NOVARTIS

Patient Safety & Pharmacovigilance

Secukinumab

AIN457

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Secukinumab
Product(s) concerned (brand name(s)):	Cosentyx®, Scapho®, Fraizeron®, Verxant®
Document status:	Final
Version number:	12.0
Data lock point for this RMP	Clinical: 07-Nov-2024; Post-marketing: 25-Dec-2023
Date of final sign off	10-Apr-2025

Rationale for submitting an updated RMP:

The EU RMP version 12.0 is prepared to reflect the completion of Study CAIN457F2304E1, which was an additional pharmacovigilance activity (Category 3 PASS) in the RMP. In addition, the post-authorization data are aligned with the PSUR (Reporting period: 26-Dec-2020 to 25-Dec-2023).

Summary of significant changes in this RMP:

- Completion of Study CAIN457F2304E1 which was an additional pharmacovigilance activity (Category 3 PASS)

Part	Major changes compared to RMP v11.1
Part I	Aligned HS indication and dosage with SmPC.
Part II	Module SI: No updates Module SII: Deletion of conclusions section to align with updated template. Module SIII: Updated to include clinical trial exposure data from Study CAIN457F2304E1. Module SIV: No updates Module SV: Aligned with the PSUR (Reporting period: 26-Dec-2020 to 25-Dec-2023). Module SVI: No updates Module SVII: Presentation of important safety concerns is updated with data from Study CAIN457F2304E1 and PSUR (Reporting period: 26-Dec-2020 to 25-Dec-2023). Module SVIII: No updates
Part III	Part III.2 and Part III.3 were updated to reflect completion of Study CAIN457F2304E1.
Part IV	None
Part V	Part V.1 Was aligned with SmPC Part V.3 Was updated to reflect completion of Study CAIN457F2304E1.
Part VI	Part VI-IIB Updated to align with SmPC. Part VI-IIC Updated to reflect completion of Study CAIN457F2304E1.
Part VII	**Annex 4**: No updates **Annex 6**: No updates

Other RMP versions under evaluation

[redacted]

Details of the currently approved RMP:

Version number: 11.1

Approved with procedure: EMEA/H/C/003729/II/0090

Date of approval (opinion date): 26-May-2023

QPPV name: Dr. Justin Daniels, PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder's QPPV. The electronic signature is available on file.

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List of abbreviations

ACR30	American College of Rheumatology 30
ADA	Anti-Drug Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
AI	Auto Injector
ANA	Antinuclear antibodies
AS	Ankylosing Spondylitis
ASAS	Assessment of Spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
BCC	Basal Cell Carcinoma
BMI	Body Mass Index
CASPAR	Classification Criteria for Psoriatic Arthritis
CD	Crohn's Disease
CHF	Congestive Heart Failure
CHMP	Committee for medicinal products for human use
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
CRSD	Carroll Rating Scale for Depression
CRP	C-reactive protein
CT	Clinical trials
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular Disease
DMARD	Disease Modifying Anti-Rheumatic Drug
EAIR	Exposure Adjusted Incidence Rate
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Enthesitis Related Arthritis
EU	European Union
EULAR	European Alliance of Associations for Rheumatology
HBV	Hepatitis B virus
HCP	Health Care Provider
HIV	Human Immunodeficiency Virus
HLT	High Level Term
HR	Hazard Ratio
HS	Hidradenitis suppurativa
JIA	Juvenile Idiopathic Arthritis
JPsA	Juvenile Psoriatic Arthritis
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonization
IFU	Instructions for Use
IM	Intramuscular
IR	Incidence Rate
IRR	Incidence rate ratio
IV	Intravenous
MACE	Major Adverse Cardiovascular Event
MI	Myocardial Infarction

MedDRA	Medical Dictionary for Regulatory Activities
NMQ	Novartis MedDRA Query
NMSC	Non-Melanoma Skin Cancer
NSAIDs	Non-steroidal Anti-inflammatory Drugs
NYHA	New York Heart Association
nr-axSpa	Non-radiographic axial spondyloarthritis
OR	Odds Ratio
NPF	National Psoriasis Foundation
PDCO	Pediatric Committee
PFS	Pre-Filled Syringe
PHQ	Patient Health Questionnaire
PIP	Pediatric Investigation Plan
PK	Pharmacokinetic
PL	Package Leaflet
PRAC	Pharmacovigilance risk assessment committee
PsA	Psoriatic Arthritis
PsO	Psoriasis
PSUR	Periodic safety update report
PT	Preferred Term
PY	Person/Patient Years
PUVA	Psoralen Plus Ultraviolet Light Therapy
RA	Rheumatoid Arthritis
RMP	Risk Management Plan
RR	Relative Risk
SAE	Serious adverse event
SCC	Squamous Cell Carcinoma
SIB	Suicidal ideation and behavior
SIR	Standardized Incidence Ratio
SMR	Standardized Mortality Ratio
SOC	System organ class
SoR	Start of Relapse
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
TNF	Tumor Necrosis Factor
UK	United Kingdom
URTI	Upper Respiratory Tract Infection
US	United States
UV	Ultraviolet
VAS	Visual Analog Scale
WoCBP	Women of Child-bearing Potential

1 Part I: Product Overview

Table 1-1 Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Secukinumab
Pharmacotherapeutic group(s) (ATC Code)	L04AC10
Marketing Authorization Holder	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Cosentyx®/secukinumab
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Secukinumab (AIN457) is a fully human monoclonal antibody.
	Summary of mode of action: Secukinumab neutralizes interleukin-17A (IL-17A) bioactivity, for the treatment of immune mediated disorders including psoriasis. Secukinumab selectively targets IL-17A, a downstream product of the Th17 cells, and leaves the other functions of Th17 cells intact. In addition, it targets IL-17A, regardless of its source. It does not directly influence the Th1 pathway, and thus is expected to leave the Th1-based host defense mostly intact. This mechanism of action may result in an improved safety profile when compared to other currently available treatment options for autoimmune diseases.
	Important information about its composition: Secukinumab is of the IgG1/κ-class produced in Chinese Hamster Ovary (CHO) cells.
Hyperlink to the Product Information	[Current approved SmPC]
Indications in the EEA	Current: **Psoriasis (Adults)** Indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. **Psoriasis (Pediatrics)** Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy. **Psoriatic arthritis** Indicated alone or in combination with methotrexate (MTX), for the treatment of active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. **Ankylosing Spondylitis** Indicated for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy. **Non-radiographic axial spondyloarthritis (nr-axSpA)**

<table>
<tr><td></td><td>Indicated for the treatment of active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs).
Juvenile Idiopathic Arthritis (JIA)
Enthesitis-Related Arthritis (ERA):
Cosentyx, alone or in combination with methotrexate (MTX), is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.
Juvenile Psoriatic Arthritis (JPsA)
Cosentyx, alone or in combination with methotrexate (MTX), is indicated for the treatment of active juvenile psoriatic arthritis in patients, 6 years of age and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.
Hidradenitis suppurativa (HS)
Indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy.</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:
Adult plaque Psoriasis
The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Each 300 mg dose is given as one subcutaneous injection of 300 mg or as two subcutaneous injections of 150 mg.
Pediatric plaque psoriasis (adolescents and children from the age of 6 years)
The recommended dose is based on body weight and administered by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Each 75 mg dose is given as 1 subcutaneous injection of 75 mg. Each 150 mg dose is given as 1 subcutaneous injection of 150 mg. Each 300 mg dose is given as one subcutaneous injection of 300 mg or as 2 subcutaneous injections of 150 mg:
<table>
<tr><th>Body weight at time of dosing</th><th>Recommended Dose</th></tr>
<tr><td><25 kg</td><td>75 mg</td></tr>
<tr><td>25 to <50 kg</td><td>75 mg</td></tr>
<tr><td>≥50 kg</td><td>150 mg (*may be increased to 300 mg)</td></tr>
<tr><td colspan="2">*Some patients may derive additional benefit from the higher dose.</td></tr>
</table>
Psoriatic arthritis
For patients with concomitant moderate to severe plaque psoriasis, please refer to adult plaque psoriasis recommendation.
For patients who are anti-TNFα inadequate responders (IR), the recommended dose is 300 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance</td></tr>
</table>

<table>
<tr><td></td><td>dosing. Each 300 mg dose is given as one subcutaneous injection of 300 mg or as two subcutaneous injections of 150 mg. For other patients, the recommended dose is 150 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Based on clinical response, the dose can be increased to 300 mg.
Ankylosing spondylitis
The recommended dose is 150 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Based on clinical response, the dose can be increased to 300 mg. Each 300 mg dose is given as one subcutaneous injection of 300 mg or as two subcutaneous injections of 150 mg.
Non-radiographic axial spondyloarthritis (nr-axSpA)
The recommended dose is 150 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing.
For all of the above indications, available data suggest that a clinical response is usually achieved within 16 weeks of treatment. Consideration should be given to discontinuing treatment in patients who have shown no response by 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks.
Juvenile Idiopathic Arthritis (JIA) [Enthesitis-Related Arthritis (ERA) and Juvenile Psoriatic Arthritis (JPsA)]: The recommended dose is based on body weight and administered by subcutaneous injection at weeks 0, 1, 2, 3, and 4, followed by monthly maintenance dosing. Each 75 mg dose is given as one subcutaneous injection of 75 mg. Each 150 mg dose is given as one subcutaneous injection of 150 mg.
<table>
<tr><th>Body weight at time of dosing</th><th>Recommended Dose</th></tr>
<tr><td>< 50 kg</td><td>75 mg</td></tr>
<tr><td>≥ 50 kg</td><td>150 mg</td></tr>
</table>
Hidradenitis suppurativa
The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. Each 300 mg dose is given as one subcutaneous injection of 300 mg or as two subcutaneous injections of 150 mg.</td></tr>
<tr><td>Pharmaceutical forms and strengths</td><td>Current:
Six formulations:
Cosentyx 75 mg/0.5 mL solution for injection in pre-filled syringe
Cosentyx 150 mg powder for solution for injection.
Cosentyx 150 mg solution for injection in pre-filled syringe.
Cosentyx 150 mg solution for injection in pre-filled pen.
Cosentyx 300 mg solution for injection in pre-filled syringe.
Cosentyx 300 mg solution for injection in pre-filled pen.</td></tr>
</table>

	In five forms: **Powder for solution for injection** The powder is a white solid lyophilisate. **Solution for injection in pre-filled syringe (150 mg/mL)** The solution is clear and colorless to slightly yellow. **Solution for injection in pre-filled pen (SensoReady pen)** The solution is clear and colorless to slightly yellow. **Solution for injection in pre-filled pen (UnoReady pen)** The solution is clear and colorless to slightly yellow. **Solution for injection in pre-filled syringe (75 mg/0.5 mL)** The solution is clear and colorless to slightly yellow.
	Proposed: None.
Is/will the product be subject to additional monitoring in the EU?	No

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1 Indication: Psoriasis

Current:

Adult plaque psoriasis

Secukinumab is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Pediatric plaque psoriasis

Secukinumab is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy.

Incidence:

A recent systematic review (Parisi et al 2020) reported rates of psoriasis that varied substantially according to geographic location. Worldwide, the incidence of psoriasis varied in adults from 30.3 per 100 000 person-years (95% confidence interval 26.6 to 34.1) in Taiwan to 321.0 per 100 000 person-years in Italy. A slight decline over time in the incidence of psoriasis was noted in the United Kingdom, between 1999 and 2013 (Springate et al 2017), while in other countries no large changes over time had been observed (Parisi et al 2020).

In children, the incidence of psoriasis increased with age, from 13.5 per 100 000 person years in 0-3 years old) to 53.1 per 100 000 person years in 14-18 years old (Parisi et al 2020).

Prevalence:

Various studies from around the world have estimated the prevalence of psoriasis.

In adults, the prevalence varied from 0.14% (95% CI: 0.05% to 0.40%) in East Asia to 1.99% (95% CI: 0.64% to 6.60%) in Australasia. Other regions with an occurrence of the disease above 1% were Western Europe (1.92%; 95% CI: 1.07% to 3.46%), central Europe (1.83%; 95% CI: 0.62% to 5.32%), high income North America (1.50%; 95% CI: 0.63% to 3.60%), and high income Southern Latin America (1.10%; 95% CI: 0.36% to 2.96%). Rates are higher when self-reported occurrence of the disease are taken into account (Parisi et al 2020).

In children, the estimated prevalence is lower than in adults. In East Asia, it was 0.2 per 1000 children (95% CI 0.1 - 0.4); in Australasia 2.2 per 1000 (0.6 – 8.1); and in Western Europe 2.1 per 1000 (1.1 to 4.1) (Parisi et al 2020). The overall prevalence of juvenile psoriasis, based on data from a large German statutory health insurance company, was reported in Germany at 4 per 1000 children. The prevalence increased from 1.3 per 1000 (1.0–1.8) at the age of 0–2 years; 1.8 at 3-6; 4.1 at 7-10; 6.1 at 11-13; and 6.7 (6.2–7.3) at the age of 14–18 years (Augustin et al 2015).

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Psoriasis appears unequally distributed across geographical regions: as reported above, the estimated prevalence in people of Asian origin is lower than in people of European or US origin. The disease is more frequent in high income countries and in regions with older populations (Parisi et al 2020). There does not seem to be agreement on whether the prevalence of psoriasis varies by gender, with some population-based studies reporting slightly higher prevalence in females than in males, e.g., Stern et al (2004) showed a prevalence of 2.5% in females and 1.9% in males, while others failed to find differences (Ferrándiz et al 2001). Regarding clinical studies of patients with moderate to severe psoriasis, these tend to include greater proportions of male patients (see e.g. Papp et al 2013).

The etiology of the disease remains unknown, but there are several factors associated to it, both genetic and environmental. Psoriasis has a large hereditary component, and many genes are associated with it, most of them involving the immune system.

Studies of factors associated with psoriasis showed a significant link between adiposity and psoriasis. An Italian case-control study (Naldi et al 2005) demonstrated that the risk of psoriasis was directly related to high body mass index (BMI): the prevalence of psoriasis was approximately twice as high in individuals with a BMI of 30 or greater compared with a BMI of <26 (multivariate odds ratio, 1.9; 95% CI, 1.2–2.8). Similarly, a cohort study with nested case-control analysis (Huerta et al 2007) reported that overweight individuals had slightly increased risk of developing psoriasis: the adjusted odds ratio (95% CI) was 1.33 (1.16–1.52) in subjects with BMI $\geq$ 30, in comparison to 1.11 (1.00–1.24) in subjects with BMI 25–29.

Prospective longitudinal data from incident case analysis (carried out in women) further suggests that increased adiposity precedes the occurrence of psoriasis (Kumar et al 2012).

Alcohol intake (Qureshi et al 2010) and smoking (Setty et al 2007a) were also shown to be positively associated with an increased risk of psoriasis in women, while vigorous physical activity was associated with a reduced risk of psoriasis incidence (Frankel et al 2012).

Plaque psoriasis affects 80% to 90% of all psoriasis subjects of all age-groups (Griffiths and Barker 2007 and Pariser et al 2007) and hence is the most common variant in pediatric subjects.

Most children manifest with plaque psoriasis in patterns similar to adult subjects and associated with significant co-morbidities.

The main existing treatment options:

The choice of treatment in patients with psoriasis should take into account disease severity, presence of psoriatic arthritis and other comorbidities (Griffiths et al, 2021). There is no international consensus on the psoriasis severity classification, which is often based on a combination of physician-reported measures (such as body surface area (BSA), Physician's Global Assessment (PGA), and the Psoriasis Area and Severity Index (PASI)) and patient-reported measures (such as the Dermatology Life Quality Index (DLQI)) (Strober et al, 2020).

Topical corticosteroids are still considered the cornerstone of treatment for patients with mild or localized psoriasis, used as monotherapy or in combination with vitamin D analogues or keratolytics. Other treatment options in these patients include topical calcineurin inhibitors, targeted phototherapy, dithranol and/or preparations (Elmets et al, 2021).

Most guidelines (Amatore et al, 2019; Gisondi et al, 2017; Menter et al 2019) suggest the use of systemic therapy in patients with moderate to severe psoriasis (e.g., in case of more extensive disease, ≥5% of BSA affected or PASI score ≥10, or concurrent psoriatic arthritis (PsA), or psoriasis localized in sensitive areas such as the face, genitals, hands or feet, scalp, or intertriginous areas, or in presence of local disease or severe symptoms recalcitrant to topical therapy). Systemic therapy includes phototherapy (broad- or narrow-band UVB light and PUVA [Psoralen Plus Ultraviolet Light Therapy]), systemic non-biological agents such as ciclosporin, methotrexate, apremilast and acitretin or systemic biological treatments such as TNF-α inhibitors, IL-12/23 inhibitors, IL-17 inhibitors or IL-23 inhibitors. Treatment options for psoriasis must be tailored to the individual patient, taking into account efficacy, side effects, availability, ease of administration, disease severity, response to previous therapies, comorbidities and family history (Elmets et al, 2019; Kaushik et al, 2019).

Few Systemic drugs for the treatment of psoriasis are approved in children, including more recently several biologic systemic therapies. In the US, etanercept (Anti-TNF-α), ustekinumab (anti-IL-12/IL-23) and ixekizumab (anti-IL-17) are approved for moderate to severe psoriasis in pediatric patients. In Europe, adalimumab (Anti-TNF-α) and secukinumab (anti-IL-17) are approved.

Children with psoriasis are often undertreated; as a result, a large number of children with moderate to severe psoriasis live with poorly controlled disease. A number of factors contribute to this under treatment, including fear of long-term adverse effects and underestimation of disease severity and symptoms. This results in poor quality of life and increased risk for other psychosocial comorbidities even in those with disease that is considered mild (Osier et al 2017, Gonzalez et al 2017). As evidence emerges that onset of systemic comorbidities may be related to poorly controlled chronic inflammation, the treatment approach for children is shifting towards a complete control of the disease (Cordoro, 2020).

Natural history of the indicated condition in the population, including mortality and morbidity:

Psoriasis is a chronic, inflammatory skin disease characterized by epidermal thickening and scaling. The diagnosis is clinical, and the disease follows a chronic course with remissions. There are several forms of the disease; site and extent can vary from trivial to major coverage. It is estimated that around 80% of sufferers have mild to moderate disease, with 20% having moderate to severe psoriasis affecting more than 5% of the body surface area or crucial body areas such as hands, feet, face or genitals (Menter et al 2008).

Because of higher rates of comorbidities (see below), psoriasis patients are at increased risk of death. The risk appears to be higher in those with severe disease. A recent systematic review and meta-analysis showed the pooled relative risk for all-cause mortality: 1.21 (95% CI 1.14-1.28) in psoriasis, 1.13 (95% CI 1.09-1.16) in mild psoriasis, and 1.52 (95% CI 1.35-1.71) in severe psoriasis. The pooled relative risks for cardiovascular mortality were 1.15 (95% CI 1.09-1.21) in psoriasis overall, 1.05 (95% CI 0.92-1.20) in mild psoriasis, and 1.38 (95% CI 1.09-1.74) in severe psoriasis. For non-cardiovascular causes, mortality risk from liver disease, kidney disease, and infection was significantly increased in psoriasis, regardless of disease severity. For non-cardiovascular causes of death, the mortality risk in liver and kidney disease was highest (Dhana et al 2019). A recent retrospective cohort study in the Danish population showed that absolute and excess mortality risks in patients with psoriasis were highest for neoplasms (Skov et al 2019).

Psoriasis can cause severe morbidity and has an important impact on the patient's quality of life including physical, psychological, social, sexual, and occupational elements (NPF 2009).

Important co-morbidities:

Psoriasis has been linked to several diseases, including PsA, cardiovascular disease and cardiovascular risk factors including diabetes mellitus, dyslipidaemia, obesity, hypertension and metabolic syndrome; aortic valve stenosis, inflammatory bowel disease, non-alcoholic fatty liver disease, kidney disease, chronic obstructive pulmonary disease, sleep apnoea, peripheral vascular disease, autoimmune hepatitis, uveitis, periodontitis, atrial fibrillation, sexual dysfunction, multiple sclerosis, osteoporosis, anxiety, depression and tumors, especially lymphoma (Dauden et al 2018).

The strongest and best investigated association is with arthritis. Psoriasis is associated with joint disease in a significant proportion of patients. PsA is considered more common in patients with more extensive skin disease; deforming PsA may however also occur in patients with little to no cutaneous involvement. Although psoriasis typically emerges years before the onset of PsA, psoriasis has been observed to develop after the emergence of PsA in some patients (Gladman et al 2005).

Several studies have shown an association between psoriasis and cardiovascular disease (CVD). In a recent meta-analysis which included all recently published good-quality observational studies about the association between psoriasis and presence of CVD (Gaeta et al 2013), patients with psoriasis showed an increased overall cardiovascular risk compared to healthy controls (risk ratio, RR=1.24; 95% CI 1.18–1.31). This was the case both for retrospective (RR=1.41; 1.16–1.72) and prospective studies (RR=1.21; 1.15–1.27). The study found that presence of psoriasis also conferred an increased risk when single outcomes were considered, i.e., myocardial infarction (RR=1.24; 1.11– 1.39), vascular disease (RR=1.27; 1.12–1.43) and overall mortality (RR=1.41; 0.97–2.04) (Gaeta et al 2013).

The cardiovascular risk might be greater in young adults (Gelfand et al 2006a).

In a recent meta-analysis of observational studies (Armstrong et al 2013a), psoriasis was associated with an increased prevalence and incidence of diabetes. The combined results from these studies suggest that psoriasis is associated with a 59% increased prevalence of diabetes. Among studies assessing the prevalence, psoriasis was associated with an odds ratio (OR) of 1.59 (95% CI, 1.38-1.83) for diabetes. Among studies that assessed incidence, psoriasis was associated with a relative risk of 1.27 (95% CI, 1.16-1.40) for developing diabetes. Patients with severe psoriasis, and especially younger patients, may have an even higher risk of developing diabetes.

A recent systematic review and meta-analysis synthesized the published data on the association of psoriasis with hypertension (Armstrong et al 2013b). According to this analysis, the odds ratio (OR) for hypertension among all patients with psoriasis was 1.58 (95% CI 1.42–1.76) compared with the general population, and it was higher in patients with severe psoriasis (OR 1.49; 95% CI 1.20–1.86 compared with the controls) than among patients with mild psoriasis (1.30; 95% CI 1.15–1.47).

Dyslipidemia, a well-established CVD risk factor, has been associated to psoriasis in the literature. A recent systematic review found a significant association between psoriasis and dyslipidemia: out of the 25 studies identified, 20 (80%) reported a significant association, with an OR for dyslipidemia ranging from 1.04 to 5.55. Among studies that assessed the severity of

psoriasis, higher odds of dyslipidemia were seen in patients with severe psoriasis (Ma et al 2013).

Other diseases which have been linked to psoriasis include cancer, in particular both Hodgkin's and non-Hodgkin's lymphoma (Schäfer 2006).

A recent systematic review and meta-analysis assessed 112 studies, to investigate the overall prevalence of cancer in patients with psoriasis: this was 4.78% (95% CI, 4.02%-5.59%), with an incidence rate of 11.75 per 1000 person-years (95% CI, 8.66-15.31) and a risk ratio of 1.21 (95% CI, 1.11-1.33) vs a reference group. There was an increased risk of several cancers, including keratinocyte cancer (RR, 2.28; 95% CI, 1.73-3.01), lymphomas (RR, 1.56; 95% CI, 1.37-1.78), lung cancer (RR, 1.26; 95% CI, 1.13-1.40), and bladder cancer (RR, 1.12; 95% CI, 1.04-1.19). No increased risk of cancer for patients with psoriasis treated with biologic agents was found (RR, 0.97; 95% CI, 0.85-1.10) (Vaengebjerg et al 2020).

Psoriasis and inflammatory bowel disease (Crohn's disease, CD and ulcerative colitis, UC) share common genetic susceptibility factors. A recent systematic review and meta-analysis, based on quantitative analysis of 93 studies, estimated the prevalence of CD and UC to be 0.7% (95% CI 0.2%–1.3%) and 0.5% (95% CI 0.3%–0.8%), respectively, among patients with psoriasis. The presence of CD or UC was significantly associated with psoriasis, with odds ratio of 2.0 (95% CI 1.4–2.9) and 1.5 (95% CI 1.2–2.0), respectively (Alinaghi et al 2020) and Crohn's disease share common genetic susceptibility factors,

Depression, suicidal ideation and behavior (SIB) have been reported in patients with psoriasis at higher rates than in the general population. Rates may vary according to the measuring instrument used, the population setting (e.g., outpatients or inpatients, socio-demographic characteristics), and the design of the study (Kurd et al 2010, Egeberg et al 2016, Wu et al 2017).

2.2 Indication: Psoriatic Arthritis

Cosentyx, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

Incidence and prevalence:

Psoriatic arthritis (PsA) is a chronic inflammatory disease with primary manifestations involving the skin and the joints (Horreau et al 2013, Jamnitski et al 2013). Psoriasis typically emerges years before the onset of PsA, however in some cases psoriasis has been observed to develop after the emergence of PsA (Gladman et al 2005).

A systematic review and meta-analysis, which included 28 studies, covering the period from January 2007 to December 2015, estimated pooled PsA prevalence and incidence rates respectively of 133 per 100,000 subjects (95% CI, 107–164) and 83 per 100,000 PY (95% CI, 41–167). The incidence of PsA in psoriasis patients is higher than in the general population. In a cross-sectional study conducted among dermatologists in the United Kingdom, Italy, France, Spain, and Germany, PsA incidence among patients with psoriasis was found to be constant over time (74 per 1000 person-years), whereas PsA prevalence increased as time passed after psoriasis diagnosis, reaching 20.5% after 30 years (Christophers et al 2010).

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

The incidence of PsA is highest among patients in their fifth decade, the male-to-female ratio is 1:1, and the disease is most frequent among Caucasians (Egeberg et al 2018). Patients with PsA tend to be older and with a longer duration of skin disease than those with psoriasis alone (Alamanos et al 2008; Ogdie et al 2013).

The main existing treatment options:

Mild cases of PsA may be treated with nonsteroidal anti-inflammatory drugs, intra-articular corticosteroid injections, and/or physical/occupational therapy. Moderate to severe disease is traditionally treated with systemic disease-modifying drugs (DMARDs) such as methotrexate, sulfasalazine, ciclosporin, or leflunomide. Biologic therapies have recently been added to the therapeutic armamentarium for PsA; however, some patients do not respond well to biologic treatment.

Significantly higher use of anti-inflammatory or immunomodulatory medications (nonsteroidal anti-inflammatory drugs, systemic corticosteroids, and conventional and biologic disease-modifying antirheumatic drugs) was observed in psoriasis patients with a PsA diagnosis than in patients without PsA (Mease et al 2013).

Natural history of the indicated condition in the population, including mortality and morbidity:

Although PsA is not considered to be as severe as RA or ankylosing spondylitis (AS), it can have a destructive course and a similar disease burden (Zink et al 2006). Flares and remissions usually characterize the course of the disease, which is variable and unpredictable, ranging from mild and non-destructive to severe, debilitating, erosive arthropathy (Gisondi et al 2010). The severity of the arthritis usually does not correlate with the severity of the skin manifestation. Left untreated, patients with PsA can have persistent inflammation, progressive joint damage, severe physical limitations and disability comparable in severity with that of patients with RA. Radiological comparisons of PsA and RA patients have demonstrated similar joint damage, especially in the hands and feet (Rahman et al 2001). A recent retrospective cohort study in the Danish population showed that survival was not significantly lower in patients with PsA than in controls (Hazard Ratio 1.06, P = 0.19). Death rates per 1000 patient-years (with 95% confidence intervals) vs. controls were 10.8 (8.9–12.8) vs. 11.6 (9.6–13.6). An increased mortality was observed only for certain infectious and parasitic diseases (HR 2.80), and for diseases of the respiratory system (HR 1.46) (Skov 2019).

Important co-morbidities:

A systematic review and meta-analysis calculated pooled prevalence estimates of individual comorbidities in PsA patients. The study showed that the top five most prevalent comorbidities were hypertension (34.2%), metabolic syndrome (28.8%), obesity (27.4%), hyperlipidaemia (24.2%), and any CVD (19.4%). Virtually all individual comorbidities had higher incidence and prevalence in PsA populations than matched controls. This review also showed high prevalence of pulmonary diseases and depression (each 12%), both of which were more common than in controls (Gupta et al 2021).

2.3 Indication: Axial spondyloarthritis (axSpA)

2.3.1 Ankylosing Spondylitis

Cosentyx is indicated for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

Incidence:

Ankylosing Spondylitis is a chronic inflammatory arthritis. Sacroilitis is the earliest recognized manifestation of AS, but peripheral joints and extra-articular structures may also be affected (Sieper et al 2002).

The incidence of AS was reported to vary between 6.4 and 7.3 per 100,000 persons in northern Europe and in white Caucasians of the US (Carbone et al 1992; Bakland et al 2005), while in Southern Europe the incidence appears to be lower. A recent review found incidence rates per 100,000 patient-years reported in 4 AS studies, varying from 0.4 (Iceland) to 15.0 (Canada) (Bohn et al 2018).

Prevalence:

The prevalence of AS is generally believed to be between 1 and 14 per 1,000 persons globally (Dean et al 2014), although uncertainty still exist given the limited number of available data. The estimated mean AS prevalence per 1,000 persons (based on 36 eligible studies from a systematic literature search) was 3.2 in North America, 2.4 in Europe, 1.7 in Asia, 1.0 in Latin America and 0.7 in Africa (Dean et al 2014).

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Ankylosing Spondylitis usually presents during the third decade of life, and rarely has onset after the age of 45 years. The reported gender ratios in AS is around 2:1 (male:female), although this estimate has also been shown to vary considerably between studies and across time. For example, in the systematic review by Dean et al 2014, the mean male:female ratio was 3.8:1 in Europe. Genetic, ethnic, racial and environmental factors are likely to influence the occurrence and clinical expression of AS. The disease is less common among black Americans than in whites, is rare in Asia and seems to be virtually nonexistent in several African populations.

In general, the AS incidence and prevalence reflect the frequency of Human Leukocyte Antigen (HLA) – B27 in the population (Gabriel and Michaud 2009). This may explain the virtual absence of the disease in South Africa, the low frequency in Japan and Greece, the higher levels in Norway compared with other European countries and the highest levels among some populations living in North America (Khan 2002). Dietetic factors such as fish oil consumption in Mediterranean diets and mild climatic factors, exposure to the sun and the ultraviolet radiation, may protect against the disease (Koko et al 2014). Chung et al (2012) showed that smoking was associated with an earlier beginning of spinal pain and a higher activity of the disease. It has also been reported that smokers with AS had more physical disability and more advanced radiological damage (Chung et al 2012).

The main existing treatment options:

According to the updated ASAS/EULAR guidelines of 2011 (Braun et al 2011), NSAIDs including COX-2 inhibitors, are recommended as first-line drug treatment for AS patients with pain and stiffness. While there is no evidence for the efficacy of oral small molecule DMARDs, including sulfasalazine and methotrexate, for the treatment of axial disease, sulfasalazine may be considered in patients with peripheral arthritis. The guidelines recommend the use of TNF blockers in the treatment of patients with advanced AS despite conventional treatments. Patients who have an inadequate response to a TNF blocker may be cycled to a second anti-TNF agent although 20-40% of the patients fail to respond to anti-TNFs (e.g., 1-year anti-TNF survival rate was reported at 74% in the Danish DANBIO registry (Glintborg et al 2010). Now, biologics targeting IL-17A, ixekizumab and secukinumab, have been approved on 05-Jun-2020 and 23-Nov-2015 respectively, for the treatment of AS, providing an alternative treatment option.

Natural history of the indicated condition in the population, including mortality and morbidity:

Excess mortality was reported in patients with AS compared to the general population (van der Horst-Bruinsma et al 2012). A recent nationwide, population-based cohort study, conducted in Sweden, similarly found that the all-cause mortality was significantly increased in patients with AS compared with the general population overall (HR=1.60, 95% CI 1.44 -1.77), and also for both men and women separately (Exarchou et al 2016).

The prognosis for patients with AS is variable and is determined, in part, by the presence of comorbities, the age at onset and treatment provided. Generally AS results in serious impairment of spinal mobility and physical function, which has an impact on quality of life (Dean et al 2014).

Important co-morbidities:

Several epidemiological studies suggested that AS patients have increased rates of major adverse cardiovascular and cerebrovascular events compared with the general population of the same age and sex. CVD mortality data, and MI and stroke data in AS patients were compared to controls. For mortality, the estimated incidence ratios (including SMRs for incidence of fatal events and HRs for overall incidence) ranged from 1.25 (1.17-1.33) to 2.14 (1.41-3.25) (Kaprove et al 1980, Darby et al 1987), i.e. from a 25% increased risk to more than double risk of CV mortality (excluding stroke) in the population of AS patients vs controls. For MI the estimated incidence rates varied from 0.23 to 0.95 per 100 patient years (Bremander et al 2011, Brophy et al 2012) over a variable period of follow-up (from 1 to more than 12 years). For cerebrovascular end-points (fatal and non-fatal stroke), the estimated incidence rates varied between 0.07 to 1.05 per 100 patient years (Darby et al 1987, Keller et al 2014), and the incidence ratios ranged from 1.00 to 2.72 showing substantial differences between the studies, partly due to the type of stroke (ischemic vs hemorrhagic), differences in duration of follow-up, and likely due to differences in baseline risk factors.

Most publications refer to single cardiovascular outcomes. In Semb et al (2012), incidence of a composite end-point of MI, hospitalization for angina, heart surgery, stroke, or transient ischemic attack was 26% in AS patients vs. 22% in controls (incidence ratio 1.18; 95%CI: 0.74-1.89).

Regarding cancer risk, a population-based cohort study from Sweden (Feltelius et al 2003) including 6621 AS patients enrolled between 1965 and 1995, showed an overall standardized incidence ratio (SIR) of 1.05 (95% CI, 0.94–1.17). No increased risk of lymphoma in AS patients compared with the general population was reported in the literature. A population-based cohort study of patients with AS and age- and sex-matched comparator subjects from the general population was conducted in Sweden (Hellgren et al 2014). In the AS cohort the crude incidence of lymphoma (based on 14 cases) was 29 per 100,000 PY (95% CI 15–46), versus 31 per 100,000 (95% CI 25–39) in the comparator group, with a HR of 0.9 (95% CI 0.5–1.6). This study did not find a marked increase of any specific lymphoma subtype either. Among the TNF inhibitor-treated patients with AS, 2 lymphomas occurred (crude incidence 25 per 100,000 PY, 95% CI 3–93), versus 12 lymphomas among non–TNF inhibitor treated AS patients (crude incidence 27 per 100,000 PY, 95% CI 14–48) (Hellgren et al 2014).

Clinically overt inflammatory bowel disease (IBD), either CD or UC, has been reported to be present in 5-10% of patients with AS. The pooled prevalence of IBD in AS was estimated at 6.8% (95% CI 6.1% - 7.7%) in a recent meta-analysis aiming at summarizing the prevalence of extra-articular manifestations among patients with AS (Stolwijk et al 2015).

Depression, suicidal ideation and behavior have been reported in patients with ankylosing spondylitis at higher rates than in the general population. Rates may vary according to the measuring instrument used, the population setting (e.g., outpatients or inpatients, socio-demographic characteristics), and the design of the study (Radford et al 1977, Hyphantis et al 2013, Wu et al 2017).

2.3.2 Non-radiographic axial spondyloarthritis (nr-axSpA)

Secukinumab is indicated for the treatment of active nr-axSpA with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to NSAIDs.

Incidence:

Since nr-axSpA is considered to be the early form of AS it may be assumed that up to 50% of the new cases reported for the overall disease entity of axSpA are early disease i.e. nr-axSpA. However, it is difficult to determine the exact incidence of axSpA due to changing criteria and differing recognition of disease not specifically associated with radiographic findings, such as nr-axSpA, diagnostic delay and misdiagnosis can be very common (Ghosh et al 2017).

Prevalence:

The prevalence of AS, the radiographic form of axSpA, has been well studied; in contrast, the epidemiology of nr-axSpA is less well established. A retrospective cohort study, in the US, found after extrapolating the data to the national level that the prevalence of nr-axSpA according to ASAS criteria is 0.35% and similar to that for AS (Strand et al 2013). However, a previous US study, based on the National Health and Nutrition Examination Survey (NHANES) and combining interviews, physical examinations, conventional radiography, and laboratory assessment, showed that the prevalence of nr-axSpA may be as high as 0.4% to 0.9%, while the general prevalence of axSpA was 0.9% to 1.4% (using the Amor and ESSG classification criteria, respectively) and that of AS about 0.5% (Reveille et al 2013).

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

While AS is more common among men, the frequency of nr-axSpA is similar between males and female. In a meta-analysis of 8 studies comprising 2236 patients with AS and 1242 patients with nr-axSpA, the proportion who were male was 70.4% of patients with AS but only 46.8% of patients with nr-axSpA (de Winter et al 2016). Thus, women with axSpA have a greater probability of being underdiagnosed if radiologic evidence of disease is required for diagnosis even though they have the same burden of disease. Clinical manifestations of axSpA usually begin in late or early adulthood (mean age of onset 26 years) while onset after the age of 45 years is rare. Ethnic distribution can be assumed to be very similar to AS (see Section 2.3.1).

The main existing treatment options:

Non-steroidal anti-inflammatory drugs are considered first-line therapy for all patients with axSpA. Traditional disease-DMARDs such as MTX and sulfasalazine are not effective in the treatment of axSpA. In the US, certolizumab, ixekizumab and secukinumab are approved for the treatment of nr-axSpA with objective signs of inflammation, whereas in Europe, several anti-TNF agents have been approved for the treatment of nr-axSpA with objective signs of inflammation as indicated by elevated CRP and/or evidence of activity on MRI for several years already. However, more than 60% of nr-axSpA patients treated with adalimumab or etanercept did not achieve an ASAS40 response in randomized clinical trials (Sieper et al 2013, Dougados et al 2014). Moreover, TNF blockade does not result in long-term remission in AS and responders usually relapse within a few weeks after interruption of treatment (Baraliakos et al 2005). While effective in treating the inflammatory symptoms, TNF antagonists do not prevent structural damage of the joints in AS (van der Heijde D et al 2008a, van der Heijde et al 2008b). Currently, there is no experimental evidence that early therapy with approved treatment options in patients with nr-axSpA can prevent or delay the occurrence of structural alterations of the axial skeleton, which usually develop over a period of up to 10 years (Robinson et al 2013).

Important co-morbidities:

Since nr-axSpA is considered an early form of AS it is assumed that the same co-morbidities may develop over time as in AS (see Section 2.3.1).

2.4 Juvenile Idiopathic Arthritis

Incidence and prevalence:

Juvenile idiopathic arthritis (JIA) is an umbrella term for a heterogeneous group of conditions, and it is the most common chronic, inflammatory rheumatic disease among children. The incidence is reported to vary between 1.6 to 23 new cases for 100,000 children/year. No countries or continents have a particular predominance; however, most populations studied are within Europe and North America (Palman et al 2018). A systematic review of 33 studies on JIA incidence reported a pooled incidence of 8.3 per 100,000 (95% CI 8.1–8.7) Caucasian children (Thierry et al 2014). These studies were based on the American College of Rheumatology (ACR) (Brewer et al 1977), European Alliance of Associations for Rheumatology (EULAR) (Wood et al 1978) and the ILAR classifications for JIA (Petty et al 2004). Oligoarthritis was the most frequent form (pooled incidence rate 3.7; 95% CI 3.5–3.9).

The pooled incidence estimates for the other individual JIA subtypes were 0.4, 1.0, 0.6, 2.0 and 0.5 per 100,000 children for polyarthritis rheumatoid factor (RF) positive, polyarthritis RF negative, systemic-onset JIA (sJIA), spondyloarthropathies including enthesitis-related arthritis (ERA) and juvenile Psoriatic arthritis (jPsA), respectively (Thierry et al 2014). The estimated global prevalence of JIA also varies widely, between 3.8 to 400 cases per 100,000 children (Thatayatikom & De Leucio 2020). The calculated pooled global prevalence according to 29 global reports was 32.6 (95% CI 31.3–33.9) per 100,000 Caucasian children (Thierry et al 2014). The pooled prevalence estimates for the individual JIA categories were 16.8, 1.0, 5.1, 3.1, 4.9 and 1.3 per 100,000 children for oligoarthritis, polyarthritis RF positive, polyarthritis RF negative, SJIA, spondyloarthropathies including ERA and jPsA, respectively. After direct standardization with the datasets providing specific age and gender information, the standardized pooled prevalence was 70.2 (62.9–78.1) per 100,000 (Thierry et al 2014). For the US, the Utah Population Database provided a prevalence of 120 per 100,000 in white populations (Thatayatikom & De Leucio 2020).

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Gender differences are recognized in JIA, with females generally more commonly affected than males, although not in all subtypes. In particular, ERA mainly affects males, and sJIA appears to affect males and females equally. From the six articles with partial or complete data on age included in a systematic review, the pooled prevalence per 100,000 was 32.9 (28.0–38.4) for the 0–4 year range, 53.0 (41.0–67.4) for the 5–9 range and 110.6 (91.2–185.1) for the 10–15 range. On this basis, the estimated number of JIA cases in Europe in 2010 were 59,174 (44,256–76,983), corresponding to 44,031 (34,046–54,426) girls and 15,143 (10,210–22,557) boys (Thierry et al 2014). Whereas in the past, generalised growth was significantly affected by JIA, most modern JIA cohorts show growth and gain weight similar to that in the healthy counterparts in the general population (Palman et al 2018).

The main existing treatment options:

In both JIA categories of ERA and JPsA, the treatment goal is to control the inflammation with NSAIDs, corticosteroids given orally or as intra-articular injections, conventional DMARDs (such as methotrexate and sulfasalazine) and anti-tumor necrosis factor (TNF) biologic agents administered either as monotherapy or in combination with other therapies (conventional DMARDs and/or NSAIDs). Per recent guidelines, corticosteroid use is advised to be used for the shortest possible duration and the lowest dose needed to control symptoms and recommendations are against the use of methotrexate as monotherapy (Ringold et al 2019, Weiss et al 2020).

There is an unmet need for new therapies with potentially higher efficacy and better safety and tolerability for these debilitating conditions in children and adolescents (Brunner et al 2020).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The actual risk factors for JIA remain poorly understood. JIA is an autoinflammatory disease, in which the immune system attacks and destroys cells and tissues (particularly in the joints)

for no apparent reason. The immune system may get provoked by changes in the environment or by errors in the gene, resulting in activation of the innate immune response and with subsequent release of inflammatory cytokines, including increased levels of IL-1 and IL-17 which play a central role in the diseases (Florence et al 2019).

The reported mortality rate of patients with JIA diagnosed between 1992 and 2001 followed for up to 9 years was 0.6% in North America (Hashkes et al 2010). Most deaths in JIA are among patients with systemic-onset JIA (sJIA). Most deaths in sJIA patients are secondary to Macrophage Activation Syndrome (MAS), infection resulting from immunosuppression, or cardiac complications (Wallace et al 1991, Weiss and Ilowite 2007).

Important co-morbidities:

Comorbid conditions in patients with JIA include co-existing autoimmune diseases. Uveitis is known to occur in 12–31% of patients with JIA (Simon et al 2020). In Italy, a single-center study of 79 patients with JIA (aged ≤ 21 years), found that 15.2% of patients had at least one autoimmune disease in addition to JIA, with autoimmune thyroid diseases, such as Graves' disease, being the most common (10.1%) (Tronconi et al 2017). In this study, Crohn's disease was present in 3.8% of patients with JIA. A cross-sectional study conducted in the US using two administrative healthcare claims databases (Truven Health MarketScan® Commercial Database and IMS PharMetrics database), to screen for the prevalence of multiple autoimmune diseases in patients with JIA and in a control group with attention deficit hyperactivity disorder, confirmed the greater prevalence of co-existing autoimmune diseases in patients with JIA compared to patients with attention deficit hyperactivity disorder. Among patients with JIA aged < 18 years, the greatest odds ratios (ORs) were seen for Sjögren's syndrome/sicca syndrome and uveitis. The large ORs suggest that patients with JIA may be more predisposed to the earlier development of autoimmune diseases than the general pediatric population (Simon et al 2020).

2.5 Indication: Hidradenitis Suppurativa (HS)

Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition that is also known as acne inversa and, historically, as Verneuil's disease. Disease epidemiology is sparse.

Incidence:

A retrospective population-based observational study using the UK Clinical Practice Research Datalink (CPRD) linked to hospital episode statistics data was performed. The mean annual incidence rate for physician-diagnosed cases from 1996 to 2013 was 28.3 per 100 000 person-years (Ingram et al 2018).

A retrospective cohort study from the US using a multi-institutional data analytics and research platform for the period 1999-2016, aimed to establish standardized incidence estimates for HS in US (Garg et al 2017a). The overall standardized incidence was 11.4 (95% CI: 11.1-11.8) per 100,000 population while the standardized incidence was 16.1 (95%CI: 15.5-16.6) per 100,000 population in females and 6.8 (95%CI: 6.5-7.2) per 100,000 population in males.

Prevalence:

A retrospective population-based observational study using the CPRD linked to hospital episode statistics data was performed to assess the point prevalence and associated comorbidities, overall point prevalence was 0.77% [95% confidence interval (CI) 0.76-0.78%] (Ingram JR et al 2018).

A retrospective cohort study from the US using a multi-institutional data analytics and research platform for the period 1999-2016 aimed to establish standardized overall and group-specific prevalence estimates for HS in US (Garg et al 2017b). Among the adult population, the crude prevalence of HS was 120.1 per 100,000 population. The age and sex standardized prevalence was as high as 172 (95% CI: 169-175) per 100,000 population in age group 30-39 years.

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

The onset of symptoms typically occurs between puberty and age of 40 years-old, with usual onset in the second or third decade of life. Based on the available evidence published in the literature, females are more likely to develop HS than males (Canoui-Poitrine F et al 2013, Garg et al 2017a, Liy-Wong C et al 2021). In a French series of 618 consecutive patients with HS, the sex ratio was 3.6:1 (Canoui-Poitrine F et al 2013). In addition, the large population-based study in the US found that the incidence of HS was higher among women; in patients between the ages of 18 - 29 years, and in the African American ethnic group (Garg et al 2017a).

Genetic susceptibility appears to be an important contributor to HS (Andersen et al 2022, Van Straalen KR et al 2020). It is estimated that approximately 41 percent of pediatric patients with HS have a family history of HS (Liy-Wong C et al 2021). Compared with other HS patients, patients with early-onset HS (onset prior to age 13) may be more likely to have a family history of the disease (Deckers IE et al 2015). Other known risk factors of the disease are higher BMIs, smoking, mechanical stress (via increasing the chance of follicular occlusion and follicular rupture) (Revuz JE et al 2008, Sartorius K et al 2009, Vazquez BG et al 2013).

The main existing treatment options:

Hidradenitis suppurativa is difficult to treat. European treatment guidelines were only developed in 2015, followed by North American clinical management guidelines in 2019. These guidelines suggest that patients should be provided with adjuvant, medical and surgical therapy (Zouboulis et al 2015, Alikhan et al 2019). Recurrent combination therapy with multiple antibiotics represents the first step to control the symptoms in patients with HS (Zouboulis et al 2015, Bettoli et al 2016, Dessinioti et al 2016). However, it is widely recognized that HS is a chronic inflammatory condition, not an infectious disease (Jemec 2012), with elevated systemic levels of inflammatory markers. Therefore, systemic anti-inflammatory agents could be a more appropriate therapeutic strategy than antibiotics. Once irreversible fibrosis occurs, medical treatment can only control some symptoms while the only option to manage the lesion is surgery (Andersen and Jemec 2017).

Currently, adalimumab, an anti-TNFα antibody, is the only biologic systemic therapy approved in adults for the treatment of moderate to severe HS (approval granted in 2015 in the US and in 2016 in Europe). Two similarly designed Phase 3 studies of adalimumab demonstrated its

superiority over placebo with respect to HS clinical response (HiSCR) responder rate at Week 12: 41.8% adalimumab vs. 26.0% placebo in PIONEER I, and 58.9% adalimumab vs. 27.6% placebo in PIONEER II. However, the maintenance of the response seen at Week 12 was not consistent during the short and long-term follow-up, with numerical decline over time (Kimball et al 2016, Zouboulis et al 2019). Besides the known immunogenicity of adalimumab, the mechanisms at the basis of the progressive loss of response are not known (Kneepkens et al 2015). In addition, as captured in the adalimumab labels, adalimumab is associated with an increased safety risk for serious infections including tuberculosis, invasive fungal infections and other opportunistic infections. An increased incidence of lymphoma and non-melanoma skin cancers has also been reported with adalimumab (Burmester et al 2013, van Lümig et al 2015).

Important co-morbidities:

Table 2-1 Disorders associated with hidradenitis suppurativa

Disorders	Odds Ratio (95% CI)	References
Metabolic syndrome	OR=1.61 [95%CI 1.36-1.89]	(Shalom G et al 2015)
	OR=2.22 [95%CI 1.62-3.06]	(Tzellos T et al 2015)
	OR=2.08 [95%CI 1.61-2.69]	(Miller IM et al 2014)
T2DM	OR=1.58 [95%CI 1.54-1.62]	(Garg A et al 2018)
Crohn's disease	OR= 2.12 [95%CI 1.46-3.08]	(Chen and Chi 2019)
Ulcerative colitis	OR=1.51, 95% CI 1.25-1.82	(Chen and Chi 2019)
Grouped auto-inflammatory disorders such as SAPHO or PAPASH or PASH syndrome	Isolated reports	
Malignancy (notable cases reports of Squamous cell carcinoma (SCC), adenocarcinoma as a complication from hidradenitis suppurativa)	SIR= 1.5 [95%CI 1.1-1.8]	(Lapins et al 2001)
Genetic disorders (e.g. KID and others)	Not estimated – only individual case reports	
Other		
Acne vulgaris	OR= 4.51 [95%CI 4.40-4.63]	
Myocardial infarction	HR=1.21 [95%CI 1.12-1.32]	(Reddy et al 2020)
	IRRs= 1.57 [95%CI 1.14-2.17]	(Egeberg et al 2016)
MACE	IRRs= 1.53 [95%CI 1.27-1.86]	(Egeberg et al 2016)
CV-associated death	IRRs=1.95 [95%CI 1.42-2.67]	(Egeberg et al 2016)
Cerebrovascular accident	HR, 1.22 [95%CI 1.14-1.31]	(Reddy et al 2020)
	IRRs= 1.33 [95%CI 1.01-1.76]	(Egeberg et al 2016)
Depression	OR=1.99 [95%CI 1.63-2.43]	(Jalenques et al 2020)
Anxiety	OR=1.97 [95%CI 1.65-2.35]	(Jalenques et al 2020)

SAPHO: synovitis, acne, pustulosis, hyperostosis, and osteitis; PAPASH: pyogenic arthritis, pyoderma gangrenosum, acne, and suppurative hidradenitis; PASH: pyoderma gangrenosum, acne, and suppurative hidradenitis; KID: keratitis-ichthyosis-deafness.

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	Relevance to human usage
Repeat dose toxicity studies	
Immune function was monitored in the 13-week subcutaneous [Study 0770712] and 26-week intravenous [Study 0770203] toxicity studies in the cynomolgus monkey with secukinumab. No immunotoxicity/immunosuppression or treatment-related infections were observed in the conducted preclinical studies. Minimal non-adverse immunomodulatory activity (effects on lymphocyte subpopulations, TDAR and NK cell activity) was observed in the 13- and 26-week toxicity studies in cynomolgus monkeys. There were no secukinumab-related macroscopic observations or adverse effects on organ weights at necropsy, no treatment-related histopathology findings or altered distribution of T and B-lymphocytes in lymphoid tissues observed in young adults or adult monkeys. No hypersensitivity reactions or infections were observed in the preclinical studies performed. A study performed in a murine model of acute oropharyngeal candidiasis [Study 1270309] as well as preclinical and clinical evidence in the literature support the role of IL-17A in fighting infections. Anti-IL17A treatment did not have a major effect on host resistance in a murine model of acute *Mycobacterium tuberculosis* infection [Study 1280723].	There is preclinical and clinical evidence in the literature supporting a role for IL-17A in fighting infections. In primary immunodeficient patients lacking IL-17-producing T cells and patients with autoantibodies against IL-17, a susceptibility to *candida albicans* and *staphylococcus aureus* was described in the literature. These primary immunodeficient patient data need to be taken with caution since other immune defense pathways are also affected in these patients [Nonclinical infection risk assessment]. Infections are included in the clinical risk management plan and infections of relevance are mentioned in the label as adverse drug reactions.
Reproduction and Development	
In a placenta transfer study [Study 0580148] and embryo fetal development study [Study 0770202] in cynomolgus monkeys, placental transfer of secukinumab was confirmed by detection of the drug in fetal serum. None of the findings in the embryo fetal development study [Study 0770202] were considered toxicologically relevant. Secukinumab was neither teratogenic nor embryotoxic. A mouse surrogate antibody BZN035 was used in the fertility and early embryonic study [Study S497027] as well as in the pre- and postnatal development study [Study S497028] in mice. Neutralization of IL-17A in the mouse did not cause adverse findings on reproduction or development. BZN035 was neither teratogenic nor embryotoxic in mice. BZN035 did not affect fertility of the adult mice nor the development of the pups exposed via the treated mother. In the pre- and post-natal mouse study, BZN035-related changes were noted in lymphocyte populations in the spleen and thymus, and in the blood at 50 and/or 150 mg/kg/dose, although no effects were noted on relative numbers of these cells. However these changes were minimal and considered non-adverse.	Animal studies do not indicate direct or indirect adverse effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development. As a precautionary measure, it is preferable to avoid the use of secukinumab in pregnancy.

Key Safety findings (from non-clinical studies)	Relevance to human usage
These mild lymphocyte changes had no effect on T-cell dependent antibody response since no BZN035-related changes in anti-KLH IgM or IgG levels were observed. Furthermore, there were no effects on lymphoid organ weights or the architecture and cellular content of the lymphoid organs in an extended histopathology assessment. There was no effect on the F2 generation.	
Genotoxicity	
Based on the ICH S6 Guideline for the Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (1997), genotoxicity studies have not been conducted for secukinumab.	-
Carcinogenicity	
In line with ICH S6 no carcinogenicity study was performed. [Nonclinical Carcinogenic Risk Assessment] because 1) secukinumab, a human monoclonal antibody, is not pharmacologically active in rodents, 2) carcinogenicity studies are not feasible in cynomolgus monkey, 3) based on the weight of evidence in the literature available to date in preclinical models, neutralizing IL-17A does not suggest an increased tumor promoting risk, and 4) the IgG1 chemical structure itself does not represent a carcinogenic risk. There is strong *in vivo* evidence supporting a role for IL-17 in promoting tumors. Anti-IL-17 may therefore have an anti-tumorigenic effect. Conversely, there is evidence supporting a role for IL-17 in tumor immuno-surveillance. Anti-IL-17 therapy may therefore impair this tumor immuno-surveillance and reduce the effectiveness of anti-tumor immune responses. Available literature data suggest that IL-17A has both pro-tumor and anti-tumor activity, depending on the model used and the types and stages of tumors transplanted. However, the effects of blocking IL-17A or other IL-17 family members on tumor growth in humans have yet to be explored. Based on non-clinical studies, secukinumab is not a potent immunosuppressant and the risk of tumor induction (e.g., skin cancer, lymphoma) by oncogenic viruses is considered to be low. Furthermore, neutralizing IL-17A should not grossly affect key anti-tumor immune defense mechanisms (Th1-type responses, CTLs and NK cells), supported by the fact that secukinumab had no adverse effects on immune function parameters (T cell-dependent antibody responses or NK cell function) and did not induce signs of lymphoproliferative disease at dose levels of up to 150 mg/kg in chronic monkey toxicology studies.	The incidence and nature of malignancies observed in clinical studies to date appear to match the expectations in the population investigated. Continued pharmacovigilance for malignancies observed in clinical studies and spontaneous reports will be part of the clinical risk management plan.
Safety pharmacology	
Slow bolus injection of secukinumab to male monkeys, at doses of 10, 30 and 100 mg/kg, produced no adverse effects on central nervous system (CNS), respiratory or cardiac function, and all parameters were within normal limits for healthy, untreated animals.	There is no preclinical or clinical evidence for any adverse effects on the CNS, respiratory or cardiac function

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

The majority of studies presented in the tables below have included a number of different secukinumab dose arms versus a single placebo arm within the same study. Most studies with secukinumab included only a limited period of placebo control and the use of active comparator control was limited to one year, thus also limiting the exposure to active controls. Moreover, nearly all patients randomized to placebo in the trials were switched/re-randomized to secukinumab treatment following the completion of the initial 12-24 week randomized phase of the study according to the study design.

Due to these study design features, both, the number of subjects treated with secukinumab and the mean exposure time to secukinumab, are significantly higher than for patients randomized to placebo or active comparators.

All extension studies, ongoing or completed, include only secukinumab-treatment arms. Patients participating in these extension studies are a subgroup of patients from the corresponding core studies; therefore, patients from the extension studies (and also from study CAIN457A2307 that recruited patients from study CAIN457A2304) are included in the total exposure counts based upon their participation in the respective core study, and not based upon their additional participation in the extension study.

Table 4-1 to Table 4-52 presents combined subject exposure numbers and subject-years, across all indications, from studies with a final or interim analysis Clinical Study Report (CSR) completed prior to 01-Oct-2021 (DLP) for M2301 and 23-Sep-2021 (DLP) for M2302. This pool represents the total number of subjects from studies using secukinumab, for which efficacy and safety data is available and has been systematically reviewed.

4.1.1 Psoriasis (Adult studies)

Induction period (Pivotal psoriasis placebo-controlled studies - Safety set)

Table 4-1 Clinical trial exposure (by duration)

Duration of exposure	AIN457 150 mg Subjects	AIN457 300 mg subjects	Any AIN457 dose Subjects	Placebo subjects	Etanercept Subjects
At least 1 month	683	685	1368	680	320
At least 3 months	15	16	31	18	8
At least 6 months	1	0	1	0	0
Subject-time (subject years)	157.2	157.5	314.6	155.4	73.0

Source: Annex 7
Month is cumulative starting from first dose
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25

Table 4-2 Exposure by age group and gender

	AIN457 150 mg		AIN457 300 mg		Any AIN457 dose		Placebo		Etanercept	
Age group	M	F	M	F	M	F	M	F	M	F
<65 years	444	190	443	199	887	389	457	194	221	84
≥65 years	41	17	33	15	74	32	29	14	8	10
≥75 years	8	2	5	1	13	3	6	4	1	2
Subject-time (Subject years)	109.8	47.4	108.8	48.7	218.6	96.1	108.7	46.8	51.6	21.4

Source: Annex 7
M: Male, F: Female
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25

Table 4-3 Exposure by Dose (if applicable)

Duration of exposure	Subjects	Subject-time (subject years)
AIN457 150 mg	692	157.2
AIN457 300 mg	690	157.5
Any AIN457 dose	1382	314.6
Placebo	694	155.4
Etanercept	323	73.0

Source: Annex 7
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25

Table 4-4 Exposure by race

Race/Ethnicity	AIN457 150 mg Subjects	AIN457 300 mg Subjects	Any AIN457 dose Subjects	Placebo Subjects	Etanercept Subjects
Caucasian/Hispanic or Latino	52	51	103	50	21
Caucasian/ South Asian	0	0	0	1	1
Caucasian/ West Asian	0	0	0	1	0
Caucasian/Russian	16	8	24	13	2
Caucasian/Mixed ethnicity	15	19	34	21	4
Caucasian/Not reported	45	61	106	51	6
Caucasian/Unknown	33	34	67	39	13
Caucasian/Other	338	331	669	335	169
Black/Hispanic or Latino	0	0	0	1	0
Black/Mixed ethnicity	0	1	1	0	0
Black/Not reported	5	2	7	4	0
Black/Unknown	2	3	5	2	0
Black/Other	6	3	9	6	0
Asian/Hispanic or Latino	1	0	1	0	1
Asian/East Asian	66	61	127	63	25
Asian/Southeast Asian	19	14	33	9	14
Asian/South Asian	38	46	84	46	31
Asian/West Asian	2	3	5	1	1
Asian/Mixed ethnicity	0	1	1	0	0

Race/Ethnicity	AIN457 150 mg Subjects	AIN457 300 mg Subjects	Any AIN457 dose Subjects	Placebo Subjects	Etanercept Subjects
Asian/Not reported	1	1	2	1	0
Asian/Unknown	1	3	4	1	2
Asian/Other	1	0	1	0	0
Native American/Hispanic or Latino	32	27	59	28	27
Native American/Not reported	1	0	1	0	0
Native American/Other	0	2	2	0	0
Pacific Islander/Mixed ethnicity	1	1	2	0	0
Pacific Islander/Not reported	0	0	0	0	1
Pacific Islander/Unknown	0	2	2	0	0
Pacific Islander/Other	0	1	1	1	0
Other/Hispanic or Latino	11	9	20	14	2
Other/East Asian	0	0	0	1	0
Other/Mixed ethnicity	1	1	2	1	0
Other/Not reported	1	0	1	0	0
Other/Unknown	1	0	1	1	0
Other/Other	2	3	5	1	2
Unknown/Hispanic or Latino	1	1	2	0	0
Unknown/Unknown	0	0	0	1	1
Unknown/Other	0	1	1	1	0
Subject-time (subject years)	157.2	157.5	314.6	155.4	73.0

Source: Annex 7
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25

Entire treatment period (All psoriasis studies - Safety set)

Table 4-5 Clinical trial exposure (by duration)

Duration of exposure	AIN457 150 mg Subjects	AIN457 300 mg Subjects	Placebo-AIN457 150 mg Subjects	Placebo-AIN457 300 mg Subjects	AIN457 150 mg SoR Subjects	AIN457 300 mg SoR Subjects	Any AIN457 150 mg Subjects	Any AIN457 300 mg Subjects	Any AIN457 dose Subjects	Placebo Subjects	Etanercept Subjects
At least 1 month	928	937	250	243	205	217	1383	1397	3394	773	320
At least 3 months	758	781	245	238	205	217	1208	1236	2867	60	301
At least 6 months	720	740	238	234	200	215	1158	1189	2727	33	290
At least 12 months	651	687	0	1	177	197	828	885	1947	29	263
Subject-time (Subject years)	759.0	783.2	185.8	181.9	197.2	212.4	1142.0	1177.5	2724.6	201.3	293.5

Source: Annex 7

SoR: Start of relapse

Month is cumulative starting from first dose

Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25

Table 4-6 Exposure by age group and gender

	AIN457 150 mg		AIN457 300 mg		Placebo-AIN457 150 mg		Placebo-AIN457 300 mg		AIN457 150 mg SoR		AIN457 300 mg SoR		Any AIN457 150 mg		Any AIN457 300 mg		Any AIN457 dose		Placebo		Etanercept	
Age group	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
<65 years	580	285	605	271	177	57	160	69	128	66	140	66	885	408	905	406	2241	959	519	225	221	84
≥65 years	55	20	50	22	11	5	11	5	7	4	8	3	73	29	69	30	165	65	33	16	8	10
≥75 years	9	2	6	2	2	1	3	2	0	1	1	1	11	4	10	5	23	9	6	4	1	2
Subject-time (Subject years)	517	242	548.8	234.4	139.4	46.4	128	53.9	130.7	66.5	145.4	67.1	787.1	354.9	822.2	355.4	1915.9	808.7	138.1	63.2	209.6	83.9

Source: Annex 7

M: Male; F: Female; Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25

Table 4-7 Exposure by Dose

Dose of exposure	Subjects	Subject-time (Subject years)
AIN457 150 mg	940	759.0
AIN457 300 mg	948	783.2
Placebo-AIN457 150 mg	250	185.8
Placebo-AIN457 300 mg	245	181.9
AIN457 150 mg SoR	205	197.2
AIN457 300 mg SoR	217	212.4
Any AIN457 150 mg	1395	1142.0
Any AIN457 300 mg	1410	1177.5
Any AIN457 dose	3430	2724.6
Placebo	793	201.3
Etanercept	323	293.5

Dose of exposure	Subjects	Subject-time (Subject years)

Source: Annex 7
SoR: Start of relapse
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25

Table 4-8 Exposure by race

Race/Ethnicity	AIN457 150 mg Subjects	AIN457 300 mg Subjects	Placebo-AIN457 150 mg Subjects	Placebo-AIN457 300 mg Subjects	AIN457 150 mg SoR Subjects	AIN457 300 mg SoR Subjects	Any AIN457 150 mg Subjects	Any AIN457 300 mg Subjects	Any AIN457 dose Subjects	Placebo Subjects	Etanercept Subjects
Caucasian /Hispanic or Latino	58	57	20	19	10	4	88	80	189	52	21
Caucasian/ South Asian	0	0	0	0	0	0	0	0	1	1	1
Caucasian/ West Asian	0	0	0	1	1	0	1	1	2	1	0
Caucasian/Russian	18	8	5	4	0	2	23	14	37	13	2
Caucasian/Mixed ethnicity	26	24	8	9	3	7	37	40	95	27	4
Caucasian/Not reported	60	82	14	16	10	10	84	108	198	51	6
Caucasian/Unknown	49	61	6	19	18	14	73	94	169	39	13
Caucasian/Other	472	461	121	108	102	111	695	680	1867	409	169
Black/Hispanic or Latino	0	0	0	0	0	0	0	0	0	1	0
Black/Mixed ethnicity	1	2	0	0	0	0	1	2	3	0	0
Black/Not reported	8	3	2	2	3	2	13	7	21	4	0

Race/Ethnicity	AIN457 150 mg Subjects	AIN457 300 mg Subjects	Placebo-AIN457 150 mg Subjects	Placebo-AIN457 300 mg Subjects	AIN457 150 mg SoR Subjects	AIN457 300 mg SoR Subjects	Any AIN457 150 mg Subjects	Any AIN457 300 mg Subjects	Any AIN457 dose Subjects	Placebo Subjects	Etanercept Subjects
Black/Unknown	2	4	1	1	0	2	3	7	10	2	0
Black/Other	7	3	3	0	0	1	10	4	17	8	0
Asian/Hispanic or Latino	1	0	0	0	0	0	1	0	1	0	1
Asian/East Asian	80	77	30	24	12	16	122	117	307	75	25
Asian/Southeast Asian	38	26	4	2	20	21	62	49	112	9	14
Asian/South Asian	59	76	17	20	16	20	92	116	212	46	31
Asian/West Asian	3	3	0	0	0	0	3	3	6	1	1
Asian/Mixed ethnicity	0	1	0	0	1	0	1	1	2	0	0
Asian/Not reported	2	1	1	0	1	0	4	1	5	1	0
Asian/Unknown	1	4	0	0	0	1	1	5	6	1	2
Asian/Other	3	2	0	0	3	2	6	4	13	1	0
Native American/Hispanic or Latino	32	28	13	13	0	0	45	41	86	28	27
Native American/Mixed Ethnicity	0	1	0	0	0	0	0	1	1	0	0
Native American/Not reported	1	0	0	0	0	0	1	0	1	0	0
Native American/Other	1	2	0	0	0	0	1	2	4	0	0

Race/Ethnicity	AIN457 150 mg Subjects	AIN457 300 mg Subjects	Placebo-AIN457 150 mg Subjects	Placebo-AIN457 300 mg Subjects	AIN457 150 mg SoR Subjects	AIN457 300 mg SoR Subjects	Any AIN457 150 mg Subjects	Any AIN457 300 mg Subjects	Any AIN457 dose Subjects	Placebo Subjects	Etanercept Subjects
Pacific Islander/Mixed ethnicity	1	1	0	0	0	0	1	1	2	0	0
Pacific Islander/Not reported	0	0	0	0	0	0	0	0	0	0	1
Pacific Islander/Unknown	0	2	0	0	0	0	0	2	2	0	0
Pacific Islander/Other	0	1	1	0	0	1	1	2	3	2	0
Other/Hispanic or Latino	11	11	2	4	1	1	14	16	31	15	2
Other/East Asian	0	0	1	0	0	0	1	0	1	1	0
Other/West Asian	0	1	0	0	0	0	0	1	1	0	0
Other/Mixed ethnicity	1	1	0	1	1	1	2	3	5	1	0
Other/Not reported	1	0	0	0	0	0	1	0	1	0	0
Other/Unknown	1	0	0	0	1	0	2	0	2	1	0
Other/Other	2	3	0	1	0	0	2	4	9	1	2
Unknown/Hispanic or Latino	1	1	0	0	2	0	3	1	4	0	0
Unknown/Unknown	0	0	0	1	0	1	0	2	2	1	1
Unknown/Other	0	1	1	0	0	0	1	1	2	1	0
Subject-time (Subject years)	759	783.2	185.8	181.9	197.2	212.4	1142	1177.5	2724.6	201.3	293.5

Race/Ethnicity	AIN457 150 mg Subjects	AIN457 300 mg Subjects	Placebo-AIN457 150 mg Subjects	Placebo-AIN457 300 mg Subjects	AIN457 150 mg SoR Subjects	AIN457 300 mg SoR Subjects	Any AIN457 150 mg Subjects	Any AIN457 300 mg Subjects	Any AIN457 dose Subjects	Placebo Subjects	Etanercept Subjects

Source: Annex 7
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25

4.1.2 Psoriasis (pediatric data)

Induction period (Psoriasis pediatric study) Safety Set

In the pediatric study A2310, the induction period was defined as from randomization through Week 12 (prior to dose). In this period the study was both active and placebo-controlled and at its completion the primary endpoint was assessed (Week 12).

Table 4-9 Clinical trial exposure (by duration)

Duration of exposure	AIN457 low dose Subjects	AIN457 High dose subjects	Any AIN457 dose Subjects	Placebo subjects	Etanercept Subjects
At least 1 month	39	39	78	40	41
At least 3 months	33	32	65	35	35
Subject-time (subject years)	9.21	9.12	18.33	9.49	9.69

Source: Annex 7
AIN457 low dose: 75 mg (in <25 kg and 25 to <50 kg) or 150 mg (≥50 kg) injections
AIN457 high dose: 75mg (in <25 kg), 150 mg (25 to <50 kg), 300 mg (≥50 kg) injections
Month is cumulative starting from first dose
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25

Entire treatment period (Psoriasis pediatric study) Safety Set

Table 4-10 Clinical trial exposure by duration – entire treatment period (Psoriasis pediatric study) Safety Set

Duration of exposure	AIN457 Low dose Subjects	AIN457 High dose Subjects	Any AIN457 Low dose Subjects	Any AIN457 High dose Subjects	Any AIN457 dose Subjects	Placebo Subjects	Etanercept Subjects
At least 1 month	39	39	55	57	112	40	41
At least 3 months	39	39	54	56	110	35	41
At least 6 months	39	38	49	53	102	0	39
At least 12 months	31	29	40	41	81	0	27
Subject-time (Subject years)	64.26	66.70	84.65	93.47	178.12	9.49	36.77

Source: Annex 7
AIN457 low dose: 75 mg (in <25 kg and 25 to <50 kg) or 150 mg (≥50 kg) injections
AIN457 high dose: 75mg (in <25 kg), 150mg (25 to <50 kg), 300 mg (≥50 kg) injections
Month is cumulative starting from first dose
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25

4.1.3 Psoriatic Arthritis

Pool A: Short term period (16 weeks) Safety set

Table 4-11 Clinical trial exposure (by duration)

Duration of exposure	AIN457 75mg	AIN457 150mg	AIN457 300mg	AIN457 10mg/kg -75mg	AIN457 10mg/kg -150mg	Any AIN457	Placebo
At least 1 month	98 (99.0)	100 (100)	98 (98.0)	199 (98.5)	200 (99.0)	695 (98.9)	299 (99.7)
At least 3 months	94 (94.9)	100 (100)	97 (97.0)	195 (96.5)	196 (97.0)	682 (97.0)	281 (93.7)
At least 6 months	0	0	0	0	2 (1.0)	2 (0.3)	0
At least 12 months	0	0	0	0	0	0	0
Subject-time (subject years)	29.8	30.9	30.2	62.1	62.5	215.5	90.4

Source: Annex 7

Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Table 4-12 Exposure by age group and gender

	AIN457 75mg		AIN457 150mg		AIN457 300mg		AIN457 10mg/kg -75mg		AIN457 10mg/kg -150mg		Any AIN457		Placebo	
Age group	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
<65	45	48	52	42	47	43	75	105	90	90	309	328	129	150
Subject-time (subject years)	13.7	14.4	16.0	13.1	14.0	13.1	23.6	32.3	27.3	28.4	94.5	101.3	39.1	44.9
≥65	2	4	3	3	4	6	9	13	6	16	24	42	6	15
Subject-time (subject years)	0.6	1.1	0.9	0.9	1.2	1.8	2.8	3.4	1.8	5.1	7.4	12.3	1.9	4.6

Source: Annex 7

Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Table 4-13 Exposure by Dose

Dose of exposure	Subjects	Subject-time (subject years)
AIN457 75mg	99	29.8
AIN457 150mg	100	30.9
AIN457 300mg	100	30.2
AIN457 10mg/kg -75mg	202	62.1
AIN457 10mg/kg -150mg	202	62.5
Any AIN457	703	215.5
Placebo	300	90.4

Source: Annex 7

Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Table 4-14 Exposure by race

Race	AIN457 75mg Subjects	AIN457 150mg Subjects	AIN457 300mg Subjects	AIN457 10mg/kg -75mg Subjects	AIN457 10mg/kg -150mg Subjects	Any AIN457 Subjects	Placebo Subjects
White	90 (90.9)	90 (90.0)	96 (96.0)	165 (81.7)	162 (80.2)	603 (85.8)	248 (82.7)
Subject-time (subject years)	27.0	27.8	28.9	50.8	50.3	184.9	74.2
Black or African American	0	0	1 (1.0)	2 (1.0)	3 (1.5)	6 (0.9)	0
Subject-time (subject years)	0	0	0.3	0.4	0.9	1.6	0
Asian	5 (5.1)	6 (6.0)	2 (2.0)	33 (16.3)	36 (17.8)	82 (11.7)	47 (15.7)
Subject-time (subject years)	1.6	1.8	0.6	10.3	11.0	25.3	14.7
American Indian or Alaska Native	0	2 (2.0)	0	0	0	2 (0.3)	0
Subject-time (subject years)	0	0.6	0	0	0	0.6	0
Native Hawaiian or other Pacific Islander	1 (1.0)	1 (1.0)	0	0	0	2 (0.3)	1 (0.3)
Subject-time (subject years)	0.3	0.3	0	0	0	0.6	0.3
Other	2 (2.0)	1 (1.0)	1 (1.0)	1 (0.5)	1 (0.5)	6 (0.9)	4 (1.3)
Subject-time (subject years)	0.6	0.3	0.3	0.3	0.3	1.8	1.2
Unknown	1 (1.0)	0	0	1 (0.5)	0	2 (0.3)	0
Subject-time (subject years)	0.3	0	0	0.3	0	0.6	0

Source: Annex 7

Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Pool A: Entire Treatment Period (Safety Set)

Table 4-15 Clinical trial exposure (by duration)

Duration of exposure	Any AIN457 75mg	Any AIN457 150mg	Any AIN457 300mg	Any AIN457	Placebo
At least 1 month	385 (98.5)	436 (99.5)	142 (97.9)	963 (98.9)	299 (99.7)
At least 3 months	374 (95.7)	416 (95.0)	133 (91.7)	923 (94.8)	281 (93.7)
At least 6 months	363 (92.8)	381 (87.0)	106 (73.1)	850 (87.3)	8 (2.7)
At least 12 months	221 (56.5)	224 (51.1)	1 (0.7)	446 (45.8)	0
Subject-time (subject years)	420.0	444.9	90.1	955.0	105.6

Source: Annex 7

Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Table 4-16 Exposure by age group and gender

	Any AIN457 75mg		Any AIN457 150mg		Any AIN457 300mg		Any AIN457		Placebo	
Age group	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
<65	162	199	201	194	63	70	426	463	129	150
Subject-time (subject years)	174.7	214.5	201.7	200.1	40.1	41.7	416.5	456.2	43.8	53.9
≥65	12	18	14	29	4	8	30	55	6	15

	Any AIN457 75mg		Any AIN457 150mg		Any AIN457 300mg		Any AIN457		Placebo	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
Subject-time (subject years)	13.3	17.5	14.0	29.2	3.1	5.2	30.4	51.9	2.3	5.6

Source: Annex 7

Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Table 4-17 Exposure by Dose

Dose of exposure	Subjects	Subject-time (subject years)
Any AIN457 75mg	391	420.0
Any AIN457 150mg	438	444.9
Any AIN457 300mg	145	90.1
Any AIN457	974	955.0
Placebo	300	105.6

Source: Annex 7

Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Table 4-18 Exposure by race

Race	Any AIN457 75mg Subjects	Any AIN457 150mg Subjects	Any AIN457 300mg Subjects	Any AIN457 Subjects	Placebo
White	318 (81.3)	367 (83.8)	139 (95.9)	824 (84.6)	248 (82.7)
Subject-time (subject years)	339.6	363.3	86.3	789.2	85.8
Black or African American	2 (0.5)	3 (0.7)	1 (0.7)	6 (0.6)	0
Subject-time (subject years)	1.5	5.1	1.0	7.5	0
Asian	65 (16.6)	60 (13.7)	3 (2.1)	128 (13.1)	47 (15.7)
Subject-time (subject years)	73.7	70.8	1.9	146.4	17.8
American Indian or Alaska Native	0	2 (0.5)	0	2 (0.2)	0
Subject-time (subject years)	0	1.5	0	1.5	0
Native Hawaiian or other Pacific Islander	1 (0.3)	2 (0.5)	0	3 (0.3)	1 (0.3)
Subject-time (subject years)	0.7	1.3	0	2.0	0.3
Other	3 (0.8)	4 (0.9)	2 (1.4)	9 (0.9)	4 (1.3)
Subject-time (subject years)	2.6	2.9	0.9	6.4	1.6
Unknown	2 (0.5)	0	0	2 (0.2)	0
Subject-time (subject years)	2.0	0	0	2.0	0

Source: Annex 7

Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

4.1.4 Axial spondyloarthritis (axSpA)

4.1.4.1 Ankylosing Spondylitis

Pool A: Short term period (16 weeks) Safety set

Table 4-19 Clinical trial exposure (by duration)

Duration of exposure	AIN457 75mg	AIN457 150mg	AIN457 10mg/kg -75mg	AIN457 10mg/kg -150mg	Any AIN457	Placebo
At least 1 month	71 (97.3)	72 (100)	123 (99.2)	125 (100.0)	391 (99.2)	189 (96.4)
At least 3 months	69 (94.5)	68 (94.4)	119 (96.0)	124 (99.2)	380 (96.4)	180 (91.8)
At least 6 months	0	0	1 (0.8)	1 (0.8)	2 (0.5)	0
At least 12 months	0	0	0	0	0	0
Subject-time (subject years)	22.1	21.6	38.3	38.9	120.9	58.3

Source: Annex 7

Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Table 4-20 Exposure by age group and gender

	AIN457 75mg		AIN457 150mg		AIN457 10mg/kg -75mg		AIN457 10mg/kg -150mg		Any AIN457		Placebo	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
<65	**50**	**20**	**45**	**25**	**84**	**33**	**82**	**40**	**261**	**118**	**136**	**51**
Subject-time (subject years)	15.1	6.0	13.8	7.2	26.2	9.8	25.7	12.4	80.9	35.5	40.1	15.2
≥65	1	2	1	1	4	3	2	1	8	7	5	4
Subject-time (subject years)	0.3	0.6	0.3	0.3	1.3	0.9	0.4	0.3	2.3	2.2	1.7	1.3

Source: Annex 7

Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Table 4-21 Exposure by Dose

Dose of exposure	Subjects	Subject-time (subject years)
AIN457 75mg	73	22.1
AIN457 150mg	72	21.6
AIN457 10mg/kg-75mg	124	38.3
AIN457 10mg/kg-150mg	125	38.9
Any AIN457	394	120.9
Placebo	196	58.3

Source: Annex 7

Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Table 4-22 Exposure by race

Race	AIN457 75mg Subjects	AIN457 150mg Subjects	AIN457 10mg/kg -75mg Subjects	AIN457 10mg/kg -150mg Subjects	Any AIN457 Subjects	Placebo Subjects
White	70 (95.9)	69 (95.8)	76 (61.3)	69 (55.2)	284 (72.1)	151 (77.0)
Subject-time (subject years)	21.1	20.7	23.3	21.4	86.5	45.1
Black or African American	0	0	0	0	0	1 (0.5)
Subject-time (subject years)	0	0	0	0	0	0.0
Asian	3 (4.1)	2 (2.8)	23 (18.5)	21 (16.8)	49 (12.4)	23 (11.7)
Subject-time (subject years)	1.0	0.6	7.3	6.6	15.5	7.0
American Indian or Alaska Native	0	1 (1.4)	3 (2.4)	8 (6.4)	12 (3.0)	3 (1.5)
Subject-time (subject years)	0	0.3	0.8	2.5	3.7	1.0
Native Hawaiian or other Pacific Islander	0	0	0	0	0	1 (0.5)
Subject-time (subject years)	0	0	0	0	0	0.3
Other	0	0	22 (17.7)	27 (21.6)	49 (12.4)	17 (8.7)
Subject-time (subject years)	0	0	6.8	8.3	15.1	4.8

Source: Annex 7
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Pool A: Entire Treatment Period (Safety Set)

Table 4-23 Clinical trial exposure (by duration)

Duration of exposure	Any AIN457 75mg	Any AIN457 150mg	Any AIN457	Placebo
At least 1 month	281 (98.9)	286 (99.7)	567 (99.3)	189 (96.4)
At least 3 months	269 (94.7)	279 (97.2)	548 (96.0)	180 (91.8)
At least 6 months	265 (93.3)	268 (93.4)	533 (93.3)	3 (1.5)
At least 12 months	222 (78.2)	219 (76.3)	441 (77.2)	0
Subject-time (subject years)	344.6	346.5	691.1	63.6

Source: Annex 7
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Table 4-24 Exposure by age group and gender

	Any AIN457 75mg		Any AIN457 150mg		Any AIN457		Placebo	
Age group	Male	Female	Male	Female	Male	Female	Male	Female
<65	188	80	194	85	382	165	136	51
Subject-time (subject years)	230.3	94.7	236.3	102.2	466.6	197.0	43.6	16.8
≥65	9	7	4	4	13	11	5	4
Subject-time (subject years)	10.6	9.0	3.4	4.6	14.0	13.6	1.8	1.4

Source: Annex 7
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Table 4-25 Exposure by Dose

Dose of exposure	Subjects	Subject-time (subject years)
Any AIN457 75mg	284	344.6
Any AIN457 150mg	287	346.5
Any AIN457	571	691.1
Placebo	196	63.6

Source: Annex 7
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Table 4-26 Exposure by race

Race	Any AIN457 75mg Subjects	Any AIN457 150mg Subjects	Any AIN457 Subjects	Placebo Subjects
White	214 (75.4)	207 (72.1)	421 (73.7)	151 (77.0)
Subject-time (subject years)	259.6	248.2	507.9	48.8
Black or African American	0	0	0	1 (0.5)
Subject-time (subject years)	0	0	0	0.0
Asian	34 (12.0)	36 (12.5)	70 (12.3)	23 (11.7)
Subject-time (subject years)	42.0	45.6	87.6	8.0
American Indian or Alaska Native	4 (1.4)	11 (3.8)	15 (2.6)	3 (1.5)
Subject-time (subject years)	4.1	14.0	18.1	1.0
Native Hawaiian or other Pacific Islander	1 (0.4)	0	1 (0.2)	1 (0.5)
Subject-time (subject years)	0.3	0	0.3	0.3
Other	31 (10.9)	33 (11.5)	64 (11.2)	17 (8.7)
Subject-time (subject years)	38.5	38.7	77.2	5.5

Source: Annex 7
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

4.1.4.2 Non-radiographic axial spondyloarthritis

Up to week 20

Table 4-27 Clinical trial exposure (by duration)

Duration of exposure	AIN457 150mg N=185	AIN457 150mg No load N=184	Placebo N=186
At least 1 month	185 (100.0)	184 (100.0)	185 (99.5)
At least 3 months	184 (99.5)	182 (98.9)	185 (99.5)
At least 5 months	182 (98.4)	178 (96.7)	158 (84.9)
Subject-time (subject years)	228.3	234.6	104.7

Source: Annex 7
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Table 4-28 Exposure by age group and gender

	AIN457 150mg Load		AIN457 150mg No Load		Placebo	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
<65	80	103	84	96	84	96
Subject-time (subject years)	104.8	119.9	108.1	121.2	108.1	121.2
≥65	0	2	0	4	0	4
Subject-time (subject years)	0	3.6	0	5.3	0	5.3

Source: Annex 7

Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Table 4-29 Exposure by Dose

Dose of exposure	Subjects	Subject-time (subject years)
AIN457 150mg Load	185	228.3
AIN457 150mg No Load	184	234.6
Placebo	186	104.7

Source: Annex 7

Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Table 4-30 Exposure by race

Race	AIN457 Load 150 mg	AIN457 No Load 150mg	Placebo
White	176 (95.1)	165 (89.7)	167 (89.8)
Subject-time (subject years)	217.1	208.0	92.4
Black or African American	0	2 (1.1)	1 (0.5)
Subject-time (subject years)	0	3.3	0.4
Asian	4 (2.2)	8 (4.3)	11 (5.9)
Subject-time (subject years)	6.2	11.0	7.0
American Indian or Alaska Native	0	2 (1.1)	0
Subject-time (subject years)	0	1.9	0
Other	5 (2.7)	7 (3.8)	7 (3.8)
Subject-time (subject years)	4.9	10.4	5.0

Source: Annex 7

Duration of exposure to study treatment is defined as the number of days on the study treatment during the considered period.

Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Entire Treatment Period (Safety Set)

Table 4-31 Clinical trial exposure (by duration)

Duration of exposure	AIN457 150mg N=185	AIN457 150mg No load N=184	Any AIN457 N=524	Placebo N=186
At least 1 month	185 (100.0)	184 (100.0)	520 (99.2)	185 (99.5)
At least 3 months	184 (99.5)	182 (98.9)	502 (95.8)	185 (99.5)
At least 6 months	182 (98.4)	178 (96.7)	470 (19.7)	79 (42.5)

Duration of exposure	AIN457 150mg N=185	AIN457 150mg No load N=184	Any AIN457 N=524	Placebo N=186
At least 12 months	121 (65.4)	130 (70.7)	314 (59.9)	42 (22.6)
Subject-time (subject years)	228.3	234.6	588.0	104.7

Source: Annex 7

Duration of exposure to study treatment is defined as the number of days on the study treatment during the considered period.
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Table 4-32 Exposure by age and gender

	AIN457 150mg Load		AIN457 150mg No Load		Any AIN457		Placebo	
Age group	Male	Female	Male	Female	Male	Female	Male	Female
<65	80	103	84	96	236	279	89	94
Subject-time (subject years)	104.8	119.9	108.1	121.2	272.3	202.4	53.5	50.0
≥65	0	2	0	4	2	7	2	1
Subject-time (subject years)	0	3.6	0	5.3	1.8	10.5	0.8	0.5

Source: [redacted]
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Table 4-33 Exposure by Dose

Dose of exposure	Subjects	Subject-time (subject years)
AIN457 150mg Load	185	228.3
AIN457 150mg No Load	184	234.6
Any AIN457	524	588.0
Placebo	186	104.7

Source: Annex 7
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

Table 4-34 Exposure by race

Race	AIN457 Load 150 mg	AIN457 No Load 150mg	Any AIN457	Placebo
White	176 (95.1)	165 (89.7)	482 (92.0)	167 (89.8)
Subject-time (subject years)	217.1	208.0	537.9	92.4
Black or African American	0	2 (1.1)	3 (0.6)	1 (0.5)
Subject-time (subject years)	0	3.3	4.7	0.4
Asian	4 (2.2)	8 (4.3)	20 (3.8)	11 (5.9)
Subject-time (subject years)	6.2	11.0	26.7	7.0
American Indian or Alaska Native	0	2 (1.1)	2 (0.4)	0
Subject-time (subject years)	0	1.9	1.9	0
Other	5 (2.7)	7 (3.8)	17 (3.2)	7 (3.8)
Subject-time (subject years)	4.9	10.4	16.8	5.0

Race	AIN457 Load 150 mg	AIN457 No Load 150mg	Any AIN457	Placebo

Source: Annex 7

Duration of exposure to study treatment is defined as the number of days on the study treatment during the considered period.

Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

4.1.5 Juvenile Idiopathic Arthritis (JIA) subtypes of Enthesitis Related Arthritis (ERA) and Juvenile Psoriatic Arthritis (JPsA)

Core study

Treatment period 1

Table 4-35 Clinical trial exposure (by duration) Safety Set

Duration of exposure	AIN457 N=86
At least 1 month	86 (100)
At least 3 months	74 (86.0)
Subject-time (subject years)	20.1

- Subject-time in subject years is calculated as a sum of individual subject duration in days divided by 365.25.
- AIN457 includes all subjects who took AIN457 during Treatment Period 1.

Source: Annex 7

Table 4-36 Exposure by age and gender

	AIN457	
Age group	Male	Female
2-<6 years	2	1
Subject-time (subject years)	0.5	0.2
6-<12 years	12	10
Subject-time (subject years)	2.8	2.4
12-<18 years	43	18
Subject-time (subject years)	10.1	4.1

- Subject-time in subject years is calculated as a sum of individual subject duration in days divided by 365.25.
- AIN457 includes all subjects who took AIN457 during Treatment Period 1.

Source: Annex 7

Table 4-37 Exposure by dose

Dose of exposure	Subjects	Subject-time (subject-years)
AIN457	86	20.1

- Subject-time in subject years is calculated as a sum of individual subject duration in days divided by 365.25.

Source: Annex 7

Table 4-38 Exposure by race

Race	AIN457
White	82 (95.3)
Subject-time (subject years)	19.1
Asian	1 (1.2)
Subject-time (subject years)	0.2

Race	AIN457
Other	3 (3.5)
Subject-time (subject years)	0.7

- Subject-time in subject years is calculated as a sum of individual subject duration in days divided by 365.25.
- AIN457 includes all subjects who took AIN457 during Treatment Period 1.

Source: Annex 7

Entire treatment period

Table 4-39 Clinical trial exposure (by duration)

Duration of exposure	AIN457 N=48	Placebo in TP2 N=38	Total N=86
At least 1 month	48 (100)	38 (100)	86 (100)
At least 3 months	47 (97.9)	38 (100)	85 (98.8)
At least 6 months	36 (75.0)	38 (100)	74 (86.0)
At least 9 months	35 (72.9)	37 (97.4)	72 (83.7)
At least 12 months	35 (72.9)	35 (92.1)	70 (81.4)
Subject-time (subject years)	71.3	70.2	141.5

- Subject-time in subject years is calculated as a sum of individual subject duration in days divided by 365.25.
- AIN457 refers to all patients who did not take any placebo (including patients who did not enter TP2).
- Placebo in TP2 refers to all patients who took placebo in TP2 and AIN457 in other treatment period/s (TP1 and/or TP3)
- Total refers to all patients who took AIN457 in at least one of the 3 treatment periods.
- Duration of exposure for the entire treatment period is defined as the time from first dose of study medication to the last dose plus 84 days or last visit (including follow-up visits) whichever occurs earlier.

Source: Annex 7

Table 4-40 Exposure by age and gender

	AIN457		Placebo in TP2		Total	
Age group	Male	Female	Male	Female	Male	Female
2-<6 years	0	0	2	1	2	1
Subject-time (subject years)	0.0	0.0	4.0	2.0	4.0	2.0
6-<12 years	4	5	8	5	12	10
Subject-time (subject years)	8.0	8.4	14.5	8.9	22.4	17.3
12-<18 years	26	13	17	5	43	18
Subject-time (subject years)	37.9	17.1	30.8	10.0	68.7	27.1

	AIN457		Placebo in TP2		Total	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**

- Subject-time in subject years is calculated as a sum of individual subject duration in days divided by 365.25.
- AIN457 refers to all patients who did not take any placebo (including patients who did not enter TP2).
- Placebo in TP2 refers to all patients who took placebo in TP2 and AIN457 in other treatment period/s (TP1 and /or TP3).
- Total refers to all patients who took AIN457 in at least one of the 3 treatment periods.
- Duration of exposure for the entire treatment period is defined as the time from first dose of study medication to the last dose plus 84 days or last visit (including follow-up visits), whichever occurs earlier.

Source: Annex 7

Table 4-41 Exposure by dose

Dose of exposure	Subjects	Subject-time (subject-years)
AIN457	48	71.3
Placebo in TP2	38	70.2

- Subject-time in subject years is calculated as a sum of individual subject duration in days divided by 365.25.
- Duration of exposure for the entire treatment period is defined as the time from first dose of study medication to the last dose plus 84 days or last visit (including follow-up visits), whichever occurs earlier.

Source: Annex 7

Table 4-42 Exposure by race

Race	AIN457	Placebo in TP2	Total
White	47 (97.9)	35 (92.1)	82 (95.3)
Subject-time (subject years)	69.5	64.0	133.5
Asian	0	1 (2.6)	1 (1.2)
Subject-time (subject years)	0.0	2.2	2.2
Other	1 (2.1)	2 (5.3)	3 (3.5)
Subject-time (subject years)	1.8	4.0	5.8

- Subject-time in subject years is calculated as a sum of individual subject duration in days divided by 365.25.
- AIN457 refers to all patients who did not take any placebo (including patients who did not enter TP2).
- Placebo in TP2 refers to all patients who took placebo in TP2 and AIN457 in other treatment period/s (TP1 and /or TP3).
- Total refers to all patients who took AIN457 in at least one of the treatment periods.
- Duration of exposure for the entire treatment period is defined as the time from first dose of study medication to the last dose plus 84 days or last visit (including follow-up visits), whichever occurs earlier.

Source: Annex 7

Extension study

As of 07-Nov-2024 (study last patient last visit), the mean duration of exposure to study treatment during the extension study F2304E1 was 1232.4 days (range 1-1527 days), with a total subject-time of 182.2 subject years. A total of 55 patients continued from the core study and enrolled into the extension study, of which 54 received study drug before discontinuing from or completing the study. By the end of the study, 24 patients (44.4%) had 4 years (208 weeks) or greater of exposure and 22 patients (40.7%) completed treatment. For the entire core and extension study treatment period, the mean (SD) duration of exposure to study treatment was 1374.8 (range 56 – 2258) days with a total subject-time of 323.7 subject years in all patients [CAIN457F2304E1 SCS].

Table 4-43 Duration of exposure to study treatment, entire treatment period (JIA subtypes of ERA and JPsA)

Duration of exposure	Any AIN457 75 mg N=19	Any AIN457 150 mg N=43	Any AIN457 300 mg N=16	Any AIN457 N=54
Any exposure - n (%)	19 (100)	43 (100)	16 (100)	54 (100)
Exposure to extension treatment – n (%)				
>= 1 weeks*	19 (100)	43 (100)	16 (100)	54 (100)
>= 52 weeks	16 (84.2)	32 (74.4)	13 (81.3)	52 (96.3)
>= 104 weeks	11 (57.9)	24 (55.8)	9 (56.3)	48 (88.9)
>= 208 weeks	7 (36.8)	6 (14.0)	1 (6.3)	24 (44.4)
Exposure in days to extension treatment				
n	19	43	16	54
Mean	917.8	842.9	804.1	1232.4
SD	582.65	535.72	471.24	389.71
Median	1043.0	919.0	893.5	1397.0
Min - Max	74 - 1527	1 - 1520	50 - 1485	1 - 1527
Subject-time				
Subject years	47.7	99.2	35.2	182.2

* This is the first dose of extension study treatment; however subjects were exposed to study treatment from the start of the core study.
Duration of exposure is defined as the time from first dose of study medication in the extension study to the last dose plus 84 days or last visit (including follow-up visits) whichever occurs earlier.
Subject-time in subject-years is calculated as the sum of individual subject durations in days divided by 365.25.
Source: [CAIN457F2304E1 SCS]

Table 4-44 Duration of exposure to study treatment, entire core and extension study treatment period (JIA subtypes of ERA and JPsA)

Duration of exposure	Any AIN457 N=86
Any exposure -n (%)	**86 (100)**
Exposure to treatment -n (%)	
>= 52 weeks	68 (79.1)
>= 104 weeks	61 (70.9)
>= 208 weeks	48 (55.8)
>= 260 weeks	41 (47.7)
>= 312 weeks	25 (29.1)
Exposure in days to extension treatment	
n	86
Mean	1374.8
SD	843.21
Median	1684.5
Min-Max	56 - 2258
Subject-time	
Subject years	323.7

Any AIN457: All subjects who received at least one dose of secukinumab treatment.
Duration of exposure is defined as the time from first dose of study medication in the core study to the last dose plus 84 days or last visit (including follow-up visits of core and/or extension), whichever occurs earlier.
Subject-time in subject-years is calculated as the sum of individual subject durations in days divided by 365.25.
Source: [CAIN457F2304E1 SCS]

4.1.6 Hidradenitis Suppurativa (HS)

Treatment period 1 (HS Phase III Studies - Safety set)

Table 4-45 Clinical trial exposure (by duration)

Duration of exposure	AIN457 Q2W N=361	AIN457 Q4W N=360	Any AIN457 N=721	Placebo N=363
At least 1 month	358 (99.2)	357 (99.2)	715 (99.2)	356 (98.1)
At least 3 months	353 (97.8)	350 (97.2)	703 (97.5)	351 (96.7)
Subject-time (Subject years)	110.7	109.7	220.4	111.1

Source: Annex 7
Month is cumulative starting from first dose
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25
Any AIN457 includes all subjects who took AIN457 during Treatment Period 1

Table 4-46 Exposure by age and gender

	AIN457 Q2W		AIN457 Q4W		Any AIN457		Placebo	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
<40	93	121	106	129	199	250	100	143

	AIN457 Q2W		AIN457 Q4W		Any AIN457		Placebo	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
Subject-time (subject years)	28.3	37.4	32.2	39.6	60.5	77.1	30.5	44.2
≥40	68	79	51	74	119	153	56	64
Subject-time (subject years)	20.7	24.3	15.5	22.4	36.1	46.7	17.3	19.1

Source: Annex 7
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.
Any AIN457 includes all subjects who took AIN457 during Treatment Period 1

Table 4-47 Exposure by Dose

Dose of exposure	Subjects	Subject-time (subject years)
AIN457 Q2W	361	110.7
AIN457 Q4W	360	109.7
Any AIN457	721	220.4
Placebo	363	111.1

Source: Annex 7
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.
Any AIN457 includes all subjects who took AIN457 during Treatment Period 1

Table 4-48 Exposure by race

Race	AIN457 Q2W Subjects	AIN457 Q4W Subjects	Any AIN457 Subjects	Placebo Subjects
Asian	35	39	74	43
Subject-time (subject years)	10.8	12.0	22.8	13.3
American Indian or Alaska Native	8	6	14	10
Subject-time (subject years)	2.7	1.9	4.5	3.2
Black or African American	33	29	62	24
Subject-time (subject years)	10.1	9.0	19.2	7.3
Native Hawaiian or other Pacific Islander	1	0	1	0
Subject-time (subject years)	0.3	0.0	0.3	0.0
White	278	285	563	282
Subject-time (subject years)	84.8	86.5	171.3	86.0
Multiple	5	1	6	4
Subject-time (subject years)	1.7	0.3	2.0	1.3
Not Reported	1	0	1	0
Subject-time (subject years)	0.3	0.0	0.3	0.0

Source: Annex 7
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.
- Any AIN457 includes all subjects who took AIN457 during treatment period 1

Entire treatment period (HS Phase III Studies - Safety set)

As of 01-Oct-2021, only 60% of the patients have completed the study (i.e. reached Week 52).

Table 4-49 Clinical trial exposure (by duration)

Duration of exposure	AIN457 Q2W N=361	AIN457 Q4W N=360	Any AIN457 Q2W N=527	Any AIN457 Q4W N=533	Any AIN457 N=1060
At least 1 month	358 (99.2)	357 (99.2)	518 (98.3)	523 (98.1)	1041 (98.2)
At least 3 months	353 (97.8)	350 (97.2)	503 (95.4)	503 (94.4)	1006 (94.9)
At least 6 months	312 (86.4)	307 (85.3)	438 (83.1)	431 (80.9)	869 (82.0)
At least 9 months	268 (74.2)	261 (72.5)	298 (56.5)	293 (55.0)	591 (55.8)
At least 12 months	139 (38.5)	131 (36.4)	139 (26.4)	131 (24.6)	270 (25.5)
Subject-time (Subject years)	313.6	309.0	413.7	411.1	824.8

Source: Annex 7
Month is cumulative starting from first dose
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25
Any AIN457 includes all subjects who took AIN457

Table 4-50 Exposure by age and gender

	AIN457 Q2W		AIN457 Q4W		Any AIN457 Q2W		Any AIN457Q4W		Any AIN457	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
<40	93	121	106	129	133	199	158	183	291	382
Subject-time (subject years)	82.1	105.5	89.0	111.6	106.1	151.8	120.0	143.5	226.1	295.3
≥40	68	79	51	74	87	108	86	106	173	214
Subject-time (subject years)	57.2	68.9	44.8	63.7	68.5	87.3	67.3	80.3	135.8	167.6

Source: Annex 7
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.
Any AIN457 includes all subjects who took AIN457

Table 4-51 Exposure by Dose

Dose of exposure	Subjects	Subject-time (subject years)
AIN457 Q2W	361	313.6
AIN457 Q4W	360	309.6
Any AIN457 Q2W	527	413.7
Any AIN457 Q4W	533	411.1
Any AIN457	1060	824.8

Source: Annex 7
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.
Any AIN457 includes all subjects who took AIN457

Table 4-52 Exposure by race

Race	AIN457 Q2W Subjects	AIN457 Q4W Subjects	Any AIN457Q2W Subjects	Any AIN457Q4W Subjects	Any AIN457 Subjects
Asian	35	39	56	59	115
Subject-time (subject years)	31.4	36.1	43.7	47.3	91.0
American Indian or Alaska Native	8	6	11	12	23
Subject-time (subject years)	5.9	4.2	7.8	7.4	15.3
Black or African American	33	29	42	44	86
Subject-time (subject years)	25.8	24.5	30.5	33.9	64.5
Native Hawaiian or other Pacific Islander	1	0	1	0	1
Subject-time (subject years)	1.0	0.0	1.0	0.0	1.0
White	278	285	410	414	824
Subject-time (subject years)	244.6	243.2	325.1	320.3	645.3
Multiple	5	1	6	4	10
Subject-time (subject years)	4.5	1.0	5.1	2.1	7.2
Not Reported	1	0	1	0	1
Subject-time (subject years)	0.5	0.0	0.5	0.0	0.5

Source: Annex 7
Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.
Any AIN457 includes all subjects who took AIN457

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
History of severe hypersensitivity reactions to secukinumab or to any of the excipients	History of hypersensitivity to the study drug or its components is a routine exclusion criterion.	No	Hypersensitivity is an important identified risk of secukinumab.
Clinically important, active infection	Immune response to active/clinically important infections may be affected by immunomodulators.	No	Infection is an important identified risk of secukinumab.
Women of child-bearing potential (WoCBP)	Pregnancy is a routine exclusion criterion for drugs in development	No	There are no adequate data from use of secukinumab in pregnant women. Label language in WoCBP: Women of childbearing potential should use an effective method of contraception during treatment.
Uncontrolled hypertension (systolic ≥ 160 mmHg and/or diastolic ≥ 95 mmHg)	At the time of finalization of the Phase III protocols, very limited information was available about the impact of exposure to secukinumab on blood pressure.	No	Experience during Phase III studies does not suggest an impact of secukinumab on the clinical course of hypertension, including use in patients with pre-hypertensive and hypertensive blood pressures that approached the level of exclusion.
Known congestive heart failure (CHF) with a New York Heart Association (NYHA) status of class III or IV	At the time of finalization of the Phase III protocols, very limited information was available about the impact of exposure to secukinumab on the status of subjects with CHF.	No	There is no evidence to suggest an increased risk of CHF among patients receiving secukinumab compared to placebo.
Known infection with the Human Immunodeficiency Virus (HIV)	At the time of finalization of the Phase III protocols, very limited information was available about the impact of exposure to secukinumab on the course of an HIV infection. Due to the potential of secukinumab to have an immunomodulatory effect,	No	Experience during Phase III studies does not suggest that secukinumab is significantly immunosuppressant, as the risk of serious infections was not increased. Vast majority of infections were of mild to moderate, and were resolved with standard of care treatment.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
	there was a theoretical possibility that it might change the course of an HIV infection.		
Known untreated malignancy, or history of malignancy of any organ system within the past five years (except for basal cell carcinoma or actinic keratosis that has been treated with no evidence of recurrence in the past 12 weeks and carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed)	At the time of finalization of the Phase III protocols, very limited information was available about the impact of exposure to secukinumab on the course of malignancies. Due to the potential of secukinumab to have an immunomodulatory effect, there was a theoretical possibility that it might change the course of malignancies.	No	There is no evidence to suggest an increased risk of malignancies among patients receiving secukinumab compared to placebo.
Neutropenia Neutrophils < 1,500/µL	Reductions in peripheral neutrophil counts may be a possible pharmacodynamic effect of systemic IL-17A blockade, based on the role of IL-17A in innate immunity and neutrophil biology. In addition, neutropenia events were reported within phase 2 results of two other anti-IL-17 compounds, brodalumab and ixekizumab.	No	Experience during psoriasis Phase 3 studies (N=3430) does not suggest that secukinumab causes severe neutropenia or leads to clinically significant infections associated with neutropenia. There were no Grade 4 neutropenia events with secukinumab and the infrequent Grade 3 events (n=18) were transient and reversible. The vast majority of the patients with Grade 3 neutropenia events had no reports of infection, while those infections that were reported were mostly mild to moderate and mainly of the upper respiratory tract. Similar patterns as in psoriasis studies were observed in PsA and AS Phase III studies. In secukinumab studies, rare cases of Grade 4 neutropenia were reported.
Live vaccinations within 6 weeks prior to exposure to secukinumab, or planned live vaccinations during the treatment with secukinumab	At the time of finalization of the Phase III protocols, very limited information was available about the impact of exposure to secukinumab on live vaccinations. Due to the potential of secukinumab to have an immunomodulatory effect, there was a theoretical possibility that it	No	A study using inactivated influenza and meningococcal vaccinations in healthy volunteers has not shown a negative impact on the efficacy or safety of these vaccines. As there is no information available on the use of secukinumab together with live attenuated vaccinations, their

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
	might change the efficacy or safety of live vaccinations.		concomitant use is not recommended, and this is reflected in the “warnings” section and in the “interactions” section of the label.
Fetal exposure in utero	Pregnancy is a routine exclusion criterion for drugs in development; there are no adequate data about in utero exposure to secukinumab.	Yes	Not applicable
Long-term safety data	Long-term observational trials are ongoing to obtain long-term data	Yes	Not applicable
Long-term efficacy data	Long-term observational trials are ongoing to obtain long-term data	No	Available data from extension clinical trials (up to 5 years) do not indicate a different efficacy profile upon long-term treatment with secukinumab. Long-term efficacy in psoriasis, psoriatic arthritis and ankylosing spondylitis is sustained when compared to the results observed in the registration trials.
Use in pediatric patients	It was not known whether secukinumab was safe and effective in children at the time of conducting pivotal clinical studies in adults. Subsequently a specific pediatric investigation plan has been undertaken.	No	The efficacy and safety of secukinumab in children has been established in psoriasis and JIA (ERA and JPsA subtypes) and will be extended to other indications as the pediatric investigation plan and dedicated trials evolve
Patients with severe hepatic impairment	Secukinumab has not been studied specifically in this patient population; no pharmacokinetic data are available in patients with hepatic impairment.	No	Secukinumab has not been specifically studied in patients with severely reduced liver function, but patients with some degree of hepatic impairment have been included in clinical trials. Well-documented cases of use of secukinumab in patients with severe hepatic impairment are monitored and reviewed in PSURs.
Patients with severe renal impairment	Secukinumab has not been studied specifically in these patient populations; no pharmacokinetic data are available in patients with renal impairment.	No	Secukinumab has not been specifically studied in patients with severely reduced kidney function, but patients with some degree of renal impairment have been included in clinical trials. Well-documented cases of use of secukinumab in patients with severe renal

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
			impairment are monitored and reviewed in PSURs.

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions due to prolonged exposure, adverse reactions due to cumulative effects and adverse reactions with long latency.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 SIV.2: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Patients with severe hepatic impairment were excluded.
• Patients with renal impairment	Patients with severe renal impairment were excluded.
• Patients with cardiovascular impairment	Patients with some degree of cardiac insufficiency (NYHA 1-2) or with controlled hypertension have been assessed in clinical trials. Patients with severe cardiac disease or uncontrolled hypertension were excluded.
• Immunocompromised patients	Patients with severe immunocompromise were excluded.
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	The study program included patients from all racial backgrounds, with a majority of them being Caucasian (Psoriasis: 75%, PsA: 85%, AS: 74%) or Asian (Psoriasis: 19%, PsA: 13%, AS: 12%). No race-related trends in total AEs or in infections and infestations were observed compared to the overall population. In addition, no meaningful differences were observed in the incidence of skin and subcutaneous disorders, gastrointestinal disorders or cardiac disorders compared to the overall population.

Type of special population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Genetic polymorphisms have not been assessed in secukinumab clinical trials not included in the clinical development program.
Other Children	The safety and efficacy of secukinumab in children aged >6 years with severe psoriasis has been studied in study CAIN457A2310. Further assessment will be derived from the ongoing study CAIN457A2311 in children with moderate psoriasis. The safety and efficacy of secukinumab was studied in study CAIN457F2304 of pediatric subject's ≥ 2 to < 18 years with juvenile idiopathic arthritis.
Elderly	Psoriasis: Across the psoriasis trials, the majority of patients were <65 years of age. Of the 3,430 plaque psoriasis patients exposed to secukinumab in clinical studies, a total of 230 were 65 years of age or older and 32 patients were 75 years of age or older. Psoriatic arthritis and Ankylosing spondylitis: Across the PsA and AS trials, the majority of patients were <65 years of age. Of the 1545 PsA and AS patients exposed to secukinumab in clinical Phase 3 studies, a total of 109 patients were 65 years of age or older and 7 patients were 75 years of age or older.

Source: RMP version 4.0 and CAIN457A2310 CSR

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

An estimate of patient exposure is calculated based on worldwide sales volume in kilogram (kg) of active substance sold until the cut-off date and the average maintenance daily dose (10 mg).

6.1.2 Part II Module SV.1.2. Exposure

The cumulative patient exposure since the International Birth Date until 25-Dec-2023 (cut-off date for PSUR 26-Dec-2020 to 25-Dec-2023) is estimated to be approximately 1,882,445 PY.

The following table provides an overall estimation of cumulative patient exposure since the international birth date, distributed by region. Data on Cosentyx sales by gender or age are not available.

Table 6-1 Cumulative exposure from marketing experience

	EU (incl. EEA and CH)	USA and Canada	Japan	ROW	Total
Cumulative exposure (patients years)	497,761	[redacted]	[redacted]	850,640	1,882,445
Source of data: [redacted]					

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

Not applicable as a potential for abuse and dependence is not anticipated based on the mechanism of action of secukinumab.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II SVII.1. Identification of safety concerns in the initial RMP submission

8.1.1 Part II Module SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable; the RMP was already approved.

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

There was no change in safety concerns since the last update.

8.3 Part II ModuleSVII.3: Details of important identified risks, important potential risks, and missing information

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

Clinical data for the important identified and potential risks detailed in this section are based on randomized clinical studies included in the development programs for psoriasis (adult and pediatric), psoriatic arthritis, axial spondyloarthritis, juvenile idiopathic arthritis and hidradenitis suppurativa.

The development programs for psoriasis, psoriatic arthritis, axial spondyloarthritis, and hidradenitis suppurativa included an initial comparison between secukinumab and placebo for the initial 12-20 weeks, before placebo patients were crossed over to secukinumab.

In the placebo-controlled periods crude incidences were provided as percentages. The assessment of long-term safety includes studies and study periods (which covered the entire treatment period) where all patients received secukinumab. Exposure-adjusted analysis (provided as the number of events per 100 patient-years) was used to compensate for the large difference in the number of patients receiving secukinumab versus placebo.

For JIA, the study (AIN457F2304) was divided into 3 parts (plus a post-treatment follow-up period) consisting of open-label, single-arm active treatment in Treatment Periods 1 and 3 and a randomized, double-blind, placebo controlled, event-driven withdrawal design in Treatment Period 2.

8.3.1.1 Important Identified risk: Infections and infestations

Table 8-1 Important identified risk – Infections and infestations: Other details

Infections and infestations	**Details**
Potential mechanisms	A potential risk of infections is associated with any immunomodulatory biologic agent. Secukinumab binds to and neutralizes the bioactivity of of human IL-17A,

Infections and infestations	**Details**
	which might lead to an increased risk for infections including those secondary to candida and with encapsulated bacteria in particular *Staphylococcus*.
Evidence source(s) and strength of evidence	In clinical studies, an increased risk for infections has been observed, mostly mild or moderate, responsive to usual treatment and not requiring discontinuation. A similar pattern of events have been identified in the post-marketing setting and medical literature (Blauvelt 2016)
Characterization of the risk:	For PsO indication in the short term, placebo-controlled period the overall incidence of infections and infestations (SOC) was higher in the secukinumab groups compared with the placebo group with no clinically meaningful differences between the low and high dose groups. The most frequently reported events for infections were upper respiratory tract infections (URTI) and nasopharyngitis. Few cases of Candida infections (including oral candidiasis, and genital candidiasis) were reported, and occurred more frequently in the any secukinumab group compared to the placebo group. In the entire treatment period the exposure-adjusted incidence per 100 patient-years of Infections and Infestations (SOC) tended to be higher in the any secukinumab group vs placebo, with no significant differences between doses, upper respiratory tract infections (URTI) continued to be the most common type of infections. Most of the infectious events were of mild to moderate severity, did not lead to treatment discontinuation and resolved after treatment. A small proportion of infections reported over the entire treatment period were SAEs (including opportunistic infections) and were not considered a significant safety signal. A similar picture was seen for the subsequent indications of psoriatic arthritis, ankylosing spondylitis, nr-axSpA, pediatric psoriasis and juvenile idiopathic arthritis. For the JIA subtypes of ERA and JPsA indication, the most common treatment-emergent adverse events by SOC were in Infections and Infestations with an exposure-adjusted incidence per 100 patient-years of 88.6. No clinically notable observations with regards to seriousness, severity or type of infections were noted [CAIN457F2304E1 SCS]. Patients with hidradenitis suppurativa are more susceptible to infections. Infection rates observed in the controlled period of clinical studies in HS (30.7% in patients treated with secukinumab compared to 31.7% in patients treated with placebo) were numerically higher to those observed in the psoriasis studies. Most of these were non-serious, mild or moderate in severity and did not require treatment discontinuation or interruption. The hidradenitis suppurativa clinical studies were conducted during the COVID-19 pandemic, during which more infections were generally reported.
Risk factors and risk groups	Severe psoriasis is recognized as a risk factor for infections (Wakkee et al 2011). Other predictors for multiple infectious diseases were the use of anti-diabetic drugs, and COPD/anti-asthmatic drugs (Wakkee et al 2011). The use of systemic psoriasis therapies does seem to increase the risk of infections, although the individual long-term safety profiles are still being investigated in real-world use. Spondyloarthropathies can be associated with an increased risk for infections with incidence rates of infection around 5.3 per 100 PY (Perez-Sola et al 2011; Grijalva et al 2011). In a recent systematic review of randomized trials, the risk of serious infections among patients with AS was 0.4 per 100 PY, while in those treated with TNF blockers the incidence was 2.2 per 100 PY (Fouque-Aubert et al 2010). In JIA, an increased risk for bacterial infections has been described (Beukelmann et al 2012). Whether treatment with biologic agents further increases the risk is not clear (Aeschlimann 2019). Using claims data, Beukelman et al found that the rate of infections requiring hospitalization was not increased in patients with JIA treated with MTX or anti-TNF, but was increased with high-dose glucocorticoids (Beukelmann et al 2012). Cultures from early, unruptured HS lesions are usually sterile. Whereas older and ruptured lesions and sinuses may demonstrate a wide variety of bacteria (eg, staphylococci, streptococci, Gram-negative rods, and anaerobic bacteria) (Sartorius

Infections and infestations	**Details**
	et al 2012). Long-standing, poorly controlled HS may lead to significant complications including infectious complications (eg, lumbosacral epidural abscess, sacral bacterial osteomyelitis) (Alikhan et al 2009). A study using National Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project (HCUP), showed that inpatients with HS had a higher prevalence (33·9% (33·1–34·6%) 95% CI) of serious infections than those without HS, with a significantly higher odds of any serious infection: aOR 2·30 (95% CI 2·21–2·39). Inpatients with HS with multifactorial comorbidities, notably cancer and HIV, appear to be at risk for developing infections. Patients with HS with long-term systemic corticosteroid use (as judged by a diagnosis of Cushing syndrome or long-term corticosteroid use) were not associated with increased infections (Lee et al 2019).
Preventability	No subpopulation at higher risk for infections on secukinumab therapy was identified in clinical studies. In particular, advanced age was not associated with a higher incidence of infections. Informing physicians and patients via the label about infections which qualify as adverse drug reactions allows to routinely include those infections (such as mucosal candida) in the questioning and physical examination. In addition, a warning on the potential of increased risk of infections may help physicians to monitor closely, recognize early and treat timely any infections associated with the use of secukinumab
Impact on the benefit-risk balance of the product	Vast majority of infections were mild to moderate, and were resolved with standard of care treatment.
Public health impact	Vast majority of infections were mild to moderate, and were resolved with standard of care treatment. No infections which would constitute a public health concern beyond the treated individual (such as reactivation of tuberculosis) were observed. There is a demonstrated risk in severe psoriasis patients of incurring high rates of infections, including infections requiring hospitalization; and an increased risk of death due to infection. However, whether these risks are associated with recent use of systemic psoriasis therapies is still not clarified and this risk is still being investigated in real-world use.
Sources	Annex 7

8.3.1.2 Important identified risk: Hypersensitivity

Table 8-2 Important identified risk – Hypersensitivity

Hypersensitivity	**Details**
Potential mechanisms	Administration of proteins such as immunoglobulin (Ig) can lead to hypersensitivity reactions. Hypersensitivity reactions to secukinumab are complex and possibly IgE-related (e.g., anaphylaxis, urticaria, and angioedema). Paradoxical reaction secondary to Th2/Th22 imbalance caused by IL-17 blockade, has led to severe eczematous eruptions and exfoliative dermatitis generalized.
Evidence source(s) and strength of evidence	Hypersensitivity events, including rare cases of anaphylactic reactions have been observed in clinical studies. The majority of events were mild to moderate. A similar pattern of events has been identified in the post-marketing setting and medical literature, although secukinumab displayed a minimal immunogenicity potential in pooled Phase III trials (Reich et al 2017).
Characterization of the risk:	In the short term placebo-controlled period for the initial indication of adult psoriasis, hypersensitivity AEs mapping to the hypersensitivity narrow SMQ were reported in a higher proportion of patients in the secukinumab dose groups and the etanercept group, which were similar to each other, compared with the placebo group. The difference vs. placebo was driven mainly by urticaria and eczema. In addition, Angioedema (HLT) was reported with low and comparable rates across the treatment groups, placebo and etanercept.

Hypersensitivity	**Details**
	For all other indications, hypersensitivity AEs were comparable in the secukinumab dose group compared with the placebo group. The most frequently reported hypersensitivity AEs across indications were urticaria and eczema and were of mild to moderate severity. For JIA, there were no SAEs reported in the secukinumab group. Two AEs of single instances with only eosinophil count increased and erythema were reported as related in ≥2 patients [CAIN457F2304E1 SCS]. In the entire treatment period the exposure-adjusted incidence per 100 patient-years of hypersensitivity AEs was higher in secukinumab group as compared to placebo in all indications except for nr-axSpA. For all indications, across the treatment periods the events related to immune/administration reactions were low or comparable between secukinumab dose groups and vs. etanercept or placebo group and were of mild to moderate severity.
Risk factors and risk groups	Patients with prior allergic reactions are at increased risk.
Preventability	Hypersensitivity reactions are included in the ADR section and Special Warnings and Precautions. In addition, patients with severe hypersensitivity reactions to the active substance or to any of the excipients are contraindicated. These risk minimization measures will help mitigate the risk.
Impact on the benefit-risk balance of the product	Potential impact on the individual patient should be carefully evaluated and managed by the treating physician on a case by case basis. Serious hypersensitivity reactions require immediate medical attention to avoid serious consequences related to the hypersensitivity reactions.
Public health impact	The potential public health impact is considered to be low, since the differences in the incidence rates between secukinumab and control groups in clinical trials were small, and the events reported were mostly mild.
Sources	Annex 7

8.3.1.3 Important potential risk: Malignant or unspecified tumors

Table 8-3 Important potential risk – Malignant or unspecified tumors

Malignant or unspecified tumors	**Details**
Potential mechanisms	Immunosuppression can potentially lead to an increase in the risk for malignancy. Previous exposure to UV therapy can also lead to an increase in the risk for skin malignancies.
Evidence source(s) and strength of evidence	Current evidence is based on clinical data (in comparison with the general population), post-marketing experience in the context of an estimated exposure of > 1.8 million patient-years, and literature review. Long-term safety data continue to be collected in the ongoing CorEvitas registry in a real-world population of moderate-to-severe psoriasis patients (including PsA patients) on secukinumab therapy.
Characterization of the risk:	In the short term placebo controlled period for the initial indication of adult psoriasis and psoriatic arthritis, the overall incidence of malignant or unspecified tumors by SMQ was similar between the secukinumab dose groups and placebo; no events were reported for etanercept group. The most frequently reported malignancy events were skin tumors, malignant or unspecified. The overall incidence of malignancies was low for ankylosing spondylitis, and no AEs were reported in the secukinumab dose groups and placebo for nr-axSpA**.** In the entire treatment period the exposure-adjusted incidence per 100 patient-years of malignant or unspecified tumors in the secukinumab dose groups was comparable to the placebo group across all the indications except for the indication of adult

Malignant or unspecified tumors	**Details**
	Psoriasis where there was a higher incidence in the placebo group compared to the active treatment groups. Malignancies related to skin were reported across all indications. However, there was no specific pattern observed for either skin or any other malignancy. Of note, for indication JIA there were no events of malignancy reported.
Risk factors and risk groups	**Psoriasis** Patients of older age, with previous skin cancer or actinic damage, family history of skin cancers, concurrent or history of immunosuppressive therapies or therapies known to increase skin cancer risk (i.e., cyclosporine, phototherapy especially PUVA) are reported to be at increased risk of NMSC. It is possible that an increased reporting of NMSC with biologics may be attributable to increased detection of skin cancer rather than increased development; however, studies comparing NMSC in patients on biologics with control patients also demonstrated increased rates of NMSC (Kamangar et al 2012). **Psoriatic Arthritis** As described in Section 2.2, the subset of PsA patients treated with DMARDS may be at increased risk of lymphoma. Evidence based conclusions cannot be reached with regard to risk groups/risk factors for NMSC in PsA patients, but it is possible that in PsA patients with plaque psoriasis, the risks may be shared with the overall psoriasis population. **Ankylosing Spondylitis** No specific risk groups or risk factors have been identified for malignancy in this patient population. **Juvenile idiopathic arthritis:** Slightly increased risk of lymphoproliferative, but not of other malignancies, has been reported, but there was no sign that the risk increased further after the introduction of DMARDs (Horne et al 2019). **Hidradenitis Suppurativa** As described in Section 2.5, there is a known increased risk of malignancies in HS patients. Squamous Cell Carcinoma (SCC) is a known complication from HS, it has been reported in individual cases and appears to be more common in men. A 2011 review of published cases of cutaneous SCC arising in HS found that SCC primarily occurred 20 to 30 years after the onset of HS (range 2 to 50 years) (Losanoff et al 2011). Approximately half of these patients died of metastatic disease. Human papilloma virus infection may be an important contributing factor to the development of SCC in lesions of HS (Lavogiez et al 2010).
Preventability	Early detection has a significant impact on progression of disease, treatment success, or even prevention if pre-cancerous lesions are addressed accordingly.
Impact on the benefit-risk balance of the product	Potential impact on the individual patient should be carefully evaluated and managed by the treating physician on a case by case basis.
Public health impact	The increased risk of malignancies in psoriasis patients has been reported in several studies, especially skin malignancies (NMSC), lymphomas and solid malignancies, and appears to be related to the use of systemic treatment, including biologic agents, although long-term assessment of the potential impact on public health is still limited and is being investigated in real-world use. In the absence of any evidence for an increased risk of malignancy in psoriatic arthritis, ankylosing spondylitis, nr-axSpA, pediatric psoriasis and JIA patients, the expected public health impact is anticipated to be low.
Sources	Annex 7

8.3.1.4 Important potential risk: Major Adverse Cardiovascular Events (MACE)

Table 8-4 Important potential risk – MACE

MACE	**Details**
Potential mechanisms	Although published data suggest a role of IL-17 in vascular inflammation and atherosclerosis, a unified concept of the relevance of IL-17 to human cardiovascular disease has yet to be defined. Research to date shows conflicting results regarding contributions of IL-17A to atherosclerotic plaque instability.
Evidence source(s) and strength of evidence	This is a therapeutic-class risk potentially associated with drugs with different mechanisms of action (e.g. TNF-inhibitors); an increased risk of MACE have not been demonstrated in patients treated with secukinumab in clinical trials and in the post-marketing setting.
Characterization of the risk	In the short term placebo-controlled period for the initial indication of adult psoriasis, the incidence of MACE cases was low (0.3%; 95%CI: 0.1, 1.2) and only in the 300 mg secukinumab group; none in placebo and etanercept groups. For all the other indications, no MACE cases were reported in any secukinumab group except in 75 mg dose group. In the entire treatment period the exposure-adjusted incidence per 100 patient-years of MACE in the secukinumab dose groups was higher for the indication of adult psoriasis and psoriatic arthritis and comparable to the placebo group for ankylosing spondylitis. No cases of MACE were reported for the indication nr-axSpA. For JIA, a serious adverse event of cerebral hemorrhage due to trauma was reported and was considered not related to secukinumab [CAIN457F2304E1 SCS]. For hidradenitis suppurativa, exposure-adjusted incidence per 100 patient-years of MACE in the secukinumab dose groups was slightly higher compared to the placebo group Across the treatment periods, the most frequently reported MACE events were myocardial infarction, acute myocardial infarction, hemorrhagic stroke and ischemic stroke and were reported as serious. Across all other indications and dose/treatment groups, no specific trend was observed.
Risk factors and risk groups	**Psoriasis and Psoriatic Arthritis** The increased cardiovascular risk in psoriasis and PsA patients is partly due to the association of psoriasis with factors that are known predictors of cardiovascular risk, including hyperlipidemia, obesity, hypertension, and diabetes. Whether an increased risk may also be linked to an independent role of psoriasis as a cardiovascular risk predictor over and above the association with these factors is still controversial, and robust data supporting a cause-effect relationship are lacking. The common role of a chronic inflammatory pathway as a contributing factor to this increased risk seems plausible and it is supported by some studies in the medical literature. **Ankylosing Spondylitis** Evidence suggests that AS patients may be at a slightly increased risk of MACE, although some studies have failed to identify any increase. No specific risk groups or risk factors have been identified within the overall population. The common role of a chronic inflammatory pathway as a contributing factor to any increased risk seems plausible and it is supported by some studies in the medical literature. **Juvenile Idiopathic Arthritis** Similarly in JIA, although several CVD risk factors are increased, no increase in CVD events was shown in patients, up to 29 years following disease onset when compared to the general population (Anderson et al 2016). **Hidradenitis Suppurativa:** As described in Section 2.5 MACE, including cerebrovascular events and myocardial infarction, as well as other risk factors for cardiovascular disease such as metabolic syndrome or T2DM or obesity are frequently associated with HS.
Preventability	The psoriasis population includes a high proportion of patients with various cardiovascular risk factors. Chronic inflammation may further increase the risk for

MACE	**Details**
	MACE events. Controlling inflammation could potentially prevent cardiovascular events.
Impact on the benefit-risk balance of the product	These events can result in disabling sequelae or death.
Public health impact	The potential public health impact of an increase in cardiovascular risk on the health of individuals can be serious, since these events can result in disabling sequelae or death.
Sources	Annex 7

8.3.1.5 Important potential risk: Hepatitis B reactivation

Table 8-5 Important potential risk-Hepatitis B reactivation

Hepatitis B reactivation	**Details**
Potential mechanisms	Hepatitis B reactivation has been reported in patients treated with other immunosuppressive drugs and biological treatments.
Evidence source(s) and strength of evidence	This is a therapeutic-class risk potentially associated with drugs with different mechanisms of action (e.g. TNF-inhibitors)**.**
Characterization of the risk:	Across the pivotal clinical trials in psoriasis, pediatric psoriasis, PsA, AS, JIA (also based on long-term treatment) and HS, no cases of Hepatitis B reactivation were reported.
Risk factors and risk groups	The risk factors for HBV reactivation during immunosuppression include history of prior inactive or resolved HBV infection. Reactivation is also more common in men, younger patients, and patients co-infected with hepatitis C virus (Motaparthi et al 2014).
Preventability	In accordance with clinical guidance for immunosuppressants, testing patients for HBV infection is to be considered before initiating treatment with secukinumab. Patients with evidence of positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation during secukinumab treatment. If reactivation of HBV occurs while on secukinumab, discontinuation of secukinumab treatment should be considered, and patients should be treated according to clinical guidelines.
Impact on the benefit-risk balance of the product	The effect of secukinumab on patients with hepatitis B infection is not known since no cases of hepatitis B reactivation have been reported in the pivotal trials.
Public health impact	The potential public health impact of hepatitis B reactivation with secukinumab is not known since there has been no clinical data of hepatitis B reactivation available to date. However, hepatitis B reactivation has been reported in patients treated with other immunosuppressive drugs and biological treatments. The clinical manifestation of hepatitis B reactivation varies significantly from asymptomatic flares to liver failure with fatal outcome.
Sources	Annex 7

8.3.1.6 Suicidal ideation and behavior

Table 8-6 Important potential risk-Suicidal ideation and behavior

Suicidal ideation and behavior (SIB)	**Details**
Potential mechanisms	To-date, the role of IL-17 (along with its receptors and antagonists) in the central nervous system is unclear. Class-G immunoglobulins (IgG), like secukinumab, are large molecules, are considered incapable of crossing the blood-brain barrier under normal conditions. In inflammatory states, low concentrations (about 300-fold lower than that of the serum) may be found in cerebrospinal fluid (Garg and Balthasar 2009). It is not clear whether these low-levels of IgG in the brain could have any effect.

Suicidal ideation and behavior (SIB)	**Details**
	Elevated levels of IL-17 have been detected in the central nervous system during inflammatory states such as seen in psoriasis and rheumatoid arthritis. IL-17 has been correlated with impaired blood–brain barrier integrity, activation of astrocytes and microglia, and disease progression in multiple sclerosis (Waisman et al 2015). Literature data also show that activation of the brain endothelium by IL-17A leads to blood-brain barrier disruption, while neutralizing IL-17A can improve the blood brain barrier tight junctions, potentially protecting the brain in the presence of systemic inflammation ally protecting the brain in the presence of systemic inflammation (Huppert et al 2010). IL-17 seems to play an important role in depression (Waisman et al 2015). IL-17A may play an important role in comorbid depression associated with psoriatic inflammation. Using a murine model of imiquimod-induced psoriasis, an enhanced expression of IL-17A in peripheral cells was associated with depression-like symptoms and increased NFκB/p38MAPK signaling and inflammation in the brain. The administration of IL-17A for 10 days lead to similar results. Finally, the administration of anti-IL17A antibody led to a reduction of the imiquimod-induced depression-like symptoms and of NFκB/p38MAPK signaling (Nadeem et al 2017).
Evidence source(s) and strength of evidence	This is a therapeutic-class risk potentially associated with drugs with different mechanisms of action (e.g. brodalumab); and no increased risk of suicidality has been identified in clinical trials and in the post-marketing settings.
Characterization of the risk:	For all indications, the number of suicidal ideation and behavior events were limited, but in general the overall incidence in the secukinumab dose groups was higher than the placebo group except for the indication of Ankylosing spondylitis and JIA where one event of SIB each was reported in placebo group. No further events were reported with long-term treatment in JIA [CAIN457F2304E1 SCS]. For hidradenitis suppurativa, there were SAEs related to suicidal ideation in patients with pre-existing medical history of depression. Psychiatric disorders (i.e., depression, anxiety) are known comorbidities and frequently associated with HS.
Risk factors and risk groups	Although no particular 'at-risk' patient subset has been identified, some studies suggest a higher risk of depression and SIB in patients with more severe forms of disease (Gupta and Gupta 1998, Kurd et al 2010, McDonough et al 2014, Jensen et al 2016). For hidradenitis suppurativa, the patients with high severity might have an impaired quality of life (QoL) as social interactions might be limited. As described in Section 2.5 there is a known association with impaired mental health notable anxiety and depression.
Preventability	As mentioned above, patients with psoriasis, PsA, AS and nr-axSpA, JIA and HS may present an increased risk for SIB, compared to the general population. It should be noted that patients with psychiatric disorders were not excluded from the secukinumab clinical trials, across all indications, according to the clinical judgment of the investigators.
Impact on the benefit-risk balance of the product	The potential individual impact can be serious, as SIB events will usually require medical attention, which may include hospitalization, and in the worst cases can be life-threatening or fatal.
Public health impact	Although the individual impact can be significant, the public health impact is not expected to be high, given that SIB events tend to be rare, even in populations with an increased risk compared to the general population.
Sources	Annex 7

8.3.2 SVII.3.2. Presentation of the missing information

Table 8-7 Missing information: Fetal exposure in utero

Fetal exposure in utero	**Details**
Evidence source	There are no adequate data from the use of secukinumab in pregnant women. Animal reproduction studies are not always predictive of human response. In a review of

Fetal exposure in utero	Details
	292 pregnancy cases in the Novartis safety database with a safety cut-off date of 25-Jun-2024 (48.3% of cases came from clinical trials, 27.1% were spontaneous reports and 24.7% were from post-marketing surveillance; 81.5% of cases were maternal and 18.5% had paternal exposure), there was no evidence for increased rates of adverse pregnancy outcomes with secukinumab compared to the observed rates for the general population (Warren et al 2018). However, only very limited conclusions can be drawn from these data due to the large amount of missing outcome data and due to the short exposure.
Anticipated risk/ consequence of the missing information:	Animal studies and limited post-marketing observation do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development. This missing information is closely monitored and presented in PSURs.

Table 8-8 Missing information: Long-term safety data

Long term safety data	Details
Evidence source	Long-term safety data (> 6 years) continue to be collected in several extension studies for all major indications including psoriasis, psoriatic arthritis, ankylosing spondylitis and hidradenitis suppurativa. Long-term safety data continue to be collected in the ongoing CorEvitas registry in a real-world population of moderate-to-severe psoriasis patients (including PsA patients) on secukinumab therapy.
Anticipated risk/ consequence of the missing information:	Available data from extension trials and cumulative post-marketing data do not indicate a different safety profile upon long-term exposure. The effects of long-term treatment on the benefit-risk profile of secukinumab from extension studies of core phase III studies and observational studies indicate that secukinumab demonstrates a favorable long-term safety profile. The overall benefit-risk profile continues to be favorable (and unchanged) in the approved indications.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Part II SVIII.1: Summary of safety concerns

Important identified risks	Infections and infestations Hypersensitivity
Important potential risks	Malignant or unspecified tumors Major Adverse Cardiovascular Events (MACE) Hepatitis B reactivation Suicidal ideation and behavior
Missing information	Fetal exposure in utero Long-term safety data

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists:

Targeted follow-up forms have not been proposed.

10.2 Part III.2. Additional pharmacovigilance activities

Psoriasis Registry study summary

Study short name and title:

Psoriasis registry study (CorEvitas formally Corrona Psoriasis Registry)

Rationale and study objectives:

The primary goal of the registry is to assess the incidence and nature of malignancies in a real-world population of moderate-to-severe psoriasis patients (including PsA patients) on secukinumab therapy.

Study design:

The Corrona registry was launched in Apr-2015, in collaboration with the National Psoriasis Foundation, to study the comparative safety of approved systemic psoriasis therapies, including the incidence and nature of malignancies, in a cohort of patients in a real world setting. The registry is designed as a prospective, multicenter, observational registry for patients with psoriasis. Its sample size of around 8000 patients (3000 on secukinumab) and a minimum of eight years of observation duration will allow detection of even rare events such as malignancies.

Study population:

Participating investigators recruit subjects with psoriasis from their own patient populations. To be eligible for enrollment into the Registry, subjects must be 18 years of age or older, must have psoriasis diagnosed by a dermatologist, and must have been started on or switched to a systemic psoriasis treatment within the previous 12 months.

Milestones:

Progress reports including data presentation to be included in DSUR/PSUR according to the regulated timelines

Interim study report submission: June-2030

LPLV: June-2032

Final study report submission: June-2033

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances.				
Category 3 - Required additional pharmacovigilance activities.				
CorEvitas Psoriasis Registry Ongoing	The primary goal of the registry is to assess the incidence and nature of malignancies in a real-world population of moderate-to-severe psoriasis patients (including PsA patients) on secukinumab therapy.	Malignant or unspecified tumors Long-term safety Suicidal ideation and behavior	Final study report submission	June-2033

11 Part IV: Plans for post-authorization efficacy studies

This section is not applicable as there are no post-authorization efficacy studies planned for secukinumab.

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important Identified Risks	
Infections and infestations	**Routine risk communication:** • SmPC Sections 4.3, 4.4, 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine
Hypersensitivity	**Routine risk communication:** • SmPC Sections 4.3, 4.4, 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine
Important potential risks	
Malignant or unspecified tumors	**Routine risk communication:** • No specific measures are required for patients receiving secukinumab - standard of care is adequate. • General knowledge about immunomodulating biologics includes awareness of potential carcinogenicity. Although no specific such risk was identified for secukinumab, prescribing doctors are expected to apply due diligence in surveying any patient on such therapy for early signs of malignancy. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • .Prescription only medicine
Major Adverse Cardiovascular events (MACE)	**Routine risk communication:** • No specific measures are required for patients receiving secukinumab - standard of care is adequate. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine.
Hepatitis B reactivation	**Routine risk communication:** • SmPC Section 4.4 **Routine risk minimization activities recommending specific clinical measures to address the risk:**

Safety concern	Routine risk minimization activities
	• In accordance with clinical guidance for immunosuppressants, testing patients for HBV infection is to be considered before initiating treatment with secukinumab. Cosentyx should not be given to patients with active hepatitis B. Patients with evidence of positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation during secukinumab treatment. If reactivation of HBV occurs while on secukinumab, discontinuation of the treatment should be considered, and patients should be treated according to clinical guidelines. **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine.
Suicidal ideation and behavior	**Routine risk communication:** • No specific measures are required for patients receiving secukinumab - standard of care is adequate. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine.
Missing information	
Fetal exposure in utero	**Routine risk communication:** • SmPC Section 4.6. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine.
Long-term safety data	**Routine risk communication:** • No risk minimization measure is considered necessary at this time. Routine risk minimization (standard of care for the target population) is considered sufficient. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine.

12.2 Part V.2. Additional Risk minimization measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

12.3 Part V.3. Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important Identified Risks		
Infections and infestations	**Routine risk minimization measures** SmPC Section 4.3, 4.4, 4.8	None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures No risk minimization measures	
Hypersensitivity	**Routine risk minimization measures** SmPC Section 4.3, 4.4, 4.8 **Additional risk minimization measures** No risk minimization measures	None
Important Potential Risks		
Malignant or unspecified tumors	None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Registry to assess incidence and nature of malignancies in a real-world population of moderate-to-severe psoriasis patients (including PsA patients) on secukinumab therapy; estimated sample size 3000, follow up period of 8 years
Major Adverse Cardiovascular Events (MACE)	None	None
Hepatitis B reactivation	**Routine risk minimization measures** SmPC Section 4.4 **Additional risk minimization measures** No risk minimization measures	None
Suicidal ideation and behavior	None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Registry to assess incidence and nature of malignancies in a real-world population of moderate-to severe psoriasis patients (including PsA) on secukinumab therapy will also be utilized to assess long-term safety, including SIB; estimated sample size 3000, follow up period of 8 years.
Missing Information		
Fetal exposure in utero	**Routine risk minimization measures** SmPC Section 4.6 **Additional risk minimization measures** No risk minimization measures	None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Long-term safety data	None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Registry to assess incidence and nature of malignancies in a real-world population of moderate-to-severe psoriasis patients (including PsA patients) on secukinumab therapy; estimated sample size 3000, follow up period of 8 years. A study to evaluate the long-term efficacy of subcutaneously administered secukinumab (provided as pre-filled syringes) with respect to JIA ACR30 response over time up to Week 308 visit in patients with active JPsA and ERA subtypes of JIA and who completed the Phase III study CAIN457F2304.

13 Part VI: Summary of the risk management plan for Cosentyx (secukinumab)

This is a summary of the risk management plan (RMP) for Cosentyx. The RMP details important risks of Cosentyx, and how these risks can be minimized, and how more information will be obtained about Cosentyx's risks and uncertainties (missing information).

Cosentyx's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Cosentyx should be used.

This summary of the RMP for Cosentyx should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Cosentyx RMP.

13.1 Part VI: I. The medicine and what it is used for

Cosentyx is authorized for:

- Psoriasis (adults)

The treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

- Psoriasis (pediatrics)

The treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy.

- Psoriatic arthritis (PsA)

The treatment of active psoriatic arthritis in adult patients as a single agent or in combination with methotrexate, when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

- Ankylosing Spondylitis

The treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

- Non-radiographic axial spondyloarthritis (nr-axSpA)

The treatment of active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs).

- Juvenile Idiopathic Arthritis (JIA)
  - Enthesitis-Related Arthritis (ERA)

    The treatment of active enthesitis-related arthritis in patients 6 years of age and older as a single agent or in combination with methotrexate (MTX), when the disease has responded inadequately to, or who cannot tolerate, conventional therapy.
  - Juvenile Psoriatic Arthritis (JPsA)

The treatment of active juvenile psoriatic arthritis in patients 6 years of age and older as a single agent or in combination with methotrexate (MTX), when the disease has responded inadequately to, or who cannot tolerate, conventional therapy.

- Hidradenitis Suppurativa (HS)

The treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. (See SmPC for the full indication).

It contains secukinumab as the active substance and it is given by subcutaneous injection [powder for solution for injection, solution for injection in pre-filled syringe or solution for injection in pre-filled pen]

Further information about the evaluation of Cosentyx's benefits can be found in Cosentyx's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link to product's EPAR summary landing page on the EMA webpage. https://www.ema.europa.eu/en/medicines/human/EPAR/cosentyx

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Cosentyx, together with measures to minimize such risks and the proposed studies for learning more about Cosentyx risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Cosentyx is not yet available, it is listed under 'missing information' below.

13.2.1 Part VI: II.A: List of important risks and missing information

Important risks of Cosentyx are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered/ taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Cosentyx. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information

refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 13-1 List of important risks and missing information

Important identified risks	Infections and infestations Hypersensitivity
Important potential risks	Malignant or unspecified tumors Major Adverse Cardiovascular Events (MACE) Hepatitis B reactivation Suicidal ideation and behavior
Missing information	Fetal exposure in utero Long-term safety data

13.2.2 Part VI: II.B: Summary of important risks

Table 13-2 Important identified risk: Infections and infestations

Evidence for linking the risk to the medicine	As with any immunomodulator, secukinumab has the potential to increase the risk of infections. In clinical studies, an increased risk for infections have been observed, mostly mild or moderate, responsive to usual treatment and not requiring discontinuation. A similar pattern of events have been identified in the post-marketing setting and medical literature (Blauvelt 2016)
Risk factors and risk groups	Severe psoriasis is recognized as a risk factor for infections (Wakkee et al 2011). Other predictors for multiple infectious diseases were the use of anti-diabetic drugs, and COPD/anti-asthmatic drugs (Wakkee et al 2011). The use of systemic psoriasis therapies does seem to increase the risk of infections, although the individual long-term safety profiles are still being investigated in real-world use. Spondyloarthropathies can be associated with an increased risk for infections with incidence rates of infection around 5.3 per 100 PY (Perez-Sola et al 2011; Grijalva et al 2011). In a recent systematic review of randomized trials, the risk of serious infections among patients with AS was 0.4 per 100 PY, while in those treated with TNF blockers the incidence was 2.2 per 100 PY (Fouque-Aubert et al 2010). In JIA, an increased risk for bacterial infections has been described (Beukelmann et al 2012). Whether treatment with biologic agents further increases the risk is not clear (Aeschlimann 2019). Using claims data, Beukelman et al found that the rate of infections requiring hospitalization was not increased in patients with JIA treated with MTX or anti-TNF, but was increased with high-dose glucocorticoids (Beukelmann et al 2012). Cultures from early, unruptured HS lesions are usually sterile. Whereas older and ruptured lesions and sinuses may demonstrate a wide variety of bacteria (eg, staphylococci, streptococci, Gram-negative rods, and anaerobic bacteria) (Sartorius et al 2012). Long-standing, poorly controlled HS may lead to significant complications including infectious complications (eg, lumbosacral epidural abscess, sacral bacterial osteomyelitis) (Alikhan et al 2009).A study using National Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project (HCUP), showed that inpatients with HS had a higher prevalence (33·9% (33·1–34·6%) 95% CI) of serious infections than those without HS, with a significantly higher odds of any serious infection: aOR 2·30 (95% CI 2·21–2·39). Inpatients with HS with multifactorial comorbidities, notably cancer and HIV, appear to be at risk for developing infections. Patients with HS with long-term systemic corticosteroid use (as judged by a diagnosis of Cushing syndrome or long-term corticosteroid use) were not associated with increased infections (Lee et al 2019).

Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.3, 4.4, 4.8 **Additional risk minimization measures** No risk minimization measures

Table 13-3 Important identified risk: Hypersensitivity

Evidence for linking the risk to the medicine	Hypersensitivity events, including rare cases of anaphylactic reactions have been observed in clinical studies. The majority of evens were mild to moderate. A similar pattern of events have been identified in the post-marketing setting and medical literature, although secukinumab displayed a minimal immunogenicity potential in pooled Phase 3 trials (Reich et al 2017).
Risk factors and risk groups	Patients with prior allergic reactions are at increased risk.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.3, 4.4, 4.8 **Additional risk minimization measures** No risk minimization measures

Table 13-4 Important potential risk: Malignant or unspecified tumors

Evidence for linking the risk to the medicine	This is a therapeutic-class risk potentially associated with drugs with different mechanisms of action (e.g. TNF-inhibitors). Current evidence is based on clinical data (in comparison with general population), post-marketing experience in the context of estimated exposure > 1.8 million patient-years and literature review.
Risk factors and risk groups	**Psoriasis:** Patients of older age, with previous skin cancer or actinic damage, family history of skin cancers, concurrent or history of immunosuppressive therapies or therapies known to increase skin cancer risk (i.e., cyclosporine, phototherapy especially PUVA) are reported to be at increased risk of NMSC. It is possible that an increased reporting of NMSC with biologics may be attributable to increased detection of skin cancer rather than increased development; however, studies comparing NMSC in patients on biologics with control patients also demonstrated increased rates of NMSC (Kamangar et al 2012). **Psoriatic Arthritis** The subset of PsA patients treated with DMARDs may be at increased risk of lymphoma. Evidence based conclusions cannot be reached with regard to risk groups/risk factors for NMSC in PsA patients, but it is possible that in PsA patients with plaque psoriasis, the risks may be shared with the overall psoriasis population. **Ankylosing Spondylitis** No specific risk groups or risk factors have been identified for malignancy in this patient population. **JIA** Slightly increased risk of lymphoproliferative, but not of other malignancies, has been reported, but there was no sign that the risk increased further after the introduction of DMARDs (Horne et al 2019). **Hidradenitis Suppurativa:** As described in Section 2.5, there is a known increased risk of malignancies in HS patients. Squamous Cell Carcinoma (SCC) is a known complication from HS, it has been reported in individual cases and appears to be more common in men. A 2011 review of published cases of cutaneous SCC arising in HS found that SCC primarily occurred 20 to 30 years after the onset of HS (range 2 to 50 years) (Losanoff et al 2011). Approximately half of these patients died of metastatic disease. Human papilloma virus infection may be an important

	contributing factor to the development of SCC in lesions of HS (Lavogiez et al 2010).
Risk minimization measures	No risk minimization measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Corrona Psoriasis Registry (CorEvitas) See section II.C of this summary for an overview of the post-authorisation development plan

Table 13-5 Important potential risk: MACE

Evidence for linking the risk to the medicine	This is a therapeutic-class risk potentially associated with drugs with different mechanisms of action (e.g. TNF-inhibitors); an increased risk of MACE have not been demonstrated in patients treated with secukinumab in clinical trials and in the post-marketing setting.
Risk factors and risk groups	**Psoriasis and Psoriatic Arthritis:** The increased cardiovascular risk in psoriasis and PsA patients is partly due to the association of psoriasis with factors that are known predictors of cardiovascular risk, including hyperlipidemia, obesity, hypertension, and diabetes. Whether an increased risk may also be linked to an independent role of psoriasis as a cardiovascular risk predictor over and above the association with these factors is still controversial, and robust data of a cause-effect relationship are lacking. The common role of a chronic inflammatory pathway seems plausible and it is supported by some studies in the medical literature. **Ankylosing Spondylitis:** Evidence suggests that AS patients may be at a slightly increased risk of MACE, although some studies have failed to identify any increase. No specific risk groups or risk factors have been identified within the overall population. The common role of a chronic inflammatory pathway as a contributing factor to any increased risk seems plausible and it is supported by some studies in the medical literature. Similarly in JIA, although several CVD risk factors are increased, no increase in CVD events was shown in patients, up to 29 years following disease onset when compared to the general population (Anderson et al 2016). **Hidradenitis Suppurativa**: As described in Section 2.5 MACE, including cerebrovascular events and myocardial infarction as well as other risk factors for cardiovascular disease such as metabolic syndrome or T2DM or obesity, are frequently associated with HS.
Risk minimization measures	No risk minimization measures.

Table 13-6 Important potential risk: Hepatitis B reactivation

Evidence for linking the risk to the medicine	This is a therapeutic-class risk potentially associated with immunomodulating drugs**.**
Risk factors and risk groups	The risk factors for HBV reactivation during immunosuppression include history of prior inactive or resolved HBV infection. Reactivation is also more common in men, younger patients, and patients co-infected with hepatitis C virus (Motaparthi et al 2014).
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.4 **Additional risk minimization measures** No risk minimization measures

Table 13-7 Important potential risk: Suicidal ideation and behavior

Evidence for linking the risk to the medicine	This is a therapeutic-class risk potentially associated with drugs with different mechanisms of action (e.g. brodalumab); and no increased risk of suicidality has been identified in clinical trials and in the post-marketing settings.
Risk factors and risk groups	Although no particular 'at-risk' patient subset has been identified, some studies suggest a higher risk of depression and SIB in patients with more severe forms of disease (Gupta and Gupta 1998, Kurd et al 2010, McDonough et al 2014, Jensen et al 2016). For hidradenitis suppurativa, the patients with high severity might have an impaired quality of life (QoL) as social interactions might be limited. As described in Section 2.5 there is a known association with impaired mental health notable anxiety and depression.
Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** CorEvitas Psoriasis Registry: See section II.C of this summary for an overview of the post-authorisation development plan

Table 13-8 Missing information: Fetal exposure in utero

Evidence for linking the risk to the medicine	There are no adequate data from the use of secukinumab in pregnant women. Animal reproduction studies are not always predictive of human response.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.6 **Additional risk minimization measures** No risk minimization measures

Table 13-9 Missing information: Long-term safety data

Evidence for linking the risk to the medicine	Long-term safety data continue to be collected in the ongoing CorEvitas registry in a real-world population of moderate-to-severe psoriasis patients (including PsA patients) on secukinumab therapy.
Risk minimization measures	No risk minimization measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** CorEvitas Psoriasis Registry: See section II.C of this summary for an overview of the post-authorisation development plan

13.2.3 Part VI: II.C: Post-authorization development plan

13.2.3.1 II.C.1. Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation for Cosentyx.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

Table 13-10 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
CorEvitas Psoriasis Registry	The primary goal of the registry is to assess the incidence and nature of malignancies in a real-world population of moderate-to-severe psoriasis patients (including PsA patients) on Cosentyx therapy.

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Not applicable.