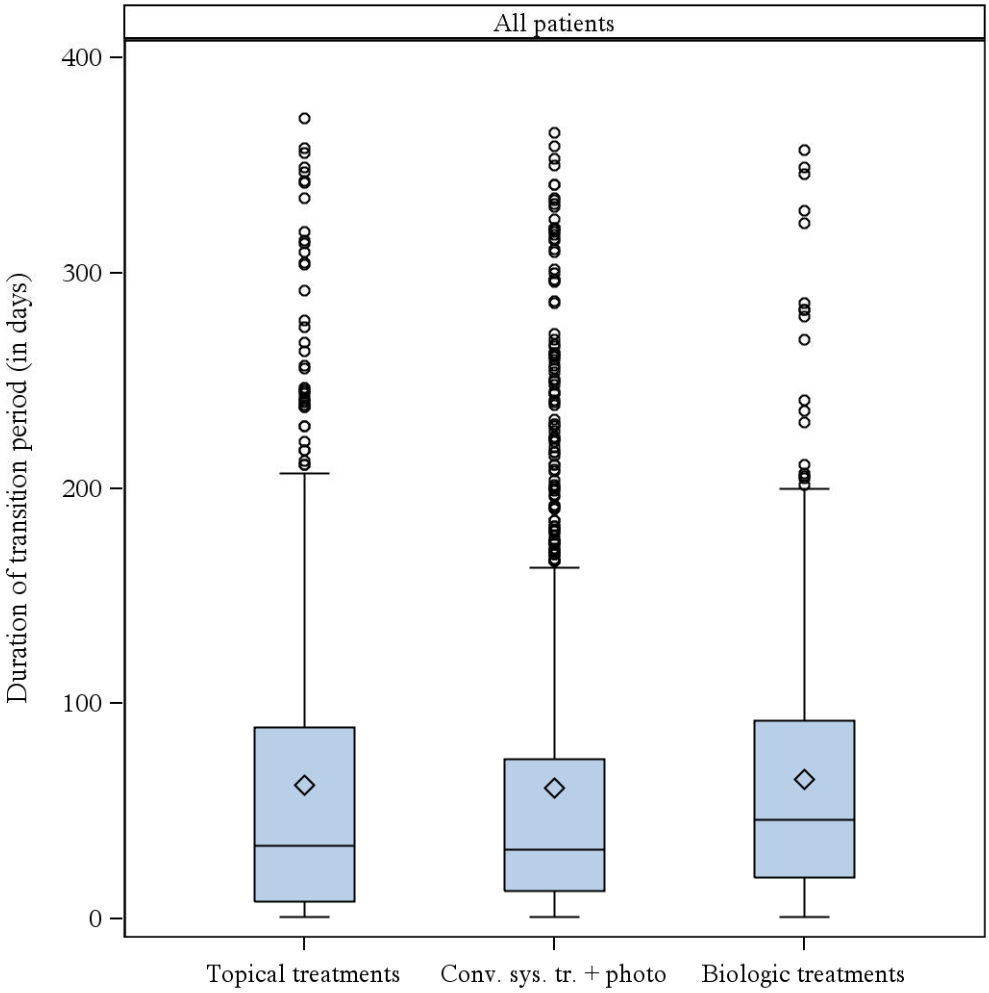
Table 10-14 Mean duration of transition periods [days] for treatment categories (all patients)

	Treatment category		
All patients (N=2502)	**Topical treatments**	**Conventional systemic treatments (incl. phototherapy)**	**Biologic treatments**
n (%)	662 (26.5)	1028 (41.1)	435 (17.4)
Mean ± SD	61.9 ± 73.4	60.6 ± 73.2	64.8 ± 62.6
Median (range)	34.0 (1-372)	32.0 (1-365)	46.0 (1-357)
IQR (1st quartile, 3rd quartile)	81 (8.0, 89.0)	61 (13.0, 74.0)	73 (19.0, 92.0)
95% confidence interval	[56.3; 67.5]	[56.1; 65.1]	[58.9; 70.7]
	Conventional systemic treatments		
Subcategories	**Fumaric acid ester**	**Methotrexate**	**Ciclosporin**
n (%)	291 (11.6)	375 (15.0)	55 (2.2)
Mean ± SD	69.9 ± 81.7	55.7 ± 65.8	62.4 ± 75.8
Median (range)	36.0 (1-359)	33.0 (1-365)	34.0 (1-310)
IQR (1st quartile, 3rd quartile)	88 (12.0, 100.0)	55 (14.0, 69.0)	68 (12.0, 80.0)
95% confidence interval	[60.4; 79.3]	[49.1; 62.4]	[42.0; 82.9]

IQR = inter-quartile range, SD = standard deviation
Source: PT-Tables 2.1.1, 2.1.3

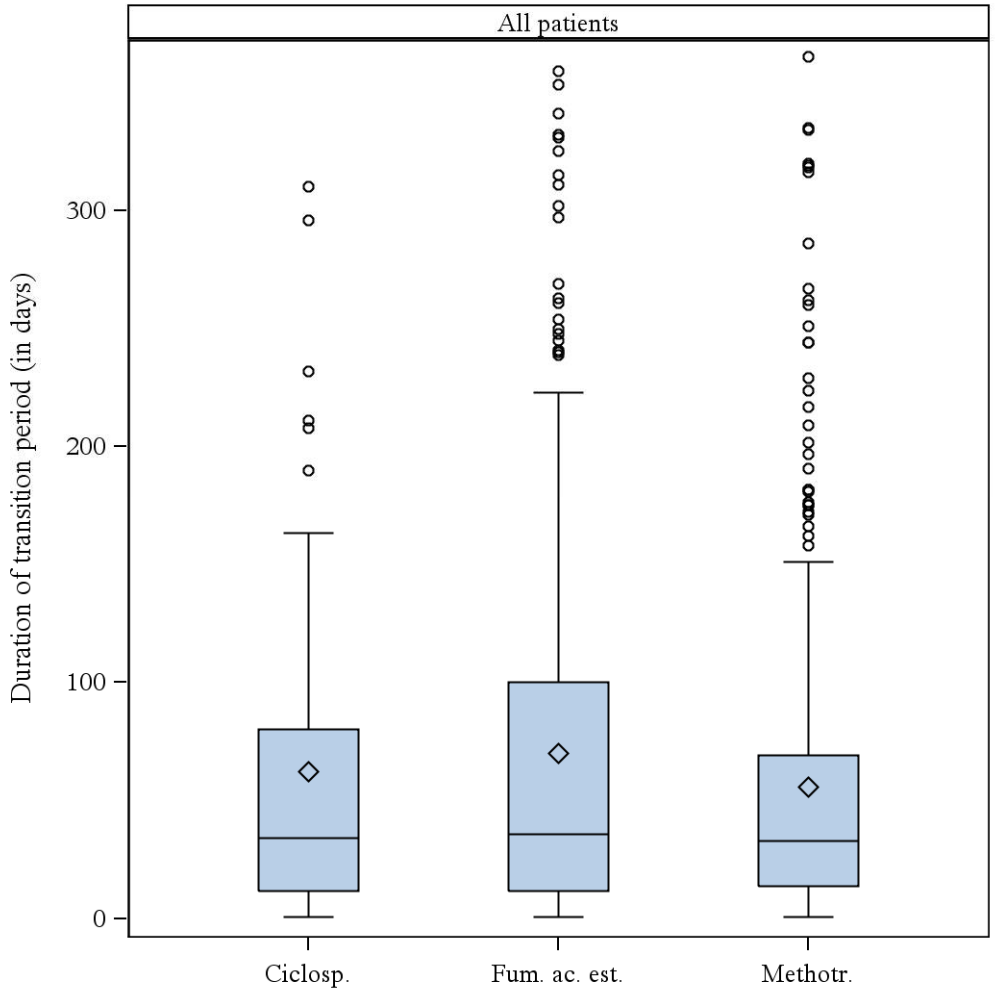
Figure 10-1 and Figure 10-2 graphically show the duration of transition periods of the treatment categories and of the 3 selected conventional systemic treatments ciclosporin, fumaric acid ester and methotrexate.

Figure 10-1 Duration of transition periods (in days) – treatment categories



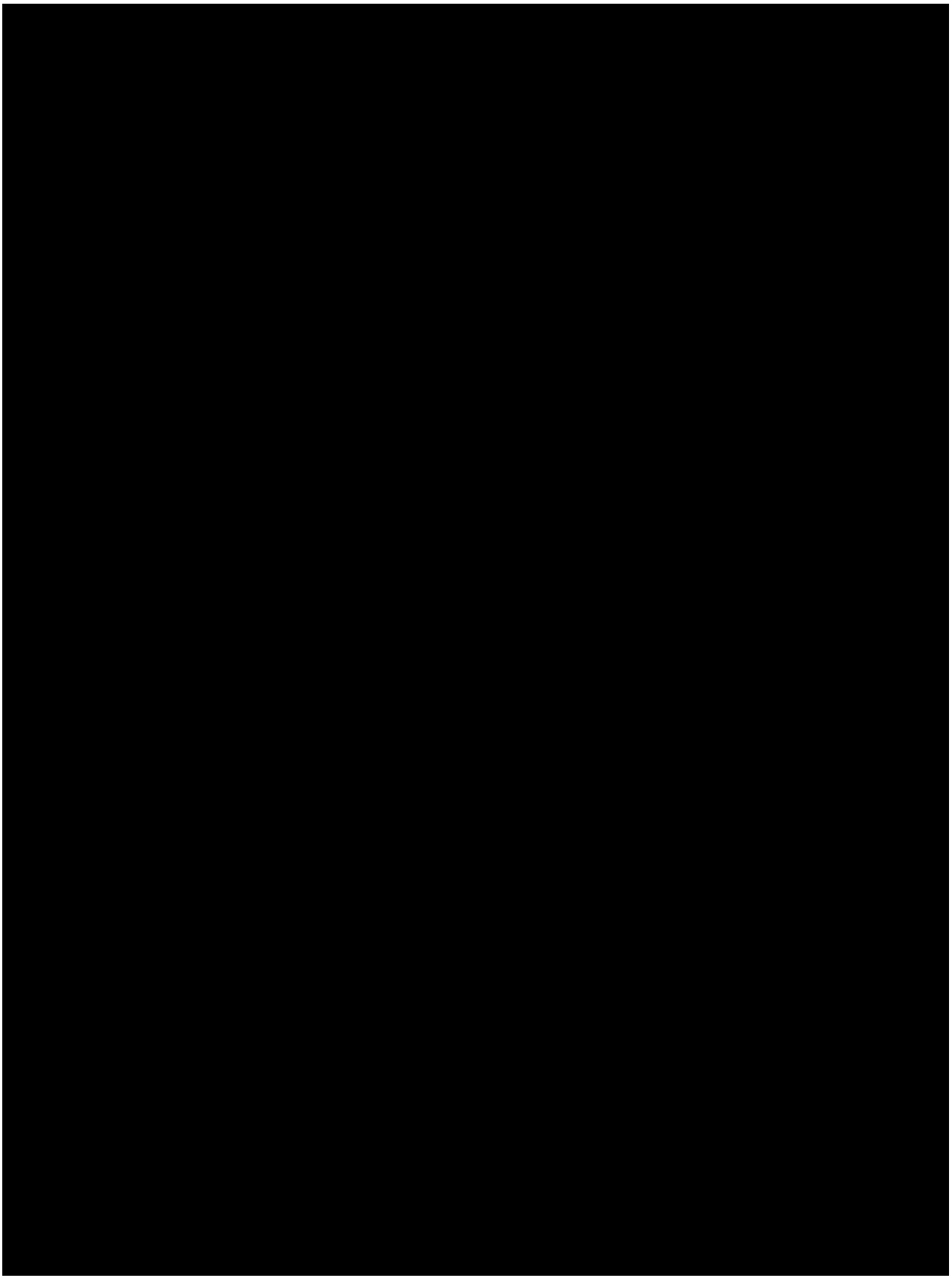
Conv.sys.tr. + photo = conventional systemic treatment including phototherapy
Source: PT-Figure 2.1.1.2

Figure 10-2 Duration of transition periods (in days) – selected conventional and systemic treatments



Ciclosp. = ciclosporin, fum. ac. est.= fumaric acid ester, methotr. = methotrexate
Source: PT-Figure 2.1.3.2 (modified by statistician)

[redacted]



[redacted]

10.4.2 Secondary endpoints

10.4.2.1 Duration of transition periods compared to treatment intervals

The proportion of patients with a transition period of ≤ 1 treatment interval, > 1 and ≤ 3 treatment intervals, > 3 and ≤ 5 treatment intervals, and > 5 treatment intervals was analysed per treatment group.

The majority of patients with prior topical and conventional systemic treatments had transition periods of >5 treatment intervals (495 patients, 82.8% and 545 patients, 70.1%, respectively). The proportion of patients with biologic treatments was largest for patients with transition periods ≤1 treatment interval (129 patients, 31.9%) and >1 and ≤3 treatment intervals (149 patients, 36.8%) as summarized in Table 10-16.

Details on topical, conventional systemic and biologic treatments are provided in PT-Tables 2.2.2, 2.2.3 and 2.2.4.

Table 10-16 Duration of transition periods compared to treatment intervals (all patients)

Duration of transition period	All patients (N=2502)	
Topical treatments	**n (%)**	**[95%-CI]**
<=1 treatment interval	30 (5.0)	[3.4 - 7.1%]
>1 and <=3 treatment intervals	53 (8.9)	[6.7 - 11.4%]
>3 and <=5 treatment intervals	20 (3.3)	[2.1 - 5.1%]
>5 treatment intervals	495 (82.8)	[79.5 - 85.7%]
Conventional systemic treatments (without phototherapy)		
<=1 treatment interval	57 (7.3)	[5.6 - 9.4%]
>1 and <=3 treatment intervals	111 (14.3)	[11.9 - 16.9%]
>3 and <=5 treatment intervals	65 (8.4)	[6.5 - 10.5%]
>5 treatment intervals	545 (70.1)	[66.7 - 73.3%]
Biologic treatments		
<=1 treatment interval	129 (31.9)	[27.3 - 36.6%]
>1 and <=3 treatment intervals	149 (36.8)	[32.1 - 41.7%]
>3 and <=5 treatment intervals	49 (12.1)	[9.1 - 15.7%]
>5 treatment intervals	78 (19.3)	[15.5 - 23.4%]

CI = confidence interval
Source: PT-Table 2.2.1

The results are shown graphically in PT-Figures 2.2.1 (all treatment categories), 2.2.2 (topical treatments), 2.2.3 (conventional systemic treatments without phototherapy), and 2.2.4 (biologic treatments).

10.4.2.2 Duration of transition periods compared to systemic terminal half-life

The majority of patients with prior conventional systemic treatments (excluding phototherapy) had transition periods of >5 systemic terminal half-lives (805 patients, 98.2%). Comparable results were observed for patients treated with fumaric acid esters, methotrexate, ciclosporin, acitretin, and apremilast, as detailed in PT-Table 2.3.2.

Among all patients with prior biologic treatments, transition periods of >5 systemic terminal half-lives were reported for approximately one third of patients (146 patients, 36.0%), periods of >1 and <=3 systemic terminal half-lives and >3 and <=5 systemic terminal half-lives were reported for a comparable number of patients (94 patients, 23.2% and 106 patients, 26.1%, respectively).

Regarding single prior biologic treatments (ustekinumab, adalimumab, etanercept, and infliximab), results were slightly different as detailed in PT-Table 2.3.3. A summary is shown in Table 10-17. The results are graphically shown in PT-Figures 2.3.1 (treatment categories), 2.3.2 (conventional systemic treatments without phototherapy), 2.3.3 (biologic treatments).

Table 10-17 Duration of transition periods compared to systemic terminal half-life (all patients)

Duration of transition period	All patients (N=2502)	
Conventional systemic treatments (without phototherapy)	**n (%)**	**[95%-CI]**
<=1 systemic terminal half-life	3 (0.4)	[0.1 - 1.1%]
>1 and <=3 systemic terminal half-lives	-	-
>3 and <=5 systemic terminal half-lives	12 (1.5)	[0.8 - 2.5%]
>5 systemic terminal half-lives	805 (98.2)	[97.0 - 99.0%]
Biologic treatments		
<=1 systemic terminal half-life	60 (14.8)	[11.5 - 18.6%]
>1 and <=3 systemic terminal half-lives	94 (23.2)	[19.1 - 27.6%]
>3 and <=5 systemic terminal half-lives	106 (26.1)	[21.9 - 30.7%]
>5 systemic terminal half-lives	146 (36.0)	[31.3 - 40.8%]

CI = confidence interval
Source: PT-Table 2.3.1

10.4.2.3 Discontinuation of concomitant psoriasis treatments by time

Discontinuation of concomitant psoriasis treatments by time was analysed as a secondary endpoint. Further information on discontinuation of concomitant psoriasis treatment is provided in section 10.3.3. [redacted] As only 1 patient received biologic treatment concomitantly, this category is not shown in Table 10-18. The respective patient discontinued after week >16-20.

Approximately half of the patients with discontinuation of concomitant topical treatment (118/236, 50.0%) and conventional systemic treatment (28/52, 53.8%) received their treatment up to week 4 and discontinued thereafter. Further details are shown in Table 10-18.

10.4.2.4 Initial treatment interval of concomitant treatments

Information on the initial treatment interval of concomitant treatments are provided per treatment group (e.g. topical steroids, topical steroids in combination with vitamin D3 analogues etc.) using sample statistics and frequency tables. Dose of topical treatments are displayed in PT-Table 2.5.1, dose of conventional treatments in PT-Table 2.5.2.

Topical treatments

Only 1 patient had concomitantly received a calcineurin inhibitor (topical treatment), this was at an initial treatment interval of four times a day (qid) which equalizes to an interval of 0.25 days (PT-Table 2.5.1).

Initial treatment intervals mainly used for administration of topical steroids were every day (qd) (47 patients, 48.0%), followed by twice daily (bid) (23 patients, 23.5%) and as needed (prn) (22 patients, 22.4%). The mean (± SD) initial treatment interval was 0.97 ± 0.65 days.

Vitamin D3 analogues were mainly given at an initial prn treatment interval (6 patients, 42.9%), followed by qd (4 patients, 28.6%), bid (3 patients, 21.4%). One patient (7.1%) had received this treatment twice a week. The mean (± SD) initial treatment interval was 1.13 ± 0.99 days.

Topical steroids in combination with vitamin D3 analogues were mainly given at an initial qd treatment interval (19 patients, 59.4%) and in each 4 patients (12.5%) either prn, twice a week or other. One patient (3.1%) had received this treatment bid. The mean (± SD) initial treatment interval was 1.40 ± 0.97 days.

Other topical treatments were mainly given prn (11 patients, 39.3%), qd (7 patients, 25.0%), bid (6 patients, 21.4%). Three patients (10.7%), received this treatment at another interval, 1 patient (3.6%) qid.

Conventional systemic treatments (including phototherapy)

A total of 2 patients (0.1%) had received concomitant acitretin at an initial and mean dose of 25.0 mg every day (mean ± SD treatment interval: 1.0 days).

One patient had received ciclosporin at an initial dose 150.0 mg, this was given twice daily.

Three patients (0.1%) received fumaric acid ester at an initial dose of 120.0 mg. Initial treatment intervals were three times a day (tid), bid and qd for 1 patient (33.3%) each. The mean (± SD) initial treatment interval was consequently 0.61 ± 0.35 days.

Methotrexate was given to 25 patients (1.0%) at a mean (± SD) initial dose of 17.8 ± 16.1 mg. It was mainly given at a weekly interval (every week) (20 patients, 80.0%), with a mean (± SD) treatment interval of 8.21 ± 4.85 days.

Phototherapy (n=11, 0.4%) was given at a mean (± SD) interval of 6.2 ± 8.8 cycles.

Details on other systemic treatments are provided in PT-Table 2.5.2.

Biologic treatments

The only patient with concomitant biologic treatment received ustekinumab at an initial dose of 90 mg and at an interval not further specified (PT-Table 2.5.3).

10.4.2.5 Measures of effectiveness and QoL per visit

Number of patients with measures of effectiveness and QoL performed per visit are displayed in PT-Table 2.6. Table 10-19 gives an overview on number of patients and documented routinely performed measurements at the regular study visits.

As expected, PASI assessment was performed for most patients over the study visits, followed by DLQI and BSA measurement. Measures as IGA, PGA, NAPSI, and PSSI were done for less than 10% of the study patients. Measurements were performed most frequently at the baseline and the end of study visit scheduled at week 24.

Table 10-19 Number of patients with documented measures at regular visits (all patients)

Visit Assessment	BL n (%)	Week 4 n (%)	Week 12 n (%)	Week 16 n (%)	Week 24 n (%)
PASI	2294 (91.7)	1746 (69.8)	1743 (69.7)	1657 (66.2)	1826 (73.0)
DLQI	941 (37.6)	628 (25.1)	645 (25.8)	587 (23.5)	684 (27.3)
BSA	410 (16.4)	277 (11.1)	286 (11.4)	260 (10.4)	328 (13.1)
IGA mod 2011	172 (6.9)	112 (4.5)	112 (4.5)	108 (4.3)	127 (5.1)
PGA	107 (4.3)	87 (3.5)	79 (3.2)	75 (3.0)	93 (3.7)
NAPSI	92 (3.7)	38 (1.5)	30 (1.2)	29 (1.2)	38 (1.5)
PSSI	73 (2.9)	31 (1.2)	29 (1.2)	25 (1.0)	25 (1.0)
IGA mod 2009	6 (0.2)	1 (0.0)	2 (0.1)	1 (0.0)	5 (0.2)

BL = baseline, BSA = body surface area, DLQI = dermatology life quality index, IGA = investigator's global assessment, NAPSI = nail psoriasis severity index, PASI = psoriasis area and severity index, PGA = physician's global assessment, PSSI = psoriasis scalp severity index
Source: PT-Table 2.6

10.4.2.6 Analysis of PASI

Clinical effectiveness of secukinumab was assessed using PASI. PASI scores can range from a value of 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.0PASI values > 10 are indicative of moderate to severe psoriasis [9].

Raw PASI and the number of patients with a PASI of 0, and a PASI below 1, 2, 3, 5, and 10 were assessed over time.

Number of patients with PASI scores (categorical) per visit are provided in PT-Table 2.7.3 and summarized in Table 10-20 for the regular study visits. The number of patients with PASI scores < 10 was constantly increasing during the study visits, indicating an improvement of psoriasis under treatment with secukinumab.

Table 10-20 PASI scores per regular study visits (all patients)

Variable	All patients (N=2502)				
	Regular study visits				
PASI score per visit	**Baseline n (%)**	**Week 4 n (%)**	**Week 12 n (%)**	**Week 16 n (%)**	**Week 24 n (%)**
	(n=2294)	(n=1746)	(n=1743)	(n=1657)	(n=1826)
PASI = 0	67 (2.9)	137 (7.8)	442 (25.4)	540 (32.6)	730 (40.0)
PASI < 1	129 (5.6)	244 (14.0)	729 (41.8)	825 (49.8)	1060 (58.1)
PASI < 2	183 (8.0)	412 (23.6)	1033 (59.3)	1110 (67.0)	1322 (72.4)
PASI < 3	216 (9.4)	588 (33.7)	1214 (69.7)	1260 (76.0)	1479 (81.0)
PASI < 5	289 (12.6)	903 (51.7)	1451 (83.2)	1426 (86.1)	1618 (88.6)
PASI < 10	558 (24.3)	1376 (78.8)	1634 (93.7)	1574 (95.0)	1756 (96.2)
PASI >=10	1736 (75.7)	370 (21.2)	109 (6.3)	83 (5.0)	70 (3.8)
PASI > 20	811 (35.4)	71 (4.1)	24 (1.4)	18 (1.1)	10 (0.5)

PASI = psoriasis area and severity index
Source: PT-Table 2.7.3

Table 10-21 provides the mean (± SD) PASI score over time for the regular study visits (baseline, weeks 4, 12, 16, and 24) and PASI reduction as % change from baseline. Details on the remaining study visits are provided in PT-Table 2.7.1 and 2.7.2. After 4 weeks of treatment with secukinumab, a mean (± SD) change from baseline of 64.8 ± 25.1 % was observed, indicating improvement which continued until the last study visit at week 24 with a mean (± SD) change from baseline of 89.7 ± 18.6 %.

P-values (mean unequal 0) were <0.001 for PASI reduction from baseline at all study visits (PT-Table 2.7.2).

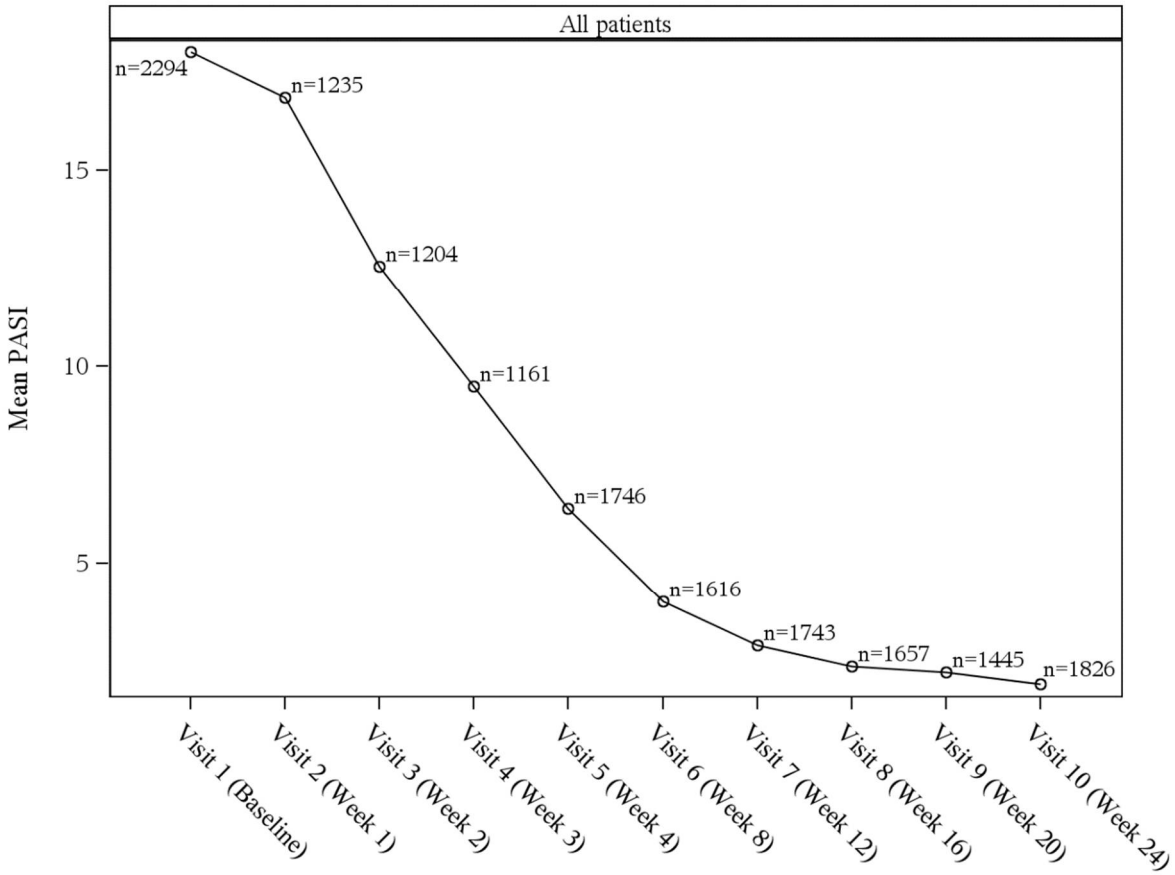
Table 10-21 PASI score during the study (all patients)

Variable	All patients (N=2502)	
PASI score **Visit (time)**	**Mean score**	**Change from baseline [%]**
Visit 1 (Baseline)		
n (%)	2294 (91.7)	-
Mean ± SD	18.0 ± 12.3	-
Median (range)	15.7 (0.0-72.0)	-
Visit 5 (Week 4)		
n (%)	1746 (69.8)	1283 (51.3)
Mean ± SD	6.4 ± 6.1	64.8 ± 25.1
Median (range)	4.8 (0.0-42.7)	70.0 (-43.3-100.0)
Visit 7 (Week 12)		
n (%)	1743 (69.7)	1266 (50.6)
Mean ± SD	2.9 ± 4.8	84.0 ± 22.2)
Median (range)	1.4 (0.0-57.8)	92.3 (-101.8-100.0)
Visit 8 (Week 16)		
n (%)	1657 (66.2)	1221 (48.8)
Mean ± SD	2.4 ± 4.2	87.4 ± 19.1
Median (range)	1.0 (0.0-50.4)	94.7 (-42.1-100.0)
Visit 10 (Week 24)		
n (%)	1826 (73.0)	1322 (52.8)
Mean ± SD	1.9 ± 3.6	89.7 ± 18.6
Median	0.6 (0.0-38.1)	97.0 (-87.5-100.0)

PASI = psoriasis area and severity index, SD = standard deviation
Source: PT-Tables 2.7.1 and 2.7.2

The continuous improvement in mean PASI during study is graphically shown in Figure 10-3 for all patients.

Figure 10-3 Mean PASI per visit (all patients)



PASI = psoriasis area and severity index
Source: PT-Figure 2.7.1

Box-and-whisker-plots of PASI per visit are provided in PT-Figure 2.7.2.

PASI response rates

PASI 50, 75, 90, and 100 response rates were assessed, for patients who had a PASI > 10 at the first visit, which correspond to the number of patients achieving at least a 50, 75, 90 or 100% reduction in PASI.

After 4 weeks under secukinumab a PASI reduction of at least 50% compared to baseline was observed for 75.1% of the patients with PASI > 10 at baseline. Reductions of 75%, 90% and 100% were documented for 41.0%, 15.0% and 4.0% of the patients, respectively. At the last study visit, after 24 weeks of secukinumab treatment, a PASI reduction of 50% was documented for 95.5% of these patients, reductions of 75%, 90% and 100% were documented for 87.4%, 72.1% and 39.9% of the patients, respectively. A summary is provided in Table 10-22.

Table 10-22 PASI response rates for patients with PASI > 10 at baseline

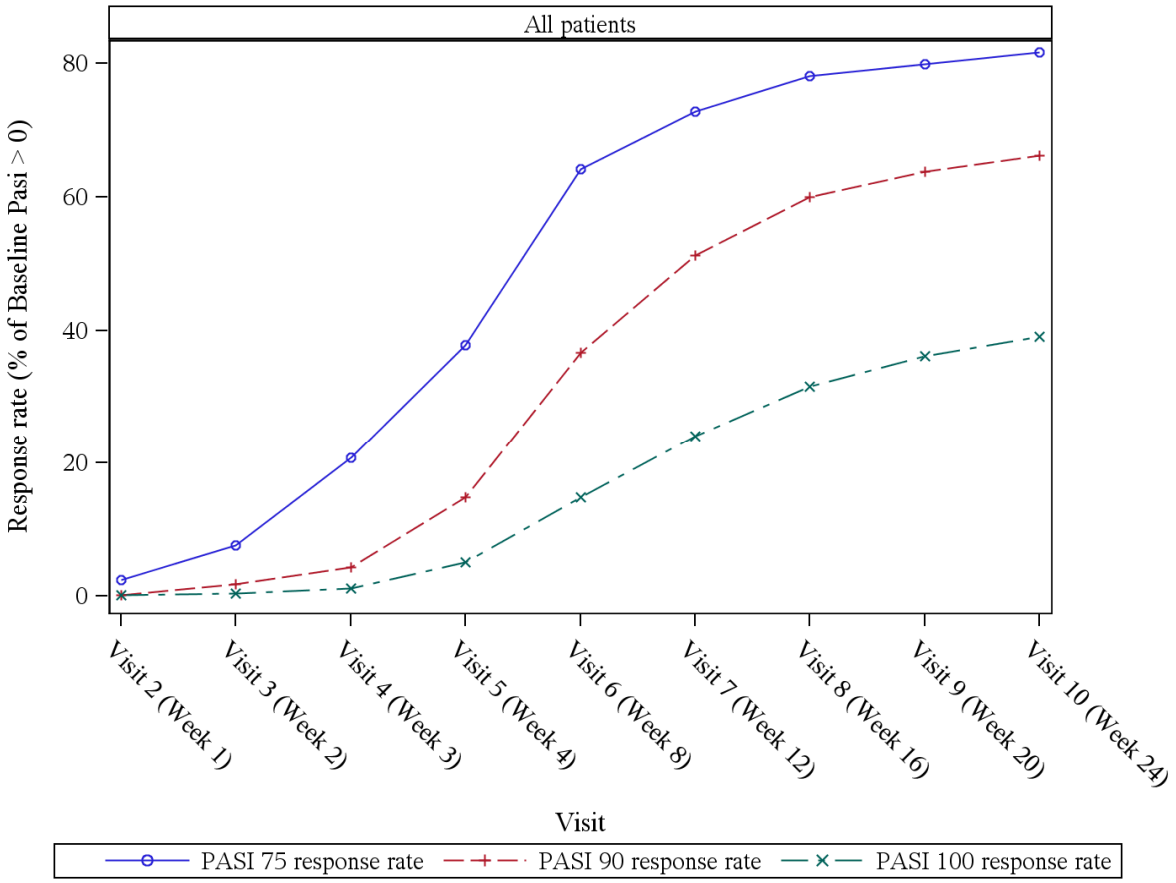
Visit Reduction	All patients (N=2502)
Visit 5 (Week 4)	
PASI reduction of at least 50% compared to baseline	75.1% (963/1283)
PASI reduction of at least 75% compared to baseline	41.0% (526/1283)
PASI reduction of at least 90% compared to baseline	15.0% (192/1283)
PASI reduction of at least 100% compared to baseline	4.0% (51/1283)
Visit 7 (Week 12)	
PASI reduction of at least 50% compared to baseline	92.3% (1168/1266)
PASI reduction of at least 75% compared to baseline	78.8% (998/1266)
PASI reduction of at least 90% compared to baseline	55.5% (703/1266)
PASI reduction of at least 100% compared to baseline	23.9% (303/1266)
Visit 8 (Week 16)	
PASI reduction of at least 50% compared to baseline	94.2% (1150/1221)
PASI reduction of at least 75% compared to baseline	83.5% (1019/1221)
PASI reduction of at least 90% compared to baseline	64.6% (789/1221)
PASI reduction of at least 100% compared to baseline	31.7% (387/1221)
Visit 10 (Week 24)	
PASI reduction of at least 50% compared to baseline	95.5% (1263/1322)
PASI reduction of at least 75% compared to baseline	87.4% (1155/1322)
PASI reduction of at least 90% compared to baseline	72.1% (953/1322)
PASI reduction of at least 100% compared to baseline	39.9% (528/1322)

PASI = psoriasis area and severity index
Note: PASI response rates are calculated only for patients with PASI > 10 at baseline.
Source: PT-Table 2.7.5.1

PASI response rates for patients with PASI > 0 at baseline and PASI > 0 at baseline by pre-treatment status are provided in PT-Tables 2.7.5.2 and 2.7.5.3.

Figure 10-4 graphically shows the course of PASI response rates (PASI 75 response rate, PASI 90 response rate and PASI 100 response rate) during the study for patients with PASI > 0 at baseline.

Figure 10-4 PASI response rates per visit for patients with PASI > 0 (all patients)



PASI = psoriasis area and severity index
Source: PT-Figure 2.7.3

PT-Figures 2.7.4, 2.7.5 and 2.7.6 provide PASI 75, PASI 90 and PASI 100 response rates.

10.4.2.7 Body surface area

BSA is measured to determine the severity of psoriasis. The total BSA affected by plaque-type psoriasis is estimated from the percentages of areas affected. The palm of hand serves as surface measure. Please refer to section 9.4.4 for a detailed description of BSA assessment in the context of PASI measurements. Details on BSA per visit and BSA reduction from baseline per visit are provided in PT-Tables 2.8.1 and 2.8.2. The course of BSA and reduction of BSA from baseline for regular study visits is shown in Table 10-23.

After 4 and 24 weeks of secukinumab treatment, a mean (± SD) reduction of 41.8 ± 38.0 % and 68.4 ± 87.6 % of involved BSA was documented, respectively.

Table 10-23 Course of BSA and reduction of BSA from baseline [%] during study

Variable	All patients (N=2502)	
BSA (%)	**Mean BSA (%)**	**Change from baseline (%)**
Visit 1 (Baseline)		
n (%)	410 (16.4)	-
Mean ± SD	19.2 ± 18.1	-
Median	14.0 (0.0-100.0)	-
Visit 5 (Week 4)		
n (%)	277 (11.1)	191 (7.6)
Mean ± SD	9.1 ± 10.6	41.8 ± 38.0
Median	5.0 (0.0-60.0)	43.3 (-100.0-100.0)
Visit 7 (Week 12)		
n (%)	286 (11.4)	194 (7.8)
Mean ± SD	4.5 ± 7.9	68.1 ± 50.8
Median	2.0 (0.0-70.0)	85.4 (-400.0-100.0)
Visit 8 (Week 16)		
n (%)	260 (10.4)	174 (7.0)
Mean ± SD	3.9 ± 8.2	76.1 ± 33.7
Median	2.0 (0.0-100.0)	87.5 (-116.7-100.0)
Visit 10 (Week 24)		
n (%)	328 (13.1)	217 (8.7)
Mean ± SD	3.1 ± 7.0	68.4 ± 87.6
Median	1.0 (0.0-100.0)	90.0 (-1000.0-100.0)

BSA = body surface area, SD = standard deviation
Source: PT-Tables 2.8.1 and 2.8.2

10.4.2.8 Effectiveness of secukinumab assessed in routine treatment

Clinical effectiveness of secukinumab as assessed in routine treatment [e.g. Investigator's Global Assessment (IGA), Physician's Global Assessment (PGA), Dermatology Life Quality Index (DLQI), Psoriasis Scalp Severity Index (PSSI), Nail Psoriasis Severity Index (NAPSI)] was documented in this NIS.

10.4.2.8.1 Investigator's global assessment

IGA modified in 2011 (IGA mod 2011) is used as a rating scale for overall disease, ranging from 0 (clear - no signs of psoriasis) to 4 (severe disease). For details please refer to section 9.4.5.

Number of patients with IGA score per visit are provided in PT-Table 2.9.1. A shift table (from baseline to last assessment) for IGA score is provided in PT-Table 2.9.2.

Table 10-24 summarizes IGA 0/1 response rates per visit (PT-Table 2.9.3). A continuous increase in the response rate 0/1 from week 1 (11.1%) to week 24 (71.7%) under secukinumab treatment was be observed. Results are shown graphically in PT-Figure 2.9.1.

Table 10-24 IGA 0/1 response rates per visit (all patients)

Visit	All patients (N=2502)
Visit 2 (Week 1)	11.1% (3/ 27)
Visit 3 (Week 2)	9.1% (2/ 22)
Visit 4 (Week 3)	20.0% (5/ 25)
Visit 5 (Week 4)	48.2% (54/ 112)
Visit 6 (Week 8)	56.5% (52/ 92)
Visit 7 (Week 12)	62.5% (70/ 112)
Visit 8 (Week 16)	66.7% (72/ 108)
Visit 9 (Week 20)	69.4% (59/ 85)
Visit 10 (Week 24)	71.7% (91/ 127)

IGA = investigator's global assessment
Source: PT-Table 2.9.3

The former IGA evaluation modified in 2009 was used for a low number of patients (n=6 at baseline) during this study. Results are provided in PT-Table 2.10.1.

10.4.2.8.2 Physician's global assessment

PGA ranges from 0 (no symptoms) to 5 (severe psoriasis) and was documented as assessed during the visit. PGA per visit is provided in PT-Table 2.11.1. A shift table is provided in PT-Table 2.11.2.

At baseline, 25 patients (23.4%) had a PGA score of 0, while 51 patients (54.8%) had this score at week 24. Vice versa declined the number of patients with higher PGA scores from baseline to week 24. Overall, this is equivalent to an improvement in psoriasis symptoms. Table 10-25 summarizes the PGA per regular visits by number of patients with different scores.

Table 10-25 PGA scores per regular study visits (all patients)

Variable	All patients (N=2502)				
	Regular study visits				
PGA score per visit	**Baseline n (%)**	**Week 4 n (%)**	**Week 12 n (%)**	**Week 16 n (%)**	**Week 24 n (%)**
	(n=107)	(n=87)	(n=79)	(n=75)	(n=93)
PGA = 0	25 (23.4)	30 (34.5)	40 (50.6)	43 (57.3)	51 (54.8)
PGA = 1	7 (6.5)	14 (16.1)	22 (27.8)	19 (25.3)	29 (31.2)
PGA = 2	8 (7.5)	19 (21.8)	14 (17.7)	13 (17.3)	10 (10.8)
PGA = 3	28 (26.2)	16 (18.4)	3 (3.8)	-	3 (3.2)
PGA = 4	20 (18.7)	4 (4.6)	-	-	-
PGA = 5	19 (17.8)	4 (4.6)	-	-	-

PGA = physician's global assessment
Source: PT-Table 2.11.1

10.4.2.8.3 Dermatology life quality index

DLQI evaluates the QoL of patients. It ranges from 0-1 (no effect at all on patient's life) to 21-30 (extremely large effect on patient's life). For details please refer to section 9.4.5.

DLQI was not measured for all patients during the study. The mean (± SD) DLQI at baseline for 941/2,502 patients was 13.7 ± 7.9. After 24 weeks of secukinumab treatment, 684/2502 patients had a mean (± SD) DLQI of 2.7 ± 4.5, this change is equivalent to a reduction in DLQI score by 73.0 ± 64.1%, indicating a large effect on patients' QoL. Table 10-26 summarizes the results during the study (regular study visits).

Table 10-26 Course of DLQI and reduction (%) from baseline during study

Variable	All patients (N=2502)	
DLQI Score	**Mean DLQI**	**Change from baseline (%)**
Visit 1 (Baseline)		
n (%)	941 (37.6)	-
Mean ± SD	13.7 ± 7.9	-
Median	14.0 (0.0-30.0)	-
Visit 5 (Week 4)		
n (%)	628 (25.1)	482 (19.3)
Mean ± SD	5.4 ± 5.4	56.1 ± 44.4
Median	4.0 (0.0-29.0)	66.7 (-300.0-100.0)
Visit 7 (Week 12)		
n (%)	645 (25.8)	472 (18.9)
Mean ± SD	3.1 ± 4.8	70.3 ± 58.5
Median	1.0 (0.0-28.0)	88.9 (-800.0-100.0)
Visit 8 (Week 16)		
n (%)	587 (23.5)	451 (18.0)
Mean ± SD	3.0 ± 4.7	70.8 ± 67.3
Median	1.0 (0.0-28.0)	92.0 (-900.0-100.0)
Visit 10 (Week 24)		
n (%)	684 (27.3)	501 (20.0)
Mean ± SD	2.7 ± 4.5	73.0 ± 64.1
Median	1.0 (0.0-30.0)	93.8 (-766.7-100.0)

DLQI = dermatology life quality index, SD = standard deviation
Source: PT-Tables 2.12.1 and 2.12.2

The number of patients with DLQI 0/1 response rates are provided in PT-Tables 2.12.3.1 and 2.12.3.2 and graphically in PT-Figure 2.12.1.

10.4.2.8.4 Psoriasis Scalp Severity Index

PSSI was assessed for 73 patients (2.9%) at the most. Mean (± SD) PSSI at baseline was 3.0 ± 6.0 (n=73), mean (± SD) PSSI after 24 weeks of secukinumab treatment was 1.2 ± 2.6 (n=25). Details are provided in PT-Tables 2.13.1 (PSSI per visit), 2.13.2 (PSSI reduction from baseline) and 2.13.3 (PSSI response rates per visit).

10.4.2.8.5 Nail Psoriasis Severity Index

NAPSI was assessed for 92 (3.7%) at the most. Mean (± SD) NAPSI at baseline was 16.7 ± 18.5 (n=92), mean NAPSI after 24 weeks of secukinumab treatment was 4.1 ± 9.3 (n=38). Details are provided in PT-Table 2.14.1 (NAPSI per visit), 2.14.2 (reduction from baseline) and 2.14.3 (NAPSI response rates per visit).

10.6 Adverse events/adverse reactions

The analysis of AEs was performed twice. Once, using investigator's assessment (PT-Tables 4 – investigator's assessment) regarding causal relationship to secukinumab and seriousness, and once using the maximum outcome of assessment of pharmacovigilance department (sponsor) and investigator's assessment, reported as "sponsor's assessment" hereafter (PT-Tables 4).

10.6.1 Summary on patients with AEs

Approximately half of the patients (1287 patients, 51.4%) had at least one AE during this NIS. Regarding AEs with suspected relationship to secukinumab, there was a difference of 1 patient between both assessment categories: investigators assessed AEs in 589 patients (23.5%) to be related to study treatment; the Sponsor assessed AEs in 590 patients (23.6%) to be related to study treatment.

Secukinumab was discontinued in 213 patients (8.5%) with AEs and in 135 patients (5.4%) with related AEs (both assessments).

In 24 patients (1.0%), secukinumab dose was increased due to an AE. This was the case for 14 patients (0.6%) with related AEs (both assessments).

In 36 patients (1.4%), secukinumab dose was reduced due to an AE. This was the case for 23 patients (0.9%) with related AEs (both assessments).

A total of 119 (4.8%) patients had at least one SAE according to investigator's assessment, 32 of them (1.3%) with a suspected relationship to secukinumab. A total of 218 patients (8.7%) had at least one SAE according to sponsor's assessment, 60 of them (2.4%) with a suspected relationship to secukinumab. Five patients (0.2%) experienced SAEs leading to death during this study (PT-Listing 4.18).

An overview on AEs is given in Table 10-27.

Table 10-27 Overview of patients with AEs investigator's and sponsor's assessment (all patients)

Patients with	Investigator's assessment (N=2502) n (%)	Sponsor's assessment (N=2502) n (%)
any AE	1287 (51.4)	1287 (51.4)
AE with suspected relationship to secukinumab	589 (23.5)	590 (23.6)
AE leading to any action with secukinumab	261 (10.4)	261 (10.4)
AE with suspected relationship to secukinumab, leading to any action with secukinumab	167 (6.7)	167 (6.7)
AE leading to secukinumab discontinuation	213 (8.5)	213 (8.5)
AE with suspected relationship to secukinumab, leading to secukinumab discontinuation	135 (5.4)	135 (5.4)
AE leading to secukinumab dose increase	24 (1.0)	24 (1.0)
AE with suspected relationship to secukinumab, leading to secukinumab dose increase	14 (0.6)	14 (0.6)
AE leading to secukinumab dose reduction	36 (1.4)	36 (1.4)
AE with suspected relationship to secukinumab, leading to secukinumab dose reduction	23 (0.9)	23 (0.9)
any SAE	119 (4.8)	218 (8.7)
SAE with suspected relationship to secukinumab	32 (1.3)	60 (2.4)
SAE leading to death	5 (0.2%)	5 (0.2%)

AE = Adverse event, SAE = serious adverse event
Source: PT-Tables 4.1 (investigator's and sponsor's assessment) and PT-Listings 4.18 (investigator's and sponsor's assessment)

PT-Tables 4.1b give an overview on patients with AEs with exposure adjusted incidence rates. Exposure adjusted incidence rates are provided in PT-Tables 4.2b.

By-patient listings of patients with non-serious AEs, non-serious AEs for patients with concomitant biologic treatments and AEs of patients not included in the analysis set are provided in PT-Listings 4.20, 4.22 and 4.24.

10.6.2 Analysis and description of AEs

The tabulation of patients with AEs and number of AEs by MedDRA PSOC and PT is provided in PT-Tables 4.2 and 4.5. If not otherwise noted, the analysis of investigator's assessment is provided, differences between investigator's and sponsor's assessments are described.

Approximately half of the patients (1,287 patients, 51.4%) experienced a total of 3,209 AEs during the observation period, equivalent to 1.28 AEs/patient (PT-Tables 4.2 and 4.5). The highest incidence was seen in patients with AEs referring to the following MedDRA SOCs:

- Infections and infestations (643 patients, 25.7%), such as nasopharyngitis (249 patients, 10.0%), oral candidiasis (51 patients, 2.0%), and tonsillitis (30 patients, 1.2%);
- Skin and subcutaneous tissue disorders (382 patients, 15.3%), with pruritus (84 patients, 3.4%), psoriasis (76 patients, 3.0%), and eczema (45 patients, 1.8%);
- General disorders and administration site conditions (242 patients, 9.7%), with fatigue (59 patients 2.4%), drug ineffective (57 patients, 2.3%), and drug effect decreased (36 patients, 1.4%).

Table 10-28 lists the number of patients with all AEs on PSOC level and the most common AEs (occurring in ≥ 1% of patients in total) on PT level during the NIS.

Table 10-28 Patients with adverse events in total by PSOC and occurring in ≥ 1% of patients on PT level

MedDRA PSOC MedDRA Preferred Term	All patients (N=2502) n (%)
Patients with any adverse events	**1287 (51.4)**
Infections and infestations	**643 (25.7)**
Nasopharyngitis	249 (10.0)
Oral candidiasis	51 (2.0)
Tonsillitis	30 (1.2)
Bronchitis	26 (1.0)
Folliculitis	24 (1.0)
Sinusitis	24 (1.0)
Skin and subcutaneous tissue disorders	**382 (15.3)**
Pruritus	84 (3.4)
Psoriasis	76 (3.0)
Eczema	45 (1.8)
General disorders and administration site conditions	**242 (9.7)**
Fatigue	59 (2.4)
Drug ineffective	57 (2.3)
Drug effect decreased	36 (1.4)
Gastrointestinal disorders	**204 (8.2)**
Diarrhea	62 (2.5)
Nausea	36 (1.4)
Musculoskeletal and connective tissue disorders	**141 (5.6)**
Arthralgia	41 (1.6)

Table 10-28 Patients with adverse events in total by PSOC and occurring in ≥ 1% of patients on PT level

MedDRA PSOC MedDRA Preferred Term	All patients (N=2502) n (%)
Respiratory, thoracic and mediastinal disorders	**134 (5.4)**
Cough	45 (1.8)
Oropharyngeal pain	31 (1.2)
Nervous system disorders	**115 (4.6)**
Headache	67 (2.7)
Injury, poisoning and procedural complications	**93 (3.7)**
Investigations	**86 (3.4)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**49 (2.0)**
Vascular disorders	**48 (1.9)**
Eye disorders	**47 (1.9)**
Psychiatric disorders	**43 (1.7)**
Depression	9 (0.4)
Metabolism and nutrition disorders	**27 (1.1)**
Blood and lymphatic system disorders	**20 (0.8)**
Cardiac disorders	**20 (0.8)**
Renal and urinary disorders	**17 (0.7)**
Reproductive system and breast disorders	**16 (0.6)**
Ear and labyrinth disorders	**10 (0.4)**
Hepatobiliary disorders	**7 (0.3)**
Immune system disorders	**7 (0.3)**
Endocrine disorders	**6 (0.2)**
Surgical and medical procedures	**4 (0.2)**
Product issues	**2 (<0.1)**
Congenital, familial and genetic disorders	**1 (<0.1)**
Pregnancy, puerperium and perinatal conditions	**1 (<0.1)**
Social circumstances	**1 (<0.1)**

MedDRA = Medical dictionary for drug regulatory activities; PT = Preferred term; SOC = System organ class
MedDRA version 21.0
Source: PT-Table 4.2 investigator's assessment

A summary of patients with AEs by exposure adjusted incidence rates is provided in PT-Tables 4.2b.

Intensity of AEs

The intensity of AEs for all patients is analysed in PT-Table 4.3 by maximum severity. In 4 patients (0.2%), information was missing.

Overall, 532 (21.3%) patients experienced AEs of mild intensity. Such AEs occurring in at least 1% of the patients on PT level were:

- 173 patients (6.9%): nasopharyngitis
- 43 patients (1.7%): pruritus

- 32 patients (1.3%): fatigue
- 31 patients (1.2%): cough
- 31 patients (1.2%): headache
- 30 patients (1.2%): diarrhea
- 25 patients (1.0%): oral candidiasis
- 25 patients (1.0%): nausea
- 24 patients (1.0%): eczema

Five hundred and thirty-eight (21.5%) patients experienced AEs of moderate intensity. Such AEs occurring in at least 1% of the patients on PT level were:

- 65 patients (2.6%): nasopharyngitis
- 34 patients (1.4%) : psoriasis
- 26 patients (1.0%): headache
- 25 patients (1.0%): diarrhea
- 24 patients (1.0%): oral candidiasis
- 24 patients (1.0%): drug effect decreased

Two hundred and thirteen (8.5%) patients experienced AEs of severe intensity. None of them occurred in ≥ 1% of the patients on PT-level.

AEs with suspected relationship to secukinumab

A total of 590 patients (23.6%) had secukinumab related AEs according to sponsor's assessment, 589 patients (23.5%) had secukinumab related AEs according to investigator's assessment (PT-Tables 4.4). The highest incidence was seen in patients with AEs referring to the following MedDRA SOCs (investigator's assessment):

- Infections and infestations (219 patients, 8.8%), such as nasopharyngitis (48 patients, 1.9%), oral candidiasis (45 patients, 1.8%), and folliculitis (10 patients, 0.4%);
- Skin and subcutaneous tissue disorders (148 patients, 5.9%), with pruritus (39 patients, 1.6%), psoriasis (32 patients, 1.3%), and eczema (10 patients, 0.4%);
- General disorders and administration site conditions (145 patients, 5.8%), with fatigue and drug ineffective (41 patients each, 1.6%) and drug effect decreased (28 patients, 1.1%).

Table 10-29 lists the number of patients with all AEs on PSOC level and the most common AEs (occurring in ≥ 1% of patients in total) on PT level during the NIS (investigator's assessment).

Table 10-29 Patients with AEs assessed as related to secukinumab on PSOC level for all patients and on PT level occurring in ≥ 1% of patients (investigator's assessment)

MedDRA PSOC MedDRA PT	All patients (N=2502) n (%)
Patients with any adverse events related to secukinumab	**589 (23.5)**
Infections and infestations	**219 (8.8)**
Nasopharyngitis	48 (1.9)
Oral candidiasis	45 (1.8)
Skin and subcutaneous tissue disorders	**148 (5.9)**
Pruritus	39 (1.6)
Psoriasis	32 (1.3)
General disorders and administration site conditions	**145 (5.8)**
Drug ineffective	41 (1.6)
Fatigue	41 (1.6)
Drug effect decreased	28 (1.1)
Gastrointestinal disorders	**83 (3.3)**
Diarrhea	29 (1.2)
Respiratory, thoracic and mediastinal disorders	**54 (2.2)**
Nervous system disorders	**46 (1.8)**
Headache	27 (1.1)
Investigations	**41 (1.6)**
Musculoskeletal and connective tissue disorders	**33 (1.3)**
Vascular disorders	**18 (0.7)**
Injury, poisoning and procedural complications	**16 (0.6)**
Eye disorders	**13 (0.5)**
Psychiatric disorders	**10 (0.4)**
Depression	0 (0.0)
Blood and lymphatic system disorders	**9 (0.4)**
Neutropenia	1 (<0.1)
Renal and urinary disorders	**9 (0.4)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**8 (0.3)**
Cardiac disorders	**4 (0.2)**
Reproductive system and breast disorders	**4 (0.2)**
Immune system disorders	**3 (0.1)**
Ear and labyrinth disorders	**2 (<0.1)**
Metabolism and nutrition disorders	**2 (<0.1)**
Product issues	**1 (<0.1)**

MedDRA = Medical dictionary for drug regulatory activities; PT = Preferred term; SOC = System organ class
MedDRA version 21.0
Source: PT-Table 4.4 (investigator's assessment)

Patients reporting MedDRA PT "psoriasis" as AE

AEs of MedDRA PT Psoriasis were reported by 76 patients (3.0%) . A summary on these AEs is provided in Table 10-30. Mostly, aggravated psoriasis (49 patients, 2.0%), exacerbation of psoriasis (12 patients, 0.5%) and psoriasis flare-up (9 patients, 0.4%) were documented. It is important to note that psoriasis is a condition recognized for its flares and exacerbations, even in patients considered under satisfactory control. Most of the flare-ups are triggered by common events such as viral infections and physical/psychological stress.

Table 10-30 Summary of patients with adverse events with MedDRA Preferred Term "Psoriasis"

MedDRA Lowest Level Term	All patients (N=2502) n (%)
Patients with adverse events with MedDRA preferred Term "Psoriasis"	**76 (3.0)**
Psoriasis aggravated	49 (2.0)
Exacerbation of psoriasis	12 (0.5)
Psoriasis flare-up	9 (0.4)
Inverse psoriasis	2 (<0.1)
Psoriasis palm & soles	2 (<0.1)
Psoriatic plaque	2 (<0.1)
Plaque psoriasis	1 (<0.1)
Psoriasis of scalp	1 (<0.1)
Psoriasis vulgaris	1 (<0.1)

MedDRA = Medical dictionary for drug regulatory activities; PT = Preferred term;
MedDRA version 21.0
Source: PT-Table 4.23 (investigator's assessment)

10.6.3 Analysis and description of SAEs

The tabulation of patients with SAEs and number of SAEs by MedDRA PSOC and PT is provided in PT-Tables 4.6 and 4.9 for investigator's and sponsor's assessment. By-patient listings of patients with SAEs except deaths are provided in PT-Listings 4.19. By-patient listings of patients with concomitant biologic treatments and SAEs are provided in PT-Table 4.21.

Sponsor assessed more AEs as serious than investigator did in the eCRF (8.7% vs. 4.8% of patients).

10.6.3.1 Seriousness

Investigator's assessment

Investigators assessed 223 AEs in 119 patients (4.8%) as serious, equivalent to 0.09 SAEs/patient (PT-Tables 4.6 and 4.9). The highest incidence was seen in patients with SAEs referring to the following MedDRA SOCs:

- Infections and infestations (33 patients, 1.3%), such as erysipelas (5 patients, 0.2%) and nasopharyngitis (3 patients, 0.1%);

- Gastrointestinal disorders (15 patients, 0.6%), with Crohn's disease (4 patients, 0.2%), diarrhea, gastritis erosive, and esophagitis (2 patients each, <0.1%);
- General disorders and administration site conditions (15 patients, 0.6%), with pyrexia (3 patients, 0.1%), condition aggravated and fatigue (2 patients each, <0.1%).

Table 10-31 summarizes patients with SAE for all PSOC and occurring in more than 1 patient on PT level.

Table 10-31 Patients with SAEs by PSOC, occurring in >1 patient on PT level (investigator's assessments)

MedDRA PSOC MedDRA PT	All patients (N=2502) n (%)
Patients with any SAE	**119 (4.8)**
Infections and infestations	**33 (1.3)**
Erysipelas	5 (0.2)
Nasopharyngitis	3 (0.1)
Staphylococcal infection	2 (<0.1)
Tonsillitis	2 (<0.1)
Gastrointestinal disorders	**15 (0.6)**
Crohn's disease	4 (0.2)
Diarrhea	2 (<0.1)
Gastritis erosive	2 (<0.1)
Esophagitis	2 (<0.1)
General disorders and administration site conditions	**15 (0.6)**
Pyrexia	3 (0.1)
Condition aggravated	2 (<0.1)
Fatigue	2 (<0.1)
Injury, poisoning and procedural complications	**14 (0.6)**
Fall	2 (<0.1)
Lumbar vertebral fracture	2 (<0.1)
Musculoskeletal and connective tissue disorders	**10 (0.4)**
Intervertebral disc protrusion	3 (0.1)
Osteoarthritis	2 (<0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**10 (0.4)**
Basal cell carcinoma	2 (<0.1)
Skin and subcutaneous tissue disorders	**10 (0.4)**
Psoriasis	4 (0.2)
Dermatitis allergic	2 (<0.1)
Pruritus	2 (<0.1)
Cardiac disorders	**9 (0.4)**
Arrhythmia	3 (0.1)
Atrial fibrillation	2 (<0.1)
Cardiac failure	2 (<0.1)
Coronary artery disease	2 (<0.1)
Myocardial infarction	2 (<0.1)

Table 10-31 Patients with SAEs by PSOC, occurring in >1 patient on PT level (investigator's assessments)

MedDRA PSOC MedDRA PT	All patients (N=2502) n (%)
Nervous system disorders	**9 (0.4)**
Headache	4 (0.2)
Dizziness	2 (<0.1)
Vascular disorders	**9 (0.4)**
Hypertension	2 (<0.1)
Hypertensive crisis	2 (<0.1)
Investigations	**6 (0.2)**
Psychiatric disorders	**6 (0.2)**
Depression	3 (0.1)
Respiratory, thoracic and mediastinal disorders	**5 (0.2)**
Metabolism and nutrition disorders	**4 (0.2)**
Immune system disorders	**3 (0.1)**
Blood and lymphatic system disorders	**2 (<0.1)**
Hepatobiliary disorders	**2 (<0.1)**
Renal and urinary disorders	**2 (<0.1)**
Renal failure	2 (<0.1)
Surgical and medical procedures	**2 (<0.1)**
Eye disorders	**1 (<0.1)**
Product issues	**1 (<0.1)**

MedDRA = Medical dictionary for drug regulatory activities; PT = Preferred term; SOC = System organ class
MedDRA version 21.0
Source: PT-Table 4.6 (investigator's assessment)

Sponsor's assessment

According to "sponsor's assessement" 403 AEs in 218 patients (8.7%) were assessed as serious, equivalent to 0.16 SAEs/patient (PT-Tables 4.6 and 4.9). The highest incidence was seen in patients with SAEs referring to the following MedDRA SOCs:

- Infections and infestations (81 patients, 3.2%), such as erysipelas (12 patients, 0.5%), nasopharyngitis, respiratory tract infection, and tonsillitis (6 patients each, 0.2%);
- General disorders and administration site conditions (24 patients, 1.0%), with pyrexia (5 patients, 0.2%), condition aggravated (3 patients, 0.1%), fatigue, and swelling (2 patients each, <0.1%);
- Musculoskeletal and connective tissue disorders (22 patients, 0.9%), with psoriatic arthropathy (10 patients, 0.4%) and intervertebral disc protrusion (4 patients, 0.2%) and arthropathy (2 patients, <0.1%);

PT-Table 4.6 summarizes patients with SAEs on MedDRA PSOC and PT level.

10.6.3.2 Intensity of SAEs

The intensity of SAEs for all patients is displayed in PT-Tables 4.7 by maximum severity for investigator's and sponsor's assessment. In 7 patients (0.3%) investigator's assessment regarding intensity was missing.

Investigators assessed SAEs in 8 patients (0.3%) as mild, in 38 patients (1.5%) as moderate and in 66 patients (2.6%) as severe.

Sponsor assessed SAEs in 47 patients (1.9%) as mild, in 95 patients (3.8%) as moderate and in 76 patients (3.0%) as severe. Both assessments are compared in Table 10-32.

Table 10-32 Intensity of SAEs investigator's and sponsor's assessment

Maximum severity	All patients (N=2502) n (%)	
	Investigator's assessment	Sponsor's assessment
Patients with any serious adverse events	**119 (4.8)**	**218 (8.7)**
mild	8 (0.3)	47 (1.9)
moderate	38 (1.5)	95 (3.8)
severe	66 (2.6)	76 (3.0)
missing	7 (0.3)	-

Source: PT-Tables 4.7 (sponsor's and investigator's assessment)

10.6.3.3 SAEs with suspected relationship to secukinumab

A total of 60 patients (2.4%) had secukinumab related SAEs according to sponsor's assessment, 32 patients (1.3%) had secukinumab related SAEs according to investigator's assessment (PT-Tables 4.8).

Investigator's assessment

The highest incidence was seen in patients with SAEs referring to the following MedDRA SOCs (investigator's assessment):

- Infections and infestations (12 patients, 0.5%), with erysipelas in more than 1 patient (2 patients, <0.1%);
- Gastrointestinal disorders (6 patients, 0.2%), with Crohn's disease in more than 1 patient (2 patients, <0.1%);
- General disorders and administration site conditions (6 patients, 0.2%), with pyrexia in more than 1 patient (2 patients, <0.1%).

The following SAEs assessed as secukinumab related by the investigators occurred in more than 1 patient:

- 2 patients (<0.1%): erysipelas, Crohn's disease, pyrexia, and headache;

Sponsor's assessment

The following SAEs assessed as secukinumab related by the sponsor occurred in more than 1 patient:

- 5 patients (0.2%): psoriatic arthropathy (also related to the underlying condition)
- 4 patients (0.2%): erysipelas
- 3 patients (0.1%): nasopharyngitis, oral candidiasis, respiratory tract infection, and leukopenia
- 2 patients (<0.1%): genital infection fungal, pneumonia, staphylococcal infection, tonsillitis, pyrexia, psoriasis, abdominal pain upper, Crohn's disease, diarrhea, and headache.

10.6.4 Deaths

A by patient listing of deaths is provided in PT-Listing 4.18.

A total of 5 patients died during this NIS after the occurrence of at least one SAE. None of the events was considered to be related to secukinumab. Table 10-33 gives an overview on SAEs with outcome death. The medical assessments of these cases indicate that the fatal outcomes were not directly linked to secukinumab treatment (see mini-narratives below).

Table 10-33 SAEs with outcome death

Center patient	Reported term/ MedDRA PT	Severity	Action taken with secukinumab
[redacted]	Atrial fibrillation/ Atrial fibrillation	Severe	Dose unchanged
	Episodes of arrhythmia/ Arrhythmia	Severe	Dose unchanged
	Renal insufficiency/ Renal failure	Severe	Not applicable
	Generalized edema as symptom/ Generalized edema	Severe	Not applicable
	Worsening of underlying disease cardiac insufficiency/ Cardiac failure	Severe	Not applicable
[redacted]	Sudden brain death/ Brain death	Severe	Not applicable
[redacted]	Seizure/ Seizure	Severe	Discontinued
	Loss of consciousness/ Loss of consciousness	Severe	Discontinued
	High-grade glioma/ Glioma	Severe	Discontinued
[redacted]	Death <suicide>/ Completed suicide	Severe	Not applicable
[redacted]	Bleeding death/ Hemorrhage		
	Pulseless electric activity/ Pulseless electrical activity		
	Thoracic hematoma after aortocoronary bypass operation/ Post procedural hematoma		
	Heart failure/ Cardiac failure		
	Rupture of venous bypass/ Vein rupture		
	Severe coronary vascular disease (ramus interventriularis anterior, ramus circumflexus and arteria coronaria dextra)/ Coronary artery disease	Severe	Discontinued

Source: PT-Listing 4.18

Fatal cases - patient narratives

[redacted]

10.6.5 Adverse events leading to any action with secukinumab

AEs were leading to any action with secukinumab in 261 patients (10.4%), this was considered to be related to secukinumab in 167 patients (6.7%) (PT-Tables 4.10 and 4.11).

Table 10-34 shows an overview on patients with AEs (overall and related) leading to any action with secukinumab.

Table 10-34 Summary of patients with AEs (unrelated and related) leading to any action with secukinumab

Action taken with secukinumab	Overall	Suspected relationship to secukinumab
Any action taken	261 (10.4)	167 (6.7)
secukinumab discontinuation	213 (8.5)	135 (5.4)
secukinumab dose increase	24 (1.0)	14 (0.6)
secukinumab dose reduction	36 (1.4)	23 (0.9)

Source: PT-Table 4.1

10.6.5.1 Discontinuation of secukinumab

Most frequent AEs (≥ 10 patients) leading to discontinuation of secukinumab without suspecting a relationship were: drug ineffective (38 patients, 1.5%), drug effect decreased (22 patients, 0.9%), psoriasis (18 patients, 0.7%), and nasopharyngitis (15 patients, 0.6%) (PT-Table 4.12).

Most frequent AEs (≥ 10% of patients) with suspected relationship leading to discontinuation of secukinumab were: drug ineffective (30 patients, 1.2%), drug effect decreased (17 patients, 0.7%) and psoriasis (11 patients, 0.4%) (PT-Table 4.13).

10.6.5.2 Secukinumab of dose increase

AEs not considered related to secukinumab leading to a dose increase in more than 1 patient were: drug effect decreased and drug ineffective (8 patients each, 0.3%), psoriasis (6 patients, 0.2%), and incorrect dose administered (2 patients, <0.1%) (PT-Table 4.14).

AEs considered related to secukinumab leading to a dose increase in more than 1 patient were: drug effect decreased and drug ineffective (6 patients, 0.2%) and psoriasis (2 patients, <0.2%) (PT-Table 4.15).

10.6.5.3 Dose reduction of secukinumab

AEs not considered related to secukinumab leading to a dose reduction in more than 1 patient were: nasopharyngitis (7 patients, 0.3%), bronchitis (4 patients, 0.2%), erysipelas (2 patients, <0.1%), and dysuria (2 patients, <0.1%) (PT-Table 4.16).

AEs considered related to secukinumab leading to a dose reduction in more than 1 patient were: nasopharyngitis (3 patients, 0.1%), bronchitis, erysipelas, and dysuria (2 patients each, <0.1%) (PT-Table 4.17).

11 Discussion

11.1 Key results

11.1.1 Baseline, demographic and treatment data

The goal of this short-term, descriptive, observational study was to determine the transition periods of prior treatments and the use of concomitant treatments of patients who receive secukinumab in routine treatment of psoriasis.

By enrollment of 2505 patients and inclusion of 2502 patients in the AS, the planned sample size of 2504 patients was almost reached.

Baseline and demographic data

Patients' mean age ± SD was 48.0 ± 14.0 years, 1545 patients (61.8%) were male. [redacted]

Since first psoriasis symptoms and start of this NIS, a mean of 19.4 ± 13.4 years (median 17.0, range: 0.0-81.0) had passed. Since first diagnosis of plaque psoriasis a mean of 17.9 ± 13.2 years (median 16.0, range: 0.0-81.0) had passed.

2,336 patients (93.4%) had one or more signs indicating high disease severity, including severe psoriasis with PASI >20, affected scalp, affected nails, affected face or a diagnosis of PsA.

Baseline PASI (n=2294 patients) was in the mean (± SD) 18.0 ± 12.3 (median 15.7, range: 0-72). A higher mean (± SD) PASI was observed in patients who have not taken part in a previous secukinumab clinical trial with 19.8 ± 11.7 (median 17.0, range: 0-72).

Mean DLQI for all patients was 13.7 ± 7.9 points. Patients who did not take part in a previous secukinumab clinical trial had a mean DLQI of 15.1 ± 7.1 points.

Mean (± SD) values for BSA, PPSI and NAPSI were comparable for all patients and for patients with higher disease severity / impact and prior systemic treatment, while they were higher in patients who did not take part in a previous clinical trial.

Prior psoriasis treatment

Last prior psoriasis treatment before secukinumab treatment initiation were mostly conventional systemic treatments (including phototherapy) (712/2502 patients, 28.5%), followed by biologic treatments (excluding secukinumab) (335/2502 patients, 13.4%), topical treatments (312/2502 patients, 12.5%), and topical & conventional systemic treatments (including phototherapy) given in parallel (278/2502 patients, 11.1%). A total of 4,078 discontinued prior therapies were recorded within 12 months prior to study baseline. Overall, insufficient response (2,252/4,078, 55.2%) and loss of efficacy (646/4078, 15.8%) were the most common reasons to discontinue prior psoriasis treatments. Discontinuation of prior treatment owing to AEs was higher for conventional systemic treatment (321/1648, 19.5%) than for biologic treatment (20/819, 2.4%) or topical treatment (6/1611, 0.4%).

Concomitant psoriasis treatment

A total of 929 patients received 1,415 topical treatments, which mostly had started before baseline (856 patients, 92.1%). Overall, 111 patients received concomitantly 122 conventional systemic treatments (including phototherapy), which also mostly had started before baseline (93 patients (83.8%). Mean (± SD) duration of treatment was 136.5 ± 65.9 days and 104.1 ± 74.4 days for topical and conventional systemic treatments (including phototherapy), respectively.

Only 1 patient received 1 biologic treatment concomitantly (ustekinumab), which had started before baseline.

A total of 1,041 patients discontinued concomitant therapies during this NIS. Improvement of disease (198 patients, 21.3% under topical treatment, 19 patients, 17.1% under conventional systemic treatments) was the main reason for this discontinuation, followed by other reasons (75 patients, 8.1% and 19 patients, 17.1%) and insufficient response (40 patients, 4.3% and 12 patients, 10.8%).

Secukinumab treatment

During the observation period, patients received a mean (± SD) number of 9.0 ± 1.8 administrations. More than half of the patients (1,321 patients, 52.8%) received 10 administrations of secukinumab per patient.

Mean (± SD) treatment interval during the initial phase was 9.5 ± 6.8 days, with the majority of patients (2133 of 2502 patients, 86.2%) having an interval of 5 to 9 days. Mean (± SD) treatment interval during the maintenance phase was 29.6 ± 4.7 days, with the majority of patients (2298 of 2502, 94.8%) having an interval of 25 to 35 days.

11.1.2 Primary endpoint

Primary endpoint was the assessment of the duration of the transition periods from prior treatments to secukinumab.

There was some variation between median transition periods associated with different types of prior treatment, with topical treatments having a much shorter median transition period of 15 days (topical treatments are restricted to topical monotherapies with a maximum transition period of 3 months due to short half-lives of topical therapies) than conventional systemic (median

32.0 days, maximum transition period of 12 months) or biologic therapies (median 46 days, maximum transition periods of 12 months) of all patients.

Regarding the prior treatment groups fumaric acid ester, methotrexate and ciclosporin, the shortest mean (± SD) transition period was reported in patients with prior methotrexate treatment (55.7 ± 65.8 days).

11.1.3 Secondary endpoints

Duration of transition periods compared to treatment interval

There were differences between treatment categories in transition periods with regard to treatment intervals. The majority of patients with prior topical and conventional systemic treatments had transition periods of >5 treatment intervals (495 patients, 82.8% and 545 patients, 70.1%, respectively). The proportion of patients with biologic treatments was largest for patients with transition periods ≤1 treatment interval (129 patients, 31.9%) and >1 and ≤3 treatment intervals (149 patients, 36.8%).

Duration of transition periods compared to systemic terminal half-life

Differences between treatment conventional systemic and biologic treatments were observed regarding the duration of transition periods compared to the systemic terminal half-life of a substance.

The majority of patients with prior conventional systemic treatments (excluding phototherapy) had transition periods of >5 systemic terminal half-lives (805 patients, 98.2%), while this was the case for approximately one third of patients (146 patients, 36.0%) with biologic treatments (periods of >1 and <=3 systemic terminal half-lives and >3 and <=5 systemic terminal half-lives were reported for 23.2% and 26.1% of the patients, respectively).

Discontinuation of concomitant psoriasis treatments

Approximately half of the patients with discontinuation of concomitant topical treatment (118/236, 50.0%) and conventional systemic treatment (28/52, 53.8%) received their treatment up to week 4 and discontinued thereafter.

Effectiveness and QoL

As expected, PASI assessment was performed for most patients throughout the study visits, followed by DLQI and BSA measurement. Measures as IGA, PGA, NAPSI, and PSSI were documented for less than 10% of the study patients. Overall, measurements were performed most frequently at the baseline and the end of study visit.

Analysis of PASI and DLQI

At visit 10 of PROSPECT (24 Weeks), patients with PASI > 10 at baseline had a PASI 75/90/100 response of 87.4%, 72.1% and 39.9%, respectively. Accordingly, at visit 10 (Week 24), patients with documented DLQI (684/2502) had a mean DLQI (± SD) of 2.7 ± 4.5.

IGA and PGA

A continuous increase in the IGA response rate 0/1 from week 1 (11.1%) to week 24 (71.7%) under secukinumab treatment was be observed indicating improvement of psoriasis. A similar result was observed regarding PGA throughout the study.

PSSI and NAPSI

Although both, PSSI and NAPSI were assessed in a very low number of patients in this NIS, results also indicate an improvement from baseline until end of study. Mean (± SD) PSSI at baseline was 3.0 ± 6.0 (n=73), mean (± SD) PSSI after 24 weeks of secukinumab treatment was 1.2 ± 2.6 (n=25). Mean (± SD) NAPSI at baseline was 16.7 ± 18.5 (n=92), mean NAPSI after 24 weeks of secukinumab treatment was 4.1 ± 9.3 (n=38).

[redacted]

11.1.4 Adverse events

Analysis of AEs was conducted using investigator's assessment regarding causal relationship to secukinumab and seriousness, and using the maximum outcome of assessment of pharmacovigilance department (sponsor) and investigator's assessment, reported as "sponsor's assessment" hereafter. Approximately half of the patients (1287 patients, 51.4%) had any AE during this NIS. Regarding AEs with suspected relationship to secukinumab, a difference of 1 patient was between both assessment categories: investigators assessed AEs in 589 patients (23.5%) to be related, sponsor assessed AEs in 590 patients (23.6%) to be related.

AEs led to any action with secukinumab in 261 patients (10.4%), and in 167 patients (6.7%) with related AEs (both assessments).

Secukinumab was discontinued in 213 patients (8.5%) with AEs and in 135 patients (5.4%) with related AEs (both assessments).

In 24 patients (1.0%), secukinumab dose was increased due to an AE. This was the case for 14 patients (0.6%) with related AEs (both assessments).

In 36 patients (1.4%), secukinumab dose was reduced due to an AE. This was the case for 23 patients (0.9%) with related AEs (both assessments).

A total of 119 (4.8%) patients had any SAE according to investigator's assessment, 32 of them (1.3%) with a suspected relationship to secukinumab.

Five patients (0.2%) experienced SAEs leading to death during this study, no relationship to secukinumab was suspected. In none of these cases the fatal outcome was directly attributed to secukinumab treatment.

Approximately half of the patients (1,287 patients, 51.4%) experienced a total of 3,209 AEs during the observation period, equivalent to 1.28 AEs/patient. The highest incidence was seen in patients with AEs referring to the following MedDRA SOCs:

- Infections and infestations (643 patients, 25.7%), nasopharyngitis (249 patients, 10.0%), oral candidiasis (51 patients, 2.0%), and tonsillitis (30 patients, 1.2%);

- Skin and subcutaneous tissue disorders (382 patients, 15.3%), pruritus (84 patients, 3.4%), psoriasis (76 patients, 3.0%), and eczema (45 patients, 1.8%);
- General disorders and administration site conditions (242 patients, 9.7%), fatigue (59 patients 2.4%), drug ineffective (57 patients, 2.3%), and drug effect decreased (36 patients, 1.4%).

AEs were mostly of mild or moderate intensity.

Overall, 589 patients (23.5%) had secukinumab related AEs according to investigator's assessment with the highest incidence seen in patients with AEs referring to the following MedDRA SOCs:

- Infections and infestations (219 patients, 8.8%), nasopharyngitis (48 patients, 1.9%), oral candidiasis (45 patients, 1.8%), and folliculitis (10 patients, 0.4%);
- Skin and subcutaneous tissue disorders (148 patients, 5.9%), pruritus (39 patients, 1.6%), psoriasis (32 patients, 1.3%), and eczema (10 patients, 0.4%);
- General disorders and administration site conditions (145 patients, 5.8%), fatigue and drug ineffective (41 patients each, 1.6%) and drug effect decreased (28 patients, 1.1%).

SAEs

As assessed by investigators in clinical routine, 223 AEs in 119 patients (4.8%) were considered as serious. These were mainly:

- Infections and infestations (81 patients, 3.2%), such as erysipelas (12 patients, 0.5%), nasopharyngitis, respiratory tract infection, and tonsillitis (6 patients each, 0.2%);
- General disorders and administration site conditions (24 patients, 1.0%), with pyrexia (5 patients, 0.2%) and condition aggravated (3 patients, 0.1%);
- Musculoskeletal and connective tissue disorders (22 patients, 0.9%), with psoriatic arthropathy (10 patients, 0.4%) and intervertebral disc protrusion (4 patients, 0.2%);

AEs leading to discontinuation of secukinumab were mainly ineffective drug or decreased drug effect, psoriasis and nasopharyngitis, regardless of a suspected relationship to secukinumab.

11.2 Limitations

Inherent limitations of non-interventional, observational studies in general are the risk of selection/ascertainment bias and the lack of a parallel control group, which complicate the interpretation of the causality between treatment and outcomes.

Furthermore, the retrospective documentation of transition periods was an inherent limitation of this study design.

11.3 Interpretation

The planned sample size had been increased after interim analyses and a total of 2,502 patients were included in the analysis set.

The study population was a representative group of patients with moderate to severe plaque type psoriasis in Germany. The baseline characteristics of the PROSPECT psoriasis patients

show that secukinumab interventional trial subjects have generally reflected the population encountered in clinical routine. [redacted]

Before PROSPECT, most subjects had received a wide range of prior recommended treatments for psoriasis, historically, as well as in the last 12 months before treatment initiation with secukinumab. The most common treatments in the year prior to starting secukinumab were conventional systemic agents, most frequently MTX or FAEs, or phototherapy.

Transition periods between prior treatments and secukinumab in clinical practice varied, but median times were longer than might be expected in clinical routine. Transition periods differed by type of prior treatment, with topical treatments having a much shorter median transition times than conventional systemic or biologic treatments. While transition times in daily routines were oftentimes shorter than those washout periods required in the context of clinical trials, the observed transition times were still longer than recommended by consensus guidelines.Less than half of the study population received concomitant therapy at baseline on top of secukinumab treatment. The most common concomitant therapies were topical steroids and vitamin D3 analogues. MTX was used most frequently as concomitant systemic therapy, with phototherapy also frequently used.

Effectiveness of secukinumab in patients with secukinumab treatment initiation at baseline, as well as in the overall patient population, was comparable to that observed in randomized controlled secukinumab trials. In clinical routine and throughout this study, clinical effectiveness was mainly assessed by PASI. Although not assessed in the majority of patients, IGA, PGA, PSSI, NAPSI, and DLQI also showed high effectiveness and improvement of quality of life, respectively, of secukinumab treatment.

Clinical safety in clinical routine as assessed by AEs/SAEs was corresponding to observations of prior studies and description of adverse reactions in the current SmPC. Incidence and pattern of (S)AEs was as expected regarding the patient population and the underlying disease.

11.4 Generalizability

The results of this NIS are consistent with findings of prior clinical studies regarding effectiveness and safety of secukinumab. This study provides insights into the daily practice with regard to secukinumab treatment of patients with moderate to severe plaque type psoriasis, washout periods of prior treatments, concomitant medication, as well as documentation practices of disease parameters, in Germany.

12 Other information

Not applicable.

13 Conclusion

In conclusion, the results of this NIS are consistent with prior efficacy and safety data observed in context of interventional clinical trials The results suggest no to minimal impact on safety and effectiveness of the shorter transition times and concomitant therapy common in the clinical

setting, but absent from clinical trials. This study will help to inform physicians in clinical practice on the transition of patients with moderate to severe psoriasis to secukinumab treatment, with or without concomitant therapy.

14 References

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Appendices

Annex 1 – List of stand-alone documents

Full data sets are available upon request.

Annex 2 – Additional information

The following appendices are provided separately on request:

Protocol and protocol amendments

Sample case report forms

List and description of investigators and other important participants in the study

Important publications referenced in the report

Tables, figures and listings