NOVARTIS

Patient Safety & Pharmacovigilance

Cosentyx®, powder for solution for injection, solution for injection, and concentrate for solution for infusion (secukinumab)

PERIODIC SAFETY UPDATE REPORT (PSUR)

Period covered by this report: 26 Dec 2020 – 25 Dec 2023
International Birth Date: 26 Dec 2014 (Japan)

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EU Qualified person for Pharmacovigilance	PD [redacted], B.Sc (Hons) PhD The assigned Global Program Safety Lead is the responsible medical safety expert for this product and is authorized by the EU-QPPV to sign this PSUR. PD [redacted] Digitally signed by PD [redacted] DN: dc=com, dc=novartis, ou=people, ou=GD, serialNumber=2481016, cn=PD [redacted] PD [redacted] Reason: I am the author of this document Date: 2024.02.22 15:01:21 +01'00' (PD [redacted], Global Program Safety Lead)
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Local brand names are available in Appendix 1.2

Executive Summary

This document is the Periodic Safety Update Report (PSUR) for Cosentyx® (secukinumab) covering the reporting interval from 26 Dec 2020 to 25 Dec 2023. The product is referred to as Cosentyx, AIN457 or secukinumab interchangeably throughout this report.

This report includes data obtained from Novartis Pharma (hereafter referred to as Novartis) and license partner, CCI . This report is being prepared by Novartis on behalf of both the companies.

A critical analysis of the efficacy and safety data revealed that the overall benefit-risk profile of Cosentyx remains favorable.

The following actions have been taken during the reporting:

- Upon request from Food and Drug Administration, the United States Prescribing Information (USPI) was updated to include Adverse drug reactions (ADR) "dyshidrotic eczema", "atopic-dermatitis-like eruptions" and "erythroderma" in the post-marketing Section 6.2 and to include warning for eczematous eruptions, including atopic dermatitis-like eruption, dyshidrotic eczema, and erythroderma in Section 5 of the USPI. (approved 24 Jul 2023)
- Upon request from The Pharmaceuticals and Medical Devices Agency, the Japan Risk Management Plan (RMP) was updated to include CCI as an important potential risk (Dec 2021)
- The European Union RMP has been updated to include the extension study CAIN457F2304E1 as additional pharmacovigilance activity
- The South African product information has been updated regarding the warning for tuberculosis reactivation. Furthermore, a local annex to the RMP was added regarding South African specific Important Comorbidities (Human Immunodeficiency Virus and Latent Tuberculosis Infection)
- The Korean national product information has been updated with a table presenting Serious and unexpected ADRs as per results from the local Post Marketing Surveillance study CAIN457AKR03.
- The Taiwanese prescribing information has been updated with inclusion of specific language about risk of hepatitis B reactivation (HBV-R) in the Warnings and Precautions section of the Cosentyx label/product information.

The cumulative safety and efficacy experience and efficacy experience for Cosentyx remains in accord with the Core Data Sheet (CDS v3.4 dated 19 Jan 2023 (corrected on 27 Mar 2023)) and the Risk Management Plan (RMP v11.1 dated 30 Sep 2022, effective 26 May 2023).

- Within the reporting interval, the Cosentyx CDS version 2.7 was updated to CDS version 2.8 (dated 19 Jan 2021) to include additional dosing information for adults with psoriasis (PsO) to allow flexible dosing. The CDS update version 3.0 (dated 31 Mar 2021), which was triggered by the periodic review of the CDS in accordance with standard Novartis practices. The CDS version 3.0 included a safety labeling change

related to Inflammatory Bowel Disease . The Warnings and Precautions section was revised to include the information from post-marketing use related to cases of new onset Inflammatory Bowel Disease, and Inflammatory Bowel Disease was added to the ADR Table 7-1of the CDS version 3.0.

- The Cosentyx CDS version 3.0 was amended to CDS version 3.1 (dated 16 Jun 2021) to include a new indication for the Enthesitis Related Arthritis (ERA) and Juvenile Psoriatic Arthritis (JPsA) categories of Juvenile Idiopathic Arthritis (JIA).
- The Cosentyx CDS version 3.1 was amended to CDS version 3.2 (dated 16 Dec 2021 and corrected 20 Dec 2021) to add the new post-marketing ADR "Dyshidrotic Eczema".
- The Cosentyx CDS version 3.2 (dated 16 Dec 2021 and corrected 20 Dec 2021) was amended to CDS version 3.3 (dated 31 Aug 2022) to add Hidradenitis Suppurativa as a new indication.
- The Cosentyx CDS version 3.3 was amended to CDS version 3.4 (dated 19 Jan 2023 and corrected on 27 Mar 2023) to include "pyoderma gangrenosum" as a new post-marketing ADR. In addition, the Instructions for Use for all approved pre-filled syringes (PFS) with Needle Safety Device (NSD) have been revised to include a "device drop statement" instructing the patients to use a new device if the PFS with NSD is dropped onto a hard surface or dropped without the needle caps.

At the beginning of the PSUR reporting interval, the effective RMP was v7.1 (dated 04 Sep 2020; effective 20 Nov 2020) which was:

- Updated to v8.3 (dated 06 May 2021; effective 16 Jul 2021) based on the Pharmacovigilance Risk Assessment Committee (PRAC) assessment report received on 25 Feb 2021 as part of procedure EMEA/H/C/003729/X/0067 submitted to register the new strength of 75 mg/0.5 ml solution for injection in pre-filled syringe. Based on GVP module V, Rev 2 and the accumulated clinical trial and post-marketing experience with secukinumab, the safety topics that have been agreed upon by PRAC for retirement from the RMP are 'Neutropenia', 'Interactions with live vaccines', 'Long-term efficacy data', 'Patients with CCI [redacted]' and 'Patients with CCI [redacted]'. Additionally, based on PRAC's recommendation, the important potential risk 'Inflammatory Bowel Disease' has been removed from the list of safety concerns.
- Further updates to the RMP (RMP v9.3 dated 01 Dec 2021; effective 20 Jan 2022) included a new flexible dosing recommendation for plaque psoriasis and psoriatic arthritis in adult patients for which some patients may derive additional benefit from Cosentyx 300 mg every 2 weeks (Q2W).
- The RMP v9.3 was further updated to RMP v10.2 (dated 07 Mar 2022; effective 20 Jun 2022) to include the new indication for the treatment of JIA in patients six years of age and older.
- Most recently, the RMP was updated to RMP v11.1 (dated 30 Sep 2022; effective 26 May 2023) to include the new indication for the treatment of Hidradenitis Suppurativa.

An overview of all important identified and potential risks as well as missing information is provided in the following table.

Conclusion and actions	Risks / missing information
There has been no change in the risk profile / missing information; it will continue to be reviewed in the next PSUR.	***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
These risks have been removed from the list of safety concerns on 06 Apr 2021, RMP v.8.1 and adopted by PRAC (EMEA/H/C/003729/X/67): There has been no change on secukinumab risk-benefit balance or have implications for public health. These risks are well characterized and documented in the CDS. Therefore, it is proposed to consider these risks as identified and potential risks not categorized as important and no longer review them in subsequent PSURs unless a validated signal arises.*	***Important identified risks*** Neutropenia ***Important potential risks*** Inflammatory bowel disease
These risks and missing information have been removed from the list of safety concerns on 06 Apr 2021, RMP v.8.1 and adopted by PRAC (EMEA/H/C/003729/X/67): The overall evaluation of data indicates neither an increased risk nor a causal relationship with Cosentyx; with no change on secukinumab risk-benefit balance or implications for public health. Therefore, it is proposed to consider them as risks / missing information not categorized as important and no longer review them in subsequent PSURs unless a validated signal arises.	***Important potential risks*** Interaction with live vaccines ***Missing information*** Patients with CCI [redacted]
This missing information has been removed from the list of safety concerns on 06 Apr 2021, RMP v.8.1 and adopted by PRAC (EMEA/H/C/003729/X/67): Based on an RMP commitment, the effects of long-term treatment on the benefit-risk profile of secukinumab are being studied in extension studies to the core phase III studies. During the reporting interval, long-term studies and cumulative post-marketing data (9 years) have confirmed the known benefit – risk profile of secukinumab on the authorized indications.	***Missing information*** Long-term efficacy data

Conclusion and actions	Risks / missing information
Based on the endorsement by PRAC in the previous PSUR (EMEA/H/C/PSUSA/00010341/202012); these missing information follow routine pharmacovigilance practices and will not be reviewed in PSURs unless a new signal arises.	***Missing information*** Patients with CCI [redacted] Patients with CCI [redacted]

PSUR: Periodic Safety Update Report

Source: EU RMP v7.1 (dated 04 Sep 2020; effective 20 Nov 2020) and RMP v11.1 (dated 30 Sep 2022; effective 26 May 2023 (Part II, Module SVIII 'Summary of the safety concerns')

* Important risks are those which could have an impact on the benefit-risk balance of the product.

During the reporting interval a total of 10 signals and one signal post the data lock point were detected. Of these 11 signals, four (Eczematous eruptions including atopic dermatitis like eruptions and dermatitis exfoliative generalized (erythroderma), Pyoderma gangrenosum Dyshidrotic Eczema and Angioedema) were confirmed as ADRs and categorized as identified risks not categorized as important. The remaining CCI [redacted] were closed as refuted.

An overview of all the request from the PRAC assessment report for previous PSUR covering period 26 Dec 2019 to 25 Dec 2020 (EMEA/H/C/PSUSA/00010341/202012 dated 08 Jul 2021), as well as other health authorities' requests is included in Appendix 6.

A summary of the product information, regulatory information, and patient exposure is provided in the following table.

Product information	
Secukinumab is an interleukin inhibitor. It is a fully human immunoglobulin G1 antibody that selectively binds to and neutralizes the proinflammatory cytokine interleukin-17A (IL-17A). Secukinumab works by targeting IL-17A and inhibiting its interaction with the IL-17 receptor, which is expressed on various cell types including keratinocytes and synoviocytes. As a result, secukinumab inhibits the release of proinflammatory cytokines, chemokines and mediators of tissue damage and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases, including psoriasis (including pediatric psoriasis), psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, juvenile idiopathic arthritis (juvenile psoriatic arthritis and enthesitis related arthritis subtypes), hidradenitis suppurativa and pustular psoriasis (Japan only). Secukinumab is to be administered subcutaneously and the product is available as: 1) 150 mg powder for solution for injection, 2) 150 mg/1 mL solution for injection as pre-filled syringe or pre-filled pen, 3) 300 mg/2 mL solution for injection as pre-filled syringe or pre-filled pen and 4) 75 mg/0.5 mL solution for injection as pre-filled syringe or pre-filled pen. For intravenous administration for psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis, a 125 mg/5 mL secukinumab solution in a single-dose vial is available in the United States only.	
Regulatory information	
Novartis is currently MAH in 110 countries worldwide.	
Exposure	
Estimated cumulative subject exposure in clinical trials (IMP only) (number of patients)	**Cumulative**
	25,394

Estimated market experience (expressed in patient treatment years	**Reporting interval**	**Cumulative**
	CCI	1,882,445

IMP: Investigational Medicinal Product: MAH: Marketing Authorization Holder

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List of abbreviations

ACR	American College of Rheumatology
ADR	Adverse Drug Reaction
AE	Adverse Event
AGEP	Acute Generalized Exanthematous Pustulosis
ANC	Absolute Neutrophil Count
AS	Ankylosing Spondylitis
ASAS	Assessment of SpondyloArthritis international Society
ax-SpA	axial SpondyloArthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
CD	Crohn's disease
CDS	Core Data Sheet
CI	Confidence Interval
CK	Creatine Kinase
CLL	Chronic Lymphocytic Leukemia
CMM	Cutaneous Malignant Melanoma
COVID-19	Corona Virus Disease-2019
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CSR	Clinical Study Report
CSU	Chronic Spontaneous Urticaria
CT	Clinical Trial
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
CVA	Cerebrovascular Accident
DAS28-CRP	Disease Activity Score 28-C-Reactive Protein
DIBD	Developmental International Birth Date
DLP	Data Lock Point
DLQI	Dermatology Life Quality Index
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
EAIR	Exposure-adjusted incidence rates
EB	Empirical Bayes
ECG	Electrocardiography / Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Enthesitis Related Arthritis
EU	European Union
EVDAS	EudraVigilance Data Analysis System
FAERS	Food and Drug Administration-Adverse Event Reporting System
GCP	Good Clinical Practice
GERD	Gastro-Esophageal Reflux Disease
GI	Gastro-Intestinal
GVP	Good Pharmacovigilance Practice
HA	Health Authority

HAQ-DI	Health Assessment Questionnaire Disability Index
HBsAb	Hepatitis B Surface Antibody
HBV	Hepatitis B Virus
HCP	Healthcare Professional
HIV	Human Immunodeficiency Virus
HiSCR	Hidradenitis Suppurativa Clinical Response
HLA	Human Leukocyte Antigen
HLGT	High-Level Group Term
HLT	High Level Term (of MedDRA)
HS	Hidradenitis Suppurativa
IBD	Inflammatory Bowel Disease
IBDU	Inflammatory Bowel Disease Unclassified
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Report
IFU	Instructions For Use
IGA	Investigator's Global Assessment
IgG1	Immunoglobulin G1
IL	Interleukin
IME	Important Medical Event
IMP	Investigational Medicinal Product
JIA	Juvenile Idiopathic Arthritis
JPsA	Juvenile Psoriatic Arthritis
LRTI	Lower Respiratory Tract Infection
LT	Life-threatening
MAA	Marketing Authorization Approval
MACE	Major Adverse Cardiovascular Events
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MR	Market Research
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribo-Nucleic Acid
MTX	Methotrexate
NIS	Non-Interventional Study
NMQ	Novartis customized MedDRA Query
NMSC	Non-melanoma Skin Cancer
NPF	National Psoriasis Foundation
nr-axSpA	non-radiographic axial SpondyloArthritis
NSAID	Non-Steroidal Anti-Inflammatory Drug
NYHA	New York Heart Association Functional Classification
PAES	Post-Authorization Efficacy Study
PASI	Psoriasis Area and Severity Index
PASS	Post-Authorization Safety Study
PBO	Placebo
PD	Pharmacodynamics

PFS	Pre-filled Syringe
PGA	Physician Global Assessment
PK	Pharmacokinetics
PMS	Post Marketing Surveillance
ppPASI	palmoplantar pustulosis Psoriasis Area and Severity Index
PRAC	Pharmacovigilance Risk Assessment Committee
PsA	Psoriatic Arthritis
Pso	Psoriasis
PSP	Patient Support Program
PSUR	Periodic Safety Update Report
PT	Preferred Term
PTY	Patient-Treatment-Year
QMO	Once in a month
QoL	Quality of Life
QPPV	Qualified Person for Pharmacovigilance
QW	Once in a week
RA	Rheumatoid Arthritis
RMP	Risk Management Plan
ROR	Reporting Odds Ratio
ROW	Rest of the World
s.c.	Subcutaneous
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SCAR	Serious Cutaneous Adverse Reactions
SCC	Squamous Cell Carcinoma
SIAQ	Self-Injection Assessment Questionnaire
SIB	Suicidal Ideation and Behavior
SJS	Stevens-Johnson Syndrome
SmPC	Summary of Medicinal Product Characteristics
SMQ	Standardized MedDRA Queries
SOC	System Organ Class (of MedDRA)
SoR	Start of Relapse
SpA	Spondylo-Arthritis
SR	Spontaneous Report
TB	Tuberculosis
TCS	Total Clinical Score
TEN	Toxic Epidermal Necrolysis
TNF	Tumor Necrosis Factor
TTO	Time-To-Onset
UC	Ulcerative Colitis
USA	United States of America
UV	Ultraviolet
WBC	White Blood Cell

1 Introduction

This document is the Periodic Safety Update Report (PSUR) for Cosentyx® (secukinumab) covering the period from 26 Dec 2020 to 25 Dec 2023 (referred to as the reporting interval in the remainder of this report). The previous PSUR covered the period from 26 Dec 2019 to 25 Dec 2020[1]. It is compiled in the format detailed in the International Council for Harmonization-E2C[2] and European Union (EU) guidelines.

This report includes data obtained from Novartis Pharma (hereafter referred to as Novartis) and license partner, CCI . This report is being prepared by Novartis on behalf of both the companies.

The product is referred to as Cosentyx, AIN457 or secukinumab interchangeably throughout this report.

The International Birth Date of Cosentyx is 26 Dec 2014 (Japan).

Secukinumab is an interleukin inhibitor. It is a fully human immunoglobulin G1 (IgG1) antibody that selectively binds to and neutralizes the proinflammatory cytokine interleukin-17A (IL-17A). Secukinumab works by targeting IL-17A and inhibiting its interaction with the IL-17 receptor, which is expressed on various cell types including keratinocytes and synoviocytes. As a result, secukinumab inhibits the release of proinflammatory cytokines, chemokines and mediators of tissue damage and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases. The product is indicated for adult patients with moderate to severe plaque psoriasis (Pso), psoriatic arthritis (PsA), ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA), and severe hidradenitis suppurativa (HS). The product is also indicated for pediatric patients with moderate to severe plaque Pso and juvenile idiopathic arthritis (JIA) subtypes juvenile psoriatic arthritis (JPsA) and enthesis-related arthritis (ERA). In Japan, secukinumab is also authorized for the treatment of pustular psoriasis (PP). For these indications, it is available as 150 mg powder for solution for injection, 75 mg/0.5 mL solution for injection (pediatric patients below 50 kg of body weight), 150 mg/1 mL solution for injection, and 300 mg/2 mL solution for injection to be delivered via subcutaneous administration. In addition, secukinumab for intravenous administration (125mg/ 5 mL concentrate solution for infusion in single-dose vial or liquid in vial at a dose of 1.75 mg/kg is approved for adult patients with PsA, AS, and nr-axSpA in the USA (Unites States of America) only.

Further details on mechanism of action, indications, pharmaceutical forms and instructions for use are presented in Appendix 1.1 (Core Data Sheet [CDS], v3.4).

2 Worldwide marketing authorization status

Cosentyx was first registered in Japan on 26 Dec 2014. Novartis and CCI (a CCI company) are currently the Marketing authorization holder (MAH) in 110 countries worldwide (see Appendix 1.2).

Cosentyx is registered in the following indication(s): moderate to severe PsO (adult and pediatric populations), PsA, axSpA (which includes AS and nr-axSpA), PP (Japan only), JIA (JPsA and ERA subtypes) and HS.

In the EU, secukinumab was approved through the centralized procedure on 15 Jan 2015 for adult moderate to severe PsO and on 31 Jul 2020 for pediatric moderate to severe PsO; on 19 Nov 2015 for PsA and AS; on 28 Apr 2020 for nr-axSpA; on 20 Jun 2022 for JIA (JPsA and ERA subtypes) and on 26 May 2023 for HS. In the USA, secukinumab was approved on 21 Jan 2015 for adult moderate to severe PsO; on 28 May 2021 for pediatric moderate to severe PsO; on 15 Jan 2016 for PsA and AS; on 16 Jun 2020 for nr-axSpA; on 22 Dec 2021 for JIA (JPsA and ERA subtypes); and on 31 Oct 2023 for HS. Details about recommended subcutaneous posology are described in Appendix 1.1'Core Data Sheet'.

In the USA, on 06 Oct 2023, the biologic license application (BLA) for Cosentyx for intravenous (i.v) administration was approved by the FDA (BLA 761349) under the same brand name and sharing the label with the subcutaneous formulation. Cosentyx for i.v. use is indicated for adults with active PsA, active AS, and active nr-axSpA with objective signs of inflammation. The approved posology for the Cosentyx for i.v. use in all three indications is as follows:

- With a loading dosage: 6 mg/kg given at Week 0 as a loading dose, followed by 1.75 mg/kg every 4 weeks thereafter (max. maintenance dose 300 mg per infusion).
- Without a loading dosage: 1.75 mg/kg every 4 weeks (max. maintenance dose 300 mg per infusion).

As Cosentyx for i.v. use is only approved and marketed in the USA, it is not presented in the company CDS. The secukinumab concentrations following the above mentioned approved i.v. dosing regimen are estimated to be within the range of the steady state concentrations following subcutaneous administration of 150 mg and 300 mg doses of Cosentyx administered every four weeks. Based on the matching of the pharmacokinetic exposures, the safety and effectiveness of intravenous Cosentyx is extrapolated from the established safety and effectiveness of subcutaneous Cosentyx in adult patients with PsA, AS, and nr-axSpA.

3 Actions taken in the reporting interval for safety reasons

Actions taken for safety reasons in the reporting interval are presented in the table below:

Table 3-1 Actions taken for safety reasons in the reporting interval

Description of the actions taken during the reporting interval	Actions taken by	Status of the actions taken	Reason for action taken
The USPI was updated to include ADRs "dyshidrotic eczema", "atopic-dermatitis-like eruptions" and "erythroderma" in the post-marketing Section 6.2 and include warning for eczematous eruptions, including atopic dermatitis-like eruption, dyshidrotic eczema, and erythroderma in Section 5 of the USPI.	Sponsor	The updated USPI was approved on 24 Jul 2023	Following the release of CDS version 3.2 (dated 16 Nov 2021, corrected on 20 Dec 2021), Novartis submitted to FDA in Jan 2022 a supplement to add "dyshidrotic eczema" in the USPI. During the review, FDA requested the addition of "atopic-dermatitis-like eruptions" and "erythroderma" as ADR in the post-marketing Section 6.2 of the USPI, as well as addition of a warning for eczematous eruptions, including atopic dermatitis-like eruption, dyshidrotic eczema, and erythroderma in Section 5 of the USPI. The USPI was approved on 24 Jul 2023. As the signal of eczematous eruptions including atopic dermatitis-like eruptions, dyshidrotic eczema, and erythroderma was validated by Novartis (29 Jun 2023), its assessment confirmed causal association of eczematous eruptions with secukinumab. As a result, the sponsor decided to amend the Cosentyx CDS to v3.5. which has been released on 19 Jan 2024.
The Japan RMP was updated to include CCI [redacted] as an important potential risk	Regulator	The Japan RMP was updated in Dec 2021	In Apr 2020, PMDA requested Novartis to revise the CCI [redacted]. Following queries, it was agreed by PMDA CCI [redacted] include it as an important potential risk in the RMP.
The EU RMP has been updated to include the extension study CAIN457F2304E1 as additional pharmacovigilance activity	Sponsor	The RMP was updated to version 10.1 in Sep 2022 to include study CAIN457F2304E1 as a category 3 study in the pharmacovigilance plan	The EU RMP version 10 was updated to version 10.1 based on the PRAC request received in 2021 during the review of the new Cosentyx indication for treatment of JIA. The indication submission dossier was based on data from the core CAIN457F2304 clinical trial; with the CAIN457F2304E1 being its extension to assess long-term efficacy, safety and tolerability in JIA patients.

Description of the actions taken during the reporting interval	Actions taken by	Status of the actions taken	Reason for action taken
The South African product information has been updated regarding the warning for tuberculosis reactivation. Furthermore, a local annex to the RMP was added regarding South African specific Important Comorbidities (HIV and Latent Tuberculosis Infection)	Sponsor	The product information has been updated and a local annex to the RMP was added as part of the procedure to register the 300mg/2mL and 75mg/0.5mL strengths.	South African HA requested to update the product information regarding the warnings for tuberculosis reactivation and to add a local annex to the RMP discussing the South African specific risk factors (HIV infection and tuberculosis infections) in Apr 2022.
The Korean national product information has been updated with a table presenting Serious and unexpected ADRs as per results from the local Post Marketing Surveillance study CAIN457AKR03.	Sponsor	The product information has been updated on 20 Oct 2022.	On 21 Dec 2021, Novartis Korea submitted to the Ministry of Food and Drug Safety (MFDS), Health Authority in South Korea, a final clinical study report for the Post Marketing Surveillance Study CAIN457AKR03 conducted in Korea between 24 Sep 2015 and 23 Sep 2021. MFDS issued a request for a label update to reflect the result of the CAIN457AKR03 study on 17 Jun 2022
The Taiwanese prescribing information has been updated with inclusion of specific language about risk of hepatitis B reactivation (HBV-R) in the Warnings and Precautions section of the Cosentyx label/product information.	Sponsor	The prescribing information has been updated, and approved on 01 Nov 2023.	On 30 Mar 2023, Novartis received a request from the Taiwanese FDA (TFDA) for inclusion of specific language about risk of HBV-R in the Warnings and Precautions section of product information of all IL-17 inhibitors registered in Taiwan including Cosentyx. The variation with the requested wording included into Cosentyx label in Taiwan was submitted on 11 Aug 2023 and approved on 01 Nov 2023.

Description of the actions taken during the reporting interval	Actions taken by	Status of the actions taken	Reason for action taken

ADR: Adverse drug reaction; CDS: Core Data Sheet; EU: European Union; FDA: Food and Drug Administration; HBV: Hepatitis B reactivation HIV: Human immunodeficiency virus; JIA: Juvenile Idiopathic Arthritis; MFDS: Ministry of Food and Drug Safety; PMDA: Pharmaceuticals and Medical Devices Agency; PI: Package Insert; PRAC: Pharmacovigilance Risk Assessment Committee; RMP: Risk Management Plan; USPI: United States Product Information

Early termination of the three clinical trials due to futility occurred during the reporting period (CAIN457Q12301 and CAIN457Q12301E1 in Lupus Nephritis, and CAIN457ADE16 in Thyroid Eye Disease). Since no safety concern was identified, the three terminated studies are described in Section 7.

4 Changes to reference safety information

Core Data Sheet (reference safety information)

The core safety information within CDS version 2.7 dated 24 Nov 2020 was in effect at the beginning of the reporting interval. The CDS is the company position and the reference safety information.

The CDS was amended six times during the reporting interval of this PSUR, the details regarding the updated versions along with the details on the updates in each version are listed below:

- The Cosentyx CDS version 2.7 was amended to CDS version 2.8 (dated 19 Jan 2021) to include additional dosing information for adults with PsO to allow flexible dosing.
- The CDS version 2.8 was updated to version 3.0 (dated 31 Mar 2021); this was triggered by the periodic review of the CDS in accordance with standard Novartis practices. The CDS version 3.0 included a safety labeling change related to "Inflammatory Bowel Disease". The Warnings and Precautions section was revised to include the information from post-marketing use related to cases of new onset Inflammatory Bowel Disease, and Inflammatory Bowel Disease was added to the ADR Table 7-1 of the CDS version 3.0.
- The Cosentyx CDS version 3.0 was amended to CDS version 3.1 (dated 16 Jun 2021) to include a new indication for the ERA and JPsA categories of JIA.
- The Cosentyx CDS version 3.1 was amended to CDS version 3.2 (dated 16 Dec 2021 and corrected 20 Dec 2021) to add the new post-marketing ADR "Dyshidrotic Eczema".
- The Cosentyx CDS version 3.2 (dated 16 Dec 2021 and corrected 20 Dec 2021) was amended to CDS version 3.3 (dated 31 Aug 2022) to add Hidradenitis Suppurativa as a new indication..
- The Cosentyx CDS version 3.3 was amended to CDS version 3.4 (dated 19 Jan 2023 and corrected on 27 Mar 2023) to include "pyoderma gangrenosum" as a new, postmarketing ADR. In addition, the Instructions for Use for all approved pre-filled syringes (PFS) with Needle Safety Device (NSD) have been revised to include a "device drop statement" instructing the patients to use a new device if the PFS with NSD is dropped onto a hard surface or dropped without the needle cap. .

The CDS version 3.4 dated 19 Jan 2023 (corrected on 27 Mar 2023) is in effect at the end of the reporting interval and this information is used as reference for the safety and benefit evaluations provided in this report (Appendix 1.1).

Note: After the reporting interval, a CDS amendment (CDS v3.5) dated 19 Jan 2024, has been released globally on 19 Jan 2024 for local implementation. The CDS was amended to include two new ADRs (Dermatitis (including eczema) and Dermatitis exfoliative generalized) which, in addition to previously included ADR Dyshidrotic Eczema (as per CDS v3.3), are considered eczematous eruptions in Section 7 Adverse Drug Reactions. A Warning and Precautions for eczematous eruptions has been added in Section 6 of the CDS.

5 Estimated exposure and use patterns

5.1 Cumulative subject exposure in clinical trials

Cumulatively, since the Development International Birth Date (DIBD, 12 Jul 2006), 25,110 adult and 284 pediatric patients received secukinumab treatment in Novartis-sponsored investigational clinical trials (CT) (either completed studies or ongoing studies with interim analysis database locks). The majority of patients were from Pso, PsA, AS, HS, and JIA. The characteristics of patients exposed to secukinumab and comparator treatments in those studies (age, sex, race distribution) are discussed below, in light of the expected characteristics of the target population for the indications.

The majority of studies 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 5-1 presents combined subject (adult) exposure numbers and subject-years, across all indications, from studies with a final or interim analysis Clinical Study Report (CSR) completed prior to 25 Dec 2023 (PSUR data lock point [DLP]). 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.

Table 5-1 Combined subject (adult) exposure to secukinumab and comparators from both completed studies and ongoing studies with interim analysis database locks

Treatment*	Number of subjects from completed studies and ongoing studies with interim analysis database locks	Number of subject-years# from completed studies and ongoing studies with interim analysis database locks
Secukinumab	25,110	39,527.14
Placebo[1]	5,445	1,805.73

*Includes adult patients as of 25 Dec 2023.

[1]Includes subjects/patients initially assigned to placebo that either switched to active treatment or remained on placebo throughout the study.

Treatment*	Number of subjects from completed studies and ongoing studies with interim analysis database locks	Number of subject-years# from completed studies and ongoing studies with interim analysis database locks

Subject-years is calculated as a sum of individual subject durations in days divided by 365.25.
Given their much smaller and unvarying numbers (compared to secukinumab and placebo), exposures to active comparators (e.g. etanercept, abatacept, ustekinumab, adalimumab) have not been included in the table.

From studies with a final or interim analysis CSR completed by 25 Dec 2023, the combined exposure to secukinumab by age and sex is provided in Table 5-2.

Table 5-2 Combined subject (adult) exposure to secukinumab by age and sex from both completed studies and ongoing studies with interim analysis database locks

Age range (years)	Number of subjects* N=25,110			
	Female		Male	
	n (%)	Subject-years (years)	n (%)	Subject-years# (years)
age <18[1]	0	0	4 (0.03)	4.44
age ≥18 and ≤65	9,518 (37.91)	14,597.31	13,878 (55.27)	22,497.66
age >65 and ≤75	745 (2.97)	1,077.19	742 (2.95)	1,067.73
age >75	115 (0.46)	141.22	108 (0.43)	141.59

* Includes adult patients as of 25 Dec 2023.
[1] The four pediatric patients in this pool were part of 'adult' trials
Subject-years is calculated as a sum of individual subject durations in days divided by 365.25.

From studies with a final or interim analysis CSR completed as of 25 Dec 2023, the combined exposure to secukinumab by racial group is provided in Table 5-3.

Table 5-3 Combined subject (adult) exposure to secukinumab by racial group from both completed studies and ongoing studies with interim analysis database locks

Racial group	Number of subjects* N=25,110	
	n (%)	Subject-years# (years)
Caucasian	20,638 (82.19)	31,807.83
Black	398 (1.59)	482.00
Asian	2,983 (11.88)	5,223.67
Unknown	63 (0.25)	90.67
Other	1,028 (4.09)	1,922.96

*Includes adult patients as of 25 Dec 2023.
Subject-years is calculated as a sum of individual subject durations in days divided by 365.25.

From studies with a final or interim analysis CSR completed as of 25 Dec 2023, the combined exposure to secukinumab by ethnicity is provided in Table 5-4.

Table 5-4 Combined subject (adult) exposure to secukinumab by ethnicity from both completed studies and ongoing studies with interim analysis database locks

Ethnicity	Number of subjects* N=25,110	
	n (%)	Subject-years# (years)
Hispanic Or Latino	2,329 (9.28)	4,040.30
Not Hispanic Or Latino	16,647 (66.30)	28,752.76
Not Reported	990 (3.94)	1,896.04
Unknown(*)	5,144 (20.49)	4,838.05

*Includes adult patients as of 25 Dec 2023.

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

(*) Includes missing information

The combined patient exposure by indication (Pso, PsA, AS, HS, JIA, others) and treatment group from studies with final or interim analysis CSR completed as of 25 Dec 2023 is provided in Table 5-5. The following studies have been used to generate Table 5-5.

Psoriasis*

CAIN457A1302, CAIN457A2102, CAIN457A2103, CAIN457A2110, CAIN457A2204, CAIN457A2211, CAIN457A2211E1, CAIN457A2212, CAIN457A2220, CAIN457A2223, CAIN457A2225, CAIN457A2302, CAIN457A2302E1, CAIN457A2303, CAIN457A2304, CAIN457A2304E1, CAIN457A2307, CAIN457A2308, CAIN457A2309, CAIN457A2310, CAIN457A2312, CAIN457A2313, CAIN457A2317, CAIN457A2318, CAIN457A2322, CAIN457A2323, CAIN457A2324, CAIN457A2325, CAIN457A2326, CAIN457A2403, CAIN457A3301, CAIN457A3302, CAIN457A3401, CAIN457AUS01, CAIN457AUS02, CAIN457AUS07, CAIN457AJP01, CAIN457ADE02, CAIN457ADE03, CAIN457ADE04, CAIN457ADE06, CAIN457ADE08, CAIN457ADE15, CAIN457AGB01, CAIN457AIT01, and CAIN457AFR01.

** The completed studies CCJM112X2101 (with six patients treated with AIN457 150 mg for up to 12 weeks) and CAIN457A2105 (with 48 patients treated once with AIN457 75/150/300 mg: single dose pharmacokinetic study in healthy volunteers) are not part of the data pool. The impact is non-significant considering the existing pool with close to 20,000 patients. Also, the exclusion only applies to exposure analysis, the cases reported from these studies have been evaluated within the relevant safety topics.*

Psoriatic arthritis

CAIN457A2206, CAIN457A2206E1, CAIN457F2306, CAIN457F2306E1, CAIN457F2312, CAIN457F2318, CAIN457F2336, CAIN457F2342, CAIN457F2354, CAIN457F2366, CAIN457F2367, CAIN457FUS01, CAIN457F3301, CAIN457F3302, and CAIN457P12302

Axial spondyloarthritis (including ankylosing spondylitis and non-radiographic axial spondyloarthritis)[1]

CAIN457A2209, CAIN457A2209E1, CAIN457F2305, CAIN457F2305E1, CAIN457F2308, CAIN457F2310, CAIN457F2314, CAIN457F2320, CAIN457FDE03, CAIN457FUS06, CAIN457H1301, CAIN457H2315, CAIN457H3301, CAIN457K2340, and CAIN457P12301.

[1] *The completed study CAIN457HDE01 (with 155 patients treated with AIN457 and 149 in the placebo arm is not part of the data pool. The impact is non-significant considering the existing pool with close to 20,000 patients. Also, the exclusion only applies to exposure analysis, the cases reported from this study has been evaluated within the relevant safety topics*

Hidradenitis suppurative

CAIN457M2301, and CAIN457M2302

Juvenile idiopathic arthritis

CAIN457F2304, and CAIN457F2304E1

Other indications (rheumatoid arthritis, Crohn's disease, uveitis, dry eye syndrome, type 1 diabetes mellitus, multiple sclerosis, polymyalgia rheumatica, asthma, overuse tendinopathy, lichen planus, and giant cell arteritis)

CAIN457A2101, CAIN457ADE11C, CAIN457F2201, CAIN457F2206, CAIN457F2208, CAIN457F2302 (combined with CAIN457F2302E1), CAIN457F2309 (combined with CAIN457F2309E1), CAIN457F2311, CAIN457A2202, CAIN457A2202E1, CAIN457A2208, CAIN457A2227, CAIN457B2201, CAIN457B2201E1, CAIN457B2203, CAIN457C2301, CAIN457C2301E1, CAIN457C2302, CAIN457C2302E1, CAIN457C2303, CAIN457C2303E1, CAIN457D2204, CAIN457S12201, CAIN457X2201, CPJMR0012201 and CPJMR009 2202

General criteria for inclusion of clinical studies into the combined subject (adult) exposure analysis are as follows:

- Investigational drug: secukinumab
- All indications evaluated with secukinumab
- Study phase: all clinical studies conducted in patients (i.e., excluding healthy volunteer studies)
- Format criteria (all must apply):
  - Data language: English (study documentation must be provided in English)
  - Statistical Analysis System data sets with Novartis standard structure: Novartis Data
  - Directory, Novartis Clinical Data Standards
  - Meeting Good Clinical Practice criteria (validation, audit trail, fully documented, etc.)
  - Novartis is sponsor and data owner
  - Study completion criterion: Completed with published CSR or ongoing with interim CSR

Table 5-5 Combined subject (adult) exposure to secukinumab by indication and treatment group from both completed studies and ongoing clinical studies with interim analysis database locks

	SECUKINUMAB									PBO[1]
	75mg Q4W	150mg Q4W	300 mg Q2W	300 mg Q4W	Any 75mg Q4W	Any 150 mg Q4W	Any 300 mg Q2W	Any 300 mg Q4W	Any dose*	
Psoriasis										
N	-	1694	165	8689	-	2117	452	10405	12782	1461
PTY	-	2667.80	179.88	9367.67	-	4197.69	304.92	13270.68	19032.74	397.12
Psoriatic arthritis										
N	99	934	-	1185	391	2308	-	2144	4648	1511
PTY	225.93	1506.36	-	1979.89	1049.03	4196.05	-	3294.28	9110.01	518.05
Axial spondyloarthritis										
N	73	1577	-	379	284	2934	-	891	3596	968
PTY	240.25	2181.05	-	622.27	985.15	4734.50	-	1299.19	7087.56	322.46
Hidradenitis suppurativa										
N	-	-	361	360	-	-	527	533	1060	363
PTY	-	-	347.08	343.10	-	-	463.89	462.24	926.53	111.11
Other indications[2]										
N	80	81	-	149	634	722	31	149	3024	1142
PTY	99.37	95.76	-	99.02	857.58	1034.22	13.50	99.02	3370.29	456.99

Includes patients as of 25 Dec 2023; N: Number of patients; PBO: Placebo; PTY: Patient Treatment Year

* Includes patients initially assigned to placebo who crossed-over to secukinumab at the specified dose; includes patients receiving i.v. loading.

[1] Includes patients assigned to placebo that either crossed-over to active treatment or remained on placebo throughout the study.

[2] Includes rheumatoid arthritis, Crohn's disease, quiescent and active noninfectious uveitis, Behçet's uveitis, dry eye syndrome, type 1 diabetes mellitus, multiple sclerosis, polymyalgia rheumatica, asthma overuse tendinopathy, lichen planus, and giant cell arteritis.

The two pediatric psoriasis studies CAIN457A2310 (completed) and CAIN457A2311 (ongoing with interim analysis / CSR as of 25 Dec 2023) and the juvenile idiopathic arthritis studies, CAIN457F2304 (completed) and CAIN457F2304E1 (ongoing), are included in this reporting period. The combined patient exposure from these studies has been used to generate the following tables:

Table 5-6 Combined pediatric subject exposure to secukinumab and comparators from completed and ongoing studies with interim analysis database locks

Treatment*	Number of subjects from completed studies and ongoing studies with interim analysis database locks	Number of subject-years# from completed studies and ongoing studies with interim analysis database locks
Secukinumab	284	798.44
Placebo[1]	41	10.33

* Includes pediatric patients as of 25 Dec 2023.

[1]Includes subjects/patients initially assigned to placebo that either switched to active treatment or remained on placebo throughout the study.

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

Table 5-7 Combined pediatric subject exposure to secukinumab by sex from completed and ongoing studies with interim analysis database locks

Age range (years)	Number of subjects* N=284			
	Female		Male	
	n (%)	Subject-years# (years)	n (%)	Subject-years# (years)
age <18	141 (49.65)	392.66	143 (50.35)	405.78

* Includes pediatric patients as of 25 Dec 2023.

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

Table 5-8 Combined pediatric subject exposure to secukinumab by racial group from completed and ongoing studies with interim analysis database locks

Racial group	Number of subjects* N=284	
	n (%)	Subject-years (years)
Caucasian	256 (90.14)	710.99
Black	3 (1.06)	7.16
Asian	6 (2.11)	20.93
Unknown	0	-
Other	19 (6.69)	59.35

* Includes pediatric patients as of 25 Dec 2023.

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

Table 5-9 Combined pediatric subject exposure to secukinumab by ethnicity from completed and ongoing studies with interim analysis database locks

Ethnicity	Number of subjects* N=284	
	n (%)	Subject-years (years)
Hispanic Or Latino	31 (10.92)	77.34
Not Hispanic Or Latino	223 (78.52)	632.35
Not Reported	18 (6.34)	53.84
Unknown(*)	12 (4.23)	34.91

* Includes pediatric patients as of 25 Dec 2023.
# Subject-years is calculated as a sum of individual subject durations in days divided by 365.25.
(*) Includes missing information

Table 5-10 Combined pediatric subject exposure to secukinumab by indication (psoriasis and JIA) and treatment group from ongoing clinical studies with interim analysis database locks

	SECUKINUMAB			PBO
	Low Dose	High Dose	Any Dose	
Psoriasis				
N	82	82	198	41
PTY	211.78	216.21	560.41	10.33
Juvenile idiopathic arthritis				
N	-	-	86	-
PTY	-	-	238.03	-

Includes pediatric patients as of 25 Dec 2023; N: Number of pediatric patients; PBO: Placebo; PTY: Patient Treatment Year
Low dose: 75-150 mg depending upon body weight group; High dose: 75-300 mg depending upon body weight group
1Includes subjects/patients initially assigned to placebo that switched to active treatment.

5.2 Cumulative and interval patient exposure from marketing experience

5.2.1 Post-authorization (non-clinical trial) exposure

An estimate of patient exposure is calculated based on worldwide sales volume in kilograms (kg) of active substance sold during the reporting interval and the average maintenance daily dose (10 mg). The sales volume of Cosentyx during the reporting interval was approximately CCI kg (active substance).

The estimated interval exposure was approximately CCI patient-treatment years (PTY). The cumulative patient exposure since the International Birth Date of the product is estimated to be approximately 1,882,445 PTY.

During the interval covered by the previous PSUR (26 Dec 2019 to 25 Dec 2020), the estimated cumulative exposure was approximately CCI PTY.

The following table provides an overall estimation of current reporting interval and previous and current cumulative patient exposure since the international birth date, distributed by region. Data on Cosentyx sales by sex or age or dose or indication are not available.

The estimated exposure is provided in the table below.

Table 5-11 Estimated post-marketing (non-clinical trial) exposure

	EEA	USA and Canada	Japan	ROW	Total
Previous cumulative exposure (PTY) (until 25 Dec 2020)	CCI	CCI	CCI		
Interval Exposure (PTY)	CCI				
Cumulative Exposure (PTY)	CCI				

EEA: European Economic Area; USA: ROW: PTY: Patient Treatment Years; Rest of the World; United States of America

Exposure from other programs which follow a specific protocol is provided in Section 7.4 'Other therapeutic use of medicinal product'.

5.2.2 Post-authorization use in special populations

There were no non-interventional studies or registries designed to obtain information on special populations and no relevant information from other post-authorization sources during the reporting interval or cumulatively.

5.2.3 Pattern of use of the medicinal product

There was no identified pattern of use of Cosentyx beyond the recommendation(s) in the CDS.

Off Label use

The objective of this section is to determine whether there were any usage patterns beyond the recommendations in the CDS of Cosentyx and whether these usage patterns, if any, induced a safety risk to the patients being treated with Cosentyx.

A search was conducted in the company safety database using MedDRA v26.1 is included in Appendix 8.

Results

Company safety database

The search retrieved 85,028 post-marketing cases during the reporting interval, and 217,988 cumulatively. Of the 217,988 cases retrieved cumulatively, in 244 cases indication and dose (relevant to off-label use) were updated and added as a follow-up information during this reporting interval. Of these 85,272 cases (85,028+244), 29,644 were HCP and 55,628 were non-HCP; 66,796 were post-marketing surveillance (PMS), 15,714 were spontaneous report (SR), 579 were literature, and 2,183 were non-valid cases.

Note: Non-valid cases are not reflected in summary tabulations as described in Section 6.3

Of these 85,272 cases,

- Based on the manual review, in 57,344 cases the reported verbatim of the indications appeared to be different from the approved indication as written in the product labels. Upon review, secukinumab was actually used for approved indications (plaque psoriasis, psoriatic arthritis, non-radiographic axial spondyloarthritis, ankylosing spondylitis, juvenile idiopathic arthritis, and hidradenitis suppurativa). Please note that Cosentyx usage for the recently approved indication for HS is not considered to be off label use in this PSUR. No off-label use was identified with regards to deviated dosing regimen from the approved label recommendations.
- In 19,050 cases indication was reported as product use for unknown/unapproved indication.
- In 2,128 cases device issues were reported, and these cases are discussed under Section 9.3 'Device issues impacting patient safety'.
- Further, 1,204 cases reported fetal exposure during pregnancy and paternal/maternal exposure during pregnancy. These cases are discussed under Section 16.3.5.1 'Fetal exposure in utero'
- In 250 cases, off-label use was reported for other medications. Secukinumab was not involved in off label use.

The remaining 5,296 cases (957 off-label indications; 4,339 off-label dose/dosing frequency/route of administration) were further analyzed below.

Off-label use for unapproved indications

- The reporting interval retrieved 957 relevant cases (458 HCP and 499 non-HCP; 510 PMS, 387 SR, 44 Literature, and 16 Non-valid cases) for use of secukinumab for off-label indications, mainly the rheumatological and dermatological conditions other than the ones approved for Cosentyx. These off-label indications are summarized in Appendix 11. No safety signal, and no use pattern aside the authorized label was identified in these cases.

Off-label by dose/dosing frequency/route of administration

- Cases with off-label dosages, dosing frequencies or/and route of administration are discussed as off-label use if it was intentional or was of unknown intention. Unintentional deviation with dosage, dosing frequency or/and route administration is discussed under Section 9.2 'Medication errors'.
- During the reporting interval, 4,339 cases were received with the reported deviation in dosage, dosing frequency, or/and route of administration. Of these, 315 were unintentional and are discussed in Section 9.2 'Medication errors', and the remaining 4,024 cases (1,311 HCP, and 2,713 non-HCP; 3,578 PMS, 372 SR, 54 Literature, and 20 Non-valid cases) are reviewed as off label use. No use pattern aside the authorized label was identified in these cases.

A total of 13,684 adverse events co-reported in these off-label cases (indication/dose/dosing frequency/route of administration) with frequency of one percent or more are mentioned in Appendix 11. Majority of these co-reported adverse events were either symptom/manifestation

that typically co-exist with approved indications and with the known safety profile of Cosentyx. No safety signal was identified.

Discussion and conclusion

Overall, the review of the off-label use cases did not find a safety concern. No pattern of use in a specific indication was identified as most of the identified off label indications are related to spondyloarthropathies. Use for covid-19 was identified in a minority of cases (n=24). The current product label is deemed appropriate with regards to approved indications and dosing recommendations.

6 Data in summary tabulations

6.1 Reference information

The coding dictionary used for the analysis of adverse events/ adverse drug reactions (AEs/ADRs) was Medical Dictionary for Regulatory Activities (MedDRA) version 26.1.

6.2 Cumulative summary tabulations of serious adverse events from clinical trials

Cumulative summary tabulations of all Serious Adverse Events (SAEs) reported in clinical trials, from the DIBD to the data lock point (DLP) of this PSUR were retrieved from the company safety database and are provided in Appendix 2.1.

The cumulative summary tabulations include both suspected and not-suspected events from cases fully processed in the company safety database, which originated from blinded and unblinded clinical trials. The tabulation is organized by MedDRA System Organ Class (SOC), by the investigational medicinal product (IMP) as well as for the comparator arm(s) (active comparators, placebo) and a no treatment arm used in the clinical development program. Respective columns and rows appear in the table only if at least one entry has been made. In the situation where a case is databased with more than one treatment arm (e.g. IMP, active comparator, placebo, or no treatment), each event from the case is counted only once and appears under one of the columns based on the following priority: IMP, active comparator, placebo, no treatment.

Adverse Events from cases which are foreseen for deactivation, deactivated cases, or cases which are considered non-valid (lacks certain criteria for a valid ICSR) are not included in the summary tabulations.

No events were defined in the protocol as “exempt” from special collection and entry into the safety database.

6.3 Cumulative and interval summary tabulations from post-marketing data sources

Cumulative and interval summary tabulations of adverse reactions reported from post-marketing data sources from the IBD to the DLP of this PSUR were retrieved from the company safety database and are provided in Appendix 2.2.

These adverse reactions are derived from cases fully processed in the company safety database, which originated from spontaneous sources, including reports from healthcare professionals, consumers, scientific literature, and competent authorities (worldwide), and from non-interventional studies and other post-marketing solicited sources such as Patient Support Programs (PSPs, as defined in Good Pharmacovigilance Practice (GVP) Module VI) [3], market research programs, and Compassionate Use or Expanded Access Programs (submitted in the EU to EudraVigilance Post-Marketing Module in accordance with GVP Module VI[3].

Serious and non-serious adverse reactions from spontaneous sources, as well as serious ADRs from non-interventional studies and other non-interventional solicited sources are presented in a single table, organized by MedDRA SOC, with interval and cumulative data presented side-by-side (Appendix 2.2). Respective columns and rows appear in the table only if at least one entry has been made.

If both serious and non-serious reactions are included in the same ICSR, the individual seriousness per reaction is reflected in the summary tabulations.

Events coming from follow-up reports of ICSRs initially received in previous reporting intervals are included in the cumulative column, but not in the interval column.

Adverse Drug Reactions from cases which are foreseen for deactivation, deactivated cases or cases which do not meet the criteria for an ICSR are not included in the summary tabulations.

7 Summaries of significant findings from clinical trials in the reporting interval

A summary of the clinically important efficacy and safety findings from clinical trials during the reporting interval is provided in the sub-sections below.

A listing of MAH sponsored interventional post-authorization safety or efficacy studies (PASS/PAES) that were completed, ongoing or planned during the reporting interval can be found in Appendix 4.1.

7.1 Completed clinical trials

During the reporting interval a total of 18 studies were completed with final CSR which included:

For these 18 clinical trials with final CSR completed during the reporting interval, there were no safety signals, and the safety findings were consistent with the known safety profile of secukinumab. The study details are presented in table below, and synopsis from each study has been enclosed within Appendix 5.

Table 7-1 Clinical trials completed during the reporting interval

Study number and title	Number of patient (treatment arm)*	Number of patients (comparator, placebo)	Safety and efficacy findings
Single agent studies			
Psoriasis (n=5)			
CAIN457A2310 A randomized, double-blind, placebo- and active controlled multicenter trial to demonstrate efficacy of subcutaneous secukinumab compared to placebo and etanercept (in a single-blinded arm) after twelve weeks of treatment, and to assess the safety, tolerability, and long-term efficacy in subjects from 6 to less than 18 years of age with severe chronic plaque psoriasis	114	48	Both doses of secukinumab (low and high) were superior to placebo in the treatment of pediatric patients with severe chronic plaque psoriasis. The efficacy was maintained through the entire treatment period. Secukinumab was safe and well tolerated at both doses. There were no dose-dependent increases in the incidence of AEs and the safety was comparable between the Any AIN457 low dose and the Any AIN457 high dose groups. Safety findings in the pediatric population in this study were similar to the long-term safety profile in the adult population. There were no new or unexpected safety signals.
CAIN457A2324 A randomized, double-blind, multicenter study assessing short (16 weeks) and longterm efficacy (up to 1 year), safety, and tolerability of subcutaneous secukinumab in subjects of body weight 90 kg or higher with moderate to severe chronic plaque-type psoriasis	331	0	Secukinumab 300 mg Q2W dose regimen was superior to the secukinumab 300 mg Q4W dose regimen in the treatment of moderate to severe chronic plaque-type psoriasis in heavier patients (>= 90 kg) with respect to the primary endpoint of PASI 90 response at Week 16. Efficacy responses beyond Week 16 were higher and sustained in the secukinumab Q2W group compared to the secukinumab Q4W group during the entire treatment period. The safety was comparable between the two dosing regimens and there were no dose-dependent increases in the incidence of AEs or risks. The safety profile was consistent with the known safety profile of secukinumab and showed no new or unexpected safety signals.
CAIN457A2325 Multicenter, randomized, double-blind, placebo-controlled, 52-week study to	118	4	Secukinumab 300 mg in 2 mL autoinjector demonstrated significantly superior efficacy over placebo in the treatment of subjects with moderate to severe chronic plaque-type psoriasis and was comparable to the efficacy

Study number and title	Number of patient (treatment arm)*	Number of patients (comparator, placebo)	Safety and efficacy findings
demonstrate the efficacy, safety and tolerability of subcutaneous secukinumab injections with 2 mL auto-injectors (300 mg) in adult subjects with moderate to severe plaque psoriasis (MATURE)			shown with secukinumab 300 mg in 2 × 1 mL PFS. Both secukinumab 2 mL autoinjector and 2 × 1 mL PFS treatments were safe, well tolerated and demonstrated a comparable safety profile. No new safety signals were identified.
CAIN457ADE08 A randomized, multicenter 28 week study to compare the efficacy and safety of combining Cosentyx (Secukinumab) (4-weekly, 300 mg s.c.) with a lifestyle intervention to Cosentyx therapy alone in adult patients with moderate to severe plaque- type psoriasis and concomitant metabolic syndrome, followed by a 28 week extension period	781	0	Secukinumab therapy is efficacious and safe in patients with psoriasis and concomitant metabolic syndrome. Lifestyle intervention is beneficial in improving symptoms associated with metabolic syndrome in patients with concomitant psoriasis and is safe to use in this patient population. In this study setting, lifestyle intervention did not improve secukinumab performance in patients with psoriasis and concomitant metabolic syndrome.
CAIN457ADE15 A randomized, double-blind, multicenter, 24-week study of subcutaneous secukinumab to assess anti-interleukin-17A treatment in plaque psoriasis patients with coexisting non-alcoholic fatty liver disease (pINPOINT)	7	3	This study was prematurely discontinued after the enrollment of 10 patients, because the recruitment was too slow to achieve the planned number of patients within a reasonable time frame. No safety issues led to the decision to terminate the study prematurely.
Psoriatic arthritis (n=3)			
CAIN457F2354 A 52-week, multicenter study to assess the time course of response to secukinumab on joint inflammation using Power Doppler ultrasonography in	83	83	Secukinumab rapidly and significantly decreased synovitis, indicating a direct effect of IL-17 inhibition on the synovium in patients with PsA. The safety profile was consistent with the established safety profile across psoriasis, PsA and axial spondyloarthritis clinical trial program and real world evidence with no new safety signals.

Study number and title	Number of patient (treatment arm)*	Number of patients (comparator, placebo)	Safety and efficacy findings
patients with active psoriatic arthritis (ULTIMATE)			
CAIN457F2367 A phase III randomized, double-blind, placebo controlled, multicenter, bridging study of subcutaneous secukinumab, to demonstrate efficacy after sixteen weeks of treatment and to assess safety, tolerability and long-term efficacy follow-up to one year in Chinese subjects with active psoriatic arthritis	41	0***	This bridging study demonstrated that the efficacy in Chinese PsA patients was consistent with that shown in the global pivotal studies. Treatment with secukinumab 150 mg and secukinumab 300 mg was well tolerated in Chinese PsA patients and showed consistency with the known safety profile of secukinumab.
CAIN457P12302 A randomized, double blind, placebo-controlled, parallel group, phase 3 multicenter study of intravenous secukinumab to compare efficacy at 16 weeks with placebo and to assess safety and tolerability up to 52 weeks in subjects with active Psoriatic Arthritis	374	7[$]	Secukinumab 6 mg/kg i.v. as an initial loading dose followed by 3 mg/kg i.v. every 4 weeks demonstrated superiority over placebo for the primary endpoint of ACR50 response at Week 16 (60/191 (31.41%) vs. 12/190 (6.32%); p<0.0001). The efficacy demonstrated by secukinumab at Week 16 was sustained up to Week 52. The safety profile of secukinumab showed no new or unexpected signals relative to the known safety profile of secukinumab.
Axial spondyloarthritis (including ankylosing spondylitis and non-radiographic axial spondyloarthritis) (n=4)^^^			
CAIN457H2315 A randomized, double-blind, placebo-controlled multicenter study of secukinumab 150 mg in patients with active non-radiographic axial spondyloarthritis to evaluate the safety, tolerability and efficacy up to 2 years, followed by an optional phase of either	543	12[$$]	The safety profile of secukinumab 150 mg and secukinumab 300 mg showed no new or unexpected safety signals during the entire treatment period and was consistent with the overall safety profile of secukinumab. In the core phase both dosing regimens of secukinumab (150 mg with or without loading) were superior to placebo across multiple endpoints including ASAS40, BASDAI, hsCRP, BASFI, SF-36 and sacroiliac joint (SIJ) edema score on MRI demonstrating significant improvement in disease activity, physical function, quality of life, and objective signs of inflammation in non-radiographic axSpA. In the optional extension phase,

Study number and title	Number of patient (treatment arm)*	Number of patients (comparator, placebo)	Safety and efficacy findings
150 mg or 300 mg randomized dose escalation for up to another 2 years			patients who were ASAS20 responders at Week 104 showed no trend for better efficacy with secukinumab 300 mg vs. secukinumab 150 mg in the 16-Week dose escalation treatment period. Patients who were ASAS20 non-responders received open-label secukinumab 300 mg in the 16-Week dose escalation treatment period and had moderate improvement across efficacy parameters.
CAIN457FUS06 A randomized, double-blind, parallel-group, multicenter study of secukinumab to compare 300 mg and 150 mg at Week 52 in patients with Ankylosing Spondylitis who are randomized to dose escalation after not achieving inactive disease during an initial 16 weeks of open-label treatment with secukinumab 150 mg (ASLeap)	322	0	The safety results in this study demonstrate that secukinumab at doses of 150 mg or 300 mg over a period of 52 weeks is safe and well tolerated. Overall, the safety results are consistent with prior experience in patients with AS treated with 150 mg and 300 mg secukinumab with no unexpected safety findings.
CAIN457HDE01 A randomized, open label multicenter trial to investigate the efficacy of a treat-to-target treatment strategy with secukinumab (AIN457) as a first-line biologic compared to a standard-of- care treatment over 36 weeks in patients with active axial spondyloarthritis (axSpA)	155	149	The study failed to demonstrate the superiority of efficacy with the T2T approach over the SOC. Besides, most of the efficacy outcomes were similar between the T2T approach and the SOC. Further studies would be required to address the research question of optimal treatment strategy in the current study population. The safety profile of secukinumab in this study was consistent with the known safety profile and there was no new or unexpected safety concerns.
CAIN457P12301 A randomized, double-blind, placebo-controlled, parallel group, phase 3 multicenter study of intravenous secukinumab to compare efficacy at 16 weeks with placebo and to assess safety	517	9#	Secukinumab 6 mg/kg - 3 mg/kg demonstrated superiority over placebo for the primary endpoint of ASAS40 response with a rapid onset of action as early as Week 4 that was sustained at all subsequent visits until and including at Week 16. Secukinumab 6 mg/kg-3 mg/kg group demonstrated superiority over placebo for all secondary efficacy endpoints which included measures of

Study number and title	Number of patient (treatment arm)*	Number of patients (comparator, placebo)	Safety and efficacy findings
and tolerability up to 52 weeks in subjects with active Ankylosing Spondylitis or non-radiographic axial SpondyloArthritis (INVIGORATE 1)			clinical response, QoL and markers of inflammation. The responses were sustained up to Week 52. The secukinumab i.v. regimen (6 mg/kg-3 mg/kg) showed no new or unexpected safety signals, and the safety profile was consistent with the known overall safety profile of secukinumab.
Juvenile Idiopathic arthritis subtypes of psoriatic and enthesitis-related arthritis (n=1)			
CAIN457F2304 A three-part randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of secukinumab treatment in Juvenile Idiopathic arthritis subtypes of psoriatic and enthesitis-related arthritis	86	0##	Secukinumab (150 mg for subjects ≥50 kg and 75 mg for subjects <50 kg) demonstrated statistically significant longer time to disease flare in Treatment Period 2 (randomized, double-blind, placebo controlled, event-driven withdrawal period) for ERA and JPsA categories of JIA in the active group versus placebo. There was a rapid improvement in all patients in almost all JIA ACR response categories which continued through Week 12 in Treatment Period 1 (open-label single arm active treatment period). The safety profile of secukinumab in this study of pediatric patients showed no new or unexpected safety signals.
Hidradenitis suppurativa (n=2)			
CAIN457M2301 A randomized, double-blind, multicenter study assessing short (16 weeks) and long-term efficacy (up to 1 year), safety, and tolerability of 2 subcutaneous secukinumab dose regimens in adult patients with moderate to severe hidradenitis suppurativa (SUNSHINE)	541 Up to week 16: 181 in AIN457 300mg sc Q2W, 180 in AIN457 300mg sc Q4W.	8###	Study M2301 met the pre-defined primary (HiSCR50 response) and all of the secondary objectives (AN count at Week 16, flare over 16 weeks, and NRS30 at Week 16) only for the secukinumab 300 mg Q2W dose regimen, but not for the secukinumab 300 mg Q4W dose regimen. The safety profile of secukinumab in subjects with HS based on secukinumab 300 mg Q2W and secukinumab 300 mg Q4W dose regimens, demonstrated to be comparable across the secukinumab Q2W and Q4W regimens and the placebo group and showed no new or unexpected safety signals compared to the well-established safety profile of secukinumab. No deaths occurred during Treatment Period 1 (up to Week 16) or during the entire study period. The incidence of AEs, SAEs or AEs leading to discontinuation of study treatment was also low, with no

Study number and title	Number of patient (treatment arm)*	Number of patients (comparator, placebo)	Safety and efficacy findings
			meaningful differences between the secukinumab dose regimens and the placebo group. Laboratory abnormalities and changes in vital signs were infrequent and did not reveal any clinically meaningful differences between secukinumab and placebo. Safety data up to Week 52, showed no new or unexpected safety signals.
CAIN457M2302 A randomized, double-blind, multicenter study assessing short (16 weeks) and long-term efficacy (up to 1 year), safety, and tolerability of 2 subcutaneous secukinumab dose regimens in adult patients with moderate to severe hidradenitis suppurativa (SUNRISE)	543 Up to week 16: 180 in AIN457 300mg sc Q2W, 180 in AIN457 300mg sc Q4W.	16[$$$]	Study M2302 met the pre-defined primary (HiSCR50 response) and the majority of the predefined secondary objectives (AN count and NRS30 at Week 16) for the secukinumab 300 mg Q2W regimen in subjects with moderate to severe HS. The primary (HiSCR50 response) and the majority of the secondary (AN count and flare) objectives were also met for the secukinumab 300 mg Q4W regimen. The safety profile of secukinumab in subjects with HS based on secukinumab 300 mg Q2W and secukinumab 300 mg Q4W dose regimens, demonstrated to be comparable across the secukinumab Q2W and Q4W regimens and placebo group, and showed no new or unexpected safety signals compared to the well-established safety profile of secukinumab. No deaths occurred during Treatment Period 1 (up to Week 16), while 2 deaths out of 543 subjects were reported during the Entire study period. The incidence of AEs, SAEs or AEs leading to discontinuation of the study treatment was also low, with no difference between the secukinumab dose regimens and the placebo group. Laboratory abnormalities and changes in vital signs were infrequent and did not reveal any clinically meaningful differences between secukinumab and placebo. Safety data up to Week 52, showed no new or unexpected safety signals.
Others (n=2)			
CAIN457ADE11C A randomized, parallel-group, double-blind, placebo-controlled, multicenter phase 2 trial to investigate the safety and	27	25	Sustained remission until Week 28 was achieved by a higher proportion of patients in the secukinumab group compared to the placebo group; therefore, the primary endpoint was met. Secukinumab was considered safe and well tolerated, and the safety profile observed in this study is in

Study number and title	Number of patient (treatment arm)*	Number of patients (comparator, placebo)	Safety and efficacy findings
efficacy of secukinumab (AIN457) in patients with giant cell arteritis (TitAIN)			line with the established safety profile of secukinumab in the secukinumab clinical development program to date.
CAIN457S12201 A proof-of-concept study to evaluate the efficacy, safety and tolerability of secukinumab 300 mg over 32 weeks in adult patients with biopsy-proven forms of lichen planus not adequately controlled with topical therapies (PRELUDE)	104	7[1]	The primary objective of this study was to demonstrate the clinical efficacy of secukinumab 300mg q4w in subjects with CLP, MLP or LPP with respect to improvement in IGA score at Week 16, compared to placebo. The primary objective was not met. The PoC criteria were not met for all 3 cohorts. The safety profile of secukinumab in subjects with LP showed no new or unexpected signals and is consistent with the known safety profile of secukinumab across other indications.
Combination studies			
None			
Studies with Adalimumab used as comparator			
CAIN457K2340 A randomized, partially-blinded, active-controlled multicenter study of secukinumab to demonstrate reduction of radiographic progression versus GP2017 (adalimumab biosimilar) at 104 weeks and to assess the long term safety, tolerability and efficacy up to 2 years in patients with active ankylosing spondylitis (SURPASS)	571	285^	The adverse event (AE) profile of secukinumab was consistent with the known safety profile. No new safety signals were observed in this study. The study did not meet its primary endpoint (mSASSS response defined as change from Baseline in mSASSS at Week 104 of ≤ 0.5). In accordance with the testing hierarchy, the secondary efficacy results were not formally tested. Subjects in the GP2017 group had a numerically higher mean change from Baseline in mSASSS. There were comparable reductions in Berlin SI joint edema score and Berlin modification of ASspiMRI-a score from Week 16 through Week 104, and the three groups (GP2017, secukinumab 150 mg and secukinumab 300 mg) did not differ in the proportion of subjects without new syndesmophytes at Week 104.

* 'Number of patients (treatment arm)' include patients that received the mentioned secukinumab dosage at least once during the trial. Secukinumab is generally taken every week for four weeks followed by dosing every four weeks but not for all studies. Patients that took placebo and switched to secukinumab will be counted in this column only and not in the placebo column.

** All patients randomized to the placebo treatment group (n=12) received secukinumab 300mg from Week 12 onwards

Study number and title	Number of patient (treatment arm)*	Number of patients (comparator, placebo)	Safety and efficacy findings

*** All 21 placebo patients switched to secukinumab

$ 7 out of 190 patients randomized to placebo did not switch to secukinumab

$$ 12 out of 186 randomized to placebo did not switch to secukinumab

9 out of 261 patients randomized to placebo did not switch to secukinumab

All patients received secukinumab during first 12 weeks of the study. After which, responders were randomized 1:1 to secukinumab or placebo. Patients experiencing a disease flare in TP2 immediately entered TP3 to receive open label secukinumab

180 patients received placebo up to week 16. After week 16, 85 patients switched to AIN457 300mg sc Q2W and 87 switched to AIN457 300mg sc Q4W.

$$$ 183 patients received placebo up to week 16. After week 16, 81 patients switched to AIN457 300mg sc Q2W and 86 switched to AIN457 300mg sc Q4W.

1 A total of 111 patients were enrolled (37 in CLP, 37 in MLP and 37 in LPP cohorts). This included 38 patients originally randomized to placebo and 73 patients originally randomized to AIN457. Placebo-treated patients without self-remission (IGA 0/1) at Week 16 (n=31) were switched to receive secukinumab starting at Week 16

^ Active control arm: GP2017 (adalimumab biosimilar)

^^^ There is a total of four completed trials for axial spondyloarthritis. The fourth clinical trial, CAIN457K2340, is listed separately as it is against an active comparator, adalimumab.

ACR: American College of Rheumatology; AE/s: Adverse Event/s; AIN457: secukinumab; AN: Abscesses and inflammatory Nodules; AS: Ankylosing Spondylitis; ASAS: Assessment of SpondyloArthritis international Society; axSpA; Axial Spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CLP: Cutaneous Lichen Planus; DLQI: Dermatology Life Quality Index; ERA: Enthesitis-Related Arthritis; HAQ-DI: Health Assessment Questionnaire Disability Index; HiSCR50: Hidradenitis Suppurativa Clinical Response, 50% reduction; HS: Hidradenitis Suppurativa; hsCRP: high-sensitivity C-Reactive Protein; IBD; Inflammatory Bowel Disease; IGA: Investigator Global Assessment ; IL: Interleukin; i.v.: intravenous; JIA: Juvenile Idiopathic Arthritis; JPsA: Juvenile Psoriatic Arthritis; kg: kilograms; LP: Lichen Planus; LPP: Lichen Planopilaris; mg: milligrams; mL: milliliters; MLP: Mucosal Lichen Planus ; MRI: Magnetic Resonance Imaging; mRNA: Messenger RNA; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; NRS: Numeric Rating Scale; NSAID: Non-Steroidal Anti-Inflammatory Drugs; PASI: Psoriasis Area and Severity Index; PFS: pre-filled syringe; PD: Pharmaco-Dynamic; PoC: Proof of Concept; PsA: Psoriatic Arthritis; PsO: Psoriasis; pt-yr: Patient-Years; q1w: once a week; Q2W: every two weeks; qwk: every week; Q4W: every four weeks; QoL: Quality of Life; SAE: Serious Adverse event; s.c.: subcutaneous; SF-36: Short Form-36 item health survey; SOC: Standard of Care T2T: Treat-to-Target; TCS: Total Clinical Score; TitAIN: Trial to InvestigaTe AIN457 in giant cell arteritis;; US: United states; Wk: Week; WORC: Western Ontario Rotator Cuff index

7.2 Ongoing clinical trials

There were 17 ongoing Novartis-sponsored interventional clinical trials.

Long-term ongoing studies within the reporting interval are included here and further described in Section 7.3 Long term follow up.

Table 7-2 Ongoing clinical trials during the reporting interval

Study number and title	Patients enrolled / planned	Treatment duration	Dosing	Safety findings
Psoriasis (n=2)				
CAIN457A2311(Week 52 interim CSR available, study ongoing for Week 224 data) A randomized, open-label, multicenter trial to assess the efficacy of s.c. secukinumab after twelve weeks of treatment, and to assess the long-term safety, tolerability and efficacy in subjects from 6 to less than 18 years of age with moderate to severe chronic plaque psoriasis	CCI / 80 42 (AIN457 Low dose: 75-150 mg depending upon body weight group) 42 (AIN457 High dose: 75-300 mg depending upon body weight group) No PBO arm; No comparator arm	208 Weeks	Secukinumab Low and High dose (Weight-based) < 25kg: High and Low dose: 75 mg > 25 kg to <50 kg: Low dose: 75 mg, High dose: 150 mg > 50 kg: Low dose: 150 mg, High dose: 300 mg s.c. qwk x 5 then q4w	No new safety findings
CAIN457A2322 A randomized, multicenter study to evaluate the effect of secukinumab 300 mg s.c. administered during 52 Weeks to subjects suffering from new onset moderate to severe	CCI / 196	52 weeks	Secukinumab: 300 mg s.c qw x 5 then 300 mg q4w	No new safety findings

Study number and title	Patients enrolled / planned	Treatment duration	Dosing	Safety findings
plaque psoriasis as early intervention compared to standard treatment with narrow band UVB (STEPIN)				
Non-radiographic axial spondyloarthritis (n=2)				
CAIN457I2301 A randomized, double-blind, placebo controlled, multicenter, phase 3 study of subcutaneous secukinumab to compare efficacy at 16 weeks with placebo and to assess safety and tolerability up to 52 weeks in Chinese participants with active non-radiographic axial spondyloarthritis	CCI / 134	52 weeks	Secukinumab 150 mg s.c qw x 4 then 150 mg s.c q4w; placebo s.c. qw x 4 then s.c. q4w up to Wk 12, switch to secukinumab 150mg s.c. q4w starting at Wk 16; Non-responders to secukinumab 150 mg at Wk 24 will receive q4w 300 mg secukinumab until Wk 48.	No new safety findings
CAIN457I2401 A multicenter study of secukinumab, with a randomized double-blind, placebo-controlled withdrawal-retreatment period, to evaluate maintenance of response in participants with non-radiographic axial spondyloarthritis who achieved remission	CCI / 340	Up to 120 weeks	Open label secukinumab 150 mg s.c qw x 4, then q4w up to Wk 52, ASDAS-CRP ID responders at Wk 52 will be randomized to: secukinumab 150 mg s.c. q4w or placebo q4w at Wk 56,	No new safety findings
Juvenile idiopathic arthritis subtypes of psoriatic arthritis and enthesitis-related arthritis (n=1)				
CAIN457F2304E1 (category 3 PASS study.) An extension study of subcutaneous secukinumab to evaluate the long-term efficacy, safety and tolerability up to 4 years in patients with Juvenile Idiopathic Arthritis subtypes of Juvenile Psoriatic Arthritis and Enthesitis related Arthritis	CCI / open*	Week 320	75 mg or 150 mg s.c. q4w from Wk 104E1 and ptitration to 300mg s.c. q4w possible at Wk108	No new safety findings
Hidradenitis suppurativa n=1				
CAIN457M2301E1 A multicenter, double-blind, randomized withdrawal extension study of subcutaneous Secukinumab to	CCI / open*	4 years	Secukinumab 300 mg s.c. Q4W, or Q2W, or placebo (until LOR), then switch to active treatment based on assigned	No new safety findings

Study number and title	Patients enrolled / planned	Treatment duration	Dosing	Safety findings
demonstrate long-term efficacy, safety and tolerability in subject with moderate to severe hidradenitis suppurativa			treatment arm (reinduction at LOR required)	
Others (n=10)				
CAIN457A02001B An open-label, multi-center protocol for patients who have completed a previous Novartis sponsored Secukinumab study and are judged by the investigator to benefit from continued Secukinumab treatment	CCI / open*	104 weeks	75 mg s.c q4w; 150 mg s.c q4w, 300 mg s.c. q4w	No new safety findings
CAIN457ADE16** A two-year multi-center phase 3 study to investigate the efficacy and safety of secukinumab in adult patients with active, moderate to severe thyroid eye disease (ORBIT), with a randomized, parallel-group, double-blind, placebo-controlled, 16-Week treatment period, and a follow-up/retreatment period	CCI / 70	Max. 108 weeks	300 mg s.c.	No new safety findings
CAIN457C22301 A randomized, parallel-group, double-blind, placebo-controlled, multicenter Phase 3 trial to evaluate efficacy and safety of secukinumab administered subcutaneously versus placebo, in combination with a glucocorticoid taper regimen, in patients with polymyalgia rheumatica (PMR) (REPLENISH)	CCI / 360	52 weeks	300 mg s.c. or 150 mg s.c. or placebo s.c. weekly for 5 weeks, followed by every 4 weeks until Week 48	No new safety findings
CAIN457FDE05 A randomized, double-blind, placebo-controlled, parallel group, multicenter, 24-Week study investigating the efficacy and safety of secukinumab compared to placebo in adult patients with moderate to severe rotator cuff tendinopathy and failure to conventional therapy (UnchAIN)	CCI / 860	12 weeks	7x PFS 300mg / 2mL	No new safety findings

Study number and title	Patients enrolled / planned	Treatment duration	Dosing	Safety findings
CAIN457O12301 A randomized, parallel-group, 24 week, double-blind, placebo-controlled, multicenter Phase 3 study to assess the efficacy and safety of secukinumab compared to placebo in adult patients with active rotator cuff tendinopathy	CCI / 234	12 weeks	300mg s.c.	No new safety findings
CAIN457O12302 A randomized, parallel-group, 24 week, double-blind, placebo-controlled, multicenter Phase 3 study to assess the efficacy and safety of secukinumab compared to placebo in adult patients with active rotator cuff tendinopathy	CCI / 234	12 weeks	300mg s.c.	No new safety findings
CAIN457Q12301** A two-year, phase III randomized, double-blind, parallel group, placebo-controlled trial to evaluate the safety, efficacy, and tolerability of 300 mg s.c. secukinumab versus placebo, in combination with SoC therapy, in patients with active lupus nephritis (SELUNE)	CCI / 400	2 years	Secukinumab s.c. (300 mg) or placebo at Baseline, Weeks 1, 2, 3, and 4, followed by s.c dosing every 4 weeks until Week 100.	No new safety findings
CAIN457Q12301E1** A three-year, open-label extension study of subcutaneous secukinumab to evaluate the long-term efficacy, safety and tolerability in patients with active lupus nephritis	CCI **/ open***	Up to 3 years	Secukinumab s.c. (300 mg) every 4 weeks	No new safety findings
CAIN457R12301 A Randomized, parallel group, double blind, placebo controlled multicenter phase III trial to investigate the efficacy and safety of secukinumab 300 mg and 150 mg administered subcutaneously verses placebo in combination with a glucocorticoid taper regimen, in patients with Giant Cell Arteritis (GCA)	CCI / 349	3-5.5years	Secukinumab s.c. (300 mg) at Baseline, Weeks 1, 2, 3, and 4, followed by s.c dosing every 4 weeks	No new safety findings

Study number and title	Patients enrolled / planned	Treatment duration	Dosing	Safety findings
CAIN457R1DE01 A randomized, parallel-group, double-blind, placebo controlled, multicenter trial to investigate the efficacy and safety of subcutaneously administered secukinumab in patients with new-onset of giant cell arteritis (GCA) who are in clinical remission and eligible for treatment with glucocorticoid-monotherapy	CCI / 146	24 weeks	Secukinumab s.c. (300 mg) at Baseline, Weeks 1, 2, 3, and 4, followed by s.c dosing every 4 weeks	No new safety findings
Combination studies				
None				
Studies with Ustekinumab used as comparator				
Psoriatic arthritis (n=1)				
CAIN457FDE04 A 28-week, randomized, double-blind, active-controlled, multicenter study to evaluate the efficacy of subcutaneously administered secukinumab compared to ustekinumab in adult patients with psoriatic arthritis and failure of TNFα-inhibitor treatment (AgAIN)	CCI / 310	24 weeks	300 mg	No new safety findings

* Since there is no planned number of patients for the extension studies, these are designated as open

** Terminated studies.

AIN457: secukinumab; AS: Ankylosing Spondylitis; ASDAS: Ankylosing Spondylitis Disease Activity Score; axSpA: Axial Spondyloarthritis; BSL: Baseline; CRP: C-Reactive Protein; CSR: Clinical Study Report; DB: Double blind; FPFV: First Patient First Screening Visit; IGA: Investigator's Global Assessment; i.v: Intravenous ; Kg: Kilograms; LOR: Loss of Response; LPLV; Last Patient Last Visit; MC: Multicenter; mg: Milligrams; ml: Milliliters; PASI: Psoriasis Area and Severity Index; PBO: Placebo; PFS: Pre-filler Syringe; PsA: Psoriatic Arthritis; PsO: Psoriasis; qwk: every week; q2w: once every 2 weeks; q4w: every four weeks; qw; every week; s.c.: Subcutaneous; SoC: Standard of Care; SpA: Spondyloarthritis; TNF: Tumor Necrosis Factor ; UVB: Ultraviolet B; Wk: Week

7.3 Long-term follow-up

Psoriasis

Pediatric study CAIN457A2310 in severe psoriasis with more than 4.5 years of treatment was completed during the reporting period.

Study CAIN457A2311 in pediatric patients with moderate to severe psoriasis with 4-year treatment is still ongoing.

Psoriatic arthritis

There were no extension or long-term core studies that had final CSR completed during the reporting period. The study CAIN457F2304E1 is ongoing in pediatric population and will provide a total of four years of follow-up data.

Axial spondyloarthritis (including ankylosing spondylitis and non-radiographic axial spondyloarthritis)

The study CAIN457H2315 providing up to a total of four years of follow-up data completed during the reporting interval.

Hidradenitis suppurativa

There were no extension or long-term core studies that had final CSR completed during the reporting period. The study CAIN457M2301E1 is ongoing and will provide a total of four years of follow-up data.

Lupus nephritis

Study CAIN457Q12301E1 was intended for Long term follow up information however it was terminated due to futility of the core study CAIN457Q12301 (refer to Section 7.2)

7.4 Other therapeutic use of medicinal product

There were three Managed Access Programs (MAPs) and eleven Post-Study Drug Supplies (PSDS) providing an access to AIN457 during the reporting period.

Table 7-3 Completed and ongoing MAPs/PSDS during the reporting period

Program Code: CAIN457I2001P	
Title of Program: Post Study Drug Supply (PSDS) Cohort Treatment Plan CAIN457I2001P to provide post-trial access to AIN457 ('SECUKINUMAB' AND 'COSENTYX') for patients benefiting from treatment in Novartis-sponsored study CAIN457H2315	
Number of participating countries: 8	**Program status:** Completed **Start Date:** 16 Aug 2018 **End Date:** 18 Oct 2023 Cumulative patients exposed: 30
Brief summary of program: Post Study Drug Supply (PSDS) Cohort to provide post-trial access to secukinumab for patients benefiting from treatment in Novartis-sponsored study CAIN457H2315	

Program Code: CAIN457H2003P	
Title of Program: Post-Trial Access Cohort CAIN457H2003P to provide access to Secukinumab (AIN457) related to clinical trial CAIN457H3301.	
Number of participating countries: 2	**Program status:** Completed **Start Date**: 15 Oct 2018 **End Date:** 27 Oct 2022 Cumulative patients exposed: 36
Brief summary of program: Post-Trial Access Cohort CAIN457H2003P to provide access to secukinumab related to clinical trial CAIN457H3301	
Program Code: CAIN457FIL01P	
Title of Program: Protocol for continuation of treatment with Secukinumab for active psoriatic arthritis and axial skeleton involvement after completion protocol CAIN457F3302 MAXIMISE (known as a randomized, double-blind, placebo-controlled, multicenter, 52 week study to assess the efficacy and safety of secukinumab 150 mg or 300 mg s.c. in patients with active psoriatic arthritis and axial skeleton involvement who have inadequate response to non steroidal anti-inflammatory drugs (NSAIDs))	
Number of participating countries: 1	**Program status:** Completed **Start Date:** 11 Jul 2019 **End Date:** 21 Aug 2022 Cumulative patients exposed: 1
Brief summary of program: Protocol for continuation of treatment with Secukinumab for active psoriatic arthritis and axial skeleton involvement after completion protocol CAIN457F3302 MAXIMISE	
Program Code: CAIN457AIL02P	
Title of Program: Post study drug supply after completion study CAIN457A3401	
Number of participating countries: 1	**Program status**: Completed **Start Date**: 01 Aug 2017 **End Date:** 30 Dec 2020 Cumulative patients exposed: 15
Brief summary of program: Post study drug supply after completion study CAIN457A3401	
Program Code: CAIN457APL01P	
Title of Program: Local PTA for the trial AIN457A2310 for Poland	
Number of participating countries: 1	**Program status**: Completed **Start Date:** 17 Jan 2022 **End Date:** 03 Aug 2022 Cumulative patients exposed: 1
Brief summary of program: Post study drug supply after completion trial AIN457A2310 in Poland	
Program Code: CAIN457AEG01P	
Title of Program: PTA for the trial AIN457A2310 for Egypt	
Number of participating countries: 1	**Program status**: Completed **Start Date**: 20 May 2022 **End Date**: 28 Nov 2023 Cumulative patients exposed: 4
Brief summary of program: Post study drug supply after completion trial AIN457A2310 in Egypt	

Program Code: CAIN457F2407I	
Title of Program: N/A - Individual Patient Request for patients with rheumatology indications	
Number of participating countries: 5	**Program status:** Ongoing **Start Date:** 24 Nov 2015 Cumulative patients exposed: 453
Brief summary of program: An Individual patient request Managed Access program in which patients who have a serious or life-threatening disease or condition, for which all currently available treatment options have been exhausted and enrollment into a clinical trial is not possible, can receive access to Secukinumab for Rheumatology indications.	
Program Code: CAIN457A2404I	
Title of Program: N/A - Individual Patient Request for patients with dermatology indications	
Number of participating countries: 13	**Program status:** Ongoing **Start Date**: 01 Feb 2016 Cumulative patients exposed: 131
Brief summary of program: An Individual patient request Managed Access program in which patients who have a serious or life threatening disease or condition, for which all currently available treatment options have been exhausted and enrollment into a clinical trial is not possible, can receive access to Secukinumab for Dermatology indications.	
Title of Program: N/A - Individual Patient Request	
Program Code: CAIN457K2001P	
Title of Program: SURPASS PSDS to provide Secukinumab and GP17 to patients coming off the SURPASS study	
Number of participating countries: 1	**Program status**: Ongoing **Start Date:** 11 Feb 2021 Cumulative patients exposed: 22
Brief summary of program: To provide Secukinumab and GP17 to patients coming off the SURPASS study	
Program Code: CAIN457AGB05P	
Title of Program: Post Trial Access to provide access to Secukinumab (AIN457) to the patients in UK	
Number of participating countries: 1	**Program status**: Ongoing **Start Date:** 13 Sep 2017 Cumulative patients exposed: 65
Brief summary of program: to provide post trail access to secukinumab to patients in UK	
Program Code: CAIN457FBR05P	
Title of Program: Post Trial Access for CAIN457F2306 in Brazil	
Number of participating countries: 1	**Program status:** Ongoing **Start Date:** 29 Sep 2017 Cumulative patients exposed: 7
Brief summary of program: to provide post access to secukinumab to patients in Brazil	
Program Code: CAIN457P12001P	
Title of Program: Post Study Drug Supply (PSDS) Cohort Treatment Plan CAIN457P12001P to provide post-trial access to Secukinumab (Cosentyx®) subcutaneous injection for patients benefiting from treatment in Novartis-sponsored study CAIN457P12301	

Number of participating countries: 2	**Program status**: Ongoing **Start Date:** 05 May 2022 Cumulative patients exposed: 13
Brief summary of program: to provide post-trial access to Secukinumab (Cosentyx®) subcutaneous injection for patients benefiting from treatment in Novartis-sponsored study CAIN457P12301	
Program Code: CAIN457P12002P	
Title of Program: Post Study Drug Supply (PSDS) Cohort Treatment Plan CAIN457P12002P to provide post-trial access to Secukinumab(Cosentyx®) subcutaneous injection for patients benefiting from treatment in Novartis-sponsored study CAIN457P12302	
Number of participating countries: 2	**Program status**: Ongoing **Start Date:** 28 Apr 2022 Cumulative patients exposed: 23
Brief summary of program: to provide post-trial access to Secukinumab(Cosentyx®) subcutaneous injection for patients benefiting from treatment in Novartis-sponsored study CAIN457P12302	
Program Code: CAIN457M2002M	
Title of Program: Managed Access Program (MAP) Cohort Treatment Plan CAIN457M2002M to provide access to Secukinumab for adult patients with Hidradenitis Suppurativa (HS)	
Number of participating countries: 8	**Program status:** Ongoing **Start Date:** 19 Dec 2022 Cumulative patients exposed: 121
Brief summary of program: to provide access to Secukinumab for adult patients with HS.	

HS: Hidradenitis Suppurativa; SC: Subcutaneous

7.5 New safety data related to fixed combination therapies

Cosentyx is neither a component of a fixed combination product or multi-drug regimen, nor a fixed combination product.

8 Findings from non-interventional studies

During the reporting interval, there was a total of four completed and eight ongoing non-interventional studies.

The Synopsis of the completed NISs are included within Appendix 5.

Table 8-1 Non-interventional studies ongoing or completed during the reporting interval

Study number	Title (abbreviated)	Number of patients	Safety and efficacy findings
Completed (n=4)			
CAIN457A1401 (imposed PASS)	Long-time observation in Japanese subjects with psoriasis or psoriatic arthritis	976	The results of this survey showed no new safety concerns from long-term

Study number	Title (abbreviated)	Number of patients	Safety and efficacy findings
			treatment with secukinumab. The long-term efficacy of secukinumab was demonstrated in patients with psoriasis and psoriatic arthritis in post-marketing surveillance.
CAIN457A1402 (imposed PASS)	Open label study in Japanese subjects w/ generalized pustular psoriasis	95	The results of this survey showed no new safety concerns from long-term treatment with secukinumab. The long-term efficacy of this drug was demonstrated in patients with pustular psoriasis in post-marketing surveillance.
CAIN457AKR03	Regulatory Post-Marketing Surveillance(PMS) for Cosentyx (Secukinumab)	1,006	No new safety or efficacy findings
CAIN457H1401 (imposed PASS	Observational study to investigate the safety and efficacy over 52 weeks in Ankylosing Spondylitis (AS) patients treated with Cosentyx (secukinumab)	86	No new safety or efficacy findings..
Ongoing (n=8)			
CAIN457A2406	A real-world, prospective, multicenter study to assess the safety and effectiveness of secukinumab (Cosentyx®) in patients aged 6 years to less than 18 years with moderate to severe chronic plaque psoriasis in China	CCI	No new safety or efficacy findings
CAIN457A2401	CorEvitas (former CORRONA) Psoriasis Registry	CCI enrolled (secukinumab – CCI; other biologics – CCI; non-biologics – CCI)	No new safety or efficacy findings
CAIN457A3403	Long-term observational, prospective study to collect in a real life setting data on the retention, effectiveness, safety, treatment pattern, quality of life, and efficiency of secukinumab in adult patients with moderate to severe plaque psoriasis, psoriatic arthritis or ankylosing	CCI	No new safety or efficacy findings

Study number	Title (abbreviated)	Number of patients	Safety and efficacy findings
	spondylitis (SERENA)		
CAIN457FDE02	Non -Interventional study to Assess the benefits of Secukinumab in biologic-naïve and inadequate responder patients with ankylosing spondylitis and psoriatic Arthritis	CCI	No new safety or efficacy findings
CAIN457ACA02 * (non-EU voluntary PASS)	PURE: Registry of patients with psoriasis in Canada and Latin America	CCI	No new safety or efficacy findings
CAIN457ACN06	A prospective multicenter study for the assessment of treatment patterns, effectiveness and safety of secukinumab in adult patients with moderate to severe plaque psoriasis in a real-world setting in China	CCI	No new safety or efficacy findings
CAIN457L1401	A Special Drug Use-results Survey to Evaluate the Safety and Efficacy of Subcutaneous Administration of Cosentyx in Pediatric Patients with Psoriasis Vulgaris, Psoriatic Arthritis, or Pustular Psoriasis	CCI	No new safety or efficacy findings
CAIN457MDE01	Long term observAtional, prospective, multicenter study to collect iN	CCI	No new safety or efficacy findings

AS: Ankylosing Spondylitis; axSpA; Axial Spondyloarthritis; PsA: Psoriatic Arthritis; Pso: Psoriasis
*Study is Post Authorization Safety Study

A listing of MAH-sponsored non-interventional PASS and PAES which was completed, ongoing or planned during the reporting interval can be found in Appendix 4.2.

8.1 Patient support programs

During the reporting interval, 66,620 cases were reported from PSPs and market research programs conducted by Novartis.

The cases are discussed under individual topics in Section 15 and Section 16. An aggregate evaluation of these cases did not reveal any new relevant safety or efficacy information.

9 Information from other clinical trials and sources

9.1 Other clinical trials

During the reporting interval a total 43 third-party Investigator Initiated Trials and Research Collaborations (RCs) were completed, two were stopped (with patients) due to low enrolment and 41 were ongoing.

Table 9-1 List of Completed, Ongoing and Stopped Investigator Initiated Trials and Research Collaborations

Study Number	Study Title	New safety findings
Completed (n=43)		
CAIN457ADE03T	A randomized, placebo-controlled, double-blind study to scrutinize the efficacy of secukinumab in patients with intrinsic (non-allergic) atopic dermatitis (SIAD)	No new safety findings
CAIN457AUS08T	Cosentyx (Secukinumab) for the treatment of adult onset pityriasis rubra pilaris: a single arm, open label exploratory trial	No new safety findings
CAIN457AUS09T	Safety and efficacy of Secukinumab in adults with Mild, Chronic Plaque - Type psoriasis.	No new safety findings
CAIN457AUS16T	A single-center, Open Label study to evaluate the efficacy and safety of secukinumab in adult patients with skin types IV-VI with moderate to severe plaque psoriasis	No new safety findings
CAIN457AUS17T	Evaluation of IL-17 activity in cutaneous dermatomyositis lesions.	No new safety findings
CAIN457AUS29T	IL-17A: A targetable marker for Sarcoidosis	No new safety findings
CAIN457F2015T	D1 Sex differences in efficacy and drug survival of tumor necrosis factor inhibitors in spondyloarthritis and psoriatic arthritis: results from the EuroSpA Research Collaboration Network	No new safety findings
CAIN457F2408T	D3 Patterns of enthesitis in patients with psoriatic arthritis and axial spondyloarthritis and effectiveness of tumor necrosis factor inhibitors - A EuroSpA collaboration study	No new safety findings
CAIN457F2410T	D6 Sex-attributable differences in patient-reported outcome measures in axial spondyloarthritis.	No new safety findings
CAIN457FDK01T	A multimodal imaging diagnostic feasibility and accuracy study to explore the association between ultrasound evaluation of the joint and nail and dynamic contrast-enhanced magnetic resonance imaging, nail bed capillaroscopy and clinical evaluation of the	No new safety findings
CAIN457FHK01T	Prevention of metacarpophalangeal joints structure damage in patients with psoriatic arthritis using secukinumab	No new safety findings

Study Number	Study Title	New safety findings
CAIN457FTH02T	Patient perspectives and treatment expectations in ankylosing spondylitis and psoriatic arthritis: a cross-sectional survey	No new safety findings
CAIN457FUS01T	What is Important to Patients with Psoriatic Arthritis: Are There Differences from What Physician Consider Important?	No new safety findings
CAIN457FUS11T	Development of referral strategy to improve the identification of axial spondyloarthritis amongst patients with chronic back pain	No new safety findings
CAIN457FUS27T	Personalized prediction models for COVID-19 outcomes in patients with immune-mediated inflammatory disease	No new safety findings
CAIN457HNL01T	An explorative study concerning the effect of secukinumab on bone metabolism in patients with ankylosing spondylitis	No new safety findings
CAIN457I2002T	D2 Handling of missing component values in Patient reported outcomes	No new safety findings
CAIN457ADK03R	IMPROVE: Incentives for healthcare management based on patient-related outcomes and value (IMPROVE) in psoriasis. A non-interventional study in patients with psoriasis to test a new outcome-based management model in a clinical setting.	No new safety findings
CAIN457FSE01R	Studies of the diagnostic validity, prevalence, incidence and mortality of psoriatic arthritis in Sweden	No new safety findings
CAIN457FBR01R	Assessment of the impact of psoriatic arthritis on functional capacity in a real-life context: A cohort study	No new safety findings
CAIN457AES13R	Search for genetic biomarkers to predict secukinumab response in psoriasis patients	No new safety findings
CAIN457FES04R	Effectiveness, retention rates and safety of secukinumab treatment in Spondyloarthrithis: results from the BIOBADASER registry.	No new safety findings
CAIN457FMY01R	Malaysian registry study to describe the burden of illness of Spondyloarthritis (SpA): MyNIAR-SpA	No new safety findings
CAIN457AMY01R	Effectiveness of secukinumab for psoriasis in real-world practice in Malaysia	No new safety findings
CAIN457FES06R	Treatment with Secukinumab in Rheumatology: A real-world, observational, multicenter, retrospective study	No new safety findings
CAIN457FBR02R	Application of the Portuguese version of Psoriatic Arthritis Screening Evaluation Tool (PASE-P) and Correlation with Clinical and Laboratory Data	No new safety findings

Study Number	Study Title	New safety findings
CAIN457HAR01R	Prevalence of diagnosed and undiagnosed axial spondyloarthritis among young people consulting because of chronic low back pain in a University Hospital in Argentina	No new safety findings
CAIN457F2014R	Describing the current COVID-19 Pandemic from the perspective of people with Rheumatic Conditions (REUMAVID)	No new safety findings
CAIN457ABR02R	SARS use of secukinumab in patients with covid-19 associated serious acute respiratory syndrome (SARS)	No new safety findings
CAIN457ANO01R	"What can drug prescriptions tell us about Norwegian psoriasis patients?"	No new safety findings
CAIN457A2405R	Exploring disease correlations and temporal disease progression and comorbidities in psoriatic disease using population-wide registry data	No new safety findings
CAIN457A2024R	A retrospective cohort study of the prevalence and Incidence of severe and rare infections among adult patients with psoriasis in Denmark: a nationwide register linkage study	No new safety findings
CAIN457AGR02R	A real-life 208 week single-center, register-based, retrospective study assessing Secukinumab survival and long-term efficacy and safety among Greek patients with moderate-to-severe plaque psoriasis, including difficult to treat manifestations such as genitals, scalp, nails and palmoplantar psoriasis	No new safety findings
CAIN457FGR02R	Comparative drug survival and effectiveness of secukinumab and TNFα inhibitors in clinical practice: analysis of a prospective single centre cohort	No new safety findings
CAIN457F2016R	Patient reported outcomes, drug adherence and clinical effectiveness of secukinumab in patients with psoriatic arthrithis and axial spondlarthritis up to 24 months: Results from the EuroSpA collaboration	No new safety findings
CAIN457AVN03R	Comorbidity burden and the treatment patterns among psoriasis patients with comorbidities in the real life setting	No new safety findings
CAIN457F2017R	Immunogenicity and safety of vaccination against Covid-19 among patients with rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, and ankylosing spondylitis treated with immunomodulatory drugs and biologics.	No new safety findings
CAIN457AFR06R	Retrospective study to describe a daily-practice cohort of psoriatic patients treated with secukinumab for skin damage and the long-term progression of psoriatic disease	No new safety findings
CAIN457FAR04R	Epidemiology of Juvenile Idiopathic Arthritis in Argentina: An retrospective study	No new safety findings
CAIN457F2020R	Long-term drug adherence and clinical effectiveness of secukinumab in patients with psoriatic arthritis and axial spondyloarthritis up to 48 months: Results from the EuroSpA collaboration	No new safety findings

Study Number	Study Title	New safety findings
CAIN457AUS10T	Secukinumab therapy for the treatment of moderate to severe plaque psoriasis with response monitoring using optical coherence tomography (OCT)	No new safety findings
CAIN457ANL02T	Prevalence of Suppurativa Hidradenitis, Atopic Dermatitis and Hand Eczema in the General population – POSH/PADHE study	No new safety findings
CAIN457ANL03T	PsoCovid	No new safety findings
Ongoing (n=41)		
CAIN457A2232T	A Randomised Controlled Trial of Secukinumab Versus Adalimumab for the Treatment of Juvenile Idiopathic Arthritis Associated Uveitis, using a Bayesian Design	No new safety findings
CAIN457ACN03T	The Effect of Secukinumab on Depression in Patients with Moderate to Severe Plaque Psoriasis: A Prospective, Single-center Study	No new safety findings
CAIN457ADE04T	PsoBest - Long-Term Benefits and Safety of Systemic Psoriasis Therapy: German Registry on the Treatment of Psoriasis with Biologics and Systemic Therapeutics	No new safety findings
CAIN457ADE12T	E-bio-study - Enthesitis biopsy study, Interventional one-arm mode-of-action study with secukinumab in patients with either PsO or PsA and active enthesitis of the epicondyle.	No new safety findings
CAIN457AFR03T	Post-registration study for secukinumab carried out using data from the psobioteq registry	No new safety findings
CAIN457AGB01T	British Association of Dermatologists Biologic Interventions Register (BADBIR)	No new safety findings
CAIN457AGB07T	A Phase II, multicentre, randomised, double-blind, placebo controlled, crossover study to evaluate the safety and efficacy of Secukinumab in patients with non- ocular Behçet's Syndrome	No new safety findings
CAIN457AUS27T	Brain morphological changes accompanied by effective biologic treatments for psoriasis and their associations with the improvement of itch, pain, and well-being.	No new safety findings
CAIN457AUS35T	Evaluating Sleep in Patients with Moderate to Severe Psoriasis.	No new safety findings
CAIN457F2301TE1	Observational study of the Psoriasis - Arthritis& Bone Program (PSARTROS) - Follow up	No new safety findings
CAIN457F2409T	D4 Treatment of peripheral arthritis in the spondyloarthritides: Joint-specific response to TNF inhibitors?	No new safety findings
CAIN457F2411T	D7 Treatment retention in SpA patients assessed with methods for interval-censored time-to-event data	No new safety findings

Study Number	Study Title	New safety findings
CAIN457FAU02T	Does "real-time" ultrasound improve medication adherence in the treatment of inflammatory arthritis?	No new safety findings
CAIN457FCA05T	Predicting Clinical and Immune Secukinumab Effects in Axial Spondyloarthritis (PreCISE.AS)	No new safety findings
CAIN457FCN01T	A non-interventional, prospective, observational, multi-center study evaluating inflammation and structural change in MRI at week 24 of active axSpA patients treated with Secukinumab in real world setting in China	No new safety findings
CAIN457FDE01T	Long-term observation of treatment with targeted therapies in axial spondyloarthritis and psoriatic arthritis - RABBIT-SpA	No new safety findings
CAIN457FFR01T	MIRIAD : Microbiota and Immune Response in patIents with Ankylosing SponDylitis treated with Secukinumab. A pilot study.	No new safety findings
CAIN457FNL02T	F-18-Flouride PET-CT monitoring of bone formation in spondyloarthritis	No new safety findings
CAIN457FNL03T	Treat to target in early psoriatic arthritis using secukinumab(Cosentyx) as first line treatment to improve outcome	No new safety findings
CAIN457FUS02T	Trabecular Bone Score and Bone Health in radiographic and non-radiographic Spondyloarthritis	No new safety findings
CAIN457FUS21T	Phase IV Open Label Study of the Effects of Secukinumab on Nail Psoriasis and non-invasive measures of enthesitis	No new safety findings
CAIN457HDK01T	TReat-to-tArget with seCukinumab in axial spondyloarthritis. IdEntification of MRI and biochemical biomarkers for disease activity, treatment response and structural damage progression (the TRACE study).	No new safety findings
CAIN457HGR01T	Integrated Multi-omics Study for the Identification of Predictive Biomarkers of Response to Secukinumab in Ankylosing Spondylitis Patients	No new safety findings
CAIN457HNL02T	Axial Spondyloarthritis Outcome	No new safety findings
CAIN457I2402T	D5 Impact of the Covid-19 pandemic on patient selection and treatment outcomes in spondyloarthritis patients treated with b/tsDMARDs across Europe	No new safety findings
CAIN457IES01T	Development of a Self-Reported Questionnaire to Early Identify Axial Spondyloarthritis in Patients with Chronic Back Pain Referred to Other Specialists Different than Rheumatologists.	No new safety findings
CAIN457R1CH01T	Predictive factors for treatment response in patients with newly-diagnosed polymyalgia rheumatica and giant cell arteritis	No new safety findings

Study Number	Study Title	New safety findings
CAIN457APT02R	Real-World Outcomes in Ankylosing Spondylitis and Psoriatic Arthritis patients treated with Secukinumab - Data from the Internal Medicine Portuguese Registry of Rheumatic Diseases (RIDAI)	No new safety findings
CAIN457AFR04R	OMCCI - Evaluation of the impact (epidemiology) of a chronic inflammatory skin disease on the daily life of people suffering from the condition	No new safety findings
CAIN457ASE02R	Real World Evidence on the use of Interleukin inhibitors/receptor antagonists in Psoriasis Patients in Sweden - Research Based on PsoReg, Regional and National Health Care Registers	No new safety findings
CAIN457FES08R	An exploratory, controlled, cross-sectional, multicenter study, comparing musculoskeletal ultrasound signal changes in psoriasis patients under suspicion of psoriatic arthritis or only skin psoriasis, before and after physical controlled exertion with dynamometer	No new safety findings
CAIN457FPT03R	CheckAP - Prevalence of PsA and performance evaluation of a PsA screening Questionnaire in the population of Portuguese patients with Psoriasis followed in Dermatology setting	No new safety findings
CAIN457LBR01R	Evaluation of the quality of life in treated psoriatic pediatric and adolescents patients	No new safety findings
CAIN457FUS26R	The Covid19 VaccinE Response in Rheumatology patients (COVER) -The SARSCoV-2 Vaccine Response and Safety in Rheumatology Patients and the Influence of Temporary Interruptions in Immunomodulatory Therapy	No new safety findings
CAIN457F2018R	Impact of national treatment guideline, schedules of reimbursement and gross domestic product on heterogeneity of patient populations across European observational spondyloarthritis registries	No new safety findings
CAIN457F2019R	Impact of national treatment guideline, schedules of reimbursement and gross domestic product on treatment outcomes in patients treated with b/tsDMARDs across European observational spondyloarthritis registries	No new safety findings
CAIN457I2003R	Distribution of sacroiliac joint and spine imaging findings in a large cohort of real-life patients with axial SpA	No new safety findings
CAIN457I2004R	Local vs. central readings of MRIs of the sacroiliac joints in patients with axial spondyloarthritis: investigation of agreement and the need for educational activities for local interpreters	No new safety findings
CAIN457ASA01R	Effectiveness of secukinumab in patients with psoriatic disease in Saudi real-world setting	No new safety findings
CAIN457I2005R	Occurrence and pattern of MRI and radiographic involvement of sacroiliac joints and spine in a European cohort of real-life patients with psoriatic arthritis	No new safety findings

Study Number	Study Title	New safety findings
CAIN457I2006R	The MRI equivalent to modified New Yort criteria-positivity on conventional radiography of the sacroiliac joints in patients with axSpA	No new safety findings
Stopped (with patients) (n=2)		
CAIN457AUS11T*	An open-label proof of concept study regarding the use of Cosentyx (Secukinumab) in patients with necrobiosis lipoidica diabeticorum (NLD)	No new safety findings
CAIN457FUS12T*	Gene expression and metabolomics profiling of synovium versus skin lesions in psoriatic patients on biological therapy	No new safety findings

*Study terminated due to low enrolment

9.2 Medication errors

Reports of medication errors, overdose, abuse, misuse, occupational exposure, and lack of therapeutic effect with no associated ADR are handled as complete case reports according to Novartis Standard Operation Procedures in the same way as symptomatic cases. Occupational exposure and lack of therapeutic effect is included in signal detection activities as part of routine pharmacovigilance activities and only presented in the PSUR if a signal is identified or upon request from a Health Authority Reports of medication errors, including overdose if unintentional, are addressed in this section.

The search criteria was updated from previous PSUR due to update in MedDRA and 15 preferred terms ('Accidental exposure to product by elderly person', 'Dosage not adjusted', 'Inappropriate schedule of product discontinuation', 'Labelled drug-genetic interaction medication error', 'Product dose confusion', 'Unadjusted dose administered', 'Use of error-prone abbreviation', 'Device safety feature issue', 'Drug effective for unapproved indication', 'Drug ineffective for unapproved indication', 'Labelled drug-genetic interaction issue', 'Product administered from unauthorised provider', 'Product temperature excursion issue', 'Therapeutic product effective for unapproved indication' and 'Therapeutic product ineffective for unapproved indication') were newly added. Hence, an impact assessment is also presented.

Methods of evaluation

A search for cases reporting medication errors was conducted in the safety database using MedDRA v26.1, and as specified in Appendix 8.

Results

Company safety database

CCI cases during the reporting interval and CCI cases cumulatively.

Out of the CCI interval cases, eight cases were also retrieved and analyzed in previous PSUR. Hence not further discussed in this section.

Of the CCI cases retrieved cumulatively, CCI cases received significant follow-up information during the reporting interval, out of which CCI cases initially received in previous reporting intervals newly reported an event related to medication error and CCI cases reported

addition of suspect drug as follow-up information during the reporting interval, and two cases received in previous reporting interval were unblinded during the reporting period.

These CCI cases are included in the analysis along with cases received during the reporting interval, adding up to a total number of evaluable cases of CCI [*Note: Case* PD [redacted] PD [redacted] *(received during reporting interval) is a continuation of case (previous PSUR case with significant follow-up information during the reporting interval) due to the data contents exceeding the database limit. Hence, the information presented in this case pair is considered only once under the case marked in bold and counted as one case in order to avoid duplication.]*

Of these CCI cases, CCI cases are either analyzed in different sections (off label use and device issues impacting patient safety) or do not reveal clinical details suggestive of unintended failure in secukinumab administration in accordance with the product label:

- In CCI cases, it was noted that the cases include a variety of clinical details such as dose and dosing frequency, drug shipment, changes in drug delivery system (device) or due to recent vaccinations. Upon medical review of each of these cases, no unintended failure or error were identified in these cases. Hence, these cases were not considered to qualify as true medication errors. Preferred terms included 'Inappropriate schedule of product administration' (n=CCI), 'Product dose omission issue' (n=CCI), 'Product prescribing error' (n=CCI 'Incorrect dose administered' (n=CCI), 'Product use issue' (n=CCI) and others (n<CCI events).
- A total of CCI cases were related to device issue. The associated medication error events in these cases were related to device issue and are discussed in Section 9.3 'Device issues impacting patient safety'.
- In CCI cases, either PT 'Product use in unapproved indication'/ 'Drug ineffective for unapproved indication'/ 'Therapeutic product ineffective for unapproved indication'/ 'Drug effective for unapproved indication'/ 'prescribed overdose'/ 'Prescribed underdose' was reported or the events were related to off label use (indication/dose /route). These also included CCI events with preferred terms 'Product prescribing error'/ 'Product prescribing issue' noted to be related to intentional use. Out of these CCI cases, CCI cases are included in Section 5.2.3 'Off-label use' based on the intent of usage of secukinumab. In the remaining CCI cases, PTs 'Drug ineffective for unapproved indication'/ 'Therapeutic product ineffective for unapproved indication'/ 'Drug effective for unapproved indication' were reported. These CCI cases were already assessed in previous PSUR off label topic and are retrieved for medication error topic for the first time during the interval as significant follow up cases due to update in MedDRA. Impact analysis of these cases is included below.
- In CCI cases 'Overdose' PT was reported. In CCI of the CCI cases, intention related to overdose was not clear. Two cases were reported with intentional overdose: in one case reason for overdose was unknown and in another overdose was related to suicidal ideation (this case is further discussed in Section 16.3.2.3 Suicidal ideation and Behavior'). One case reported potential overdose but was not confirmed due to limited information. The remaining five cases reported unintended overdose. These five cases are included in medication error cases discussed below.

- In CCI cases, the medication error event was related to other suspect drugs (omalizumab, methotrexate, carbamazepine, unspecified psychiatric medication, sildenafil, heroin, mitrazapine, amitriptyline, gabapentin and alcohol etc.).

The distribution of the remaining CCI cases plus the five unintentional overdose cases (i.e., CCI in total) (CC CT, CCI non-valid, CC literature, CCI PMS, CCI SR; CCI HCP and CCI non-HCP) is presented in the Table 9-2 below (*Note: Non-valid cases are not reflected in summary tabulations as described in Section 6.3)*. Adverse events were reported with 'Overdose' in three out of five cases which included 'Fatigue', 'Ascites', 'Skin tightness', 'Rheumatoid arthritis', 'Pain in extremity', 'Arthralgia', 'Pruritus' and 'Confusional state'. The patient with the reported 'Confusional state' event received different delivery system (from 150 mg prefilled syringe to 300 mg injections) and was confused by the device change and administered two injections of 300 mg leading to overdose (coded to Confusional state in MedDRA). In the case reporting 'Ascites' there is limited information in the case regarding the causal etiology, time to onset, medical history and risk factors. The available information in the case doesn't warrant any suspicion to relate the event to secukinumab.

Table 9-2 Frequency of cases based on medication error category

Medication error category*	Number of cases
Medication error with AE	CCI
Medication error without AE	CCI
Intercepted error	CCI
Potential error	CCI
Total	CCI

AE: Adverse Event.

*In cases reporting >1 events of medication error, categorization was performed on single medication error event of interest

Medication error with adverse event

The CCI medication error cases with AEs (CCI SR, CCI PMS; CC Literature and CC Non-valid; CCI HCP, CCI non-HCP) contained CCI events. The top five medication error events are presented in Table 9-3. The top five adverse events co-reported with medication errors are presented in Table 9-4. These adverse events were mainly the clinical signs and symptoms of underlying conditions or are expected for secukinumab without increased severity. No new safety concerns were identified.

Table 9-3 Frequency of Medication error events

Medication error event*	Count
Inappropriate schedule of product administration	CCI
Product dose omission issue	CCI
Product storage error	CCI
Product use issue	CCI
Incorrect dose administered	CCI

*Frequency of top five preferred terms are presented in the table

Table 9-4 Frequency of adverse events co-reported with 'Medication error'

Additional adverse events with medication error events*	Count
Psoriasis	CCI
Pain	CCI
Arthralgia	CCI
Pruritus	CCI
Fatigue	CCI

* Frequency of top five preferred terms are presented in the table

Medication error without adverse event

There were CCI medication error cases without AEs (CC CT, CC Non-valid, CCI PMS, CCI SR; CCI non-HCP and CCI HCP) contained CCI medication error events. The top five medication error events reported are presented in Table 9-5. The most frequently reported medication error was 'Product storage error'. As per CDS V 3.4, secukinumab should be stored in refrigerator at 28°C. The pre-filled syringe and pre-filled pen only are not to freeze and if necessary, may be stored unrefrigerated for a single period of up to four days at room temperature, not above 30°C. Upon analysis it was noted that in the cases the drug was stored at room temperature or elevated temperatures due to human error.

Table 9-5 Frequency of medication error events

Medication error event*	Count
Product storage error	CCI
Product temperature excursion issue	CCI
Inappropriate schedule of product administration	CCI
Incorrect dose administered	CCI
Product dose omission in error	CCI

* Frequency of top five preferred terms are presented in the table

Intercepted error

There were CCI cases (CCI PMS and CC SR; CC HCP and CCI non-HCP) reporting intercepted medication error events. The intercepted errors events reported are presented in Table 9-6. The most frequently reported intercepted error was 'Intercepted product administration error'. These cases were noted to be related to incorrect prescription in most of the cases.

Table 9-6 Frequency of intercepted medication error events

Intercepted Medication error event*	Count
Intercepted product administration error	CCI
Intercepted product storage error	CC
Intercepted product dispensing error	CC
Intercepted medication error, Intercepted product prescribing error, Intercepted product selection error	CC each

Potential error

There were CCI cases (CCI PMS, CCI SR, CC non-Valid, C CT; CCI HCP and CCI non-HCP) reporting potential error events. The top five events are presented in Table 9-7. The reported dispensing error was mostly related to dispensing of incorrect dose or quantity.

Table 9-7 Frequency of potential medication error events

Potential Medication error event*	Count
Product dispensing error	CCI
Product prescribing issue, Product prescribing error	CCI each
Product packaging issue	CCI
Product label confusion	CC
Circumstance or information capable of leading to medication error, Drug monitoring procedure not performed	CC each

* Frequency of top five potential errors are presented in the table

Impact analysis of the cases that were retrieved cumulatively due to addition of Preferred terms

Cumulatively CCI cases were retrieved with 15 PTs newly added due to change in search criterion. These CCI cases reported a total of CCI adverse events (CCI serious and CCI non-serious; CCI medication error events and CCI other adverse events). A review of these cases did not identify any safety concern that could impact the safety profile of secukinumab.

Discussion and conclusion

Based on the review of new information related to medication error (reported mostly by non-HCP's) available during the reporting interval, no safety concern was identified. Adverse events reported concomitantly with medication error are either related to the background indication (e.g. psoriasis, pain, arthralgia, etc.), COVID 19 pandemic or in line with the safety profile of secukinumab (e.g. nasopharyngitis). The instructions for prescribers in the CDS are deemed adequate. Therefore, no changes to CDS are warranted. The MAH will continue to monitor MEs as standard practice.

9.3 CCI

The details of the search criterion used to retrieve cases are included in Appendix 8.

The search criterion was updated from previous PSUR and two PTs (CCI) were newly added. Hence, an impact assessment has been also presented.

Results

Company safety database

The search in the Novartis safety database retrieved CCI cases in this PSUR reporting interval and CCI reported cumulatively.

Out of the CCI cases reported cumulatively, CCI cases initially received in previous reporting intervals newly reported information related to 'Device issues impacting patient safety' as

follow-up information during the reporting interval and were retrieved for the first time and are analyzed along with the reporting interval cases (total CCI cases).

These CCI cases (2 CT, CCI PMS, CCI SR, CCI non-valid *[of note, the 13 non-valid cases are not reflected in the summary tabulations as described in Section 6.3]*) reported a total of CCI events (CCI serious, and CCI non-serious) related to device issues.

The reported descriptions (verbatim) of device issues varied without specified patten. An overview of the most frequently (≥5% of the CCI cases) MedDRA PTs related to device issues is provided in the table below.

Table 9-8 Most frequently reported events related to device issues

Preferred term	Number of events
CCI	

Of the CCI cases, CCI cases reported other events (CCI serious, CCI non-serious) along with device related issues. These events mainly pertained to deviated dosing frequency, omitted dose, accidental spills of the drug solutions (coded to Accidental exposure to product in MedDRA PT), injection site pain, and underlying psoriasis. An overview of the most frequently (≥2% of the events) co-reported events by seriousness is provided in the table below.

Table 9-9 Most frequently co-reported events by seriousness

Preferred term	Number of events		
	Serious	Non-serious	Total
CCI			

The SAEs in these reported device issues were mainly an underlying clinical signs/symptoms or pneumonia. No safety signal was identified. An overview of the most frequently (≥1% of the CCI cases) co-reported serious events is provided in the table below.

Table 9-10 Most frequently co-reported serious events

Preferred term	Number of events
Psoriatic arthropathy	CCI
Pain	CCI
Arthralgia	CCI
Ankylosing spondylitis	CCI
Psoriasis	CCI
Pneumonia	CCI

CCI

Of these CCI cases, CCI cases (CCI PMS, CCI SR) reported events with CCI. In six cases, the CCI was not reported. In the remaining CCI cases, the cause of death was not associated with the device issue.

CCI

Of these CCI cases, in CCI cases a CCI was performed. CCI

.

In CCI cases, the CCI

.

Impact analysis of the cases that were retrieved cumulatively due to addition of PTs

Cumulatively no cases were retrieved with PT 'Product sterility issue', and CCI cases were retrieved with PT 'CCI'. These CCI cases reported a total of CCI AEs (CCI device issues [all non-serious] and CCI other AEs [all non-serious]). The review of these cases did not reveal any safety hazard that could impact the safety profile of Cosentyx.

Discussion and conclusion

CCI issues reported have not indicated a consistent CCI. Adverse events in these reported device issues were either anticipated given the established safety profile or related to underlying indications for Cosentyx. Analysis of the reports of CCI did not reveal any safety hazard that could impact the safety profile of Cosentyx. The CDS includes adequate wording for the CCI. No further actions are warranted at this stage.

9.4 CCI

9.4.1 CCI from POP20150553

There was CCI

Of the CCI cases, CCI cases with CCI were identified pertaining to Cosentyx. Of these CCI cases, CCI cases were included in the reporting interval analysis and under the respective safety sections. The remaining CCI cases were reported as CCI cases in the previous reporting intervals and non-significant information was received during follow-up and no new safety information was identified.

9.4.2 CCI

During the reporting interval, it was identified that, in certain cases, the CCI .

A retrospective review of the cases was performed. A total of CCI Cosentyx cases were identified in which the CCI . For that reason, the CCI . Upon identification of the issue, the CCI .

Based on the review of the cases performed, no impact on the safety was noted.

10 Non-clinical data

No non-clinical *in vivo* or *in vitro* studies were ongoing or completed during the reporting interval.

11 Literature

Relevant publications containing important new safety information published during the reporting interval were retrieved from the three publicly accessible, bibliographic databases Medline, Embase and Biosis Previews and by full text screenings in subscribed medical journals.

The search criteria cover products containing secukinumab and were inclusive of pregnancy outcomes (including termination) with no adverse outcomes, use in pediatric populations, compassionate supply, named patient use, lack of efficacy, asymptomatic overdose, abuse or misuse, medication error where no AEs occurred, or "near misses" and important non-clinical safety results.

With the exclusion of publications describing individual case reports which have been included in Appendix 2.2 'Cumulative and interval summary tabulation of serious and non-serious ADRs from post-marketing data sources', publications containing important safety findings related to secukinumab are presented below.

A total of 10 publications were retrieved during the current reporting interval of which are presented in relevant sections as follows:

Zheng Y et al (2023): Toxicity signals associated with secukinumab: A pharmacovigilance study based on the United States Food and Drug Administration Adverse Event Reporting System database[4].

This publication aimed to explore the clinical characteristics, outcomes and time to onset of the four main toxicities of secukinumab using post-marketing data utilizing data from the United States Food and Drug Administration Adverse Event Reporting System (FAERS) database from 2015 to 2021, using disproportionality analysis. Toxicities were defined based on the standardized Medical Dictionary for Regulatory Activities queries. Two disproportionality methods were used to detect potential signals: information component (IC) and reporting odds ratio (ROR). The signals were defined as ROR025 > 1 and IC025 > 0. A total of 73,945,398 records were included in this study, of which 300,665 records were related to secukinumab. diarrhea (N = 3538), nasopharyngitis (N = 3458), pruritus (N = 4277) and rash (N = 3270) were the most common adverse events. Inflammatory bowel disease (IC025/ROR025 = 3.25/9.69), genital candidiasis (IC025/ROR025 = 3.46/11.54), dermatitis psoriasiform (IC025/ ROR025 = 1.94/4.04) and anosmia (IC025/ROR025 = 1.62/3.17) had the highest IC025 values of all toxicities. The time to onset of the four toxicities was mainly concentrated in the first month. Some patients simultaneously presented with two or more toxicities.

Shu Y et al (2022): Post-Marketing Safety Concerns With Secukinumab: A Disproportionality Analysis of the FDA Adverse Event Reporting System[5].

Disproportionality analysis of US FDA Adverse Event Reporting System (FAERS) data identified many signals for secukinumab-related adverse events (AEs), some of which were new and unexpected. FAERS data from the first quarter of 2015 (when secukinumab was approved by the FDA) to the third quarter of 2021 were used to investigate secukinumab-related AEs. During the study period, there were 89,228 reports with secukinumab as the primary suspected drug which included a total of 254,886 AEs. Overall, 257 signals of secukinumab-induced AEs in 19 system organ classes were identified. Significant signals included infections, respiratory disorders, skin and soft tissue disorders, immune system disorders, ear disorders and labyrinth disorders. Unexpected significant AEs included injection site pain, vessel puncture site hemorrhage, injection site nerve damage, arthralgia, swollen joints, musculoskeletal stiffness, hypokinesia and genital ulceration.

***MAH Comment**: The authors described their findings from their disproportionality analyses of spontaneous cases with a variety of different AEs reported for secukinumab relative to other drugs, as captured in the US Food and Administration Adverse Event Reporting System (FAERS) database. The disproportionately reported AEs as described in the two articles included the known safety risks such as infections as well as some that are currently not causally associated with secukinumab. Due to the inherent limitations of the spontaneous reports, a signal of disproportionality based on spontaneous reports does not automatically confirm a causal association with a suspected drug, rather it is a hypothesis generating technique (Michel et al 2017[6]). The impossibility to confirm the causal relationship between secukinumab and the reported AEs in the data source precludes medical assessment. Shu et al[5] acknowledged this limitation and stated that the disproportionality analysis only provided an evaluation of the signal strength, which was only statistically significant, neither quantified risk nor existed causality. Additionally, the article by Zheng et al 2023[4] revealed unclear objectives, it was claimed in the abstract that the objective was to explore the clinical characteristics, outcomes and time to onset of four main toxicities of secukinumab using post-marketing data, whereas in the main body of the article it is stated that the authors performed this pharmacovigilance study based on data from the FAERS, aiming to detect signals of potential toxicities of secukinumab.*

Neither the study objective was targeted by their methods, results, or the conclusions. Signal detection (including disproportionality analyses) is in place within Novartis, allowing ongoing evaluation of the safety profile for Cosentyx, results of signal monitoring during the reporting period are in Section 15. No further action is warranted given these two articles.

Megna M et al (2022): Eczematous drug eruption in patients with psoriasis under anti-interleukin-17A: does interleukin-22 play a key role?[7]

Background: Eczematous drug eruption (EDE) is a spongiotic skin reaction in response to systemic medications. To date, EDE has been described in patients treated with anti-interleukin (IL)-17A monoclonal antibodies with a prevalence of 2.2%–12.1%. **Aim**: To describe the clinical and histological features and the skin cytokine milieu in patients with EDE induced by anti-IL-17A biologics. **Methods**: This was a prospective study, enrolling patients with psoriasis who developed EDE during treatment with two anti-IL-17 biologics, ixekizumab and secukinumab, from June 2019 to April 2021. Skin biopsies were taken from all patients: a 5-mm lesional biopsy (LB) and a 3-mm nonlesional biopsy (NLB). The LB sample was split into two parts, one for histological examination and the other for cytokine profile evaluation. **Results:** During the study period, treatment with an anti-IL-17A drug was given to 289 patients of whom 8 (2.8%) developed EDE during the treatment. Histopathological evaluation suggested a diagnosis of spongiotic dermatitis in all eight patients. Cytokine gene expression showed a predominance of T helper (Th)2/Th22 cytokines in EDE lesions with a large increase in IL-4, IL-22 and S100A7 levels in both LB and NLB samples compared with healthy skin. IL-4, IL-22 and S100A7 were significantly higher in LB compared with NLB samples. IL-26 levels were also significantly increased in both LB and NLB compared with healthy skin, whereas low levels of IL-23A were found in both LB and NLB. **Conclusion:** Eczematous drug eruption skin lesions have mainly Th2/Th22 features, with IL-22 playing a major role in their pathogenesis. EDE seems to be the result of an imbalance towards a Th2/Th22 response, secondary to the blockade of IL-17A activity.

***MAH Comment**: The authors provide evidence of Th2/Th22 imbalance secondary to IL-17 bock. This mechanism is recognized as paradoxical activity resulting in ADRs for secukinumab that were identified during the reporting period including atopic dermatitis like eruptions including dyshidrotic eczema and exfoliative dermatitis generalized, plus pyoderma gangrenosum (see Section 16.2.1, Section 16.2.2, and Section 16.2.3). Overall, the analysis of all the identified events linked with this mechanism shows no change in the benefit / risk of secukinumab. The secukinumab CDS has been updated accordingly, no further risk minimization measures are deemed to be necessary at this stage.*

The other seven articles are presented in:

- **Section 16.3.1.1 "Infections and infestations":**
  - Dernoncourt A et al (2022): COVID-19 in DMARD-treated patients with inflammatory rheumatic diseases: Insights from an analysis of the World Health Organization pharmacovigilance database[8].
  - Kridin K et al (2022): Risk of COVID-19 infection, hospitalization, and mortality in patients with psoriasis treated by interleukin-17 inhibitors[9].
  - Hasan MJ et al (2021): Secukinumab in severe COVID-19 pneumonia: Does it have a clinical impact?[10]

- Elewski BE et al (2021): Association of secukinumab treatment with tuberculosis reactivation in patients with psoriasis, psoriatic arthritis, or ankylosing spondylitis[11].
- Akdogan N et al (2021): Serial Quantiferon-TB Gold test results in 279 patients with psoriasis receiving biologic therapy[12].

- **Section 16.3.5.1 "Fetal exposure in utero"**
  - Nguyen H et al (2021): A systematic review of the safety of non-TNF inhibitor biologic and targeted synthetic drugs in rheumatic disease in pregnancy[13].
  - Babuna Kobaner G et al (2020): Use of biologic therapies for psoriasis during pregnancy and long‐term outcomes of exposed children: A 14‐year real‐life experience at a tertiary center in Turkey and review of the literature[14].

***MAH Comment**: Overall, the literature review has identified one publication that provides biologic plausibility for new secukinumab ADRs that were identified during the reporting period. Other than this, literature review shows safe secukinumab use during the COVID 19 pandemic, and no new or significant safety findings related to secukinumab were retrieved from published peer-reviewed scientific literature or made available as unpublished manuscripts during the reporting interval.*

12 Other periodic reports

This section is not applicable since this is the single PSUR prepared for the multiple indications and formulations of Cosentyx.

13 Lack of efficacy in controlled clinical trials

There were no results from CTs indicating lack of efficacy which could have a direct impact on subject safety.

14 Late-breaking information

There were no potentially important safety, efficacy, or effectiveness findings, nor regulatory changes, that arose during the preparation of the PSUR after the DLP.

A CDS amendment (CDS v3.5) dated 19 Jan 2024, has been released globally to include two new ADRs (Dermatitis (including eczema) and Dermatitis exfoliative generalized) which, in addition to previously included ADR Dyshidrotic Eczema (as per CDS v3.3) (for details see Section 4).

A new ADR of angioedema is being proposed for the CDS amendment and the SmPC to include sections warning and precautions and ADR.

Post DLP the signal of CCI [redacted] was identified it is discussed in detail in Section 16.2.6.

15 Overview of signals: new, ongoing and closed

15.1 Signals

During the reporting interval, 10 signals were detected during the reporting interval, and one signal (CCI) was detected and validated post DLP.

Of these 11 signals, signals eczematous eruptions including atopic dermatitis like eruptions and dermatitis exfoliative generalized (erythroderma), pyoderma gangrenosum, dyshidrotic eczema and angioedema were closed and confirmed.

The remaining seven signals CCI were closed as refuted as the MAH evaluation was conclusive of no causal association with secukinumab.

The evaluation of validated signals is presented in detail in Section 16.2.

For an overview, reference is made to Appendix 3. The signals are categorized as closed using the definitions described in GVP Module VII[15].

15.2 Health authority requests

In the final Pharmacovigilance Risk Assessment Committee (PRAC) assessment report for previous PSUR covering period 26 Dec 2019 to 25 Dec 2020 (EMEA/H/C/PSUSA/00010341/202012 dated 08 Jul 2021) the MAH was also asked to:

- Provide a review of new cases reporting CCI during the reporting interval of the next PSUR. This review should also include a discussion on whether, based on all available evidence, an update of the product information is warranted. The topic is presented in Section 16.2.4 for the PSUR.
- Submit a cumulative review on angioedema related cases from both clinical trials and post-marketing data using the MedDRA PT Angioedema. The cumulative review should include a table with case details including case ID, source, age, gender, time to onset, dechallenge/rechallenge, outcome, any confounding factors such as concomitant medication or medical history, reported causality assessment and MAH´s conclusion. In addition, a summary and discussion of the most noteworthy cases should also be provided as well as well as the case narratives (ICSR) of these cases. This review should also include an analysis and discussion whether, based on the available evidence, an update of the product information is warranted. The requested review is included in the Section 16.2.5.
- The MAH is requested to present, if available, the observed vs expected number of events and standardized incidence ratio for each type of malignancy compared with the general population. The presentation of the requested incidence ratio is done in Section 16.3.2.1.

In addition to review of topics, the PRAC also requested the following two clarifications:

- The MAH is requested to present a summary of the data reviewed and conclusions drawn from the cumulative review of the topics CCI , requested by the Australian health authority in 2016.

- ***MAH Response:*** In response to earlier applications by the MAH to extend the treatment indications for Cosentyx® (secukinumab) to include active PsA and AS in May 2015, the Advisory Committee on Prescription Medicines (ACPM) at the Therapeutic Goods Administration (TGA) advised inclusion of "CCI " to the CCI .
  In Feb 2016, Novartis received the RMP Advice – Round 2 and performed a comprehensive review of CT and safety data pertaining to CCI from both PsA and AS. The review of the databases did not suggest any clinically significant risk of CCI for patients receiving secukinumab when compared to controls, and specifically the imbalance in CCI between secukinumab and placebo bear no clinical relevance on the overall CCI safety of secukinumab in both PsA and AS clinical programs. Therefore, there was no justification to add CCI " to the list of important potential risks in the RMP. This information was submitted and no further request from TGA was received by Novartis.
  In addition, in the previous PSUR (reporting period: 26 Dec 2019 to 25 Dec 2020) Novartis performed a new cumulative review of cases of CCI , including information from literature and data from Empirica signal system; pre-clinical studies; clinical studies and Novartis safety database, and was included in an CCI
  The overall evaluation from the cases presenting sufficient information did not reveal any new safety information, pattern, or new signal for the topics "CCI CCI ". An update to the CDS was not warranted and Novartis continued to assess CCI under routine pharmacovigilance procedures and will present in future PSURs or CCI , only if a validated signal is identified.
  Novartis has not received additional questions from the TGA after this and routine pharmacovigilance procedures have not identified any new safety concerns for the topics of CCI ".
- Overall, and as highlighted in previous PSUR ARs, the MAH continues to exclude most of the cases from further review due to limited information included in the cases which hampers the assessment of the cumulative reviews. The MAH is reminded that it is the MAH responsibility to follow-up case reports in order to obtain enough information for a clinical assessment. The MAH should consider redefining the criteria used for excluding the cases when conducting cumulative reviews; and revise the procedures in place to ensure completeness of the ICSR in order to obtain data of good quality which can be assessed. Future PSURs cumulative reviews are expected to be more complete and of better quality.
  MAH response*:* Regarding documentation of cases, the MAH would like to continue to assure that appropriate follow up measures are in place and adequate follow up attempts are made to receive complete information for case documentation and assessment. For Cosentyx, the majority of cases come from post marketing sources, prominently from PSPs (73% for current reporting interval) followed by SRs (18% for current reporting interval). Of these, majority of cases may have limited information due to following reasons:
  - Novartis only receives the information provided by the PSP external service providers. The PSP external service providers are informed that all available information should

be transferred to Novartis as per Global PSP AE training slides and Patient Oriented Programs Vigilance contract provisions. As the majority of PSP reports did not have consent to follow up with the reporters, it is difficult to obtain clinically meaningful details in the cases. Additionally, due to local data privacy regulations in many cases Novartis is not able to contact the patient´s physician to obtain more information related to the initial case, including the event/product-specific questionnaire/checklist.

- In general, the follow-up process is dependent on the willingness of the HCP or patient to provide additional information. For the most part, either HCPs have not given consent or HCPs have no additional information to report, or patients did not give consent to contact their physicians to get additional information.

Regarding, redefining the criteria used for excluding the cases when conducting cumulative reviews, the MAH would like to clarify that no case is excluded from aggregate analysis. Minimum criteria to establish causal association is set preliminary to the PSUR data lock point and in this is applied to all cases that are retrieved according to the search strategy. To determine that causality cannot be judged because information is insufficient or contradictory and/or data cannot be supplemented or verified, the following criteria were followed:

- Absence of relevant information in the narrative despite of contact attempts.
- (e.g., absence of information on temporal exposure with suspected drug [not limited to dates], unclarity about confounders [no clear description of medical history or concomitant medications that], no information about effect of suspected medication discontinuation or re-exposure).
- Narrative with lack of chronological order regarding course of events (signs and symptoms), concomitant drugs / co- morbidities.
- Contradictory information (e.g., the patient received suspected drug with concomitant use of other biologics for the same indication, which is unlikely).

For the PSUR, all cases are accounted for the analysis of frequency, severity, pattern of use, pattern of report (e.g., clustered reports) etc. The data analysis of cases with limited information and follow up details are included in the individual safety topics of interest as required. The MAH will continue to review and assess any important information including outcome of events that might enable a meaningful assessment.

Lastly, the MAH would like to highlight that even though a proper causality assessment may not be done for these cases due to limited information about outcome of events in these cases, they are all included in the pooled totality of the data for signal detection as a part of routine pharmacovigilance activity and are, as well, an integral part of the PSUR data set used to conclude on the impact of each safety concern on the benefit-risk balance of the product.

For an overview of all requests from previous assessment reports as well as other HA requests (including those categorized as signals, risks or missing information), reference is made to Appendix 6.

Details on sources of information and general methods applied for evaluating HA requests are presented in Appendix 7.

16 Signal and risk evaluation

16.1 Summary of safety concerns

At the beginning of the PSUR reporting interval, the effective RMP was v7.1 (dated 04 Sep 2020; effective 20 Nov 2020) which was updated to v8.3 based on the PRAC AR received on 29 Apr 2021.

Safety concerns at the beginning of the reporting interval are presented in Table 16-1.

Table 16-1 Safety concerns at the beginning of the reporting interval

Current safety concerns	Comment
Important identified risks*	
Infections and infestations	Addressed in Sections 16.3.1.1 and Appendix 9.1.1
Hypersensitivity	Addressed in Section 16.3.1.2 and Appendix 9.1.2
Neutropenia#	Addressed in Table 16-16 and Section 16.4.1.1
Important potential risks*	
Malignant or unspecified tumors	Addressed in Section 16.3.2.1 and Appendix 9.2.1
Major Adverse Cardiovascular Events (MACE)	Addressed in Section 16.3.2.2 and Appendix 9.2.2
Suicidal ideation and behavior	Addressed in Section 16.3.2.3 and Appendix 9.2.3
Hepatitis B reactivation	Addressed in Section 16.3.2.4 and Appendix 9.2.4
Inflammatory bowel disease#	Addressed in Table 16-16 and Section 16.4.2.1
Interaction with live vaccines#	Addressed in Table 16-16 and Section 16.4.2.2
Missing information	
Fetal exposure in utero	Addressed in Sections 16.3.5.1 and Appendix 9.3.1
Long-term safety data	Addressed in Sections 16.3.5.2 and Appendix 9.3.2
Patients with CCI [redacted]#	Addressed in Table 16-16 and Section 16.4.3.1
Long-term efficacy data$	This missing information has been removed from the list of safety concerns on 06 Apr 2021, RMP v.8.1 and adopted by PRAC (EMEA/H/C/003729/X/67): Based on an RMP commitment, the effects of long-term treatment on the benefit-risk profile of secukinumab are being studied in extension studies to the core phase III studies. During the reporting interval, long-term studies and cumulative post-marketing data (9 years) have confirmed the known benefit – risk profile of secukinumab on the authorized indications. This topic is presented in detailed in the relevant sections of the PSUR.
Patients with CCI [redacted]**	Based on the endorsement by PRAC in the previous PSUR (EMEA/H/C/PSUSA/00010341/202012); these missing information follow routine pharmacovigilance practices and will not be reviewed in PSURs unless a new signal arises.
Patients with CCI [redacted]**	

Source: EU RMP v7.1 (dated 04 Sep 2020; effective 20 Nov 2020), (Part II, Module SVIII 'Summary of the safety concerns').

* Important risks are those which could have an impact on the benefit-risk balance of the product.

On 6th April 2021, RMP v.8.1 was adopted by PRAC within procedure EMEA/H/C/003752/X/67 as per recommendation the Risk/Missing Information was removed from the list of safety concerns taking into account that the information provided in the PI is considered sufficient to minimize the risk and there are not currently additional Pharmacovigilance activities or additional risk minimization measures in place for this safety concern.

$ On 6th April 2021, RMP v.8.1 was adopted by PRAC within procedure EMEA/H/C/003752/X/67 in which Long-term efficacy was removed from the list of safety considering that available data from extension clinical trials (up to 5 years) and cumulative post-marketing data (6 years) do not indicate a different efficacy profile.

** As pre PRAC EMEA/H/C/PSUSA/00010341/202012 it was endorsed that as this safety concern has been removed in RMP v8.1, this topic does not need to be presented in future PSURs and should be monitored through routine pharmacovigilance activities moving forward,

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Note: The RMP effective at the end of the reporting interval was v11.1 (dated 30 Sep 2022; effective 26 May 2023).

At the beginning of the PSUR reporting interval, the effective RMP was v7.1 (dated 04 Sep 2020; effective 20 Nov 2020) which was updated multiple times during the reporting interval the list of changes are as below:

- Updated to v8.3 (dated 06 May 2021; effective 16 Jul 2021) based on the Pharmacovigilance Risk Assessment Committee (PRAC) assessment report received on 25 Feb 2021 as part of procedure EMEA/H/C/003729/X/0067 submitted to register the new strength of 75 mg/0.5 ml solution for injection in pre-filled syringe. Based on GVP module V, Rev 2 and the accumulated clinical trial and post-marketing experience with secukinumab, the safety topics that have been agreed upon by PRAC for retirement from the RMP are 'Neutropenia', 'Interactions with live vaccines', 'Long-term efficacy data', 'Patients with CCI [redacted]' and 'Patients with CCI [redacted]'. Additionally, based on PRAC's recommendation, the important potential risk 'Inflammatory Bowel Disease' has been removed from the list of safety concerns.
- Further updates to the RMP (RMP v9.3 dated 01 Dec 2021; effective 20 Jan 2022) included a new flexible dosing recommendation for plaque psoriasis and psoriatic arthritis in adult patients for which some patients may derive additional benefit from Cosentyx 300 mg every 2 weeks (Q2W).
- The RMP v9.3 was further updated to RMP v10.2 (dated 07 Mar 2022; effective 20 Jun 2022) to include the new indication for the treatment of JIA in patients six years of age and older.
- Most recently, the RMP was updated to RMP v11.1 (dated 30 Sep 2022; effective 26 May 2023) to include the new indication for the treatment of Hidradenitis Suppurativa.

16.2 Signal evaluation

Of the nine signals identified during the reporting interval six signals were refuted and three were categorized as identified risks not categorized as important (new ADRs leading to CDS update).

Table 16-2 Signals closed during the reporting interval

Categorization following signal evaluation	Signal
Identified risk not categorized as important	Eczematous eruptions including atopic dermatitis like eruptions and dermatitis exfoliative generalized (erythroderma)
	Pyoderma gangrenosum
	Dyshidrotic Eczema
	Angioedema
Refuted (false) signal	CCI [redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	CCI [redacted]

Details on sources of information and general methods applied for signal evaluation are presented in Appendix 7.

16.2.1 Eczematous eruptions including atopic dermatitis like eruptions and dermatitis exfoliative generalized (erythroderma)

The signal was confirmed as Identified Risk not categorized as important and the CDS was amended for "eczematous eruptions, atopic dermatitis-like eruptions, dyshidrotic eczema and erythroderma" in CDS sections 6. "Warnings & Precautions" and 7. "Adverse Drug Reactions". (CDS v3.5, dated 19 Jan 2024) with HLT dermatitis (uncommon frequency) and the term Dermatitis exfoliative generalized in the Table 7-2 as an ADR from spontaneous reports and literature (frequency not known), as no AE in the pivotal PSO program has been reported (see Section 14). The proposal was endorsed since the cases are typically not serious, are reversible, detectable and monitorable, and can be managed by dose modification and routine medical care and the fact that Cosentyx is almost exclusively prescribed by dermatologists and rheumatologists who are familiar with this type of ADRs (for a detailed overview of see Appendix 10.1).

16.2.2 Pyoderma gangrenosum

The signal was endorsed as Identified Risk not categorized as important and "Pyoderma gangrenosum" was added to the CDS (CDS v3.4, 19 Jan 2023, corrected 27 Mar 2023) as a post-marketing ADR based on biological plausibility, disproportionality across multiple databases (for a detailed overview of see Appendix 10.2).

16.2.3 Dyshidrotic Eczema

The signal was endorsed as Identified Risk not categorized as important and "dyshidrotic eczema" was added to the CDS (CDS v3.2, 16 Dec 2021 corrected 20 Dec 2021) as ADR (uncommon) based on biological plausibility, disproportionality across multiple databases (for a detailed overview of see Appendix 10.3)..

16.2.4 CCI

Source or trigger of signal

During the previous PSUR, a cumulative review of CCI cases with secukinumab from all available sources was assessed per PRAC request (22 Dec 2020). This signal (EPITT nº 19653) was triggered by nine UK cases of CCI associated with secukinumab which raised a disproportionality score..

Per MAHs assessment, a total of CCI cases were identified. Of them, CCI were serious cases, CCI (CCI cases could be better explained by alternative causes with CCI cases (CCI reported CCI representing less than CCI of the infections reported in the previous reporting period; which supports the fact that secukinumab treated patients who develop CCI do not necessarily develop CCI. There were no fatal cases reported and of the three life threatening cases, one case reported CCI as a sequela of hypersensitivity, the second event was explained by Moyamoya disease, and the remaining case had limited information precluding proper medical assessment. No noteworthy cases were identified. Though CCI hit for CCI PT 'CCI' (CCI in Europe and/or all) with secukinumab in EVDAS database, no disproportionality was observed in Empirica, WHO Vigibase and FDA AERS. Lastly, no relevant data from sources such as literature, pre-clinical, clinical trials and non-interventional studies was identified. The MAH concluded that the collected evidence did not provide any evidence to suggest any direct or indirect effect of secukinumab treatment on CCI.

Subsequently, in the PRAC recommendation (procedure no.: EMEA/H/C/PSUSA/00010341/202012), the PRAC Rapporteur agreed with the MAH position; however, given the seriousness of the reaction and the fact that relevant information precluding a complete assessment was missing in the majority of the cases, "the MAH is requested to provide a review of new cases reporting CCI during the reporting interval of the next PSUR. Completeness of the data submitted should be ensured. This review should also include a discussion on whether, based on all available evidence, an update of the product information is warranted".

On 17 May 2022, the Saudi Food and Drug Authority (SFDA) independently published a recommendation for all health care professionals to be aware of the safety signal of CCI associated with the use of Secukinumab. SFDA claimed that the signal originated as a result of their routine pharmacovigilance monitoring activities. Novartis was not contacted to provide an assessment of this signal.

Background

CCI is a CCI condition in which function of the CCI is partially or completely lost. It is often idiopathic but, in some cases, associated with CCI Two major types are distinguished: CCI) and CCI). Diagnosis can usually be made clinically while patient history often helps in evaluating the underlying etiology. Idiopathic CCI is treated with CCI and, in severe cases, CCI . Treatment of

CCI depends on the underlying cause. Most cases of idiopathic CCI heal completely within three weeks[16, 17].

There have been CCI side effects reported with tumor necrosis factor-α (TNF-α) inhibitors. Clinical presentation of CCI events associated with biologic agents are varied but include CCI, among others.

Literature suggests the plausibility of an association between biological therapy of psoriasis and CCI complications, which could be linked with the known CCI of some of the monoclonal antibodies used in this disease. Currently, there are no data on any CCI side effects occurring with secukinumab [18].

Method(s) of evaluation

A search was conducted in the Novartis safety database using the MedDRA version 26.1 and is included in Appendix 8.

All cases retrieved via the search were reviewed to make a medical assessment.

The focus of analysis is to assess causal association between secukinumab and events of CCI.

Noteworthy cases are defined as any well documented case with no apparent confounding factors and will be presented.

Results

Cumulative reporting rate in the clinical database

During the entire treatment period, the incidence rate of CCI' (by search CCI [HLT]) for Any AIN457 dose was CCI% (95% CI CCI). No significant dose-response effect was identified. (Source: Table 10 Incidence of PSUR risk (all indications) Entire treatment period Safety Set).

Company safety database

Reporting interval analysis

The above-mentioned search criteria retrieved a total of CCI cases in this PSUR reporting interval and CCI cases reported cumulatively.

Of the CCI cases retrieved cumulatively; CCI cases initially received in previous reporting intervals had newly reported relevant events. Additionally, CCI case received in the previous reporting interval was unblinded during the reporting period. These CCI cases are included in the analysis of cases received during the reporting interval.

The distribution of these CCI interval cases and CCI cumulative cases by report type and seriousness is presented in the table below:

Table 16-3 Distribution of cases of 'CCI ' during the reporting interval and cumulatively

Report type	Reporting interval*					Cumulative				
	HCP		Non-HCP		Total	HCP		Non-HCP		Total
	Serious	Non-serious	Serious	Non-serious		Serious	Non-Serious	Serious	Non-serious	
CT	CCI									
PMS	CCI									
Literature		CCI								
SR	CCI									
Total	CCI									

Source: Company Safety Database as of 25 Dec 2023

A case is considered serious only if the most relevant event retrieved by the search is serious.

*Interval data comprise cases initially received during the current reporting interval and cases initially received during previous reporting intervals which were unblinded during the reporting interval or in which either related event of 'CCI ' was newly received as a follow-up or secukinumab was newly added as co-suspect drug to a case that contained an event of 'CCI '.**Regarding the unblinding of the 3 CT cases from previous reporting period (PD) in all cases the treatment received was secukinumab.

CT: Clinical Trials; HCP: Health Care Professional; PMS: Post marketing Surveillance; SR: Spontaneous Report

The age/age group was reported in CCI (CCI) of the cases. The distribution of the CCI cases analyzed during the reporting interval by age group and gender is presented in the table below:

Table 16-4 Distribution of CCI cases during reporting interval by gender and age group

Gender	Age Group*			Total
	Adult age group (18 to 65 years)	Elderly age group (>65 years)	Not Reported	
Female	CCI			
Male	CCI			
Not reported	CCI			
Total	CCI			

*The cases where the age group was reported but the patient's age was unknown are included in the respective age group category.

These CCI cases encompassed CCI adverse events associated with CCI and are summarized by seriousness and TTO in the table below.

Table 16-5 Overview of Preferred terms of CCI and related time to onset reported

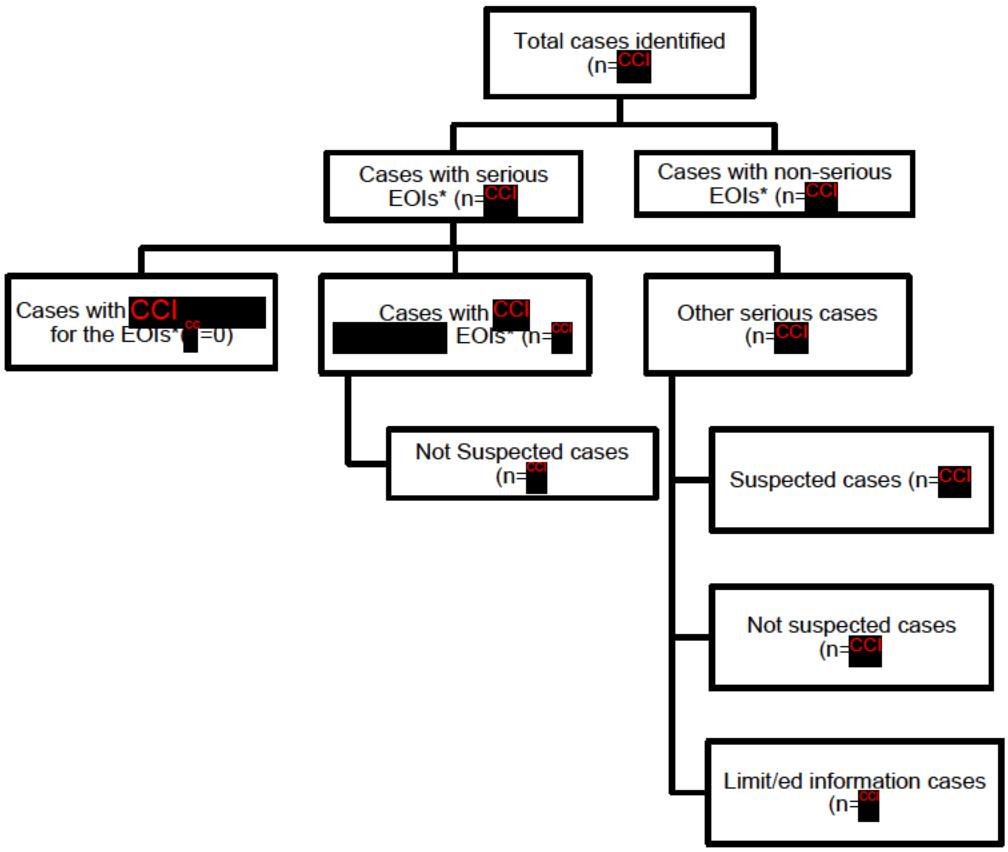
Preferred terms	Time to onset						Total
	8 days to 14 days	15 days to 6 months	>6 Months to 1 year	>1 year to 2 years	>2 years	Not Reported	
Serious Preferred terms							**46**
CCI							
Non-serious Preferred terms							CCI
CCI							
Total	CCI						

Of the CCI events, TTO was reported for CCI %) events, and the onset latency ranged from CCI to CCI and CCI approximately. Based on the table above, the number of events reported with acute onset (TTO <14 days) are only CCI %) of total CCI events.

Out of the total CCI cases with CCI relevant events of CCI , the outcomes were reported for CCI %) events, in the majority of these (CCI %) the event completely recovered / was improving / patient recovered with sequelae. For CCI %) events, the outcome was reported as condition unchanged while for CCI event (CCI %), the outcome was condition deteriorated.

The distribution of CCI cases retrieved during the reporting interval for this analysis is presented in the figure below:

Figure 16-1 Overview of [redacted] cases retrieved for the during the reporting interval



*Case seriousness is based on EOI, EOI: Event Of Interest

Of the [redacted] relevant cases, [redacted] were serious and [redacted] were non-serious.

Of the [redacted] serious cases, [redacted] case was reported with [redacted] EOI (n=[redacted] and [redacted] cases reported [redacted] non-fatal/non-LT EOIs.

[redacted] of the cases reported a [redacted] outcome for [redacted].

Cases with [redacted]

- Case (NVSC2023CN156524, spontaneous, HCP) concerned 70-year-old male, with concomitant treatment with mecobalamin and thiamine, who received secukinumab for the treatment of psoriasis. Sixteen days after the first dose (9 days post last known dose) started [redacted]). Post 26 days of first dose (19 days after last known dose), the [redacted] after which the symptoms

were in remission. CCI showed no abnormality. Treatment with secukinumab was discontinued (in total 2 doses received).

Despite of temporal association, no information about pre-existing risk (e.g. CCI) was included in the case, and considering the etiopathogenesis of CCI as an CCI which cannot be explained by the mechanism of action and pharmacological profile of secukinumab, causal role is assessed as not suspected for the event CCI and subsequent CCI .

Other serious cases (n=CCI

In CCI cases, CCI events of interest were reported including CCI) and CCI (n=CCI Of these CCI cases, CCI (CCI cases described time to onset, which ranged from eight days to 2,020 days.

- In CCI out of CCI cases, causality with secukinumab was considered as suspected based only in temporal causal association; however no definitive causal association could be established due to presence of risk factors (n=CCI or limited information (n=1; no consent for follow up).
- Of the remaining CCI cases, CCI cases were assessed as not suspected with secukinumab and the events related to CCI could be attributed to underlying conditions (e.g. COVID-19, recurrent / other infections, cerebrovascular accident).
- The remaining CCI cases had limited information and despite multiple follow-ups attempts additional information was not available for a meaningful medical assessment (lost to follow up n=5 and consent to contact was denied n=1).

Non serious cases (n=CCI)

Of the CCI non-serious cases, CCI case was assessed as suspected due to temporal association, however the patient's underlying current condition of blood pressure changes could have contributed to the onset of the event. CCI cases were assessed as not suspected and can be better explained by underlying infections, multiple comorbidities, brain injury and concomitant immunosuppressive therapy. The remaining three cases had limited information.

The assessment of the relevant cases did not identify any noteworthy case and precluded any definitive role of secukinumab in causing CCI . No new safety finding was identified from the analysis.

Cumulative data summary

In the remaining CCI cases, no new information was received that would change the previous assessment and was consistent with the findings from the cumulative data review in the previous PSUR.

Disproportionality analysis

Eudravigilance data

The results of disproportionality reporting analyses for CCI [redacted] with secukinumab in EudraVigilance Data Analysis System (EVDAS) are presented in the table below.

Table 16-6 Disproportionality scores for CCI [redacted]

Event (Preferred Term)	EVDAS				
	Total case count	SDR ALL	ROR ALL	ROR Europe	ROR Asia
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EVDAS: EudraVigilance Data Analysis System; ROR: Reporting Odds Ratio; SDR: Signals of Disproportionate Reporting

There is a disproportionality hit for PT ('CCI [redacted]') with secukinumab in EVDAS database (CCI [redacted] in CCI). The review of the hit from EVDAS did not reveal any new information related to the safety profile of secukinumab.

Empirica, FDA AERS and WHO VigiBase data

The Empirica, Food and Drug Administration AERS (Adverse event reporting system) and WHO VigiBase database were used for disproportionality analysis. All drug-event pairs were included, regardless of whether the drug was suspected (S) as a cause of the event or considered a concomitant (C) medication.

Results of disproportionality reporting analyses for CCI [redacted] with secukinumab in these databases are presented in the table below.

Table 16-7 Disproportionality scores from Empirica, WHO Vigibase and FDA AERS

Event Variable	EB 05 scores		
	Empirica*	WHO Vigibase**	FDA AERS***
CCI [redacted]	[redacted]	[redacted]	[redacted]

AERS: Adverse event reporting system; EB05: lower limit of the 90% confidence interval for the Empirical Bayesian Geometric Mean; FDA: Food and Drug Administration; WHO: World Health Organization

* Data Source: Company Safety Database as of 25 Dec 2023;

**data till 2023Q3 Vigibase (S+C) was used

***data till 2023Q3: AERS (S + C)

Based on the CCI [redacted], there is no disproportionality apparent for the HLT 'CCI [redacted]' in Empirica, WHO Vigibase and FDA AERS.

Please note that data mining scores are hypothesis generating and do not provide sufficient evidence on causality but instead suggest the necessity of extending the evaluation to other data sources.

Discussion

Overall, from the CCI cumulative cases, no noteworthy cases have been identified and only CCI cases (CCI of cumulative cases, identified in the reporting period) remain as suspected based only on temporal plausibility; however, no definitive causal association can be drawn from these cases mainly due to either presence of risk factors or lack of adequate case documentation (e.g. dechallenge, confirmation of absence of pre-existing risks, etc.).

Similar to the previous reporting period, a minority of cases with CCI such as CCI , and CCI (unspecified) were identified (n= current period, total CCI cumulatively [CCI

From the analysis of the identified risk of CCI (Section 16.3.1.1), cumulatively there were CCI cases of CCI . Therefore, these CCI cases of CCI reporting preceding CCI represent CCI percent of these CCI cases. This supports the fact that secukinumab treated patients CCI .

From the cases reporting sufficient information, the patients either had risk factors as plausible explanation or precluded any definitive role of secukinumab in causing CCI in the reporting period, cumulative CCI

Cumulatively, there were CCI reported and there were CCI cases reported (CCI not suspected and not assessable; and reporting period, not suspected).

No trends/patterns or risk factors for CCI were identified during the cumulative review.

CCI . The review of information from EVDAS, Empirica, WHO Vigibase and FDA AERS did not reveal any new information related to the safety profile of secukinumab. Lastly, it is important to note that with an extensive patient post-marketing exposure (1.8 million patient-years), only CCI reported cases of CCI were identified; accounting the CCI the identified cases do not show a pattern of increased incidence in the population exposed to secukinumab.

No information about biologic plausibility linking IL-17 inhibition with CCI has been identified upon literature review, and no relevant data pertaining to this signal from other data sources such as literature, pre-clinical, clinical trials, and non-interventional studies.

Conclusion

A comprehensive analysis of data from all sources, including published literature, and post-marketing safety data did not provide evidence of any direct or indirect effect of secukinumab treatment on CCI . Therefore, upon two consecutive reviews the MAH concludes that there is lack of evidence supporting a causal association between CCI and secukinumab exposure. An update to the CDS/SmPC is not currently warranted and no updates to the RMP are deemed necessary.

Novartis will continue to monitor CCI under routine pharmacovigilance procedures, and this topic will not be presented in future PSURs unless a validated signal is identified.

16.2.5 Angioedema

Source or trigger of signal

In the PRAC assessment report for the previous PSUR (26 Dec 2019 to 25 Dec 2020), Novartis was requested to submit a cumulative review on angioedema related cases from both clinical trials and post-marketing data using the MedDRA PT Angioedema. The cumulative review should include a table with case details including case ID, source, age, gender, time to onset, dechallenge/rechallenge, outcome, any confounding factors such as concomitant medication or medical history, reported causality assessment and MAH´s conclusion. In addition, a summary and discussion of the most noteworthy cases should also be provided as well as well as the case narratives (ICSR) of these cases. This review should also include an analysis and discussion whether, based on the available evidence, an update of the product information is warranted. Novartis has conducted the review and the analysis and recommendations are provided below.

Background relevant to the evaluation

Angioedema is a self-limited, localized swelling of the skin or mucosal tissues, which results from extravasation of fluid into the interstitium due to a loss of vascular integrity. Angioedema may occur in isolation, accompanied by urticaria, or as a component of anaphylaxis. Upon the underlying mechanism angioedema can be classified as[20]:

- Mast cell-mediated etiologies (IgE-mediated and direct mast cell activation [non-IgE related]), in which release of mast cell-derived mediators increase vascular permeability. Mast cell-mediated angioedema is associated with urticaria and/or pruritus in most cases. May present as part of an allergic reaction or anaphylaxis.
- Bradykinin-mediated etiologies, in which angioedema results from the generation of bradykinin, leads to increased vascular permeability. These forms of angioedema are not associated with urticaria and/or pruritus, may present with abdominal symptoms due to bowel wall edema and are diagnosed and treated differently from other types of angioedema.
- Etiologies of unknown mechanism.

Clinical features and diagnosis

Angioedema can be a benign and transient condition that can also be life-threatening when it leads to airway obstruction. The diagnosis of angioedema is made clinically based on a suggestive history and physical findings. Laboratory tests may be helpful in confirming an underlying allergy or a complement disorder. However, routine laboratories are normal in many cases of angioedema and therefore, not diagnostic Zuberbier et al 2014.[21]

Angioedema can be distinguished clinically from other forms of edema (e,g, peripheral or localized edema), by the following characteristics:

- Onset in minutes to hours and spontaneous resolution in hours to a few days.
- Asymmetric distribution.

- Tendency not to involve gravitationally dependent areas.
- Involvement of face, lips, larynx, and bowels.
- Association of some forms of angioedema with other signs and symptoms of allergic reactions or anaphylaxis.

Method of Evaluation

The details of the search criteria used to retrieve cases are included in Appendix 8.

Noteworthy case definition: A well-documented HCP / medically confirmed case describing angioedema event with suspected causal association based on plausible time to onset, positive de-challenge or re-challenge and without any other plausible alternative explanation or apparent confounding factors.

The focus of analysis is based on causal association between angioedema and secukinumab exposure.

Results

Cumulative reporting rate in the clinical database and other sources

In the clinical trial database encompassing over 6,000 subjects across multiple indications and doses, the above-mentioned search retrieved one case of angioedema during the short-term period with placebo-controlled exposure between 12 and 24 weeks. This single case was reported for AIN457 10mg/kg - 75 mg (non-pivotal study), this event was non-serious, but led to study treatment discontinuation. Likewise, a single non serious case was reported in the placebo group (Source: Table a211 1-1.2 Exposure-adjusted incidence rates for treatment emergent adverse events for angioedema by event and preferred term – entire study period Compound Pool 17 Safety Set).

During the entire treatment period (ETP) with exposure beyond 52 weeks, encompassing over CCI subjects across multiple indications and doses, CCI cases were identified. The exposure adjusted incidence rates (EAIR) for Any AIN457 dose was CCI (Table a211 1-1.2).

From the development programs, four serious cases were identified (all of them assessed by both investigators and Novartis as not suspected due to alternative causal association); two of them lead to treatment discontinuation), the remaining cases (n=21) corresponded to non-serious mild- moderate events. (Source: Table 10 Incidence of PSUR risk (all indications) Entire treatment period Safety Set).

When EAIR analysis was splitted by dose, slightly CCI was observed. No events of angioedema were reported in the Any AIN457 low dose / high dose [pediatric] (N=CCI / N=CCI (Table a211 1-1.2). EAIRs are summarized by dose in the table below.

Figure 16-2 EAIR for Angioedema by dose – Entire treatment period

Source: Table a211 1-1.2

Company safety database

The search in the Novartis safety database retrieved a total of CCI cases in this PSUR reporting interval and CCI cases reported cumulatively (including the four serious clinical trial cases described above). An outline of the evidence collected is presented in the table below.

Table 16-8 Overview of 'Angioedema'

Evaluation	Angioedema
Biological Plausibility	Administration of proteins such as immunoglobulin (Ig) can lead to hypersensitivity reactions. Hypersensitivity reactions including urticaria and rare cases of anaphylaxis were reported in the development programs for secukinumab and are currently included in the CDS (warning and precautions and adverse drug reaction sections). Based on this precedent, IgE-mediated

Evaluation	**Angioedema**				
	mast cell activation can be a possible mechanism associated with angioedema occurrence after secukinumab exposure.n.				
ICSR analysis	**Total: CCI evaluable cases** - CCI SR, CCI PMS, 01 literature, 04 CT - CCI cases were reported by HCP and CCI were non-HCP cases.				
Severity Analysis	Of the CCI evaluable cases, 139 (98%) were designated as serious as per IME/DME list. CCI cases (CCI included Hospitalizations and CCI case (0.7%) to CCI Total CCI high severity cases = CCI cases cumulatively were reported (CCI 2%). No fatalities among CCI evaluable cases were reported.				
PT (event)	**Fatal**	**Life threatening**	**Other serious**	**Non-serious**	**Total***
Angioedema	CCI				
*The total number is greater than the number of overall angioedema cases, since some cases had more than one episode of angioedema. $These three non-serious cases are from health authority (primarily from physician) for which the IME/DME convention do not apply.					
Causality assessment					
(events)	**CT**	**PMS**	**SR**	**Lit**	**Total**
Noteworthy	0	CCI		1	CCI
Suspected (CNBR)	0	CCI	CCI	0	CCI
Not suspected (confounded)	4	CCI		0	CCI
Not assessable	0	CCI		0	CCI
Reporting disproportionality	AERS EB05 = CCI VIGIBASE EB05 = CCI Eudravigilance ROR (-) All CCI No disproportionality reporting.				

AERS: Adverse event Reporting System; CI: Confidence Interval; CNBR: Cannot Be Ruled Out, CT: Clinical Trial, DME: Designated Medical Event; Lit: Literature, EVDAS: Eudravigilance Data Analysis System, F: Fatal; IME: Important Medical Event; ICSR: Individual Case Safety Report, LT: Life-Threatening; n=number; PT: Preferred Term; PSUR: Periodic Safety Update Report, PMS: Post-Marketing Study, ROR: Reporting Odd Ratio; SR: Spontaneous Report.

Total CCI cases reported CCI events related to angioedema. Of these CCI cases, in CCI cases (CCI events) causal relationship was suspected (including CCI noteworthy cases), in CCI cases (CCI events) causal relationship was not suspected, and the remaining CCI cases (CCI events) had limited information.

- In CCI cases, causal relationship was assessed as suspected. In these CCI cases, the time to onset since the last secukinumab dose ranged from few hours/immediate to five days; and occurred mainly after the initial secukinumab doses (second to fifth dose). In eight cases, the events were described after long term exposure (ranged from 62 to 485 days). In CCI out of CCI suspected cases, Cosentyx was discontinued/temporarily interrupted, in five cases, there was no change in Cosentyx therapy, and in the remaining CCI cases, action taken was unknown/ not reported (n=CCI and not applicable (n=CCI Of these CCI cases, corrective treatment medications were reported in 18 cases (mainly antihistamines and corticosteroids). De-challenge was positive in CCI cases, and re-challenge was positive in CCI cases out of the

CCI suspected cases. In 38 cases (mainly non-HCP cases), causal association was established based on plausible temporal relationship, absence of confounders and de/re-challenge positive in some cases. Noteworthy criteria were identified for the remining CCI cases.

- In 48 cases, the causal relationship was assessed as not suspected due to identification of confounders including concurrent conditions (preexisting allergies [drug, food and insect bite], underlying autoimmune disorder), and concomitant medications (amlodipine, omalizumab, perindopril, candesartan, NSAIDS, sulfa drugs, ixekizumab, etc.).
- In the remaining CCI cases, there was no information available or partial information available to make a comprehensive medical assessment; these cases remain as not assessable. Of these CCI cases, CCI cases (CCI %) were lost to follow-up either at initial attempts or after diligent follow-up attempts; in CCI cases (CCI %) follow-up is ongoing; in 10 cases CCI %) follow-up was not possible due to insufficient contact information or was not allowed as there was no consent to contact the reporter/ Novartis FU conventions for non-serious events/HA case; in four cases (CCI %), follow-up was complete but no relevant information received.

The details of these CCI cases; suspected cases (n=CCI confounded (n=CCI and not assessable (n=CCI and are mentioned in detail in the Appendix 12.1, and the remaining CCI noteworthy cases (narratives in Appendix 12.2) were discussed in detail in the below table. .

Table 16-9 Noteworthy cases of angioedema (n=13)

Case Number/ Source/ HCP or Non-HCP/ Patient age in years/ Gender/ Indication/ Dose details	Confounding Medical history and Concurrent conditions	Confounding Concomitant medications	TTO (days) from first Secukinumab dose/ TTO (days) from most recent/last Secukinumab dose	Seriousness/ Action Taken/ Event Outcome/ De-challenge/ Re-challenge/ As reported causality	MAH Conclusion
PD PD SR/ HCP/ PD PD PsA, Pso/ 300 mg SC QMO	No	No	2-3 days	MS/ No Change/ Complete Recovery/ NA/ Pos/ Suspected	The patient developed pruritus and oral candidiasis along with angioedema, the events occurred since the initial dose and afterwards three consecutive episodes (re-challenge positive). Angioedema resolved after treatment with antihistamines, and outcome of other events

Case Number/ Source/ HCP or Non-HCP/ Patient age in years/ Gender/ Indication/ Dose details	Confounding Medical history and Concurrent conditions	Confounding Concomitant medications	TTO (days) from first Secukinumab dose/ TTO (days) from most recent/last Secukinumab dose	Seriousness/ Action Taken/ Event Outcome/ De-challenge/ Re-challenge/ As reported causality	MAH Conclusion
					were not reported. There were no confounders.
PD [redacted] SR/ HCP/ NR/ PD [redacted] Product used for unknown indication/ Unknown	No	No	1 year/ 1 day	MS/ Treatment Temporarily Interrupted/ Condition Unchanged/ Pos/ Pos/ Not assessable	The patient developed angioedema one day after receiving Cosentyx (after one year of stable treatment), the events recurred with the following two doses (re-challenge positive for two times). There were no confounders.
PD [redacted] PD SR/ HCP/ PD PD Pso/ 300 mg SC Q4W	No	No	127/ Unspecified (reported as immediate)	MS, H/ Treatment Temporarily Interrupted/ Complete Recovery/ NA/ Pos/ Suspected	The patient developed lip, facial, and peripheral edema (while on stable treatment for 127 days), the events are described after each secukinumab dose (re-challenge positive). All events resolved with treatment (antihistamine) until last secukinumab dose (D 116), it was discontinued after severe

Case Number/ Source/ HCP or Non-HCP/ Patient age in years/ Gender/ Indication/ Dose details	Confounding Medical history and Concurrent conditions	Confounding Concomitant medications	TTO (days) from first Secukinumab dose/ TTO (days) from most recent/last Secukinumab dose	Seriousness/ Action Taken/ Event Outcome/ De-challenge/ Re-challenge/ As reported causality	MAH Conclusion
					event requiring hospitalization. There were no confounders
PD [redacted] / SR/ HCP/ PD PD Pso/ 300 mg SC QW	No	No	7/ 1	MS, LT/ Treatment Discontinued/ Recovered with Sequelae/ Pos/ NR/ Suspected	The patient received total two secukinumab dose and after the second dose, developed angioedema and dyspnea. After discontinuation of secukinumab, symptoms improved (de-challenge positive). There were no confounders.
PD [redacted] SR/ HCP/ PD PD Pso/ 300 mg	No	No	7/ 1	H/ NR/ Condition Improving/ NR/ NR/ Suspected	The patient developed urticaria after first dose, and angioedema and worsening of skin reaction after second dose requiring hospitalization. Cutaneous lesions evolved to erythrodermic reaction after third dose. The

Case Number/ Source/ HCP or Non-HCP/ Patient age in years/ Gender/ Indication/ Dose details	Confounding Medical history and Concurrent conditions	Confounding Concomitant medications	TTO (days) from first Secukinumab dose/ TTO (days) from most recent/last Secukinumab dose	Seriousness/ Action Taken/ Event Outcome/ De-challenge/ Re-challenge/ As reported causality	MAH Conclusion
					patient was on on cyclosporine, (not related to severe skin reactions or angioedema), no other confounders. All events improved with Cosentyx treatment discontinuation and treatment with high dose corticosteroids.
PD [redacted] / SR/ HCP/ NR/ PD Product used for unknown indication/ 300 mg	No	No	5/ 5	MS/ Treatment Discontinued/ Complete recovery/ Unk/ Pos/ Not assessable	The patient developed urticaria, and eye lid edema along with angioedema, which started 5 days after first dose. The subject received three more doses and after each consecutive dose developed angioedema (re-challenge positive). All events were controlled with intravenous diphenhydramine. There were no confounders.

Case Number/ Source/ HCP or Non-HCP/ Patient age in years/ Gender/ Indication/ Dose details	Confounding Medical history and Concurrent conditions	Confounding Concomitant medications	TTO (days) from first Secukinumab dose/ TTO (days) from most recent/last Secukinumab dose	Seriousness/ Action Taken/ Event Outcome/ De-challenge/ Re-challenge/ As reported causality	MAH Conclusion
PD [redacted] / Lit/ HCP/ PD PD PP/ PsA/ 150 mg SC QD (2 DF), 300 mg SC QW	No	No	33/ 12 hours	MS/ Treatment Discontinued/ Complete Recovery/ Pos/ Pos/ Suspected	The patient developed urticaria after initial doses, and later developed lip edema, facial edema, peripheral edema, rash, and type I hypersensitivity along with angioedema after third and fourth secukinumab doses (re-challenge positive). All events resolved after treatment with hydroxyzine 25 mg QD. There were no confounders.
PD [redacted] SR/ HCP/ PD PD Pso/ 2 DF SC QW, 2DF SC QMO	No	No	17/ 2	MS/ Treatment Discontinued/ Condition Improving/ Pos/ Pos/ Suspected	The patient developed face edema, rash maculo-papular along with angioedema after third and fourth secukinumab doses (re-challenge positive). All events resolved after treatment with

Case Number/ Source/ HCP or Non-HCP/ Patient age in years/ Gender/ Indication/ Dose details	Confounding Medical history and Concurrent conditions	Confounding Concomitant medications	TTO (days) from first Secukinumab dose/ TTO (days) from most recent/last Secukinumab dose	Seriousness/ Action Taken/ Event Outcome/ De-challenge/ Re-challenge/ As reported causality	MAH Conclusion
					prednisone. There were no confounders.
PD [redacted] / SR/ HCP/ PD PD Pso/ 300 mg SC QMO	No	No	1/ short time after dosing	MS, H/ NR/ Complete Recovery/ NR/ Pos/ Not assessable	The patient developed dermatitis exfoliative along with angioedema, after 2 initial doses (re-challenge positive). The second dose led to hospitalization. Later angioedema resolved in 10 days with systemic treatment. There were no confounders.
PD [redacted] SR/ HCP/ 55/ M/ AS/ 150 mg SC	No	No	9/1	H/ Treatment Discontinued/ Complete Recovery/ NA/ NA/ Suspected	The patient developed urticaria along with angioedema, one day after the second dose, which lead to hospitalization. Both events resolved after treatment with intravenous loratadine 10 mg. There were no confounders.

Case Number/ Source/ HCP or Non-HCP/ Patient age in years/ Gender/ Indication/ Dose details	Confounding Medical history and Concurrent conditions	Confounding Concomitant medications	TTO (days) from first Secukinumab dose/ TTO (days) from most recent/last Secukinumab dose	Seriousness/ Action Taken/ Event Outcome/ De-challenge/ Re-challenge/ As reported causality	MAH Conclusion
PD [redacted] SR/ HCP/ PD [redacted] Pso, PsA/ 300 mg SC QMO	No	No	333/ 25	MS, H/ Treatment discontinued/ Complete Recovery/ Pos/ Pos/ Not assessable	The patient developed swelling face, eczema, dermatitis exfoliative, hypersensitivity along with two consecutive episodes of angioedema (re-challenge positive), in which the second episodes lead to hospitalization. Secukinumab was discontinued and angioedema, swelling face, and dermatitis exfoliate events resolved subsequently. There were no confounders.
PD [redacted] SR/ HCP/ NR/ NR/ Product used for unknown indication/ 300 mg SC QMO	No	No	NR/ 1	MS/ Treatment Temporarily Interrupted/ Complete Recovery/ Pos/ Pos/ Not assessable	The patient developed two episodes of angioedema after secukinumab injections (re-challenge positive), and secukinumab discontinued, and angioedema

Case Number/ Source/ HCP or Non-HCP/ Patient age in years/ Gender/ Indication/ Dose details	Confounding Medical history and Concurrent conditions	Confounding Concomitant medications	TTO (days) from first Secukinumab dose/ TTO (days) from most recent/last Secukinumab dose	Seriousness/ Action Taken/ Event Outcome/ De-challenge/ Re-challenge/ As reported causality	MAH Conclusion
					resolved. There were no confounders.
PD [redacted] SR/ HCP/ PD PD Pso/ 300 mg SC	No	No	31/ unspecified (reported as after each dose	MS/ Treatment discontinued/ Complete Recovery/ NR/ Pos/ Suspected	The patient developed anaphylaxis, pharyngeal edema along with angioedema of uvula after each secukinumab dose (re-challenge positive) from Jul to Oct 2015. Last event of angioedema was severe and required emergency care. The allergist suspected on secukinumab reaction and discontinued subsequently all events resolved. There were no confounders.

AS: Ankylosing Spondylitis; DF: Dosage Form; H: Hospitalization; HCP: Health Care Professional; LT: Life-threatening; PSO: Psoriasis; F: Female; M: Male; MS: Medically Significant; NA: Not Applicable; NR: Not Reported; Pso: Psoriasis, PsA: Psoriatic Arthropathy; PP: Pustular Psoriasis; PMS: Post-Marketing Surveillance; QMO: Evey month; QW: Every Week; Q4W: Every four weeks; SC: Subcutaneous; SR: Spontaneous Report; TTO: Time to Onset.

Severity Analysis

Of the [redacted] evaluable cases, 125 ([redacted] were designated as serious by Novartis as per IME/DME list; however, these cases were reported as not serious, and were typically reversible, detectable by patients and health care professionals, and monitorable by treating physicians, and were managed by routine medical care and dose modification. Twelve cases ([redacted] required hospitalization and one case (0.7%) disability was reported as seriousness criteria.

The case reporting disability ([redacted]) was assessed as not suspected, due to identification of other medications that provided better alternative causal association (Perindopril and candesartan).

Total [redacted] high severity cases were reported ([redacted] these correspond to life-threatening (LT) cases. In two of these LT cases ([redacted] [noteworthy case] and [redacted]) based on plausible temporal relationship and positive rechallenge the causality is assessed as suspected. In other two cases ([redacted], both CT) causality was assessed as not suspected due to identification of other medications that provided better alternative causal association (lisinopril and ibuprofen). [redacted] among [redacted] cases were reported.

Discussion

Angioedema is anatomically self-limited, localized subcutaneous (or submucosal) swelling, which results from extravasation of fluid into interstitial tissues. Mast cell-mediated etiologies, in which angioedema results from release of mast cell-derived mediators that increase vascular permeability is associated with urticaria and/or pruritus in most cases, and it's related with allergic or anaphylactic reactions. Data regarding the epidemiology of angioedema are limited, although it affects both adults and children and is not a rare disorder[20].

Data from the development programs reported a single angioedema case in the placebo-controlled period, and overall, along the entire treatment period (n= 25,349) 25 cases were identified, corresponding to an EAIR of 0.06 / 100 PYs. From these cases, four were SAEs, yet alternative causal association was identified in these cases therefore were assessed as not related (both investigators and Novartis). Overall, the angioedema cases reported in the development programs corresponded to non-serious mild- moderate events (the severe events corresponded to the SAEs described above).

When EAIR analysis was splitted by dose, slightly high frequency in AIN457 300 mg Q2W regimen was observed; yet this should be interpreted with caution due to the low number of cases, differences on exposure length for the different dose regimen and overlap of the 95% confidence intervals among the different doses; therefore, the difference between doses may not be significant.

In the Novartis safety database 138 cases were identified from the post-marketing experience. A total of 51 (35%) cases were assessed as suspected, from them 13 corresponded to well documented cases with plausible temporal association, rechallenge positive, and lack of confounders. The remaining events were assessed as suspected on basis of plausible temporal association, absence of confounders and de/re-challenge positive in some cases. From the suspected cases it is observed that most occur following dosing (range 12 hours to five days)

and mainly after the initial secukinumab doses (2nd to 5th dose); nonetheless, some cases (n=8 out of 51) were described after long term exposure (range 62 to 485 days). In addition to angioedema co-reported AEs included urticaria, lips, facial, and eyelid edema, rash, type I hypersensitivity, and anaphylaxis. Out of the 51 suspected cases two corresponded to LT cases, these cases had dyspnea and laryngeal edema as co-reported events, in seven cases hospitalization was required to control symptoms and the remaining cases corresponded to mild-moderate events, reported as non-serious (upgraded to serious due to IME designation) that were managed with oral antihistaminics.

No reporting disproportionality was observed in internal or external health authority databases (AERS, Vigibase, EVDAS); and provided the broad secukinumab exposure (more than 1.8 million PTYs) the 142 identified cases (51 suspected) do not have an impact to public health.

Conclusions

Based on the review of the collected evidence the following conclusion is drawn:

- A causal association for angioedema and secukinumab is confirmed, thus this adverse event is considered as new adverse drug reaction for secukinumab.
- Since evidence from the clinical database is limited to 25 cases out of 25,394 exposed patients across indications for the entire treatment period, no cases were identified in the pivotal trials, and the confirmatory evidence comes from the post-marketing experience, the CDS Section 7, Table 7-2 (ADRs) will be updated with the PT angioedema (frequency not known).).
- An update to the Warnings and Precautions Section for Hypersensitivity reactions, to include angioedema is deemed appropriate due to 1) serious cases requiring hospitalization (up to CCI and 2) prescribers should consider treatment discontinuation in severe cases.

  These changes are proposed to be used for corresponding changes in the EU SmPc and National Prescribing Information (NPI) documents.
- Since the identified angioedema cases were mild – moderate in severity, reversible, monitorable by patients and treating physicians, manageable with improvement after standard of care treatment initiation or discontinuation of secukinumab; the ADR of angioedema is considered of low impact. In addition, language in the CDS about serious allergic reactions already exists in the CDS. For all this, no change in the safety profile of secukinumab is identified.
- Since angioedema is deemed of low clinical impact, an update of the CDS / international labels is considered adequate for risk minimization, and no additional Risk Minimization Measures are necessary at this stage; therefore, no RMP update is required.
- The overall benefit/risk profile of secukinumab remains favorable.

16.2.6 CCI [redacted]

Table 16-10 Overview and Evaluation of Refuted Signal – CCI [redacted]

Signal	CCI [redacted]
Source of signal	Health Authority (Saudi Arabia Food and Drug Authority).

Signal	CCI
Background relevant to the evaluation	The signal has been originated as a result of HA routine pharmacovigilance monitoring activities. The SFDA identified one CCI and CCI cases that were consider sufficient to validate this signal.
Methods of evaluation/data sources	• Novartis safety database (NSDB): Cumulative up to 25 Dec 2023- Terms: PT CCI, MedDRA version 26.1. • Literature search: Cumulative up to 25 Dec 2023. Source: Causaly®. Terms: CCI AND Secukinumab, AIN457, Cosentyx, Interleukin-17A Antagonist • Novartis EMPIRICA (reporting disproportionality)
Results	**Biological plausibility:** Not identified **Reporting disproportionality**: Not identified. **NSDB**: total of CCI CCI cases serious, CCI Fatal and CCI LT CCI) suspected, CCI cases not suspected due to confounders and CCI cases not assessable **Relevant publications:** Not identified.
Discussion and Conclusions	Based on the assessment of the clinical, postmarketing, literature and disproportionality data no temporal associated could not be established. No causal association can be confirmed between CCI and secukinumab exposure. **Signal refuted.**

CT: Clinical trial; Lit: Literature; MedDRA: Medical Dictionary for Regulatory Activities; PMS: Post marketing surveillance; SR: Spontaneous report

16.2.7 CCI

Table 16-11 Overview and Evaluation of Refuted Signal – CCI

Signal	CCI
Source of signal	Health Authority (Saudi Arabia Food and Drug Authority). The signal has been originated as a result of HA routine pharmacovigilance monitoring activities.
Background relevant to the evaluation	No information was provided by the HA.
Methods of evaluation/data sources	• Novartis safety database (NSDB): Cumulative up to 09 Dec 2022- Terms: PT CCI PT CCI, MedDRA version 25.1. • Literature search: Cumulative up to 01 Dec 2022. Source: Causaly®. Terms: CCI AND • Secukinumab, AIN457, Cosentyx, Interleukin-17A Antagonist

Signal	CCI
	• Novartis EMPIRICA (reporting disproportionality)
Results	**Biological plausibility**: Not identified **Reporting disproportionality**: Not identified. **NSDB:** total of CCI cases (CCI) - CCI cases serious, only CCI lead events serious (CCI [not suspected] – CCI LT [Not assessable]) - All cases secondary to co-reported primary events (exception CCI cases – CCI serious (H) / CCI NS – both not assessable) **Relevant publications:** Not identified.
Conclusions	Based on the assessment of the clinical, postmarketing, literature and disproportionality data no temporal associated could not be established. No causal association can be confirmed between CCI and secukinumab exposure. **Signal refuted.**

CT: Clinical trial; HA: Health Authority; Lit: Literature; MedDRA: Medical Dictionary for Regulatory Activities; PMS: Post marketing surveillance; SR: Spontaneous report

16.2.8 CCI

Table 16-12 Overview and Evaluation of Refuted Signal – CCI

Signal	CCI
Source of signal	Health Authority (Saudi Arabia Food and Drug Authority). The signal has been originated as a result of HA routine pharmacovigilance monitoring activities.
Background relevant to the evaluation	No information was provided by the HA.
Methods of evaluation/data sources	• Novartis safety database (NSDB): Cumulative up to 09 Dec 2022- Terms: PT CCI , MedDRA version 25.1. • Literature search: Cumulative up to 01 Dec 2022. Source: Causaly®. Terms: CCI • AND • Secukinumab, AIN457, Cosentyx, Interleukin-17A Antagonist • Novartis EMPIRICA (reporting disproportionality)
Results	**Biological plausibility:** Not identified

Signal	CCI
	Reporting disproportionality: Not identified. **NSDB:** total of CCI cases (CT, NIS, PSP, SR, Lit) - CCI cases serious: CCI lead events serious ([not suspected] – 0 LT). All cases secondary to co-reported primary events (mainly) or pre-existing conditions. - Lit cases: - PD CCI serious / not suspected. Secukinumab used for AS, in context of CRF due to disease progression after multiple DMTs (including adalimumab, infliximab and golimumab); - PD serious / not suspected. Secukinumab used for PSO, CCI in context of IgA nephropathy (long term immune complex deposit). - PD CCI non-serious / not suspected. Secukinumab used for described without context (the case refers to pruritic eczema) the patient had historical condition of calculus ureteric. - PD serious / not suspected. Secukinumab used for PSO, CCI in context of IgA nephropathy (long term immune complex deposit - **Relevant publications** (other than case reports): Not identified.
Discussion and Conclusions	Based on the assessment of the clinical, postmarketing, literature and disproportionality data no temporal associated could not be established. No causal association can be confirmed between CCI and secukinumab exposure. **Signal refuted.**

CT: Clinical trial; Lit: Literature; MedDRA: Medical Dictionary for Regulatory Activities; PMS: Post marketing surveillance; SR: Spontaneous report

16.2.9 CCI

Table 16-13 Overview and Evaluation of Refuted Signal –CCI

Signal	CCI
Source of signal	Health Authority (Saudi Arabia Food and Drug Authority). The signal has been originated as a result of HA routine pharmacovigilance monitoring activities.
Background relevant to the evaluation	No information was provided by the HA.
Methods of evaluation/data sources	- Novartis safety database (NSDB): Cumulative up to 09 Dec 2022- Terms: PT CCI . MedDRA version 25.1. - Literature search: Cumulative up to 01 Dec 2022. Source: Causaly®. Terms: CCI . AND Secukinumab, AIN457, Cosentyx, Interleukin-17A Antagonist

Signal	CCI
	- Novartis EMPIRICA (reporting disproportionality)
Results	**Biological plausibility**: Not identified **Reporting disproportionality**: Not identified. **NSDB:** total of CCI cases (CCI CT, CCI MAP, CCI NIS, CCI PSP, CCI SR) - CCI cases serious, CCI lead events serious (CCI [not assessable] – CCI LT [Not assessable / not suspected]) - All cases secondary to co-reported primary events or pre-existing condition. **Relevant publications:** Not identified
Discussion and Conclusions	Based on the assessment of the clinical, postmarketing, literature and disproportionality data no temporal associated could not be established. No causal association can be confirmed between CCI and secukinumab exposure. **Refuted signal.**

CT: Clinical trial; Lit: Literature; MedDRA: Medical Dictionary for Regulatory Activities; PMS: Post marketing surveillance; SR: Spontaneous report

16.2.10 CCI

Table 16-14 Overview and Evaluation of Refuted Signal – CCI

Signal	CCI
Source of signal	Health authority (EMA PRAC)
Background relevant to the evaluation	Details on the signal source, assessment and MAH conclusions and PRAC conclusions are in the Signal assessment report on CCI and Cosentyx CCI), see Appendix 10.4
Methods of evaluation/data sources	
Results	
Discussion and Conclusions	A comprehensive analysis of data from all sources, including published literature, clinical trials and post-marketing experience, indicates that treatment with secukinumab does not increase the risk of CCI or other types of vasculitis, and a significant number of the cases retrieved in the search conducted had alternative explanations for the development of vasculitis. For these reasons, no product information amendment, no update to the Risk Management Plan, and no targeted communication is warranted at this time. This analysis is consistent with the established safety profile of Cosentyx as part of the continuous pharmacovigilance activities. The PRAC agreed with the MAH excepting for the PT hypersensitivity vasculitis the EU SmPC was updated accordingly.

16.2.11 CCI

Table 16-15 Overview and Evaluation of Refuted Signal – CCI

Signal	CCI
Source of signal	Internal - routine Empirica, reporting disproportionality monitoring.

Signal	CCI
Background relevant to the evaluation	During routine Empirica review of hits for May 2023, CCI noteworthy cases for the drug event combination Cosentyx and CCI were identified. The type of CCI). A new search in Empirica with cases up to June 2023 retrieved CCI cases with CCI . Which revealed CCI and CCI of the literature cases required further investigation.
Methods of evaluation/data sources	Novartis safety database (NSDB): Cumulative up to 31 May 2023 - Terms: CCI . MedDRA version 26.0
Results	**Biological plausibility**: Not identified **NSDB:** Total of CCI cases identified: CCI PSP, CC Spontaneous cases, CC literature cases CC literature cases. - CCI PSP cases corresponded to the program CCI in the US. The case review identified that the source document the event CCI with many other suspected medications (including secukinumab) with no clear connection (PSP form included all conditions and concomitant / past medications with no chronologic order). Per case processing conventions, secukinumab remains as suspected medication. However, most of the cases lack of clear information in the forms. These and other reported cases from this PSP program, will remain as not suspected, due to the inconsistencies in the source data. - From the 2 literature cases that were identified as erroneously attributed to Secukinumab (the involved drug was Ustekinumab). Request for case nullification has been processed. The publication[23] concerned a PD years, PD that after six doses of secukinumab, developed multiple black macules limited to the resolving lesions of psoriasis. The lesions were not accompanied by pruritus or pain. Histopathology: increased prickle cell layer, club-shaped rete ridges, Munro's micro abscess, and mild infiltration of inflammatory cells into the upper layer of the dermis. Action taken with secukinumab, and outcome are unknown. Based on a temporal association role of secukinumab could not be excluded. - The remaining CCI events were confounded CCI or had limited information for a proper assessment.
Discussion and Conclusions	Based on the assessment of the clinical, postmarketing, literature and disproportionality data no temporal associated could not be established. No causal association can be confirmed between CCI and secukinumab exposure. **Refuted signal.**

CT: Clinical trial; Lit: Literature; MedDRA: Medical Dictionary for Regulatory Activities; PMS: Post marketing surveillance; SR: Spontaneous report

16.3 Evaluation of risks and new information

An evaluation of new information relevant to previously recognized identified and potential risks, and an update on missing information, are provided in the following sections.

Details on sources of information and general methods applied for evaluating important identified risks, important potential risks, and missing information are presented in Appendix 7.

During the reporting interval on 06 Apr 2021, RMP v.8.1 was adopted by PRAC within procedure EMEA/H/C/003729/X/67 (CHMP Opinion 20 May 2021) in which the following risks/ Missing information were removed from the list of safety concerns taking into account that the information provided in the product information is considered sufficient to minimize the risks and there are not currently additional Pharmacovigilance activities or additional risk minimization measures in place for these safety concerns. These topics are not considered safety concerns (i.e., important identified risk, important potential risk or missing information [(GVP) - Annex I - Definitions (Rev 4)][24]) and are briefly summarized in the below table:

Table 16-16 Summary of the risks/missing information not considered as safety concerns in RMP v8.1

Risks/missing information	Focus of Analysis and/or Noteworthy Definition	Comparison of post-marking RR per 100 PY [N, (RR)]				Summary of the cases
		26Dec2018 – 25Dec2019	26Dec2019 – 25Dec2020	26Dec2020 – 25Dec2023	Cumulative till 25Dec2023	
Identified Risk						
Neutropenia	Focus of Analysis: The medical review focus is to identify increases in frequency or severity of neutropenia which is listed in the current CDS. Noteworthy Definition: Well-documented, confirmed case of PG (full criteria), with plausible exposure to secukinumab and confounders free (pre-existing condition which are part of the criteria diagnostic were not considered confounders)	CCI			)	A total of CCI cases (CCI , all in post-marketing) were received during the interval, including CCI serious cases CCI cases) and CCI non-serious cases CCI cases). CCI was reported in CCI cases CCI PD the CCI), the patient experienced CCI In PD the patient experienced CCI was not reported. Compared to the last PSUR, no increased severity was identified in these cases. The post-marketing RR has been stable.

Risks/missing information	Focus of Analysis and/or Noteworthy Definition	Comparison of post-marking RR per 100 PY [N, (RR)]				Summary of the cases
		26Dec2018 – 25Dec2019	26Dec2019 – 25Dec2020	26Dec2020 – 25Dec2023	Cumulative till 25Dec2023	
Potential Risk						
Inflammatory bowel disease	Focus of Analysis: All cases retrieved via the above mentioned search were reviewed to make a medical assessment. Noteworthy Case Definition: Case with a confirmed diagnosis (e.g. imaging or biopsy) of IBD including CD and UC	CCI [redacted]	[redacted]	[redacted]	[redacted]	A total of CCI cases (CCI initial, CCI follow-up) including 12 CT cases) were received during the interval. A history of prior IBD was identified in CCI of the CCI cases.[a] Clinical nature of these IBD cases were similar; no fatal or life-threatening gastrointestinal complications were recognized as to be related to IBD in the cases with prior IBD. Compared to the last PSUR, no increased severity was identified in these IBD cases. The post-marketing RR has been stable.
Interaction with live vaccines	Focus of Analysis: All cases retrieved via the above mentioned search were reviewed to make a medical assessment. Noteworthy Case Definition Case reporting an interaction between Cosentyx and a co-suspect or concomitant live vaccine, followed by an SAE.	0 (0.00)	0 (0.00)	CCI [redacted]	[redacted]	A total of CCI cases (all post-marketing) were received during this interval. No significant follow-up to the previously received cases was identified. The most common event was “crying” (N=CCI Vaccinations were almost exclusively reported for COVID-19 vaccines. No concomitant live vaccine was reported in these cases. The increasing number of the cases may have resulted from mass immunization in response to the COVID-19 pandemic. These

Risks/missing information	Focus of Analysis and/or Noteworthy Definition	Comparison of post-marking RR per 100 PY [N, (RR)]				Summary of the cases
		26Dec2018 – 25Dec2019	26Dec2019 – 25Dec2020	26Dec2020 – 25Dec2023	Cumulative till 25Dec2023	
						reports do not suggest a possible interaction of secukinumab with vaccines.
Missing Information						
CCI [redacted]	The medical review focused on identification of any new trends/differences in the safety profile of Cosentyx in the sub-group of patients with CCI [redacted]	NA	NA	NA	NA	A total of CCI [redacted]) were received during the interval including 15 cases in CT). CCI [redacted]. When received, three fourths of these reports did not have CCI [redacted]. Compared to the last PSUR, no increased severity was identified.

[a] In pooled clinical trials for secukinumab, 77% of the patients with a history of IBD did not experience IBD flare.[25]

CT: Clinical Trial; IBD: Inflammatory bowel disease; NA: Not applicable; PSUR: Periodic Safety Update Report.

For each of these important risks or missing information, a search was conducted in the Novartis global safety database using the MedDRA version 26.1 to retrieve all the relevant cases (refer to Appendix 8 for the search criteria).

During the reporting period of this PSUR, routine pharmacovigilance has not identified any new safety information for the topics above described. The review did not change the previous safety conclusions on these risks / missing information. Therefore, it is concluded that the CDS/SmPC contains sufficient information to address the retired risks (neutropenia and IBD) and contains an adequate warning for Interaction with live vaccines. Other than routine pharmacovigilance, no further action is deemed necessary for patients with CCI [redacted].

Accounting that the above summarized risks/missing information have been removed from the RMP, that do not have an impact on the risk-benefit balance for secukinumab, nor on public health and hence, are not considered safety concerns anymore; the MAH proposes that these safety topics will be monitored via routine pharmacovigilance procedures and will not be presented in subsequent PSURs unless new safety information emerges.

16.3.1 New information on important identified risks

16.3.1.1 Infections and infestations

Background relevant to the evaluation

'Infections and infestations' is an important identified risk in the Cosentyx RMP.

The Cosentyx CDS includes, under Section 6 'Warning and Precautions', information that Cosentyx has the potential to increase the risk of infections. Adverse drug reactions (ADRs) listed in the CDS include nasopharyngitis, upper respiratory tract infection, rhinitis, pharyngitis, sinusitis, tonsillitis, oral herpes, oral candidiasis and tinea pedis. Mucosal and cutaneous candidiasis are also included in the CDS as post-marketing ADRs with unknown frequency.

In psoriasis registration CTs, events of "Infections and infestations", the most frequently affected SOC, occurred less frequently based on exposure-adjusted incidence rate per 100 PTY in the any Cosentyx dose group and etanercept groups compared to the placebo group (90.5 and 91.4 vs. 100.1, respectively). However, cautions should be exercised when interpreting these differences due to the nature of the study design where >95% of the patients randomized to placebo were switched to active treatment after the initial 12 weeks or 16 weeks of placebo treatment. Therefore, there was a large difference in the amount of exposure between active treatment and placebo. There was a small increase in exposure-adjusted incidence rate (EAIR) per 100 PTY for infections overall with 300 mg vs. 150 mg (90.5 vs. 83.9). Some specific infections, notably oral candidiasis and oral herpes, showed the opposite trend of being more frequent with any Cosentyx dose compared to placebo and etanercept, and also a higher rate with 300 mg vs. 150 mg Cosentyx. Some infection-related AEs, such as upper respiratory tract infection, viral upper respiratory tract infection, oral herpes and oral candidiasis, occurred more frequently per 100 PTYs in any Cosentyx dose group compared to placebo and etanercept groups.

In both PsA and AS registration CTs, upper respiratory tract infection was the most common type of infection followed by *Candida* infection. There were no events of reactivation of viral hepatitis or latent tuberculosis (TB) reported in the entire treatment period of studies. The EAIR of infections and infestations, in the entire treatment period, was higher for the 300 mg dose

than for the 150 mg and 75 mg doses. A small proportion of infections reported over the entire treatment period were SAEs, with few serious upper respiratory tract infections and only one SAE of oral candidiasis. In AS clinical trials, the exposure-adjusted incidence of infections and infestations in the entire treatment period was higher in the any Cosentyx group (68.8 per 100 PTY) vs. placebo (63.8). A small proportion of infections reported over the entire treatment period were SAEs.

Secukinumab was studied in one double-blind, placebo-controlled, event-driven, randomized trial in 86 pediatric patients aged 2 to less than 18 years old with JPsA and ERA. The safety profile reported in this trial was consistent with the safety profile of secukinumab, including infections and upper respiratory tract infections being the most frequently reported AEs.

Likewise, in HS registration studies, the events of "Infections and infestations", the most frequently affected SOC. Folliculitis and upper respiratory tract infections were the two most frequent AEs, the rate of fungal infections remained higher for subjects who received 300 mg every two weeks (14.7/100 subject-years) compared to subjects who received 300 mg every 4 weeks (10.1/100 subject-years). The majority of the cases were reported as non-serious, non-severe, and resolved with anti-fungal treatment.

An increased risk of infections is potentially associated with any immunomodulatory biologic agent. Blockade of IL-17A may lead to an increased risk of fungal infections, including *Candida* infections, and may lead to an increased risk of infections by encapsulated bacteria, in particular *Staphylococcus spp*. Severe psoriasis is recognized as a risk factor for infection [26].

Based on the PRAC PSUR assessment report recommendation (EMEA/H/C/PSUSA/00010341/202012), dated: 08 Jul 2021, the closure of topics '[redacted]' and '[redacted]' will be accepted. Hence, MAH has closed the monitoring of these topics in future PSURs. However as per the PRAC recommendation for the next PSUR, "*the MAH should continue monitoring through routine pharmacovigilance activities new cases of* [redacted] *and submit all the relevant evidence within the section on the new information gathered on the important identified risk of Infections and infestations"*, the [redacted] are discussed below in respective sub-section.

Method of evaluation

A reporting interval search (26 Dec 2020 to 25 Dec 2023) and a cumulative search (until DLP 25 Dec 2023) was conducted in the company safety database using MedDRA version 26.1 to retrieve the relevant cases with "Infection and Infestation". Please refer to Appendix 8 for MedDRA search criteria.

Noteworthy case definition: A -documented HCP / medically onfirmed case describing infectious event with increased severity (fatal or life-threatening) and suspected causal association based on plausible time to onset, positive de-challenge or re-challenge and without any other plausible alternative explanation or apparent confounding factors.

Focus of Analysis: Due to their potential relevance in assessing the benefit-risk profile of Cosentyx, the medical review focused on serious cases of the following infections: Opportunistic infections, Central nervous system (CNS) infections and inflammation, Mycobacterial infections, Fungal infections, including esophageal candidiasis, Herpes

infections, including herpes zoster, staphylococcal infections, CCI [redacted] and COVID-19.

Results

Literature:

Five relevant literature (three relavant to COVID-19 and two relevant to Mycobacterial infection) have been identified showing any association between "Infection and infestation" and secukinumab. These literature have been discussed below:

Dernoncourt a et al (2022): COVID-19 in DMARD-treated patients with inflammatory rheumatic diseases: Insights from an analysis of the World Health Organization pharmacovigilance database[8].

This article aimed to determine whether the use of disease-modifying antirheumatic drugs (DMARDs) is linked to the risk of COVID-19 among patients with inflammatory rheumatic diseases (IRDs) using a disproportionality analysis of the World Health Organization pharmacovigilance database between 01 Jan 2020, and 10 Jun 2020. The frequency of COVID-19 reports for all DMARD classes (both conventional synthetic DMARDs and biologic DMARDs including secukinumab) identified was compared with that for all other reports for all other drugs and quoted as the reporting odds ratio (ROR) (95% confidence interval [CI]). Among 980,446 individual case-safety reports voluntarily recorded in the database, 398 identified COVID-19 in DMARD-treated patients with IRDs. There were 177 (44.5%) patients with rheumatoid arthritis (RA), 120 (30.1%) with ankylosing spondylitis (AS), 93 (23.4%) with psoriatic arthritis (PsA), and 8 (2.0%) with juvenile idiopathic arthritis. Most of the cases of COVID-19 occurred in patients taking anti-TNF agents (84.2%), resulting in a significant disproportionality signal (ROR [95% CI]: 8.31 [7.48-9.23]) - particularly in patients with RA, AS or PsA. With regard to other biologic DMARDs, only a few cases featured anti-IL-17 agents (22 of 398), secukinumab (ROR [95% CI]: 2.98 [2.18–4.08]).

Kridin K et al (2022): **Risk of COVID-19 infection, hospitalization, and mortality in patients with psoriasis treated by interleukin-17 inhibitors [9].**

This article aimed to evaluate the risk of COVID-19, COVID-19-associated hospitalization, and mortality among patients with psoriasis treated by IL-17 inhibitors. A population-based cohort study was performed to compare psoriasis patients treated by IL-17I (n = 680) with those treated by methotrexate (n = 2153) and non-systemic/non-immunomodulatory treatments (n = 138,750) regarding the incidence of COVID-19 and its complications. The use of IL-17I was not associated with an increased risk of COVID-19 infection [adjusted HR for IL-17I vs. methotrexate: 0.91 (95% CI, 0.48-1.72); IL-17I vs. non-systemic/non-immunomodulatory treatments: 0.92 (95% CI, 0.54-1.59)]. IL-17I was associated with comparable risk of COVID-19-associated hospitalization [adjusted HR for IL-17I vs. methotrexate: 0.42 (95% CI, 0.05-3.39); IL-17I vs. non-systemic/non-immunomodulatory treatments: 0.65 (95% CI, 0.09-4.59)] and COVID-19-associated mortality [adjusted HR for IL-17I vs. methotrexate: 7.57 (95% CI, 0.36-157.36); IL-17I vs. non-systemic/non-immunomodulatory treatments: 7.05 (95% CI, 0.96-51.98)]. In a sensitivity analysis, neither secukinumab nor ixekizumab imposed an elevated risk of any of the outcomes of interests.

Hasan MJ et al (2021): Secukinumab in severe COVID-19 pneumonia: Does it have a clinical impact?[10]

This publication aimed to review evidence of using IL-17A inhibitor (secukinumab) as targeted therapy in COVID-19 pneumonia among the admitted patients with confirmed severe COVID-19 pneumonia. 17 patients were treated with secukinumab plus baricitinib (SNB-BCB group) and another 17 patients received only baricitinib (BCB group). Compared to patients in BCB group, patients in SNB-BCB group showed more normal breathing function within 48 h of therapy initiation ($P = 0.180$); less requirement of ICU and intubation support ($P < 0.05$), shorter length-of-ICU stay ($P = 0.042$), and less 30-day m ortality rate ($P = 0.033$).

MAH Comment: *While Amandine et al 2022[8] identified that there was a significant disproportionality for secukinumab (n=22 subjects; ROR [95% CI]: 2.98 [2.18–4.08]) along with other DMARDs; however, remarked that regardless of the disproportional reporting of COVID-19 in patients exposed to DMARDs, of most cases (70.1%) considered serious, only 13.3% of the patients were hospitalized and only 3.3% died. These results are consistent with the low reported mortality rate in cohort studies of this population. In the population based cohort study by Kridin et al 2021[9] it was identified that the use of IL-17i was not associated with an increased risk of COVID-19 or its complications in patients with psoriasis, rather supported the continuation of IL-17i treatment during the pandemic. Lastly, Md J. Hasan et al 2021[10] concluded that secukinumab plus baricitinib may actually reduce the severity of cytokine storm in severe COVID-19 which may ultimately improve clinical outcomes and survival in patients with severe COVID-19 pneumonia. Novartis is in alignment with the conclusions of these publications, which are similar to the observed reporting rate for COVID 19 in the reporting period and morbi-mortality rates of COVID 19 observed in patients exposed to secukinumab.*

Elewski BE et al (2021): Association of Secukinumab Treatment With Tuberculosis Reactivation in Patients With Psoriasis, Psoriatic Arthritis, or Ankylosing Spondylitis[11].

This pooled cohort study aimed to assess the association of secukinumab with reporting of active TB development, TB reactivation, and latent tuberculosis infection (LTBI) activation as an adverse event (AE) in patients with psoriasis, psoriatic arthritis, or ankylosing spondylitis using data from 28 clinical trials of secukinumab. Data from a total of 12 319 patients was analyzed, (8819 patients had psoriasis, 2523 had psoriatic arthritis and 977 had ankylosing spondylitis) from the start of treatment in the individual studies through 25 Dec2018. Reporting of active TB or LTBI as an AE over a 5-year period using exposure-adjusted incidence rates (EAIR; incidence rates per 100 patient-years). LTBI as an AE during secukinumab treatment was reported in 13 patients (0.1% of 12 319). Of these 13 patients, six had a prior positive LTBI test result, and seven were newly diagnosed as having LTBI. Four of the seven patients had psoriasis (EAIR, 0.03; 95% CI, 0.01-0.07), 1 had psoriatic arthritis (EAIR, 0.02; 95% CI, 0.00-0.11), and two had ankylosing spondylitis (EAIR, 0.08; 95% CI, 0.01-0.28). No cases of active TB were reported. This study found that LTBI reported as an AE after secukinumab treatment was uncommon and appeared to support the use of secukinumab in chronic systemic inflammatory conditions.

Akdogan N et al (2021): Serial Quantiferon-TB Gold test results in 279 patients with psoriasis receiving biologic therapy[12].

This publication aimed to determine the risk of LTBI reactivation by Quantiferon-TB Gold (QFT) assay in psoriatic patients treated with biologics in 11 years' follow-up, along with chest radiography alterations. This retrospective study included 279 patients with plaque-type and/or pustular, or nail psoriasis who were treated with biologics, and had results for =2 LTBI tests. The QFT outcomes were defined according to the baseline and the follow-up QFT results; seroconversion as from negative to positive, seroreversion as from positive to negative, persistently seronegative as invariantly negative, persistently seropositive as invariantly positive, and other any result was accepted as indeterminate. Demographic features, the presence and the type of any chest X-ray abnormality was noted during the follow-up. Of 279 baseline QFT tests, the vast majority were negative (n = 193; 69%), with a less of positive (n = 86; 31%). Ten (5.2%) of 193 patients converted from negative to positive QFT status after starting biologic therapy (P < 0.001) during 11 years' follow-up. Although these 10 patients exhibited seroconversion of QFT from negative to positive, only one patient was diagnosed with active TB. QFT seroconversion rate was highest among the patients treated with anti-TNF drugs, followed by anti-IL12/23 drug, and the lowest on anti-IL17. There was no statistically significant difference among biologics as regards with QFT seroconversion risk (P = .09).

***MAH Comment**: The findings of the study by Elewski et al 2021[11] show that there was a scarce spontaneous reporting of new LTBI and no reports of active cases of TB or LTBI reactivation while undergoing secukinumab treatment, providing a broader understanding of the safety of secukinumab and support the long-term use of secukinumab in chronic systemic inflammatory conditions. It is further supported by the review of serial Quantiferon-TB Gold test (QFT) results in 279 patients with psoriasis receiving biologic therapy by Neslihan et al 2020[12] where the QFT seroconversion rate is reported to be the lowest on anti IL 17 therapy when compared to other biologicals. The conclusions drawn in these publications are in alignment with the results observed during the reporting period.*

Cumulative reporting rate in the clinical database and other sources

The cumulative EAIR for the entire treatment period for SOC 'Infections and infestations' across all indications, for any AIN457 dose was CCI PTY. Consistent with the mechanism of action and the overall risk for infection, patients treated with CCI . Overall, the incidence rates remained comparable between the previous PSUR and the current reporting period PSUR [Incidence rate ratio CCI)].

The EAIR of CCI ' in the Novartis Clinical Database, across all indications, was low CCI) per 100 PTY], no dose trend was observed for CCI . (Source: Table 18 Change in the incidence rates relative to the last review period of treatment emergent adverse events of special interest by PSUR risks, by treatment group Entire treatment group Safety Set)

In the CorEvitas registry EAIR per 100 PTY for overall serious infections and pneumonia, respectively: Secukinumab CCI (CCI) and CCI (CCI) Non-IL-17 biologics: CCI (CCI)

and 0.5 (0.4, 0.6) Non-biologic systemic therapies: 1.2 (0.6, 2.0) and 0.2 (0.1, 0.7) (Source: Table 18-4)

Company Safety Database

The search in the Novartis safety database retrieved a total of 16,023 cases in this PSUR reporting interval and 46,425 cases reported cumulatively. . Of the 16,023 cases, two cases were also retreived and analyzed in previous PSUR.Hence not further discussed in this section. (Total cases: 16,021). Of the 46,425 cases retrieved cumulatively, 1,222 cases initially received in previous reporting intervals newly reported an event related to "Infection and Infestation" as follow-up information during the reporting interval.

Of the 17,243 (16,021+1,222) cases received during the reporing interval, 6,625 cases were excluded from further analysis due to the broad search criteria. Further, one case (PD [redacted] identified as continuation of Case PD [redacted] and two cases, PD [redacted] and PD [redacted] identiifed as continuation of Case PD [redacted] hence these three cases excluded from the analysis (Interval= 17,240 Cumulative= 46,422).The remaining 10,615 cases of special interest, as detailed in the "Methods of evaluation" section are discussed below.

An outline of the distribution of these cases by report type and seriousness is presented in the table below.

Table 16-17 Overview of 'Infection and Infestation' in the reporting interval

Evaluation	Infection and Infestation				
ICSR analysis	Total: CCI cases Of the evaluable CCI cases identified in the reporting period, CCI SR, CCI PMS, 127 CT, 70 literature; and CCI were reported by HCP and CCI were Non-HCP cases				
Severity Analysis	Of the CCI evaluable cases, CCI (CCI%) were serious. The proportion of CCI cases during the reporting interval is slightly CCI [redacted]. Due to their potential relevance in assessing the benefit-risk profile of secukinumab, the medical review focused on serious cases of the following infections:				
	Fatal	**Life threatening**	**Other serious**	**Non-serious**	**Total***
CNS Infection and inflammation	CC [redacted]	CC [redacted]	CCI	[redacted]	CCI
Mycobacterial infections	CC [redacted]	CC [redacted]	CCI	[redacted]	CCI
Staphylococcal Infection	CC [redacted]	CC [redacted]	CCI	[redacted]	CCI
Opportunistic infections	CC [redacted]	CC [redacted]	CCI	[redacted]	CCI
Herpes infections,	CC [redacted]	CC [redacted]	CCI	[redacted]	CCI

Evaluation	Infection and Infestation				
including herpes zoster					
Fungal infection including esophageal candidiasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious cutaneous Infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
* The total case numbers of each sub-topics (n=12,684) will be higher than the overall case numbers (n=10,615), due to overlapping of cases (n= 2,069) in one, two or more sub-sections. Similarly the total number of serious case numbers in each sub-topics (2,514) will be greater than the overall serious cases (2,042) due to overlapping of cases (n= 472) in one, two or more sub-sections.					
Causality assessment of Serious infection cases	**Evaluation**				
	CT	**PMS**	**SR**	**Lit**	**Total**
Noteworthy	0	[redacted]	[redacted]	0	[redacted]
Suspected (CNBR)	3	[redacted]	[redacted]	4	[redacted]
Not suspected (confounded)	62	[redacted]	[redacted]	14	[redacted]
Not assessable	56	[redacted]	[redacted]	11	[redacted]
Frequency Analysis	The reporting rate of the current PSUR reporting interval is less to the previous PSUR interval and higher than the cumulative period, and could be attributed to the inherent nature of solicited reporting The reporting rate of serious cases are less to the previous PSUR interval and cumulative period. No new safety findings could be identified (Source: Table 16-18 and Table 16-19)				

CNBR: Causal role cannot Be Ruled Out, CNS: Central Nervous System: CT: Clinical Trial, COVID-19: Corona Virus Disease-19, F: Fatal, ICSR: Individual Case Safety Report, Lit: Literature, LT: Life-Threatening, n=Number, PT: Preferred Term, PSUR: Periodic Safety Update Report, PMS: Post-Marketing Study, SR: Spontaneous Report, QFT: Quantiferon Test

Opportunistic infections

A total of 292 serious cases were reported with opportunistic infection. These 292 serious cases included [redacted] cases of mucocutaneous candidiasis, esophageal candidiasis, [redacted] and discussed under the sub-topic 'Fungal infections'. Of the remaining [redacted] cases, [redacted] cases (including [redacted] cases and [redacted] cases) included events of tuberculosis, [redacted] and are discussed under the sub-topics 'Mycobacterial infections' and 'Herpes infections' respectively. The remaining 28 cases are discussed below.

The relevant events reported in these 28 serious cases are as follows: CCI [redacted]), Opportunistic infection (n=5), CCI [redacted]

Of the 28 serious cases, in two cases, causality with secukinumab cannot be completely ruled out due to temporal causal association (TTO: 15 days and three months respectively) however, no definitive causal association could be established due to limited information regarding one or more factors including relevant medical history, concomitant medications, event/therapy nature and circumstances.

In 11 serious cases, the causality was assessed as not suspected/confounded due to underlying patient's medical condition such as diabetes mellitus and concomitant immunosuppressant drugs such as methotrexate, betamethasone, prednisolone, etanercept and cyclosporine.

In remaining 15 serious cases, the causality was not assessable due to limited information, thus precluding further medical assessment. Of the 15 cases, 10 cases (10/15, 66.7%) were lost to follow-up (lost to follow-up at initial (n=3), at follow-up (n=6)) and consent not given to contact the reporter (n=1) and in remaining five cases (5/15, 33.3%) follow-up denied or not allowed.

No noteworthy cases were identified during the reporting interval.

Herpes infections including herpes zoster

A total of 65 serious cases were reported with herpes infections. The relevant events (frequency>1) reported in these 65 serious cases are as follows: Herpes zoster (n=30), Oral herpes (n=14), CCI [redacted] each), Herpes virus infection (n=5) and CCI [redacted]).

Of the 65 serious cases, in four cases, causality with secukinumab cannot be completely ruled out due to temporal causal association (TTO range from 10 days to 1.2 years) however, no definitive causal association could be established due to limited information regarding one or more factors including relevant medical history, concomitant medications, event/therapy nature and circumstances.

In 21 serious cases, the causality was assessed as not suspected/confounded due to underlying patient's medical condition such as diabetes mellitus, and concomitant immunosuppressant drugs such as methotrexate, prednisolone, beclomethasone, adalimumab and apremilast.

In the remaining 40 serious cases including one case reported with CCI [redacted]), the causality was not assessable due to limited information, thus precluding further medical assessment. Of the 40 cases, 28 cases (28/40, 70%) were lost to follow-up (lost to follow-up at initial (n=5), at follow-up (n=23)) and in remaining 12 cases (12/40, 30%) follow-up denied or not allowed.

No noteworthy cases were identified during the reporting interval.

Fungal infections including oesopheageal candidiasis

A total of 180 serions cases were reported with fungal infection. These 180 serious cases included CCI and discussed under the sub-topic 'Oppurtunistic infections'. The remaining 171 cases are discussed below.

The relevant events (frequency >2) reported in these 171 serious cases are as follows: Oesophageal candidiasis (n=50), Oral candidiasis (n=32), Fungal infection (n=23), Candida infection (n=20), CCI), CCI), Fungal oesophagitis (n=8), CCI , Genital candidiasis (n=5 each), CCI , CCI), Oral fungal infection, CCI , Fungal skin infection, Fungal pharyngitis and Tinea pedis (n=3 each).

Of the 171 serious cases, in seven cases, causality with secukinumab cannot be completely ruled out due to temporal causal association (TTO ranges from one day to five years) however, no definitive causal association could be established due to limited information. regarding one or more factors including relevant medical history, concomitant medications, event/therapy nature and circumstances.

Of the remaining 164 serious cases, CCI and CCI . CCI the other cause of death was reported as COVID-19, systemic lupus erythematosus, pericarditis, type II diabetes mellitus and pneumonia/pancytopenia in context to myelodysplastic syndrome which could explain the fatality. CCI . In all fatal cases, there was no information on TTO and autopsy findings which precluded further assessment.

In CCI reported with CCI), there was limited information available regarding patient's relevant medical history, TTO, clinical course of event, relevant concomitant medications, and status of underlying diseases results, thus precluding further medical assessment.

In 66 serious cases, the causality was assessed as not suspected/confounded due to underlying patient's medical condition such as diabetes mellitus, chronic kidney disease, chronic renal failure and immunosuppressant drugs such as methotrexate, methylprednisolone, beclomethasone, prednisolone, betamethasone, etanercept and adalimumab.

In remaining 93 serious cases, the causality was not assessable due to limited information available, thus precluding further medical assessment. Of the 93 cases, 59 cases (59/93, 63.4%) were lost to follow-up (lost to follow-up at initial (n=5), at follow-up (n=54)) and in remaining 34 cases (34/93, 36.6%) follow-up denied or not allowed.

No noteworthy cases were identified during the reporting interval.

Mycobacterial infections

A total of 207 serious cases were reported with mycobacterial infeciton. The relevant events (frequency>1) reported in these 207 serious cases are as follows: Tuberculosis (n=156), CCI Latent tuberculosis (n=11), Pulmonary tuberculosis (n=6), CCI),

CCI
).

Of the 207 serious cases, in six cases, causality with secukinumab cannot be completely ruled out due to temporal causal association (TTO ranges from two months to two years) however, no definitive causal association could be established due to limited information regarding one or more factors including relevant medical history, concomitant medications, event/therapy nature and circumstances.

Of the remaining 201 serious cases, CCI
, hepatic cirrhosis, CCI , type II diabetes mellitus, deep vein thrombosis, breast cancer stage III and systemic lupus erythematosus which could explain the CCI In all CCI cases, there was no information on TTO or autopsy findings which precluded further assessment.

In CCI
, seven cases were confounded by patient's underlying conditions such as diabetes mellitus, chronic respiratory infections/recent chronic infection episode and use of concurrent immunosuppressant drugs such as methotrexate, etanercept and adalimumab. In remaining two cases, there was limited information, thus precluding further medical assessment.

In 42 serious cases, the causality was assessed as not suspected/confounded due to underlying patient's medical condition such as diabetes mellitus, benign mediastinal tumor, reactivation of tuberculosis (history of previous tuberculosis infection), malignant neoplasm, chronic kidney disease, sarcoidosis, and use of immunosuppressant drugs such as methotrexate, methylprednisolone, beclomethasone, prednisolone, betamethasone, ixekizumab, etanercept, certolizumab and adalimumab.

In remaining 143 serious cases, the causality was not assessable due to limited information available, thus precluding further medical assessment. Of the 143 cases, 113 cases (113/143, 79%) were lost to follow-up (lost to follow-up at initial (n=12), at follow-up (n=101)) and in remaining 30 cases (30/143, 21%) follow-up denied or not allowed.

No noteworthy cases were identified during the reporting interval.

Central nervous system (CNS infections) and Inflammations

A total of 85 serions cases were reported with CNS infections and inflammation. These 85 serious cases included CCI
) and discussed under the sub-topic 'CCI '. The remaining 81 serious cases are discussed below.

The relevant events (frequency>1) reported in these 81 serious cases are as follows: CCI
Central nervous system infection (n=2 each)

Of the 81 serious cases, in two cases, causality with secukinumab cannot be completely ruled out due to temporal causal association (TTO ranges from six months to 2.4 years) however, no definitive causal association could be established due to limited information regarding one or more factors including relevant medical history, concomitant medications, event/therapy nature and circumstances.

Of the remaining 79 serious cases, CCI was reported with CCI and CCI cases were reported with CCI . In case reported with CCI), the CCI , which was confounded by immunosuppressant drug mycophenolate mofetil, however there was no information on TTO and autopsy findings which precluded the further assessment.

Of the CCI cases reported with CCI was confounded by use of immunosuppressant drug methotrexate while in remaining two cases, there was limited information.

In 17 serious cases, the causality was assessed as not suspected/confounded due to underlying patient's medical condition such as spinal disorder/spinal osteoarthritis, cerebral thrombosis, cerebrovascular accident, pseudotumor cerebri, idiopathic intracranial hypertension, CCI complication, intervertebral degeneration/spinal stenosis, procedure related complications (such as craniectomy, Intervertebral disc operation and discectomy) and use of immunosuppressant drug methotrexate, etanercept and adalimumab.

In remaining 58 serious cases, the causality was not assessable due to limited information available, thus precluding further medical assessment. Of the 58 cases, 32 cases (32/58, 55.2%) were lost to follow-up (lost to follow-up at initial (n=1), at follow-up (n=31)) and in remaining 26 cases (26/58, 44.8%) follow-up denied or not allowed.

No noteworthy cases were identified during the reporting interval.

Staphylococcal infections

A total of 98 serious cases were reported with staphylococcal infection. The relevant events (frequency>1) reported in these 98 serious cases are as follows: Staphylococcal infection (n=57), Furuncle (n=16), Cellulitis staphylococcal (n=5), Staphylococcal bacteraemia (n=4), CCI , Staphylococcal abscess (n=3 each), CCI and CCI each).

Of the 98 serious cases, in three cases causality with secukinumab cannot be completely ruled out due to temporal causal association (TTO ranges from six months to 2.4 years) however, no definitive causal association could be established due to limited information regarding one or more factors including relevant medical history, concomitant medications, event/therapy nature and circumstances.

In 26 serious cases, the causality was assessed as not suspected/confounded due to underlying patient's medical condition (such as diabetes mellitus, neoplasm malignant, chronic kidney disease, renal impairment,) and immunosuppressant drugs (such as methotrexate, methylprednisolone, beclomethasone, prednisolone, hydrocortisone and ciclosporin).

In remaining 69 serious cases including CCI (PT=Staphylococcal infection) of interest, the causality was not assessable due to limited

information, thus precluding further medical assessment. Of the 69 cases, 39 cases (39/69, 56.5%) were lost to follow-up (lost to follow-up at initial (n=2), at follow-up (n=37)), four cases (4/69, 5.8%) with follow-up completed and in remaining 26 cases (26/69, 37.7%) follow-up denied or not allowed.

No noteworthy cases were identified during the reporting interval.

CCI [redacted]

A total of 883 serious cases were reported with Serious cutaneous infection. These 883 serious cases included 26 cases of furuncle, Staphylococcal abscess, Wound infection staphylococcal, Cellulitis staphylococcal, Staphylococcal skin infection and are discussed under the sub-topic 'Staphylococcal infections'. Of the remaining 857 cases, 121 cases (including CCI [redacted] cases and CCI [redacted] cases) included events of Herpes Zoster and other Herpes infection, Candida infection and related events, CCI [redacted] and are discussed under the sub-topics 'Herpes infections' 'Mycobacterial infections', 'CNS infection and inflammations' and 'Fungal infection' respectively. The remaining 736 cases are discussed below.

The relevant events (frequency>25) reported in these 736 serious cases are as follows: Cellulitis (n=281), Hidradenitis (n=71), Folliculitis and Localised infection (n=47 each), Erysipelas (n=43), Wound infection (n=41), Postoperative wound infection (n=32) and Abscess (n=27).

Of the 736 serious cases, in 25 cases, causality with secukinumab cannot be completely ruled out due to temporal causal association (TTO ranges from five days to seven years) however, no definitive causal association could be established due to limited information.

Of the remaining 711 serious cases, CCI [redacted] cases were reported with CCI [redacted] and CCI [redacted] cases were reported with CCI [redacted]. Of these CCI [redacted] cases reported with CCI [redacted] events with CCI [redacted], (PT Folliculitis (n=23), Wound infection (n=9), Postoperative wound infection (n=2) and Cellulitis, CCI [redacted] each)), in CCI [redacted] cases, the other cause of death was reported as deep vein thrombosis, road traffic accident, SLE, pericarditis, diabetes mellitus, hepatic cirrhosis and breast cancer etc. which could explain the fatality. In remaining CCI [redacted] cases, there was limited information available for further assessment. In all fatal cases, there was no information on TTO and autopsy findings which precluded the further assessment.

Of the CCI [redacted] cases reported with CCI [redacted] event of interest (PT Folliculitis (n=13), Wound infection (n=5), Abscess (n=3), Cellulitis and Hidradenitis (n=2 each), Erysipelas, CCI [redacted] infection, CCI [redacted] CCI [redacted] each)), 22 cases were confounded by underlying conditions such as diabetes mellitus, gangrenous appendicitis and immunosuppressant drugs such as methotrexate, prednisolone, hydrocortisone, adalimumab and etanercept. While in remaining seven cases, the causality was not assessable due to limited information, thus precluding further medical assessment.

In 271 serious cases, the causality assessment was confounded due to underlying patient's medical condition such as diabetes mellitus, tooth infection, pre-existing cellulitis, renal impairment, skin malignancies, COPD etc. and use of immunosuppressant drugs such as methotrexate, prednisolone, adalimumab, etanercept, rituximab, betamethasone, hydrocortisone and golimumab; hence not suspected.

In remaining 377 serious cases, the causality was not assessable due to limited information, thus precluding further medical assessment. Of the 377 cases, 215 cases (215/377, 57%) were lost to follow-up (lost to follow-up at initial (n=42), at follow-up (n=173)), 72 cases (72/377, 19.1%) with follow-up completed and in remaining 90 cases (90/377, 23.9%) follow-up denied or not allowed.

No noteworthy cases were identified during the reporting interval.

CCI

A total of CCI serious cases were reported with CCI . The relevant events (one case reported more than one event per case) reported in these CCI serious cases are as follows: CCI each).

Of these 704 serious cases, in 20 cases including CCI , causality with secukinumab cannot be completely ruled out due to temporal causal association (TTO ranges from three months to five years) however, no definitive causal association could be established due to limited information regarding one or more factors including relevant medical history, concomitant medications, event/therapy nature and circumstances.

In case reported with CCI), there was no information available on TTO for comprehensive further assessment.

Of the remaining CCI serious cases, CCI cases were reported with CCI and CCI were reported with CCI . Of the CCI , CCI)] were confounded by other co-morbid conditions (such as chronic obstructive pulmonary disease, diabetes mellitus, chronic kidney disease, etc.) and immunosuppressant drugs such as methotrexate, betamethasone, prednisolone and etanercept. In the remaining CCI], there was limited information available on medical history, concomitant medication, clinical course of events, TTO, action taken with drug and CCI details for comprehensive medical assessment.

Of the CCI cases reported with CCI event of interest [PT= CCI r cases were confounded by patient's comorbid conditions such as diabetes mellitus, atrial fibrillation and immunosuppressant drugs such as methotrexate, cortisone, prednisolone and adalimumab. In the remaining 14 cases, there was limited information for a comprehensive medical assessment.

In 183 serious cases, the causality was assessed as not suspected/confounded due to underlying patient's medical condition (e.g. bronchial asthma/chronic obstructive pulmonary disease, chronic renal failure, etc.)

In remaining 412 serious cases, the causality was not assessable due to limited information thus precluding further medical assessment. Of the 412 cases, 261 cases (261/412, 63.3%) were lost to follow-up (lost to follow-up at initial (n=11), at follow-up (n=250), 32 cases (32/412, 7.8%)

with follow-up completed and in remaining119 cases (119/412, 28.9%) follow-up denied or not allowed.

No noteworthy cases were identified during the reporting interval.

Frequency Analysis / Post-marketing Reporting Rate

The reporting rate of 'Infections and infestations' since PSUR 1 is presented in the table below. The reporting rate for this period is lower than that of previous PSUR reporting interval and higher than the cumulative period.

Table 16-18 Infections and infestations: comparison of reporting rates in PSUR periods and cumulative from post-marketing source

	PSUR 26Dec14 - 25Jun15	PSUR 26Jun15 - 25Dec15	PSUR 26Dec15 - 25Jun16	PSUR 26Jun16 - 25Dec16	PSUR 26Dec16 - 25Dec17	PSUR 26Dec17 - 25Dec18	PSUR 26Dec18 - 25Dec19+	PSUR 26Dec19 - 25Dec20+	PSUR 26Dec20 - 25Dec23+	Cumulative up to 25 Dec 2023
Cases (n)	178	495	712	1,136	2,584	6524	6,468	5,828	17,060	45,549
Exposure (PTY)	[redacted]	[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]
Reporting rate (per100 PTY)	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

n: Number; PSUR: Periodic Safety Update Report; PTY: Patient Treatment Years.

+ The total number of cases includes all those initially received during the reporting interval as well as all those received in previous reporting intervals, which received significant follow-up information during the current reporting interval, as well as additional cases, if any, retrieved in current reporting interval owing to update in case retrieval logic.

Table 16-19 Reporting rate of cases reporting serious infections in PSUR periods and cumulative from post-marketing source

	PSUR 26Dec14 - 25Jun15	PSUR 26Jun15 - 25Dec15	PSUR 26Dec15 - 25Jun16	PSUR 26Jun16 - 25Dec16	PSUR 26Dec16 - 25Dec17	PSUR 26Dec17 - 25Dec18	PSUR 26Dec18 - 25Dec19*	PSUR 26Dec19 - 25Dec20+	PSUR 26Dec20 - 25Dec23+	Cumulative up to 25Dec23
Serious cases (n)	CCI									
Exposure (PTY)			CCI							
Reporting rate (per 100 PTY)	CCI									

n: Number; PSUR: Periodic Safety Update Report; PTY: Patient Treatment Years.

+ The total number of cases includes all those initially received during the reporting interval as well as all those received in previous reporting intervals, which received significant follow-up information during the current reporting interval, as well as additional cases, if any, retrieved in current reporting interval owing to update in case retrieval logic

Discussion

The majority (80.8%) of the cases of special interest retrieved for the risk of 'Infections and infestations' were reported as non-serious, which is consistent with the established safety profile of Cosentyx. Of the assessment performed for the selected types of infections, the cases were either confounded, (mostly by concomitant use of immunosuppressants e.g. MTX, cyclosporine, adalimumab, prednisolone etc.; or by underlying medical conditions e.g. diabetes, etc.); or contained partial case information, which was not sufficient to establish any definite causal relationship with secukinumab. No noteworthy cases were identified during the reporting interval. Though number of CCI and CCI cases has slightly CCI %) as CCI cases; nonetheless, provided the broad exposure during the interval period (more than CCI CCI PTYs), no CCI incidence of CCI is observed in secukinumab exposed population compared to the general population, where the CCI .

There was no new safety information from epidemiology and CTs during the reporting interval. In comparison to previous reporting interval and cumulative period, there was decrease in reporting rate for both overall infection and serious infections. During the reporting interval five relevant literatures were identified with conclusions aligned with the results observed during reporting period. Based on the assessment of all cases, no new safety finding, trend in frequency or severity was observed for the cases reporting serious infections.

Conclusion

The review of the data received during the reporting interval did not provide any new information pertaining to 'Infection and Infestations' or its subtopics. No increased reporting frequency was identified upon the review of the interval. CCI [redacted]

Overall, the data collected during the reporting interval is consistent with the known safety profile of Cosentyx with no new safety concerns identified. No update to the risk characterization is required. The wording for infections included in the current CDS in the section warning and precautions and ADRs is considered adequate for risk minimization.

In addition, after a thorough review of the available data from multiple sources, there is no evidence for a specific causal association between CCI [redacted] and CCI [redacted] with secukinumab therapy. Also, the status of the pandemic does not warrant close monitoring CCI [redacted] in future PSURs, unless a validated signal is identified. Both topics will continue to be monitored under routine pharmacovigilance activities.

For the following PSURs, the MAH will continue presenting focused analysis of Opportunistic infections, Central nervous system (CNS) infections and inflammation, Mycobacterial infections, Fungal infections, including esophageal candidiasis and Herpes infections.

For a complete characterization of the risk, please refer to Appendix 9.1.1.

16.3.1.2 Hypersensitivity

Background relevant to the evaluation

Hypersensitivity is an important identified risk in the Cosentyx RMP. Hypersensitivity reactions, including urticaria (frequency: common) and rare cases of anaphylactic reactions are listed in the CDS as ADRs, and included in the 'Contraindications' and 'Warning and Precautions' sections.

In the psoriasis registration trials, a higher incidence per 100 PTYs of hypersensitivity AEs mapping to 'Hypersensitivity' Standardized MedDRA Queries (SMQ) (narrow) was noted for secukinumab and etanercept compared with placebo (11.9 for any 300 mg secukinumab dose, 10.7 for any 150 mg secukinumab dose, and 9.7 for etanercept vs. 4.5 for placebo). This difference vs. placebo was mainly driven by eczema (particularly for secukinumab), urticaria, dermatitis, contact dermatitis and allergic rhinitis. 'Angioedemas' (HLT of MedDRA) were less frequent per 100 PYs for secukinumab and etanercept compared to placebo (0.5, 0.5 and 0 for any 300 mg, any 150 mg and etanercept vs. 1.0 for placebo), with no difference between the two secukinumab doses. A review of hypersensitivity events in PsA and AS and more recently JIA and HS registration studies was consistent with the findings from the psoriasis program.

During the reporting interval, two signals pertaining to hypersensitivity reactions were assessed:

Hypersensitivity vasculitis cases were reviewed in a signal procedure (EMEA/H/C/003729/SDA/011, Section 16.2.10 CCI [redacted]

in 2021. Available scientific data indicate a generally pro-inflammatory vasculitis-promoting role of IL-17A, and inhibition of IL-17A by secukinumab would therefore be expected to be beneficial in vasculitic disease conditions (e.g. Giant Cell Arteritis currently being assessed in a phase III study); rather than having a role in the development of CCI and other CCI Per MAH, the review of the cumulative cases did not support a causal relationship between secukinumab and CCI or other CCI Nevertheless, for the event of hypersensitivity vasculitis only, the PRAC Rapporteur disagreed with the MAH and requested its inclusion as new ADR (frequency rare) in SmPC. In line with the MAH position, currently the secukinumab CDS does not include this event as ADR.

Eczematous eruptions, including atopic dermatitis like eruptions and exfoliative dermatitis generalized (erythroderma) were assessed as a signal Section 16.2.1, in 2023. Based on the identification of biological plausibility with dual mechanism of action as both a paradoxical reaction and a hypersensitivity reaction, along with evidence from post-marketing secukinumab cases with disproportionate reporting for eczema and exfoliative dermatitis, Novartis confirms the causal association. Update to the CDS with the high-level term dermatitis with frequency uncommon, and the term dermatitis exfoliative generalized is to be included as an ADR from post-marketing (frequency not known). Off note, current Cosentyx SmPC includes exfoliative dermatitis (frequency rare). In addition, update to the Warnings and Precautions Section for Eczematous eruptions, including dermatitis-like and Exfoliative reactions was deemed appropriate due to 1) serious cases requiring hospitalization (up to CCI and 2) prescribers should consider treatment discontinuation for some cases.

In the PRAC assessment report for previous PSUR (26 Dec 2019 to 25 Dec 2020), the Novartis was requested to submit a cumulative review on angioedema related cases from both clinical trials and post-marketing data using the MedDRA PT Angioedema. Novartis has conducted the review, and the analysis and recommendations are provided below.

Methods of evaluation

The details of the search criteria used to retrieve cases are included in Appendix 8.

Noteworthy case definition: A well-documented HCP / medically confirmed case describing hypersensitivity event with increased severity (fatal or life-threatening) and suspected causal association based on plausible time to onset, positive de-challenge, or re-challenge and without any other plausible alternative explanation or apparent confounding factors.

Focus of Analysis: Based on change in frequency and severity of serious cases reporting significant hypersensitivity reactions as compared to the previous reporting interval and cumulative period.

Results

Cumulative reporting rate in the clinical database and other sources

The cumulative exposure adjusted incidence rate (EAIR) for the entire treatment period for 'Hypersensitivity' (identified by MedDRA SMQ narrow) across all indications, for Any AIN457 dose was 7.32 (95% CI 7.05 - 7.61) per 100 PTY. Patients treated with Cosentyx 300 mg presented a higher EAIR (per 100 PYs) of hypersensitivity reactions when compared to patients receiving 150 mg [7.98 (95% CI 7.56 – 8.42) for 300 mg Q4W, 12.26 (95% CI 9.86 –

15.07) for 300 mg Q2W vs. 6.58 (95% CI 6.15 – 7.04) for 150 mg]. Overall, the incidence rates remained comparable between the previous PSUR and the current reporting period PSUR [Incidence rate ratio 1.02 (95% CI 0.97, 1.08)]. (Source: Table 18 Change in the incidence rates relative to the last review period of treatment emergent adverse events of special interest by PSUR risks, by treatment group Entire treatment group Safety Set).

In the CorEvitas Registry, IR per 100 PTY for severe and anaphylactic reactions was comparable for secukinumab [CCI)] and for non-biologic system therapies [0.0 (CI 0.0 - 0.3)]. (Table 18-5)

Company safety database

Reporting interval analysis

The search in the Novartis safety database retrieved a total of 6,526 cases in this PSUR reporting interval and 18,045 cases reported cumulatively. Of the 18,045 cases retrieved cumulatively, 618 cases received in previous reporting intervals newly reported an event related to hypersensitivity reactions as follow-up information during the reporting interval.

A total of 7,144 cases are included in the analysis during the reporting interval; an outline of their distribution by report type and seriousness is presented in the table below.

Table 16-20 Overview of 'Hypersensitivity' in the reporting interval

Evaluation	**Hypersensitivity**				
ICSR analysis	**Total: CCI evaluable cases (CCI events)** CCI SR, CCI PMS, 46 literature, 8 CT. CCI HCP cases; CCI non-HCP cases.				
Severity Analysis	CCI (11%) out of the CCI were serious cases (CCI events); of them in CCI cases (1,032 serious events) were recorded as lead events. Due to their potential relevance in assessing the benefit-risk profile of secukinumab, the medical review focused on serious cases of the significant hypersensitivity reactions (see PTs below), which correspond to CCI cases (CCI events). The proportion of CCI cases during the reporting interval is CCI than the CCI and CCI				
Events (PT)	**Fatal**	**Life threatening**	**Other serious**	**Non-serious**	**Total***
Anaphylactic Reaction	0	CCI	CCI	0	CCI
Angioedema	0	CCI	CCI	0	CCI
Cutaneous Vasculitis	0	CCI	CCI	0	CCI
Dermatitis exfoliative generalised	0	0	CCI	0	CCI
Skin necrosis	0	0	CCI	0	CCI
Anaphylactic Shock	0	0	CCI	0	CCI

Evaluation	Hypersensitivity				
Dermatitis exfoliative	0	[redacted]	[redacted]	0	[redacted]
Circulatory collapse	[redacted]	0	[redacted]	0	[redacted]
Stevens-Johnson syndrome	0	0	[redacted]	0	[redacted]
Shock	0	[redacted]	[redacted]	0	[redacted]
Drug reaction with eosinophilia and systemic symptoms	0	[redacted]	[redacted]	0	[redacted]
Erythema multiforme	0	0	[redacted]	0	[redacted]
Henoch-Schonlein purpura	0	0	[redacted]	0	[redacted]
Anaphylactoid Reaction	0	[redacted]	[redacted]	0	[redacted]
Toxic skin eruption	0	0	[redacted]	0	[redacted]
Acute generalized exanthematous pustulosis	0	0	[redacted]	0	[redacted]
Hypersensitivity vasculitis	0	0	[redacted]	0	[redacted]
Toxic epidermal necrolysis	0	0	[redacted]	0	[redacted]
Mast cell activation syndrome	0	0	[redacted]	0	[redacted]
Cross sensitivity reaction	0	0	[redacted]	0	[redacted]
Others[+]	[redacted]	[redacted]	[redacted]	0	[redacted]

*The total numbers of each event (PT) can be greater than the overall serious significant hypersensitivity reaction cases due to case overlap.

[+]Fatal and Life-threatening reported with cause of death other than hypersensitivity reactions.

Causality assessment (events)	Evaluation				
	CT	PMS	SR	Lit	Total*
Noteworthy	0	[redacted]	[redacted]	2	[redacted]
Suspected (CNBR)	0	[redacted]	[redacted]	1	[redacted]
Not suspected (confounded)	1	[redacted]	[redacted]	0	[redacted]
Not assessable	0	[redacted]	[redacted]	0	[redacted]

[*]The total count of causality assessment table will be greater than the overall serious significant hypersensitivity reaction cases since one case may appear in more than one sub-topic.

Evaluation	Hypersensitivity
Frequency Analysis	The reporting rate of the current PSUR reporting interval is less compared to the previous PSUR interval and to the cumulative period. No new safety findings could be identified (refer Table 16-22).

CNBR: Causal role cannot Be Ruled Out, CT: Clinical Trial, Lit: Literature, F: Fatal; ICSR: Individual Case Safety Report, LT: Life-Threatening; n=number; PT: Preferred Term; PSUR: Periodic Safety Update Report, PMS: Post-Marketing Study, SR: Spontaneous Report

Anaphylactic Reaction (n=CCI Anaphylactic Shock (n=CCI Anaphylactoid Reaction (n=CCI

CCI cases contained CCI events of anaphylactic reaction, CCI events of anaphylactic shock, and three events of anaphylactoid reaction. No noteworthy cases were identified.

In CCI cases, one case was assessed as not suspected due to long latency from last secukinumab injection (21 days) to develop an acute anaphylactic reaction and in 16 other cases event was reported due to either concurrent conditions (iodine sensitivity, tobacco use, allergy to bee stings) in three cases or other medications (methotrexate, sulfa drugs, infliximab, adalimumab, and amoxicillin/clavulanic acid) in thirteen cases (includes one life-threatening event of anaphylactic reaction).

In the other CCI cases (includes CCI of anaphylactoid reaction) there was no information available or partial information available to make a comprehensive medical assessment; these cases remain as not assessable. Of these CCI cases, in CCI cases (CCI %) follow-up is ongoing; CCI cases (CCI %) were lost to follow-up either at CCI

CCI

immediate, within few hours to 15 days (median range: seven days). Cosentyx was discontinued/temporarily interrupted in CCI cases, no change in Cosentyx in CCI cases, and in the remaining nine cases, action taken was unknown/not reported and not applicable. Of these CCI cases, corrective treatment medications were prescribed in two cases. Outcome was reported as complete recovery in five cases, condition unchanged in two cases, and unknown/not reported in CCI cases. De-challenge was positive in four cases.

Angioedema (n=35)

As requested by PRAC, please see Section 16.2.5 for cumulative review of angioedema.

Cutaneous vasculitis (n=CCI Hypersensitivity vasculitis (n=CCI CCI

CCI cases contained CCI events of cutaneous vasculitis, CCI events of CCI and one event of hypersensitivity vasculitis.

In CCI cases (event: cutaneous vasculitis), the causal relationship was not suspected, due to history of rheumatic purpura, and hepatitis C in two cases (includes CCI life-threatening case), concurrent conditions (sarcoidosis, and smoking) in two cases, and other medications (felodipine, metoprolol succinate, sulfasalazine, methotrexate, golimumab, cephalexin,

ciprofloxacin, diclofenac, naproxen, cyclosporine, and atorvastatin) in six cases. In another case (event: hypersensitivity vasculitis), the causality was not suspected due to implausible TTO (event occurred four months after Cosentyx discontinuation).

In 10 cases (nine cutaneous vasculitis and CCI) there was no information available or partial information available to make a comprehensive medical assessment; these cases remain as not assessable. Of these CCI cases, CCI cases (CCI) were lost to follow-up either at initial attempts or after diligent follow-up attempts; in two cases CCI %) follow-up is ongoing; in two cases (CCI %) follow-up was not possible due to insufficient contact information or was not allowed as there was no consent to contact the reporter; in two cases (CCI follow-up was complete but no relevant information received.

In CCI cases (CCI), causality is assessed as suspected, in which the TTO ranged from six days to 43 days. In these cases, Cosentyx was discontinued, and outcome was reported as complete recovery/condition improving. De-challenge was positive in two cases. There were no confounders in these cases.

The remaining three noteworthy cases which reported cutaneous vasculitis are mentioned in table below.

Table 16-21 Noteworthy cases of cutaneous vasculitis during reporting interval (n=3)

Case ID/ Age/ Gender/ Report type/ HCP/ Indication/ Medical history/ Past medications/ Concomitant medications	Seriousness criteria/ TTO (days)/ treatment provided	Action taken/ Outcome/ De-challenge/ Re-challenge	Case information
PD PD PD Lit/ HCP/ Hidradenitis/ Cardiac failure chronic, type 2 diabetes mellitus/ Adalimumab/ NR	MS/ NR/ Corticosteroids	Treatment discontinued/ Condition improving/ NA/ NA	Relevant investigations included skin biopsy (findings compatible with immune complex vasculitis), dermatologic examination (revealed palpable purpuric papules, and pustules on lower extremities), direct immunofluorescence analysis (revealed only C3 deposition within capillary walls), and high C-reactive protein level along with low C4 level.
PD PD PD Lit/ HCP/ PsA/ NR/ Methotrexate, Adalimumab/ NR	MS, H/ NR/ Prednisone, Cyclosporine	Treatment discontinued/ Complete Recovery/ NA/ NA	Relevant investigations showed CIC C1Q level (2620 ug/ml- normal value 0.00-16 ug/ml) and immunoglobulin A level (8130 g/l-normal value 0.70-4.00 g/l). Biopsies from two different ulcerative lesions on the gluteus region showed perivascular inflammatory cell infiltrate, mainly neutrophils and their fragmentation. Dermal vessels showed swelling of endothelial cells and deposits of strongly eosinophilic strands of fibrin within and around the vessel wall. Extravasation of

Case ID/ Age/ Gender/ Report type/ HCP/ Indication/ Medical history/ Past medications/ Concomitant medications	Seriousness criteria/ TTO (days)/ treatment provided	Action taken/ Outcome/ De-challenge/ Re-challenge	Case information
			erythrocytes was also present along with dermal oedema. These findings confirmed the diagnosis of leukocytoclastic vasculitis, which the patient developed after eight months of receiving secukinumab.
PD [redacted] PD [redacted] PMS/ HCP/ AS/ Drug hypersensitivity/ NR	H/ 39/ Prednisolone	Treatment discontinued/ Complete Recovery/ NA/ NA	The patient developed cutaneous vasculitis (confirmed by skin biopsy), 10 days after the last dose of Cosentyx (total five doses received).

CIC: Circulating immunocomplexes; F: Female; H: Hospitalization; HCP: Health Care Professional; Lit: Literature; M: Male; MS: Medically Significant; NA: Not Applicable; NR: Not Reported; PMS: Post-Marketing Study; PsA: Psoriatic Arthritis; PT: Preferred Term

Company Comment: Based on the relevant investigation details provided, considering reasonable temporal relationship, improvement of event post discontinuation of secukinumab, and lack of confounders (recent infection, other drug intake or auto-immune etiology), the causality is assessed as suspected in the above three cases.

Dermatitis exfoliative (n=7), Dermatitis exfoliative generalized (n=16)

Twenty-three cases contained seven events of dermatitis exfoliative, and 16 events of dermatitis exfoliative generalized. Comprehensive analysis of 18 of these 23 cases which led to the CDS update is presented in the clinical overview (data cut 03 Aug 2023) Section 16.2.1.

Of the remaining five cases, in four cases (event: dermatitis exfoliative generalized), the causality was assessed as not suspected, due to concomitant medication acitretin in one case, and event occurred due to aggravation of underlying conditions (psoriasis) and concurrent conditions (basal cell carcinoma) in three cases. In one case (event: dermatitis exfoliative), there was no information available to make a comprehensive medical assessment; this case remain as not assessable. This case was lost to follow-up.

Severe cutaneous adverse reactions (CCI [redacted])

Twenty-one cases contained CCI [redacted] (includes dermatitis exfoliative event). No noteworthy cases were identified.

In CCI [redacted] cases (including CCI [redacted]), exact TTO from last Cosentyx administration was unknown, and the causality was assessed as not suspected, since event could be either confounded by concomitant medications (omalizumab, losartan, vancomycin, and acyclovir) or event recovered without any change in Cosentyx therapy (negative rechallenge),

or there was no confirmatory diagnosis of CCI reported and investigator did not attribute CCI to Cosentyx or any other drugs).

In CCI cases (event: CCI) one case had concurrent staphylococcal infection, the event occurred two months after discontinuation of Cosentyx in the second case and the in the third case the patient recovered without any change in Cosentyx therapy (negative rechallenge), hence causality was assessed as not suspected.

In CCI cases CCI , and CCI each)] there was no or partial information available to make a comprehensive medical assessment; these cases remain as not assessable. Of these 10 cases, in five cases (5/10, 50%) follow-up is ongoing, in four cases (4/10, 40%) follow-up was not possible due to insufficient contact information or was not allowed as there was no consent to contact the reporter; and one case (1/10, 10%) was lost to follow-up.

CCI , where causality is assessed as suspected, the patient developed CCI each), in which TTO ranged from six days to 19 days (median range: 14 days) from the last dose of Cosentyx administration. Cosentyx was discontinued/temporarily interrupted in two cases, action taken was reported as unknown/no change in three cases. Outcome was reported as condition improving in two cases, and not reported/unknown in other three cases. De-challenge was positive in one case.

CCI

CCI cases contained CCI events of CCI , and no noteworthy cases were identified.

Of these 14 cases, in four cases skin necrosis developed as a result of the progression of underlying conditions (plaque psoriasis, psoriatic arthropathy) and was not related to or occurred as a consequence of any form of hypersensitivity reactions. Hence these cases are not considered relevant for further discussion in terms of hypersensitivity reactions.

In the remaining CCI cases, there was no information available or partial information available to make a comprehensive medical assessment; these cases remain as not assessable. Of these CCI cases, six cases (6/10, 60%) were lost to follow-up; in two cases (2/10, 20%) follow-up is ongoing, and in two cases (2/10, 20%) follow-up was not possible due to insufficient contact information or was not allowed as there was no consent to contact the reporter.

CCI

CCI cases contained CCI events of CCI (includes CCI cases), and CCI events of CCI (includes CCI). In none of these cases, events circulatory collapse and shock were related to or occurred as consequence of any form of hypersensitivity reactions. These events developed in context of other antecedent conditions/events and included gastroenteritis, aspiration pneumonia, underlying COVID-19, sepsis, multiple organ dysfunction syndrome, cardiomyopathy, anuria, hepatic failure, and renal failure. Hence, these cases are not considered relevant for further discussion in terms of hypersensitivity reactions.

CCI

CCI case reported CCI and CCI case reported CCI with CCI however there was no information on the relevant medical history,

concomitant medications, relevant investigations, detailed clinical course, and outcome of event which precluded a comprehensive medical assessment in both cases.

Severity analysis

While the CCI [redacted]
a medical review determined that CCI [redacted]

Apart from the CCI cases of CCI and the CCI [redacted].

Of the CCI , the CCI was reported due to multiple conditions which could explain the fatality. There was no information on TTO, CCI , detailed clinical course of the events which precluded comprehensive medical assessment. In all these cases, there was limited scope for follow-up as these were received from health authorities.

In the CCI which reported CCI ,

- In CCI the causal relationship was assessed as not suspected, since the events (drug hypersensitivity, urticaria, infusion related reaction) reported due to medications other than secukinumab in three cases, and one case (event: urticaria) was reported due to underlying conditions.
- In CCI cases (hypersensitivity n=3, urticaria n=1) the causal relationship was assessed as suspected. In all CCI cases, the TTO was reported as one day. Corrective treatment medications (betamethasone, dexchlorpheniramine) were prescribed in one case and not reported in other three. In all these four cases, Cosentyx was discontinued, outcome was reported as complete recovery/condition improving, and de-challenge was positive, and no information on re-challenge.
- In the remaining CCI cases (hypersensitivity, rash, infusion related reaction, urticaria, drug hypersensitivity, eye swelling, rash pruritic, CCI , and injection related reaction), there was limited information available on TTO, clinical course of the events, relevant investigations performed, which precluded comprehensive medical assessment. In all these cases, there was limited scope for follow-up as these were received from health authorities.

Frequency Analysis / Post-marketing Reporting Rate

The reporting rate of 'Hypersensitivity' has been compared in the table below. The reporting rate for this period is lower than the rate observed in previous reporting interval and cumulatively.

Table 16-22 Hypersensitivity: comparison of reporting rates in PSUR periods and cumulative

	PSUR 26Dec 14 - 25Jun 15	PSUR 26Jun 15 - 25Dec 15	PSUR 26Dec 15 - 25Jun 16	PSUR 26Jun 16 - 25Dec 16	PSUR 26Dec 16 - 25Dec 17	PSUR 26Dec 17 - 25Dec 18	PSUR 26Dec 18 - 25Dec 19	PSUR 26Dec 19 - 25Dec 20	PSUR 26Dec 20 - 25Dec 23*	Cumulative
Cases (n)									CCI	
Exposure (PTY)									CCI	
Reporting rate (per 100 PTY)	CCI									

n: Number; PSUR: Periodic Safety Update Report; PTY: Patient Treatment Years.

* Cases considered in the analyses include those initially received during the reporting interval as well as those received in previous reporting intervals in which 'Hypersensitivity' was newly received as a follow-up or secukinumab was newly added as co-suspect drug to a case that contained an event of 'Hypersensitivity', during the current reporting interval, as well as additional cases, if any, retrieved in current reporting interval owing to update in case retrieval logic

Cumulative data summary

The above-mentioned search retrieved 18,045 cases cumulatively, of which 6,527 cases were discussed under the reporting interval analysis. The remaining 11,518 cases were reviewed in the previous PSURs. Out of these 11,518 cases, 617 cases received significant follow-up information during the reporting interval, however, the newly added information was not clinically significant and did not alter the previous case assessment. No noteworthy case was identified, and the analysis revealed no new safety concerns.

Discussion

During the reporting period the following safety findings led to CDS / EU SmPC update. Analysis of eczematous eruptions (including dermatitis like eruptions and exfoliative dermatitis generalized) reported in patients exposed to secukinumab, revealed causal association with secukinumab based on biological plausibility as paradoxical reaction (due to Th2/Th22 imbalance caused by IL-17 blockage), several of these cases were in the clinical circumstances of allergic reactions; for which the hypersensitivity component cannot be excluded.

As requested by the PRAC in the last PSUR period, the analysis of cases reported cumulatively for angioedema showed causal relationship with secukinumab, this and the fact that other IgE mediated allergic reactions (urticaria and anaphylaxis) are linked to secukinumab, confirm causal association between angioedema and secukinumab. Within this PSUR, the MAH confirms angioedema as a new ADR and proposes a CDS update (see Section 16.2.5).

The PRAC requested the inclusion of hypersensitivity vasculitis in the EU SmPC. In this sense, the Chapel Hill 1994 consensus on the classification of vasculitides excluded the term because

of a lack of specificity of clinical (palpable purpura) and histologic presentation (LCV), as well as the inability to describe the precise immune mechanism that caused the small vessel vasculitis, and patients who previously would have been classified as having hypersensitivity vasculitis are now diagnosed with cutaneous small vessel vasculitis if vasculitis is limited to the skin[28]. No direct link between IL-17 inhibition and leukocytoclastic vasculitis has been identified to date (other than the case reports). Based on the review of cases reported with event cutaneous vasculitis (n=22) during the reporting period, three suspected (two literature and one PMS) cases were identified out of a total 68 cumulative cases. Overall, is still concluded that this is limited evidence to confirm causal association, particularly accounting the broad secukinumab exposure in post-marketing setting (plus 1.8 million PTYs).

All and all, these new safety findings during the reporting period are considered that do not modify the benefit risk profile of secukinumab, provided that most of the cases correspond to events of mild-moderate in severity, a minority of cases led to hospitalization and no fatal cases assessed as suspected to secukinumab were identified. Therefore, the benefit risk profile is still considered positive for the authorized and investigational indications.

The review of all other cases related to hypersensitivity reactions during this reporting period do not reveal any new safety information on hypersensitivity reactions. There was no new information from non-interventional/observational studies and CTs during the reporting interval. No increase in reporting frequency was identified based on post marketing reporting rate for this period as compared to that in previous and cumulative reporting interval. CCI [redacted].

The CT data does not show a change in the incidence rates between reporting periods.

Conclusion

Based on the review of the collected evidence, the following conclusions are drawn.

- Hypersensitivity reactions are complex, possibly not only Ig-E related, while most event are related with classic allergic reactions (e.g. urticaria and atopic dermatitis), long-latency events may occur (severe eczematous reactions, isolated cases of severe angioedema).
- CDS update has been made in section 6 "warnings and precautions" and section 7 "Adverse drug reactions" to include eczematous eruptions, atopic dermatitis-like eruptions, and erythroderma, along with SmPC update. As there was no change in the benefit-risk profile of secukinumab, this was not included in the RMP.
- Based on the cumulative review of cases reported with angioedema, a causal association for angioedema and secukinumab was confirmed, the CDS section 7, table 7-2 "Adverse drug reactions" is being updated with PT angioedema (frequency not known), along with proposal to update SmPC and NPI documents.
- New adverse drug reactions identified during the reporting period do not change the benefit-risk profile for secukinumab.

The review of data pertaining to the risk of 'Hypersensitivity' received during the reporting interval does not change the safety profile of Cosentyx. For the following PSURs the MAH will continue presenting focused analysis of Hypersensitivity reactions.

The overall characterization of this identified risk is presented in Appendix 9.1.2.

16.3.2 New information on important potential risks

16.3.2.1 Malignant or unspecified tumors

Background relevant to the evaluation

'Malignant or unspecified tumors' is an important potential risk in the Cosentyx RMP and is not listed in the CDS as an ADR.

Available literature data suggest that IL-17A has both pro-tumor and anti-tumor activity. In general, medicines that affect the immune system (immunosuppressants or immunomodulators), like Cosentyx, may in theory increase the risk of developing cancer. There is no adequate data available about the use of Cosentyx in patients who have a history of malignancy or who have a known malignancy. Currently, there is no evidence that Cosentyx increases the risk of cancer.

Results from the clinical trials in psoriasis, PsA and AS population show that secukinumab does not confer an increased risk for malignancy. The incidence of malignancies including skin tumors was low and comparable across the secukinumab dose groups and placebo.

Data from the psoriasis registration program, including studies and study periods where all patients received secukinumab, revealed a higher incidence of AEs related to malignant or unspecified tumors in the placebo group compared with the active treatment groups (exposure-adjusted rates per 100 PTY were 1.49 for placebo vs. 0.96 for any secukinumab dose and 0.68 for etanercept) and no evidence for dose-response effect (0.77 for Cosentyx 300 mg vs. 0.97 for Cosentyx 150 mg).

As part of post-approval commitments during submission for PsA and AS new indications, Swissmedic requested the assessment of basal cell carcinoma cases in the PSUR. The assessment is presented below under 'Skin cancer.'

In the PRAC PSUR assessment report (Procedure no: EMEA/H/C/PSUSA/00010341/202012) on previous PSUR, the HA has agreed to the proposal made by the MAH to only review the five top reported types of malignancies in the subsequent PSURs.

"As malignancies have been followed since the first PSUR for the last six years with no new safety finding identified, the MAH has proposed to only review the five top reported types of malignancies in the subsequent PSURs. This approach is endorsed by the assessor.

For the next PSUR, the MAH is requested to present the observed vs. expected number of events and standardized incidence ratio for each type of malignancy compared with the general population, provided this information is available to the MAH."

Methods of evaluation

The details of the search criteria used to retrieve cases are included in Appendix 8.

Noteworthy Case Definition: A case with a physician confirmed diagnosis of malignancy (serious events) with supportive imaging/histopathology results.

Results

Company safety database

The search in the Novartis safety database retrieved a total of CCI cases in this PSUR reporting interval and CCI cases reported cumulatively. Of the CCI cases retrieved cumulatively, CCI cases initially received in previous reporting intervals newly reported an event related to 'Malignant and unspecified tumors' as follow-up information during the reporting interval. One case PD was a continuation of another case PD and hence is only counted only once.

A total of CCI cases are included in the analysis of cases received during the reporting interval; an outline of the distribution of these cases by report type and seriousness is presented in the table below.

Table 16-23 Distribution of cases reporting events of 'Malignant or unspecified tumors' during the reporting interval and cumulatively

Report type	Reporting interval*					Cumulative				
	HCP		Non-HCP		Total	HCP		Non-HCP		Total
	Serious	Non-serious	Serious	Non-serious		Serious	Non-Serious	Serious	Non-serious	
SR	CCI									
PMS	CCI									
Lit	15	0	0	0	15	35	0	0	0	35
CT	19	0	0	0	19	245	1	0	0	246
Total	CCI									

* Cases seriousness determined based on seriousness of the most relevant event

Source: Company Safety Database as of 25 Dec 2023;

CT: Clinical Trials; HCP: Health Care Professional; Lit: Literature; PMS: Post Marketing Surveillance; SR: Spontaneous Report

These CCI cases reported CCI AEs (CCI Serious and CCI non-serious). The most commonly reported five malignancies were identified based on the High-level group term (excluding the HLGT Miscellaneous and site unspecified neoplasms malignant and unspecified). The order of the frequencies is consistent with the last PSUR. All other malignancies were reported in less than 5% of the CCI cases for the interval.

Table 16-24 Distribution of events of 'Malignant or unspecified tumors' (greater than 5%) as per the HLGT

HLGT	Number of events**
Skin neoplasms malignant and unspecified*	CCI
Miscellaneous and site unspecified neoplasms malignant and unspecified	CCI
Breast neoplasms malignant and unspecified (incl nipple)*	CCI
	CCI

HLGT	Number of events**
[redacted]	CCI
[redacted]	[redacted]

*Top five malignancies that are further analyzed
**Each case may report more than one type of malignancy event

The MedDRA PTs reported in ≥5% of the CCI cases for each of these top five malignancies are listed in the below table.

Table 16-25 Preferred terms reported in each of the top five malignancies

HLGT	Number of events	Preferred term	Frequency
Skin neoplasms malignant and unspecified	CCI	CCI	CCI
		Skin cancer	CCI
		[redacted]	[redacted]
		[redacted]	[redacted]
		Neoplasm skin	CCI
Breast neoplasms malignant and unspecified (incl nipple)	CCI	Breast cancer	CCI
		CCI	CCI
		CCI	CCI
CCI	CCI	CCI	CCI
		CCI	CCI
		CCI	CCI
		CCI	CCI
		CCI	CCI
CCI	CCI	[redacted]	[redacted]
		CCI	CCI
CCI	CCI	[redacted]	[redacted]
		CCI	06

*Including one event of 'Basal cell carcinoma metastatic'.
**Including six events of 'Lung neoplasm'.

As shown in the table below, duration of secukinumab treatment can only be assessed for 24% of the events, and time to event onset can only be assessed in approximately 44% of the events. Malignancy onset within six months of secukinumab initiation would not be related secukinumab (implausible temporally).[29] The time to onset of the malignancy event with respect to the treatment duration for the top five malignancies is given in below table.

Table 16-26 Overview of the malignancy event time to onset by treatment duration for the top five malignancies

	Time to event onset						
Treatment duration	< 6 months	≥6 - <12 months	≥1 - <2 years	≥2 - <3 years	≥3 years	Unknown	Total events
<6 months	CCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6-12 months	CCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥1 - <2 years	CCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Time to event onset						
Treatment duration	**< 6 months**	**≥6 - <12 months**	**≥1 - <2 years**	**≥2 - <3 years**	**≥3 years**	**Unknown**	**Total events**
≥2 - <3 years	0	0	CCI	[redacted]	[redacted]	[redacted]	[redacted]
≥3 years	0	CCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	CCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	CCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The assessment of the top five malignancies (excluding miscellaneous and site unspecified neoplasms) is summarized in below table. Causality was not suspected in all but two cases (further described in this section).

Table 16-27 Overview of assessment of events reported from the top five malignancies

	Skin neoplasms malignant and unspecified							
	CCI			All*	CCI			
Number of cases/ AEs	CCI			CCI	266**/ 280	181/ 186	126/ 128	101/ 101
Fatal cases	0	0	CCI		CCI			
Assessment of the AEs								
Implausible temporal association								
TTO within 6 months	CCI							
Event onset ≥1 year after Cosentyx discontinuation	CCI							
Confounded*								
Prior cancer or prior chemo/radiotherapy	CCI							
Current conditions/ risk factors such as UV therapy	CCI							
Concomitant/ co-suspect medications	CCI							
Insufficient info for causality assessment/ Lost to follow-up	CCI							
Causality cannot be excluded	0	0	0	0	0	CCI	0	0

*Each case may report more than one type of malignancy and may contain more than one type of confounding factors and hence, the total case/ AE count may not match with the total of individual rows.

**Of these 266 cases, six cases were male

The two cases where the causality with Cosentyx cannot be excluded based on the plausible temporal relationship, and absence of alternate explanations in one case are presented below.

- PD (PMS, HCP): This case refers to an elderly PD patient with no relevant medical history who received Cosentyx for the treatment of psoriasis. The patient developed CCI 11 months and two days after the first dose and was treated with radiotherapy. Therapy with Cosentyx was discontinued. The outcome of the event was reported as condition unchanged.
- Company comment: Based on the available information and plausible time to onset and absence of alternate explanations, the causal association of the event could not be excluded. However, there is no information on risk factors and investigation results, hence, definite assessment could not be made.
- PD (SR, HCP): This case refers to a PD-year-old PD patient with no relevant medical history who received Cosentyx for the treatment of spondylarthritis. The patient developed CCI around two years after the first dose. Therapy with Cosentyx was discontinued and it was reported that the patient fully recovered from the event in four months. Treatment for the reported malignancy was not reported.
- Company comment: Based on the available information and plausible time to onset a causal association of the event could not be excluded.

Frequency Analysis

Post-marketing reporting rate of 'Malignant or unspecified tumors' is provided in the below table. The reporting rate for this period is lower compared to the rate observed in previous and cumulative reporting interval, considering all malignant and unspecified neoplasms.

Table 16-28 Malignant or unspecified tumors: comparison of reporting rates in PSUR periods and cumulative

	PSUR 26Dec14 - 25Jun15	PSUR 26Jun15 - 25Dec15	PSUR 26Dec15 - 25Jun16	PSUR 26Jun16 - 25Dec16	PSUR 26Dec16 - 25Dec17	PSUR 26Dec17 - 25Dec18	PSUR 26Dec18 - 25Dec19*	PSUR 26Dec19 - 25Dec20	PSUR 26Dec20 -25Dec23	Cumulative
Cases (n)	CCI									
Exposure (PTY)	CCI									
Reporting rate (per 100 PTY)	CCI									

n: Number; PSUR: Periodic Safety Update Report; PTY: Patient Treatment Years.

Cumulative data summary

A total of CCI individual case safety reports of malignancies have been cumulatively received, including 246 cases received from clinical trials. Of the CCI cases, CCI cases have been discussed above, in the reporting interval analysis. In the remaining cases, no new significant safety information was received during the reporting interval. During the current interval, the post-marketing reporting rates per 100 patient-years was approximately 50% lower than the

previous three reporting intervals. Incidence rates in clinical trials are summarized separately in this section below. In all 3,801 cases, the five most commonly reported malignancies (based on the High-level group term, excluding the HLGT Miscellaneous and site unspecified neoplasms malignant and unspecified) were Skin neoplasms malignant and unspecified, Breast neoplasms malignant and unspecified (incl nipple). CCI [redacted] Of the 3,555 cumulative post-marketing cases, CCI [redacted] were identified in 512 cases (including 68 cases reported with other type of malignancies. Prior or pre-existing malignancies, or prior chemo- or/and radiotherapies were reported in CCI [redacted] %) of the CCI [redacted] cases. Treatment duration and time to first occurrence of malignancies can only be assessed in CCI [redacted] and CCI [redacted] of the post-marketing cases, respectively. In CCI [redacted] post-marketing cases, malignancies were reported within six months after receiving the first dose of secukinumab. The cumulative review of these case reports did not identify any new or significant information impacting the safety profile of Cosentyx.

Cumulative rate in the clinical database and other sources

The cumulative EAIR for the entire treatment period for SMQ 'Malignant or unspecified tumors' across all indications, for any AIN457 dose was 0.81 (95% CI 0.72 - 0.90) per 100 PTY. No dose-response effect was identified. Similarly, the incidence rates remained comparable between the previous PSUR and the current reporting period PSUR [Incidence rate ratio 0.99 (95% CI 0.84, 1.16)] (Source: Table 18 Change in the incidence rates relative to the last review period of treatment emergent adverse events of special interest by PSUR risks, by treatment group Entire treatment group Safety Set).

Additionally, the observed vs. expected number of malignancies, as indicated by the standardized incidence ratios (SIR) were estimated using the US general population in SEER as reference adjusting for age and sex. CCI [redacted]

Table 16-29 Observed vs. expected number of events and SIR for overall malignancies[1] compared with the general population in SEER program, by treatment groups – Clinical Trial data - entire treatment period - Safety Set

Treatment Group	Observed Events, N	Expected Events [2]	SIR	95% CI	Exposure (PTY)
Any secukinumab 75 mg Q4W	CCI [redacted]	CCI [redacted]	CCI [redacted]	CCI [redacted]	[redacted]
Any secukinumab 150 mg Q4W	CCI [redacted]	CCI [redacted]	CCI [redacted]	CCI [redacted]	[redacted]
Any secukinumab 300 mg Q4W	CCI [redacted]	CCI [redacted]	CCI [redacted]	(CCI [redacted]	[redacted]
Any secukinumab 300 mg Q2W	CCI [redacted]	CCI [redacted]	CCI [redacted]	(CCI [redacted]	[redacted]
Any secukinumab dose	CCI [redacted]	CCI [redacted]	CCI [redacted]	(CCI [redacted]	[redacted]

[1] Excluding non-melanoma skin cancers (NMSC);

[2] Expected number of cases: calculated by multiplying the incidence rate and the PTY.

Indications included are PsA, AS, and Pso

CI: Confidence Interval; N: number of events; PTY: patient-treatment years; SEER: Surveillance, Epidemiology, and End Results Program from the National Cancer Institute (United States); SIR: standardized incidence ratio.

Table 16-30 Observed, Expected number and standardized incidence ratios (SIRs) for malignancies (top 5 except NMSC) compared with the general population in SEER, by treatment group - Entire treatment period Safety Set

Treatment Group	Observed Events	Expected Events*	SIR	95% CI	Exposure (Pat-Yrs)
Skin neoplasms malignant and unspecified					
Any AIN457 75 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 150 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 300 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 300 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Breast neoplasms malignant and unspecified (incl nipple)					
Any AIN457 75 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 150 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 300 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 300 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
Any AIN457 75 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 150 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 300 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 300 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
Any AIN457 75 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 150 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 300 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 300 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
Any AIN457 75 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 150 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 300 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 300 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AIN457 dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

^Expected number of cases: calculated by multiplying the incidence rate and the PTY

The [redacted]

CCI

CCI

Appendix 14).

CCI

A meta-analysis comparing biologics to conventional systemic therapies in psoriasis patients

CCI

CCI

In addition, analyses comparing clinical trial data to US general population (using SEER data)

CCI

The CCI observed while comparing the secukinumab exposed CT population (mainly PsO and PsA patients) to the US general population SEER data has the same limitations as discussed for studies Burmester et al 2013[37]; Leonardi et al 2019[38]).

Therefore, based on available data in the observational studies as well as studies comparing CT data to SEER national registry, no definite conclusion on CCI in biologically treated PsO or PsA patients can be drawn, due to the major limitations discussed above especially the lack of adjustment for important confounding factors.

In the CorEvitas (PsO registry) the CCI for secukinumab was CCI was CCI/100 PTY for both secukinumab (95% CCI) and non-IL-17 biologics (95% CCI) and was <CCI/100 PTY (95% CI CCI) for non-biologic systemic therapies). The observed risk of skin melanoma in secukinumab, other non-IL-17 biologics and the conventional systemic therapy exposed PsO and PsA patients remains similar.

All and all, CCI for secukinumab exposed patients over the suspected correlation between PsO and PsA patients is observed

Table 16-31 Comparison of incidence rates per 100 PYS of malignancies (excluding NMSC)

	N	PYR	Rate	95% CI	
Secukinumab	CCI	CCI	CCI	CCI	CCI
Other non-IL-17 biologic therapies	CCI	CCI			
Non-biologic systemic therapies	CCI	CCI			
Overall	CCI	CCI	CCI	CCI	

Discussion

Patients with psoriasis and other immunological conditions such as PsA and AS are at an increased risk of developing malignancies. AEs of malignancies were reviewed in post-marketing reports, pooled clinical trials, and in the CorEvitas registry, focusing the top five most commonly reported malignancies. Cumulative exposure to secukinumab was significant including more than 1.8 million patient-years in post-marketing experiences, of these, more than CCI of exposure were added during the 3-year reporting interval. Post-marketing reporting rate was lower in this reporting interval than the previous reporting period. This could be due to the COVID-19 pandemic causing restricted access to healthcare system, or due to the largely increased exposure while malignancy reporting might have not yet been kicked off. In any case, even though clinical details were lacking for dosing information and time to onset in most post-marketing cases, when relevant information was provided, causality may be excluded due to pre-existing malignancy or short time to onset. No new safety information was identified from the post-marketing reports received during the interval.

In pooled clinical trials, the cumulative EAIR for all malignancies was low and comparable to the previous reporting period. The overall incidence of malignancies excluding NMSC in clinical trial was comparable with the US general population. CCI

CCI . Upon review of CCI), it was observed that CCI were reported in PsO and PsA trials; and in most cases, pre-existing risk factors were identified for these patients (CCI , CCI). In up to CCI cases the investigators assessed the event as "not suspected" with secukinumab, in the remaining cases reported as "suspected" by investigators yet similar risk factors were identified.

The conclusion of the available information in the literature review aligns on the association between secukinumab /IL-17 inhibitors, other biologics exposed PsO/PsA patients and unexposed patients to malignancy risk are in line with the findings of the clinical and safety databases. Therefore, it can be concluded that there is no observed increased risk in secukinumab-exposed patients CCI .

In the CorEvitas registry, CCI

No relevant publications that associate malignancies occurrence with secukinumab or IL-17 exposed patients was identified during the reporting period.

Conclusion

No new safety information was identified from the post-marketing reports received during the interval, nor from the cumulative CorEvitas registry data. CCI Also available information in literature suggests that there is no increased risk of CCI in patients treated with secukinumab as compared to PsO and PsA subjects (with / without exposure to other Il-17 inhibitors and biologics); therefore, the baseline indication risk cannot be ruled out. The overall characterization of this potential risk is presented in Appendix 9.2.1.

16.3.2.2 Major Adverse Cardiovascular Events (MACE)

Major adverse cardiovascular event as a composite of non-fatal MI, stroke and cardiovascular death is listed as an important potential risk in the Cosentyx RMP. Neither MACE nor its individual events are listed in the CDS as ADRs.

Several studies suggest that patients with chronic inflammatory conditions, including psoriasis, PsA and AS, have an increased cardiovascular (CV) risk. In particular, patients with severe psoriasis show an increased mortality risk, largely attributable to cardiovascular death, driven by the association of psoriasis with known cardiovascular risk factors like hyperlipidemia, obesity, hypertension and diabetes[41]. Severe psoriasis has also been suggested to be independently associated with increased risks of myocardial infarction (MI), stroke and CV death. Epidemiological studies suggest that PsA and AS patients may also have increased rates of major adverse cardiovascular and CV events compared with the general population of the same age and sex. The prevalence of all heart diseases in patients with psoriasis in the US was

estimated at 14.3%, compared with 11.3% for the general US population[42]. In a meta-analysis[43], patients with psoriasis showed an increased overall CV risk compared to healthy controls (risk ratio, RR=1.24; 95% CI 1.18–1. 31).

Although published data suggest a role of IL-17 in vascular inflammation and atherosclerosis, a unified concept on the relevance of IL-17 to human CV disease has yet to be defined. Interleukin-17 is postulated to mediate chronic inflammation, atherosclerosis, and thrombosis, and has been found to infiltrate within vascular plaques and induce proinflammatory response of vascular smooth muscle cells, suggesting its role in the pathogenesis of atherosclerosis. In addition, low serum levels of IL-17 have been shown to be associated with a higher risk of MACE in a retrospective cohort of 981 patients.

Based on published literature [44-69], the rates of MACE per 100 PTY vary between 0.65 to 1.64 for severe Pso and for 0.46 to 0.57 for PsA, compared to the unexposed (general) population, where the corresponding rates were 0.55 and 1.16 for severe Pso; and 0.35 and 0.50 for PsA (information is scarce on AS and mild Pso).

In the assessment report for PSUR (26 Dec 2018 to 25 Dec 2019), the PRAC asked the MAH should continue presenting results from CORRONA/CorEvitas registry for data pertaining to the risk of MACE in next PSURs. This is provided within the results section below.

Methods of evaluation

A search was conducted in the Company Safety Database using MedDRA (version 26.1). Refer to Appendix 8 for search criteria. The focus of analysis aims to determine causality in noteworthy definition cases, and to determine how reporting frequency changed over time.**Noteworthy Case Definition:**

Stroke

- All HCP reported serious cases, OR
- Non-HCP reported cases with supportive imaging results (e.g. computed tomography, magnetic resonance imaging)

Myocardial infarction (MI)

- All HCP reported serious cases OR
- Non-HCP reported cases that meet the following criteria:
  - Characteristic course of cardiac pain PLUS confirmation on electrocardiogram (ECG), or Creatine kinase (CK)-MB elevations or troponin increases.

CV death

All cases from the SOCs of ‘Cardiac disorders’ and ‘Vascular disorders’ with a fatal outcome.

Results

Cumulative reporting rate in the clinical database and other sources

The cumulative EAIR for the entire treatment period for NMQ ‘Major adverse cardiovascular events (MI, stroke, cardiovascular death)’ across all indications, for any AIN457 dose was CCI [redacted]. No significant dose-response effect was identified. Similarly,

the incidence rates remained comparable between the previous PSUR and the current reporting period PSUR [Incidence rate ratio CCI].(Source: Table 18 Change in the incidence rates relative to the last review period of treatment emergent adverse events of special interest by PSUR risks, by treatment group Entire treatment group Safety Set).

Data from the CorEvitas registry is included in below table, per PRAC's request (The MACE cases from CorEvitas are already included in the respective PSURs for assessment). Therefore, MACE events as captured in the CorEvitas registry were summarized cumulatively with data cut-off same as the DLP for this PSUR.

The incidence rate for MACE events in secukinumab-treated patients was comparable to non-IL-17 biologic therapies and non-biologic systemic therapies. No difference was observed between the different biologic therapies for MI, stroke, CV death, or for composite MACE events.

Table 16-32 Data from CorEvitas for MACE: Targeted Adverse Event Table among Patients Exposed to Cosentyx, other Biologic therapies, non-biologic systemic therapies, and Overall (Incidence Rates per 100 Person-Years)

Event	Secukinumab				Non-IL-17 Biologic therapy				Non-biologic Systemic therapy				Overall			
	N	PTY	Rate	95% CI	N	PTY	Rate	95% CI	N	PTY	Rate	95% CI	N	PTY	Rate	95% CI
MACE	CCI	CCI			CCI	CCI			CCI	CCI			CCI	CCI		
Myocardial infarction	CCI	CCI			CCI	CCI			CCI	CCI			CCI	CCI		
Stroke	CCI				CCI	CCI			CCI	CCI			CCI	CCI		
Cardiovascular death	CCI				CCI	CCI			CCI	CCI			CCI	CCI		

CI= Confidence Interval; MACE: Major Adverse Cardiovascular Events; N=Number; PTY= Patient-Treatment-Year

Non-IL-17 Biologic comparators: Adalimumab (Humira), Adalimumab-atto (Amjevita), Adalimumab-abdm (Cyltezo), Etanercept (Enbrel), Etanercept-szzs (Erelzi), Infliximab (Remicade), Infliximab-dyyb (Inflectra), Infliximab abda (Renflexis), Golimumab (Simponi), Certolizumab (Cimzia), Risankizumab (Skyrizi), Tildrakizumab (Ilumya), Guselkumab (Tremfya), Ustekinumab (Stelara).

Non-biologic comparators: Apremilast (Otezla), Cyclosporine, Methotrexate, Acitretin

Company safety database

Reporting interval analysis

The search retrieved a total of CCI cases in this PSUR reporting interval and CCI reported cumulatively with at least any one of the MACE categories: MI, stroke, or/and CV death.

Of the CCI cases retrieved cumulatively, CCI cases initially received in the previous reporting intervals newly reported an event related to MACE as follow-up information during the reporting interval. These CCI cases are included in the analysis along with CCI cases (i.e., CCI cases in total) received during the reporting interval.

The table below illustrates the distribution of cases with PTs related to MACEs, both for the current reporting period and cumulatively.

Table 16-33 Distribution of cases reporting events of 'Major adverse cardiovascular events' during the reporting interval and cumulatively

Report type	Reporting interval^					Cumulative^				
	HCP		Non-HCP		Total	HCP		Non-HCP		Total
	Serious	Non-Serious*	Serious	Non-Serious		Serious	Non-Serious*	Serious	Non-Serious	
CT	19	0	0	0	19	186	0	0	0	186
Lit	4	0	0	0	4	13	0	0	0	13
PMS	CCI									
SR	CCI									
Total	CCI									

HCP: Healthcare professional; CT: Clinical trial; PMS: Post-marketing surveillance; SR: Spontaneous report; Lit: Literature. ^A case is considered serious only if the most relevant event retrieved by the search is serious.

#Interval data comprise cases initially received during the current reporting interval and cases initially received during previous reporting intervals in which an 'event of interest' was newly added as a follow-up information.

* These cases were retrieved by the search criteria but none of these cases involved myocardial infarction (MI) or stroke events. Additionally, the cause of death retrieved through the search criteria for CV death, did not result from a cardiovascular etiology.

Source: Company Safety Database as of 25 Dec 2023

The patients' demographics are presented in the table below Gender and age groups appears to be evenly distributed. There were cases reported for CCI), CCI and CCI), respectively. CCI of the CCI cases were CCI and CCI). The CCI presented with CCI while the CCI had a reported cardiac disorder (n=1), CCI . However, insufficient details were provided for the fetus. The 3rd case was a CCI -months-old CCI patient with history of deep vein thrombosis enrolled in a managed access program (MAP). The patient received secukinumab CCI mg/sc to treat severe skin dermatitis, multiple allergies and metabolic wasting syndrome for two years. Within 14 days after discontinuation of secukinumab, the patient experienced cardiac arrest, brain injury, cerebral ischemia, and subdural hematoma. The clinical

circumstance leading to fatal cardiac arrest was not available, but subdural hematoma would suggest severe head injury. The pre-existing deep vein thrombosis may also be a risk factor.

Table 16-34 Demographic distribution of cases reporting events of 'Major adverse cardiovascular events' during the reporting interval.

Age group	Female	Male	Not reported	Total
Adult (18-69 Y)	CCI			
Elderly (70-199 Y)	CCI			
CCI				
Not reported	17	18	11	46
Total	CCI			

Y: Years

The review of the 911 cases is summarized in the below table. In this review, fatal myocardial infarction (MI) and fatal stroke cases are counted as cardiovascular (CV) deaths. All CV death events are summarized in the table below. No noteworthy cases were identified.

Table 16-35 Comprehensive Analysis of 'Major adverse cardiovascular events' cases received during the reporting interval period

Cases	Non-Fatal MI		Non-fatal Stroke		Both Non-fatal MI and Non-Fatal Stroke		CV Death		Total
	HCP	Non-HCP	HCP	Non-HCP	HCP	Non-HCP	HCP	Non-HCP	
Pre-existing CV risks	CCI								
Limited information $	CCI								
Not MACE*	CCI								
Noteworthy case	CCI								
Total	CCI								

MACE: Major Adverse Cardiovascular Events, HCP: Health Care Professional, CV: Cardiovascular, MI: Myocardial infraction

$ Also contain all Non-HCP cases without diagnostic reports.

* Further explained in this section.

The identified pre-existing cardiovascular risks included ischemic heart diseases, arrhythmia, cerebrovascular conditions, thrombo-embolisms, hypertension, coronary artery disease, myocardial infractions, thrombocyte hyper-aggregation, cerebral artery occlusion, arteriosclerosis, diabetes, dyslipidemia, cigarette smoking, or/and alcoholism and also concomitant use of adalimumab, ustekinumab, tacrolimus, omalizumab, tocilizumab, certolizumab, methotrexate, golimumab.

Causality assessment was precluded in CCI (CCI cases due to lack of relevant clinical details including medical history, concomitant medications, relevant diagnostic reports, details of secukinumab administration, or/and event time to onset. Of these CCI cases, CCI cases (CCI, CCI CCI were lost to follow-up either at initial attempts or after diligent follow-up attempts; in 143 cases (CCI follow-up is ongoing; in CCI cases (CCI %) follow-up was not possible due to insufficient contact information or was not allowed as there was no consent to contact the reporter/ Novartis FU conventions for non-serious events/HA case; in CCI cases (CCI follow-up was complete but no relevant information received.

In CCI %) of the 911 cases, the MACE identified by the search criteria are determined not to be an outcome of cardiovascular conditions. This includes cerebral hemorrhage due to accidental injuries, or the identified cardiovascular death events were not secondary to any cardiovascular condition. Details of all these case IDs and causes of death are presented in Appendix 13.

Table 16-36 Overview of Preferred terms of 'Cardiovascular death'

Preferred terms	Count of Preferred term
CCI	
Total	CCI

Frequency Analysis / Post-marketing Reporting Rate

Frequency analysis from post-marketing cases for MACE is presented in the table below. The reporting frequency for MACE events has been stable since Jun 2016. The reporting rate for this period appeared to be less than the rate observed in the previous reporting intervals.

Table 16-37 Reporting rate of Major Adverse Cardiovascular Events

Report Type	PSUR 26Dec14 – 25Jun15	PSUR 26Jun15 - 25Dec15	PSUR 26Dec15 - 25Jun16	PSUR 26Jun16 - 25Dec16	PSUR 26Dec16 - 25Dec17	PSUR 26Dec17 -25Dec18	PSUR 26Dec18 - 25Dec19	PSUR 26Dec19 - 25Dec20	PSUR 26Dec20 – 25Dec23*	Cumulative (till 25Dec23)
Total Cases (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient exposure in PTY	CCI	[redacted]					[redacted]	[redacted]	[redacted]	[redacted]
Reporting rate (per 100 PTY)	CCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

n: Number; PSUR: Periodic Safety Update Report; PTY: Patient Treatment Years

*Cases considered in the analyses include those initially received during the reporting interval as well as those received in previous reporting intervals in which "Major adverse cardiovascular events" was newly received as a follow-up or cases received in previous reporting interval were unblinded during the reporting period.

Cumulative Data Summary

In the previous analyses on the MACE events, no new safety concern had been raised. Analysis of the current interval cases continue to confirm the previous safety conclusions regarding the MACE events. Further, with significantly increased post-marketing exposure, the reporting rate did not increase. Overall, there has been no new safety information on MACE that would impact the current safety profile of secukinumab.

Discussion

Major adverse cardiovascular events was reviewed in post-marketing reports, in the CorEvitas registry, and in pooled data from CTs. No noteworthy case was identified during the interval. Furthermore, significant amount of the CV death cases was not secondary to a cardiovascular etiology but retrieved by the broad search criteria. The post-marketing reporting rate did not increase (instead, a trend of decrease) after exposure exceeded 1.8 million patient-years. Similarly, the incidence rate in pooled CTs did not change, and no safety signal was identified either. Overall, this review did not identify any new information with respect to MACE. In the CorEvitas registry, cardiovascular comorbidities were common. The real-world incidence rate for MACE in secukinumab-treated patients did not differ from non-IL-17 biologic therapies or from non-biologic therapies.

Conclusion

The data pertaining to the risk of 'Major adverse cardiovascular events' received during the reporting interval are consistent with the known safety profile of Cosentyx. The evaluation revealed no new safety information in regard to this risk. The overall characterization of this identified risk is presented in Appendix 9.2.2.

16.3.2.3 Suicidal ideation and behavior

Background relevant to the evaluation

Suicidal ideation and behavior (SIB) have been a topic of close monitoring since the first Cosentyx PSUR, based on a safety signal related to brodalumab, an IL-17 receptor inhibitor.

Suicidal ideation and behavior has been included as an important potential risk in the Cosentyx RMP, since version 3.0, dated 04 Jan 2018, based on PRAC's request that "*although causality has not been established, SIB meets the criteria as important potential risk because a potential biological mechanism cannot be completely ruled out since the biological role of IL-17 receptor ligands is still largely unknown, and consideration of the potential public health impact*".

Depression, suicidal ideation and cases of completed suicide have been reported in patients with Pso, PsA and AS at higher rates than in the general population. In a cross-sectional study conducted in Italy, 294 dermatological outpatients and 172 inpatients were administered the Patient Health Questionnaire (PHQ) to assess mental health. The overall prevalence of suicidal ideation (as measured by the relevant PHQ item) in the entire group of patients with dermatologic conditions was 8.6% (95% CI 6.2%-11.5%). Suicidal ideation was present in 10% (95% CI 4.4% - 18.7%) of the 80 patients with psoriasis [(70)]. In a UK population-based cohort study conducted using data collected from patients' electronic medical records (General Practice Research Database) from 1987 to 2002, the unadjusted incidences of clinical diagnoses of depression, anxiety, and suicidality in patients with psoriasis were 2.59, 2.09, and 0.09 per 100 person-years, respectively. Comparing data recorded in psoriasis patients with a control group from the general population, a history of suicidality was more common in psoriasis patients than in controls (mild psoriasis 0.71% vs 0.39%, $p<0.001$; severe psoriasis 1.01% vs 0.38%, $p<0.001$). These rates are lower than those reported in other studies cited above, since they are based on clinical diagnoses as recorded in the medical record, rather than on direct assessment through questionnaires. The age- and sex-adjusted hazard ratio (HR) for receiving a clinical diagnosis of suicidality in patients with psoriasis compared with controls was 1.44 (95% CI 1.32-1.57), and the adjusted HR of suicidality appeared to be higher in patients with severe psoriasis (1.51; 95% CI 0.92-2.49) than with mild psoriasis (1.44; 95% CI 1.32-1.57)[(71)].

In patients with psoriatic arthritis, the prevalence of depression and anxiety seems to be even higher than in psoriasis. A study conducted in Canada [(72)] reported a prevalence of depression and anxiety of 36.6% and 22.2%, respectively, in patients with psoriatic arthritis, compared with 24.4% and 9.6% in patients with psoriasis alone.

Rates of suicidal behaviors and treated depression in patients with psoriatic arthritis in comparison to non-psoriatic arthritis patients were recently estimated using the UK Clinical Practice Research Datalink [(73)]. The rates of suicidal ideation and suicide attempt were similar: 0.04 per 100 PY for suicidal ideation in both cohorts, 0.13 (95%CI: 0.10–0.16) vs 0.12 (95% CI: 0.11–0.13) respectively for suicide attempt [IRR 0.99 (95% CI: 0.67–1.47), and 1.07 (95% CI: 0.86–1.34), respectively]. Psoriatic arthritis patients had a slightly higher rate of treated depression compared to non- psoriatic arthritis patients [IRR 1.38 (95% CI: 1.27–1.49)].

A nationwide population-based retrospective cohort study performed in Taiwan reported that AS might increase the risk of a subsequently newly diagnosed depressive disorder; the adjusted HR for depressive disorders in subjects with AS was higher than those of the controls during

follow-up (HR 1.72, 95% CI 1.30-2.26) [74]. Similarly, a population-based cohort study conducted in Sweden found the incidence of physician-diagnosed depression to be higher in AS patients than in the general population seeking healthcare. The incidence of depression in AS patients was 16.8 per 1,000 patient-years, with the standardized depression rate ratio significantly elevated in subjects with AS versus those without (1.63; 95% CI 1.40-1.89) [75].

Method(s) of evaluation

A cumulative search was conducted in the Novartis Safety Database using the MedDRA version 26.1 and is included in Appendix 8.

All cases retrieved via the search were reviewed to make a medical assessment.

Noteworthy case was defined as any well-documented case with no apparent confounding factors and will be presented.

Results

Cumulative reporting rate in the clinical database and other sources

The cumulative EAIR for the entire treatment period for SMQ 'Suicide/self-injury' across all indications, for any AIN457 dose was 0.08 (95% CI 0.05 - 0.11) per 100 PTY. No significant dose-response effect was identified. Similarly, the incidence rates remained comparable between the previous PSUR and the current reporting period PSUR [Incidence rate ratio 1.06 (95% CI 0.6, 1.88)].(Source: Table 18 Change in the incidence rates relative to the last review period of treatment emergent adverse events of special interest by PSUR risks, by treatment group Entire treatment group Safety Set).

In the CorEvitas Registry, IR per 100 PTY was comparable for Secukinumab [CCI), Non-IL-17 biologics [CCI) and for Non-biologic systemic therapies [CCI). No completed suicide case was reported.

Company safety database

The search in the Novartis safety database retrieved a total of 92 cases in this PSUR reporting interval and 315 cases reported cumulatively. Of the 315 cases retrieved cumulatively, 11 cases received significant follow-up information during the reporting interval where cases initially received in previous reporting intervals newly reported an event related to 'Suicidal ideation and behavior' as follow-up information during the reporting interval, and two cases received in previous reporting interval were unblinded during the reporting period.

From the 105 cases, three cases were excluded from this analysis to avoid duplication (*Note: Case* PD *is a continuation of previous PSUR interval case* PD *; case* PD *is continuation of case* PD *(both received during reporting interval), case* PD *is continuation of case* PD *(both received during reporting interval) due to the data contents exceeding the database limit. Hence, the information presented in three case pairs is considered only once under the primary case (marked in bold) and counted as one case in order to avoid duplication).*

Total 102 cases are included in the analysis of cases received during the reporting interval; an outline of the distribution of these cases by report type and seriousness is presented in the table below.

Table 16-38 Overview of 'Suicidal ideation and behavior' in the reporting interval

Evaluation	**Suicidal ideation and behavior**				
ICSR analysis	**Total evaluable:** CCI PMS, CCI SR, 4 CT, 1 lit; and CCI were reported by HCP and 55 were non-HCP cases.				
Severity Analysis*	Of the CCI evaluable cases* during the interval, CCI %) were serious. The proportion of fatal/life-threatening cases during the reporting interval is less CCI %); life threatening case CCI %)] than the proportion of CCI cases cumulatively CCI %); CCI)].				
Count of events	**Fatal**	**Life threatening**	**Other serious**	**Non-serious**	**Total**
Suicidal ideation	0	CCI			
Suicide attempt	0	CCI			
Intentional self-injury	0	0	CCI	0	CCI
CCI		0	0	0	CCI
Depression suicidal	CCI	CCI		0	CCI
Suicidal behaviour	0	CCI		0	CCI
Intentional overdose	0	CCI		2	CCI
Suicide threat	0	0	CCI	0	CCI
Self-injurious ideation	0	0	CCI		
Causality assessment	**Evaluation**				
	CT/NIS	**MAP/PSP**	**SR**	**Lit**	**Total**
Noteworthy	0	0	0	0	0
Suspected (CNBR)	0	0	CCI	0	1
Not suspected (confounded/alternative explanation)	4/10	CCI		1	CCI
Not assessable	0/2	CCI	CCI	0	CCI
Frequency Analysis	The reporting rate of the current PSUR reporting interval is less than the previous PSUR interval and comparable to the cumulative period. No new safety findings could be identified (refer Table 16-39).				
Reporting disproportionality	No reporting disproportionality has been identified in the reporting period in the safety database (EMPIRICA; EBO5 0.201) or the external databases EVDAS.				

CNBR: Cannot Be Ruled Out, CT: Clinical Trial, EVDAS: Eudravigilance Data Analysis System, HCP: Health Care Professional; ICSR: Individual Case safety Report; Lit: Literature; MAP: Managed Access Program; NIS: Non-Interventional Study; PMS: Post-Marketing Study, PSP: Patient Support Program; PSUR: Periodic Safety Update Report, SR: Spontaneous Report

Evaluation	Suicidal ideation and behavior

*Cases considered in the analyses include those initially received during the reporting interval as well as those received in previous reporting intervals in which an 'event of interest' was newly received as a follow-up or cases were unblinded during the reporting interval

Reporting interval analysis

The total CCI cases retrieved during the interval were analyzed and summarized below (of these CCI cases, CCI cases reported more than one PT relevant to event of interest):

- Of the CCI cases reporting CCI events of 'CCI ' (CC PMS and CC SR):
  - In CCI case the role of secukinumab was suspected considering plausible temporal association. Time to onset was 211 days since first dose and secukinumab was received until one month prior to the event. Although there are insufficient details in the case related to medication history and concomitant medications; the role of secukinumab could not be ruled out. It was unknown if an autopsy was performed.
  - CCI cases had confounding factors: CCI cases were confounded by medical history of psychiatric issues and alcohol intake and/or concurrent condition of depression and attention deficit hyperactivity disorder and the remaining case was confounded by concomitant drug methylprednisolone. Autopsy was not performed in one case and was unknown if performed in remaining two cases.

    Note: One of these cases, also reported additional events of Suicide attempt' and 'Depression Suicidal'.
  - The remaining case had partial or lack information; hence meaningful assessment was precluded. It was unknown if an autopsy was performed.
- Of the CCI cases reporting CCI events of **'intentional overdose', 'intentional self-injury' and 'self-injurious ideation'** (CCI PMS and CC SR)**:**
  - CCI cases had confounding factors including concomitant depression, anxiety, panic attacks, marijuana use, physical abuse from wife and/ or historic conditions of anxiety, major depressive disorder, suicidal ideation, suicide attempt, post-traumatic stress disorder and cutting herself in three cases; underlying psoriasis and concurrent condition of depression in one case. CCI case was confounded by concomitant drugs: clonazepam. The remaining two cases were confounded by both concurrent condition of depression and concomitant drugs: amitriptyline, sertraline and citalopram.

    Note: One of these cases, also reported additional events of 'Suicidal Ideation'.
  - The remaining CCI cases had partial information that limited full assessment; hence remained as not assessable.
- Of the CCI cases reporting CCI events of **'Depression suicidal'**, **'Suicidal behaviour'** and **'Suicidal ideation'**. One case of Depression suicidal is discussed above with 'CCI '. Another case of suicidal ideation is discussed above with self-injurious ideation. Of the remaining CCI cases (CC CT, CCI PMS, CCI SR and CC literature report) reporting CCI events:
  - A total of CCI cases had confounding factors: Out of these CCI cases, CCI cases were confounded by underlying indication of psoriasis/ ankylosing spondylitis flare/relapse and/or delayed drug delivery. Nine cases were confounded by concurrent conditions (e.g. depression, anxiety, etc). Further, nine cases were confounded by concomitant drugs such as clonazepam, mirtazapine, amitriptyline, duloxetine, CCI

alprazolam, celecoxib, hydromorphone, lisdexamfetamine, adalimumab and zolpidem. Five cases were confounded by both concomitant drugs clonazepam, duloxetine, fluoxetine, lorazepam and mitrazipine and concurrent conditions. Further, two cases were confounded by underlying indication of psoriasis/ ankylosing spondylitis and concomitant drugs amitriptyline, carbamazepine and gabapentin. In the remaining case onset latency was implausible as time to onset of event was one day after initiation of secukinumab treatment.

Note 1: CCI of these cases, also reported additional event of Suicide attempt'.

Note 2: CCI cases (PT Suicidal Ideation) were reported from the CorEvitas Registry during the reporting interval.

- The remaining CCI cases had partial information that limited full assessment; hence remained as not assessable. Out of the CCI cases, CCI cases were lost to follow up, in CCI cases follow-up is denied or not allowed and CCI case had insufficient reporter contact details. Hence it is unlikely to receive any new or missing information on the event. In two cases follow up is complete but no relevant information is received. Follow up is ongoing in one case. In the remaining two cases, no information regarding follow-up is available.

- Of the CCI cases reporting CCI events of **'suicide attempt'** and **'Suicide Threat'.** CCI case of 'suicidal attempt' was discussed above with 'Completed suicide'. CCI more CCI of 'suicidal attempt' was discussed above with 'Suicidal ideation'. The remaining CCI cases reporting CCI events are discussed below (CCI CT, CCI PMS and CCI SR):
  - A total of CCI cases, had confounding factors that included: CCI cases were confounded by concurrent conditions miscarriage, depression, anxiety, tinnitus affecting patient mentally; CCI cases had both concurrent conditions depression, suicide attempts, alcohol use and concomitant drugs clonazepam, duloxetine, bupropion and gabapentin as confounding factors; CCI cases were confounded by concomitant drugs: diphenhydramine and adalimumab. The other CCI remaining cases, one case was confounded by underlying indication of ankylosing spondylitis and concurrent condition of mental disability and the CCI case was confounded by concurrent condition of mental disorder but was concomitantly receiving indomethacin.
  - The remaining CCI cases had partial information that limited full assessment.

Frequency Analysis / Post-marketing Reporting Rate

The reporting rate of 'Suicidal ideation and behavior' since first PSUR is compared in the table below. The reporting rate for this period is less than the rate observed in the previous and comparable to cumulative reporting interval.

Table 16-39 Suicidal ideation and behavior: comparison of reporting rates in PSUR periods and cumulative

	PSUR 26Dec14 - 25Jun15	PSUR 26Jun15 - 25Dec15	PSUR 26Dec15 - 25Jun16	PSUR 26Jun16 - 25Dec16	PSUR 26Dec16 - 25Dec17	PSUR 26Dec17 - 25Dec18	PSUR 26Dec18 - 25Dec19	PSUR 26Dec19 - 25Dec20	PSUR 26 Dec 20 - 25 Dec 23*	Cumulative (till 25 Dec 2023)
Cases (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exposure (PTY)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reporting rate (per 100 PTY)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

n: Number; PSUR: Periodic Safety Update Report; PTY: Patient Treatment Years.
*Cases considered in the analyses include those initially received during the reporting interval as well as those received in previous reporting intervals in which "Suicidal ideation and behavior' was newly received as a follow-up or cases received in previous reporting interval were unblinded during the reporting period.

Cumulative data summary

The above-mentioned search retrieved [redacted] cases cumulatively (excluding [redacted] cases duplicate cases), of which [redacted] cases were received in the reporting interval analysis and have been discussed above. The remaining [redacted] cases were reviewed in the previous PSURs. Overall, the new information reported did not reveal any changes to previous case assessments or the overall risk.

Discussion

Patients with psoriasis, psoriatic arthritis and ankylosing spondylitis have higher rate of depression, anxiety, suicidal ideation and completed suicide compared to the general population[70]. All cases analyzed during the interval were either confounded ([redacted]%]) or had limited information ([redacted]%]) that precluded assessment; except [redacted] case assessed as suspected ([redacted] considering temporality. No noteworthy case was identified using the MedDRA version 26.1 (SMQ) 'Suicide/self-injury'. However, from the cases with sufficient information, and on an aggregate level, there was no clinical pattern suggestive of a causal association. Review of data from non-interventional (including from CorEvitas Registry) and clinical trials also did not reveal any new safety information. Additionally, the post-marketing reporting rate does not indicate any increased frequency of SIB. No disproportionality is observed in Empirica/EVDAS and no imbalances are noted in the CT incidence.

Conclusion

The overall evaluation of the data indicates neither an increased risk nor a causal relationship of the risk of SIB with Cosentyx. Most the cases received during the interval were assessed to be not suspected/ not assessable. An update to the CDS/SmPC is not warranted. Data from multiple sources do not suggest an increased risk or causal association. 'Suicidal ideation and behavior' have been followed closely for over a period of about 17 years since DIBD and about nine years since IBD with no evidence of significant risk or changes in the reporting rates. The review of the data received during the reporting interval did not provide any new information pertaining to SIB. The MAH will continue monitoring in the subsequent PSURs. For a complete characterization of the risk, please refer to Appendix 9.2.3.

16.3.2.4 Hepatitis B reactivation

Background relevant to the evaluation

Hepatitis B reactivation is an important potential risk in the RMP. Reactivation of hepatitis B virus (HBV) infection can occur, spontaneously or upon immunosuppression, in chronic active and chronic inactive carriers. It can also rarely occur in patients with resolved or occult infections. In chronic inactive carriers or in patients with resolved infection, spontaneous reactivation is not uncommon, reported in one study to vary between 6.3% in a one-year to 15% over a four-year period[76]. Reactivation rates are higher (around 50%) after the administration of chemotherapy and anti-TNF[77]. Hence, the use of anti-TNF in patients with psoriasis who are HBV carriers is usually not recommended and antiviral prophylaxis may be required. Moreover, hepatitis B reactivation has been reported in patients treated with other immunosuppressive drugs and biological treatments. On 30 Mar 2023 Novartis received notification from the Taiwanese HA requesting all the MAHs of IL-17 inhibitors (including COSENTYX, TALTZ and LUMICEF) to update the local label Warning and precaution section with HBV reactivation language suggested by the authority (see Section 3). Across the registration program in psoriasis, pediatric psoriasis, PsA, AS, JIA and HS patients, no cases of hepatitis B reactivation were reported.

Methods of evaluation

A search was conducted for the reporting interval in the Company Safety Database using the MedDRA (version 26.1) and is included in Appendix 8.

Note: A manual review was performed to include cases in which only reactivation Hepatitis B was reported in the current PSUR.

Noteworthy case was defined as a case of hepatitis B, for which reactivation can be characterized (e.g., by serology tests).

Results

Cumulative reporting rate in the clinical database

The cumulative EAIR for the entire treatment period for HLT 'hepatitis viral infections' across all indications, for any AIN457 dose was CCI (95% CI CCI) per 100 PTY. With no change in the incidence rates despite the number of patients in clinical trials. None of the CCI

cases from this HLT corresponded to true Hepatitis B virus reactivation.(Source: Table 18 Change in the incidence rates relative to the last review period of treatment emergent adverse events of special interest by PSUR risks, by treatment group Entire treatment group Safety Set).

Company safety database

Reporting interval

The above-mentioned search strategy retrieved a total of CCI cases during the reporting interval and CCI cases reported cumulatively.

Of the CCI cases retrieved cumulatively no case reported any significant follow up information.

On the manual review of the CCI cases, four (3 Lit and CCI SR) cases of suspected hepatitis B reactivation was identified and a review of these four cases HBV-R is presented in the table below:

A review of the CCI cases HBV-R is presented in the table below:

Table 16-40 Hepatitis B reactivation cases

Case ID **Age/ Gender/ Indication/ Reporter's causality/ Report type**	**Time to onset (days)*/ Action taken (drug disposition)/ Intervention or treatment required/** **Clinical outcome/** **Dechallenge/rechallenge information**	**Concomitant medications/ Relevant medical history/ Seriousness**	**HBV clinical and diagnostic data** **Narrative synopsis** ***Novartis causality assessment***
PD [redacted] PD Y/PD [redacted] Psoriatic arthropathy/ Not assessable/ SR	NR/NR/NR/Complete Recovery/Unk	Methotrexate; Leflunomide; Sulfasalazine; Cyclosporine; Neurontin; Cymbalta;Tramadol/ Oligoarthritis; Synovial disorder; Fasciitis; Plantar fasciitis; Psoriatic arthropathy; Osteopenia; Diarrhoea; Bell's palsy; Acute sinusitis; Urinary tract infection /Serious	CCI [redacted]
PD [redacted] NR/PD [redacted] Psoriasis/ Suspected/Lit	336/Drug stopped/ Entecavir/NR/Unknown	NR/NR/Serious	CCI [redacted]

Case ID **Age/ Gender/ Indication/ Reporter's causality/ Report type**	**Time to onset (days)*/ Action taken (drug disposition)/ Intervention or treatment required/** **Clinical outcome/** **Dechallenge/rechallenge information**	**Concomitant medications/ Relevant medical history/ Seriousness**	**HBV clinical and diagnostic data** **Narrative synopsis** ***Novartis causality assessment***
			CCI [redacted]
PD [redacted] NR/NR Axial spondyloarthritis/ Suspected/Lit	NR/NR/NR/NR/Unkown	NR/NR/Serious	CCI [redacted]

Case ID **Age/ Gender/ Indication/ Reporter's causality/ Report type**	**Time to onset (days)*/ Action taken (drug disposition)/ Intervention or treatment required/** **Clinical outcome/** **Dechallenge/rechallenge information**	**Concomitant medications/ Relevant medical history/ Seriousness**	**HBV clinical and diagnostic data** **Narrative synopsis** ***Novartis causality assessment***
PD [redacted] NR/NR Axial spondyloarthritis/ Suspected/Lit	NR/NR/NR/NR/Unkown	NR/NR/Serious	CCI [redacted]

ALT: Alanine Transaminase; AST: Aspartate aminotransferase; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B reactivation; Lit: Literature; NR: Not reported; TTO: Time to Onset; Unk: Unknown

Frequency Analysis / Post-marketing Reporting Rate

The reporting rate of 'Hepatitis B reactivation' since PSUR 1 is compared in the table below. As observed to-date, the potential risk of hepatitis B reactivation is extremely low.

Table 16-41 Hepatitis B reactivation: comparison of reporting rates in PSUR periods and cumulative

	PSUR 26Dec 14 - 25Jun 15	PSUR 26Jun 15 - 25Dec 15	PSUR 26Dec 15 - 25Jun 16	PSUR 26Jun 16 - 25Dec 16	PSUR 26Dec 16 - 25Dec 17	PSUR 26Dec 17 - 25Dec 18	PSUR 26Dec 18 - 25Dec 19*	PSUR 26Dec 19 - 25Dec 20+	PSUR 26Dec 20 - 25Dec 23+	Cumulative (till 25 Dec23)
Cases (n)*	0	0	0	0	0	CCI	CCI	CCI	CCI	CCI
Exposure (PTY)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CCI	[redacted]	[redacted]	[redacted]	[redacted]
Reporting rate (per 100 PTY)	CCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

n: HBV: Hepatitis B reactivation; Number; PSUR: Periodic Safety Update Report; PTY: Patient Treatment Years.

*Cases considered in the analyses include those initially received during the reporting interval as well as those received in previous reporting intervals in which 'Hepatitis B reactivation' was newly received as a follow-up or secukinumab was newly added as co-suspect drug to a case that contained an event of 'Hepatitis B reactivation' during the current reporting interval.

Note: The cumulative numbers may no add the previous numbers as there is change the approach for case analysis focusing only on true HBV Cases

Cumulative data summary

The above-mentioned search criteria retrieved CCI cumulatively. On the manual review of these cases cumulatively CCI cases of suspected of hepatitis B reactivation, of which four cases are analyzed in the reporting interval.

Of the remaining CCI cases reviewed in the previous PSURs, none reported any significant follow-up information during this reporting interval, hence not analyzed further.

Discussion

Hepatitis B reactivation is an important potential risk in the RMP. Based on the cumulative analysis, Novartis' position is that the identified CCI cases reporting reactivation do not provide any conclusive evidence that confirms the association between HBV-R and exposure to secukinumab. Of note, cumulatively in CCI cases, the patients had a history of biologic use with ustekinumab, etanercept or adalimumab, for which a risk of HBV-R is included in the prescribing information (Warnings and Precautions and ADR sections).

During the reporting period, only CCI [redacted]

CCI [redacted] Furthermore, the evidence published by this author, shows that most of the patients did not experience reactivation (reactivation reported in n=6/37, 16.2%) despite that all these 37 patients were at high risk of reactivation. Moreover, among these six patients, three had chronic HBV infection and received anti-HBV prophylaxis, two had chronic HBV infection but did not receive anti-HBV prophylaxis, and one patient had occult HBV infection and did not receive antiviral prophylaxis(78).

No new evidence from the literature or other sources implicating a definitive association of secukinumab or other IL-17 inhibitors with the event of HBV-R has been identified in the reporting period.

Lastly, it is important to note that with an extensive patient exposure from both post-marketing (more than 1.8 million patient-years) and clinical studies (+25,000 patients), only CCI reported cases of HBV-R were identified and none of them were reported in clinical studies. Based on the current analysis, Novartis' position is that CCI cases during the reporting interval do not support causal association of HBV-R and secukinumab, and no change benefit / risk profile for this important potential risk is observed.

Conclusion

The data pertaining to the risk of 'Hepatitis B reactivation' received during the reporting interval is consistent with the known safety profile of Cosentyx. The evaluation revealed no new safety concerns in regard to this risk. No update to the risk characterization is deemed to be required. The overall characterization of this potential risk is presented in Appendix 9.2.4.

16.3.3 New information on other identified risks not categorized as important

There are no identified risks not categorized as important for Cosentyx.

16.3.4 New information on other potential risks not categorized as important

There are no potential risks not categorized as important for Cosentyx.

16.3.5 Update on missing information

16.3.5.1 Fetal exposure in utero

Background relevant to the evaluation

'Fetal exposure in utero' is considered as missing information in the Cosentyx RMP as there is no adequate data from use of Cosentyx in pregnant women. According to the CDS, animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development. Because animal reproduction studies are not always predictive of human response, Cosentyx should be used during pregnancy only if the benefits clearly outweigh the potential risks.

It is not known whether secukinumab is excreted in human milk. As immunoglobulins are excreted in human milk, caution should be exercised when Cosentyx is administered to a woman who is breast-feeding.

Method(s) of evaluation

The details of the search criteria used to retrieve cases are included in Appendix 8.

Noteworthy case definition: The medical review will focus on cases with abnormal pregnancy outcomes, with focus on HCP confirmed diagnosis of fetal developmental anomalies, fetal malformation, and/or birth defects associated with exposure to Cosentyx.

Results

Company safety database

Reporting interval analysis

The search in the CCI [redacted] cases reported cumulatively.

Of the CCI cases reported cumulatively, CCI cases (CCI during reporting interval) did not contain any information related to pregnancy or breast feeding and are retrieved due to broad search criteria, in another CCI cases (four during reporting interval), the pregnancy was reported around 1-2.5 years after last dose of Cosentyx and hence not considered related to Cosentyx. All these CCI cases were not further discussed. In addition, 16 cases (all reporting interval) were continuation of other cases due to narrative character limit, hence considered as a single case. Of the remaining CCI cases, in 16 cases initially received in previous reporting intervals had newly reported information related to 'Fetal exposure in utero' as follow-up information during the reporting interval and are analyzed along with the reporting interval cases.

An overview of the reporting interval (CCI and cumulative (CCI cases is presented is presented in the table below by case type and seriousness (based on the seriousness of the most relevant event pertaining to the topic of fetal exposure in utero).

Table 16-42 Distribution of cases reporting events of 'Fetal exposure in utero' during the reporting interval and cumulatively

Report type	Reporting interval					Cumulative				
	HCP		Non-HCP		Total	HCP		Non-HCP		Total
	Serious	Non-serious	Serious	Non-serious		Serious	Non-Serious	Serious	Non-serious	
SR	CCI [redacted]									
PMS	CCI [redacted]									
Literature	3	3	0	0	6	12	26	0	0	38
CT	4	15	0	0	19	45	213	0	0	258
Total	CCI [redacted]									

Source: Company Safety Database as of 25 Dec 2023

CT: Clinical trials; HCP: Health care professional; PMS: Post marketing surveillance; SR: Spontaneous report

Reporting interval analysis

Of the 1,198 cases, 1,160 cases reported exposure during pregnancy, 68 cases reported exposure during breastfeeding (including 30 cases reported both pregnancy and breastfeeding).

Exposure during pregnancy

These 1,160 cases described 1,070 pregnancies, of which 955 were after maternal exposure and 114 after paternal exposure and one pregnancy was after both maternal and paternal exposures.

The overview of the pregnancy outcomes in these 1,070 pregnancies are presented below.

Table 16-43 Overview of the pregnancy outcomes

Pregnancy outcome	Count
CCI	

*Limited information available regarding the nature or etiology of abortion
**Includes CCI pregnancies where the outcome of the pregnancy is pending
#Includes CCI pregnancy where one of the twin babies was born, and CCI was reported. Counted under both outcomes.
##CCI pregnancy reported exposure during first trimester

The pregnancies reporting adverse outcomes are analyzed below.

Abortion

- Of the CCI pregnancies reporting spontaneous abortion,
  - In CCI pregnancies the spontaneous abortion was not related to Cosentyx and was confounded by an accident (slipping from bed), concurrent uterine fibroids, ectopic pregnancy, endometrioses, heterozygous factor 5 leiden mutation, autoimmune disease, hypothyroidism, and multiple sclerosis.; co-suspect adalimumab; patient's medical

history of abortion, infertility, and underlying risk factors of advanced maternal age, nicotine use and obesity.

- In CCI pregnancies, limited information regarding mother's medical and obstetric history, concomitant medications, event onset latency precluding complete medical assessment. Of these CCI was lost to follow-up or reporter consent was not available.

- Of the eight pregnancies reporting voluntary termination of pregnancy, in CCI cases, the pregnancy was terminated due to CCI , in the five cases, reason for abortion was not specified. These cases had limited information precluding complete medical assessment and five cases were lost to follow-up or reporter consent was not available.
- In CCI pregnancies, the details regarding the nature and etiology of abortion were not provided; and were lost to follow-up as reporter consent was not available.

CCI

- In CCI pregnancy, CCI
- In CCI pregnancy, the fetal death occurred due to cervical dilation and was not related to Cosentyx.
- In one pregnancy, CCI was reported due to CCI (unspecified) and this case was lost to follow-up.
- In CCI pregnancies, limited information regarding one or more factors of mother's medical and obstetric history, concomitant medications, event onset latency, any abnormalities in baby during birth, and other investigation details precluded complete medical assessment. Of these eight pregnancies, four were lost to follow-up or reporter consent was not available.

CCI

- Of the CCI cases reporting CCI in the newborn
  - In CCI cases, details of the CCI were not reported.
  - In one case, CCI of the baby was observed at 37 gestation weeks of gestation; delivered via C-section. The CCI ests conducted post birth were normal and no developmental delays or other relevant illness was observed.
  - In CCI pregnancy, CCI was reported but limited information available regarding onset of events, relevant medical and obstetric history, risk factors and concomitant medications, precluded complete medical assessment. This case was lost to follow-up.
- CCI pregnancies reporting CCI However, limited information available and lost to follow-up precluded complete medical assessment.
- In CCI) was CCI . CCI with sequelae from CCI . No further details were available.

CCI

- In CCI pregnancies, CCI of the baby was reported.

- In CCI pregnancies, the CCI was due to CCI .
- In four pregnancies, the pre-mature birth of baby was confounded by the mother's underlying conditions such as thyroid disorder, hypertension, obesity, maternal age and multifetal pregnancy.
- In CCI pregnancies, limited information regarding one or more factors of mother's medical and obstetric history, concomitant medications and event onset latency precluded complete medical assessment. Of these CCI pregnancies, CCI lost to follow-up or reporter consent was not available.

- In CCI case, CCI birth of the baby was reported. No congenital or developmental disorders noted.

Other adverse events in the baby

- Of the CCI pregnancies reporting other adverse events in newborn
  - In four pregnancies, the events of CCI re confounded by the use of milk thickeners, poor feeding effort by the newborn, concomitant use of ibuprofen, salbutamol and complications during labor.
  - In CCI pregnancies, limited information regarding one or more factors of mother's medical and obstetric history, concomitant medications, event onset latency, and other investigation details precluded complete medical assessment. Of these seven pregnancies, five were lost to follow-up or reporter consent was not available.

Exposure during breastfeeding

- Of the CCI cases reporting exposure via breastfeeding
  - In CCI cases, no adverse events were reported.
  - In CCI cases, CCI was reported (CCI cases were linked [mother-baby]). Limited information regarding medical history, concomitant medications, outcome of event precludes complete assessment. These cases were lost to follow-up.
  - In CCI was reported. The patient received Cosentyx one week before pregnancy hence, the event was considered not related to Cosentyx.

Cases with pending pregnancy outcome during previous PSUR reporting interval

In CCI cases, below follow-up information regarding pregnancy outcome was reported during the reporting interval.

- Live birth was reported in CCI cases.
  - In CCI cases, normal newborn was reported.
  - In CCI cases, one was CCI birth, and CCI newborn CCI was reported. No further details were reported in these cases.
- CCI cases were lost to follow-up and no further follow-up information is expected in these cases.

Discussion and conclusion

Cosentyx is not recommended for use during pregnancy unless the potential benefits of using Cosentyx outweigh the potential risks. The information received during the reporting interval is limited and the analysis of the available data does not reveal any new safety information. A cumulative overview of this missing information is presented in Appendix 9.3.1.

There has been no change in the risk profile / missing information; it will continue to be reviewed in the next PSUR.

16.3.5.2 Long-term safety data

Long-term safety data continue to be collected in several extension studies on the authorized indications (including ongoing studies CAINA2311 pediatric PsO, CAINF2311E1 pediatric PsA, CAINM2301E1 HS [adults] and completed studies CAINA2310 pediatric PsO CAIN2315 AS [adults]). The review of the interval data did not change the previous safety conclusions on these long-term studies. There has been no change in the benefit risk profile / missing information; it will continue to be reviewed in the next PSUR.

Details regarding Long term efficacy are presented in Section 7.3 and Section 17.

A cumulative overview of this missing information is presented in Appendix 9.3.2

16.4 Characterization of risks

Important identified and potential risks are characterized and missing information is described below based on the totality of information available and cumulative safety experience.

Based on the risk evaluation presented in Section 16.3, the risk characterization of the following identified and potential risks and the missing information does not require an update and therefore is aligned with the content of RMP version 11.1]. The corresponding tables of these risk characterizations have been included in Appendix 9:

Important identified risks:

- Infections and infestations
- Hypersensitivity

Important potential risks

- Malignant or unspecified tumors
- Major Adverse Cardiovascular Events (MACE)
- Suicidal ideation and behavior
- Hepatitis B reactivation

Missing information

- Fetal exposure in utero
- Long-term safety data

No special actions have been taken or are being proposed for the above risks and missing information. These topics will be evaluated again in the next PSUR.

In addition, for the important identified risk Neutropenia, for the important potential risk Inflammatory bowel disease and Interaction with Live vaccine and the missing information Patients with CCI or CCI, no update to the characterization is warranted, it is proposed to no longer review these risks and missing information in subsequent PSURs unless a new signal arises as presented in the following sub-sections are presented.

16.4.1 Important identified risks

16.4.1.1 Neutropenia

Based on the new information and risk evaluation presented in Section 16.3, the characterization of the risk did not require an update; table below reflects the previous as well as current risk characterization. The known risk profile remains unaltered and valid.

Table 16-44 Characterization of Neutropenia

Parameter	Updated	Detailed information
Frequency	No	The post-marketing reporting rate and cumulative reporting rate from the clinical database do not indicate any increase in frequency.
Potential mechanism(s)	No	Reductions in peripheral neutrophil counts may be a possible effect of systemic IL-17A blockade, based on roles of IL17A in innate immunity and neutrophil biology.
Reversibility	No	Grade 3 and 4 neutropenia was rarely reported; in most cases, neutropenia was mild and transient, not requiring secukinumab discontinuation
Risk factors	No	Neutropenia is associated with an increased risk of infections, and severe psoriasis is recognized as a risk factor for infections. The use of systemic immunomodulatory therapies in psoriasis does seem to increase the risk of infections, although the individual long-term safety profiles are still being investigated in real-world use.
Preventability	No	Listing neutropenia in the label as an adverse drug reaction will allow for early detection, and thus mitigate the risk. This appears to be a standard risk for other biologics i.e. anti TNFs (including Enbrel (etanercept)/Humira (adalimumab)).
Strength of evidence	No	Current evidence is based on a clinical data, literature, and post marketing experience.
Impact on the individual patient	No	Potential impact on the individual patient should be carefully evaluated and managed by the treating physician on a case by case basis.
Impact on public health	No	The potential public health impact is considered to be low since the difference in the occurrence of neutropenia between secukinumab and control groups in clinical trials is small. Moreover, no clinically significant adverse events were associated with the development of neutropenia in secukinumab psoriasis clinical trials, and no patients discontinued the study due to neutropenia.

Parameter	Updated	Detailed information
Impact on the benefit-risk balance	No	The new information received in the reporting interval does not change the benefit-risk profile of Cosentyx

Sources: Risk Management Plan version 7.1, Core Data Sheet version 3.4
IL: InterLeukin; TNF: Tumor Necrosis Factor

Actions taken or proposed

Based on the results of the risk evaluation performed in Section 16.3 and a reinforced, unchanged risk profile, no special actions have been taken during the reporting period for this risk. Provided that neutropenia has been removed from the list of safety concerns on 06 Apr 2021, RMP v.8.1, that no change on secukinumab risk-benefit balance has been identified, nor implications for public health are deemed due to this risk; and that it is well characterized and documented in the CDS; the MAH proposes to consider this risk as identified risk not categorized as important and no longer review it in subsequent PSURs unless a validated signal arises.

16.4.2 Important potential risks

16.4.2.1 Inflammatory bowel disease

Based on the new information and risk evaluation presented in Section 16.3, the characterization of the risk did not require an update; table below reflects the previous as well as current risk characterization. The known risk profile remains unaltered and valid.

Table 16-45 Characterization of Inflammatory bowel disease

Parameter	Updated	Detailed information
Frequency	No	The post-marketing reporting rate and cumulative reporting rate from the clinical database do not indicate any increase in frequency.
Potential mechanism(s)	No	The current literature is not conclusive. There is evidence to suggest that IL-17 may have a protective role in the gut mucosa against bacterial infection from exposures through the alimentary tract.
Reversibility	No	There is no information on reversibility
Risk factors	No	The majority of the cases reported had a history of IBD. Since IBD is a chronic recidivating condition, it cannot be concluded that these patients had an undue additional risk compared to their background incidence of flares.
Preventability	No	A warning on IBD exists in the Core Data Sheet/SmPC which will increase the level of awareness among physicians and patients to properly monitor and manage patients with active IBD.
Strength of evidence	No	Current evidence is based on clinical data, literature, and post marketing experience.
Impact on the individual patient	No	Due to the severity of the condition, the impact on individual patients may be significant, potentially requiring chronic immunosuppressive medications and surgical interventions.
Impact on public health	No	Because of the low overall incidence of IBD related adverse events (which may or may not exceed the background incidence of IBD in

Parameter	Updated	Detailed information
		psoriasis patients), the potential public health impact is considered to be low.
Impact on the benefit-risk balance	No	There is no change to the existing benefit risk profile of Cosentyx based on the information retrieved in this reporting interval.

Sources: Risk Management Plan version 7.1, Core Data Sheet version 3.4

IBD: Inflammatory Bowel Disease; IL: InterLeukin; SmPC: Summary of Medicinal Product Characteristics

Actions taken or proposed

Based on the results of the risk evaluation performed in Section 16.3 and a reinforced, unchanged risk profile, no special actions have been taken during the reporting period for this risk. Provided that IBD has been removed from the list of safety concerns on 06 Apr 2021, RMP v.8.1, that no change on secukinumab risk-benefit balance has been identified, nor implications for public health are deemed due to this risk; and that it is well characterized; the MAH proposes to consider this risk as not categorized as important and to no longer review in subsequent PSURs unless a validated signal arises.

16.4.2.2 Interaction with live vaccines

Based on the new information and risk evaluation presented in Section 16.3, the characterization of the risk did not require an update; table below reflects the previous as well as current risk characterization. The known risk profile remains unaltered and valid.

Table 16-46 Characterization of Interaction with live vaccines

Parameter	Updated	Detailed information
Frequency	No	Not applicable, since there have been no post-marketing cases of interactions with live vaccines.
Potential mechanism(s)	No	Immunomodulatory nature of secukinumab may reduce immune responses to live attenuated vaccines or may render a recipient prone to infectious manifestations (including secondary transmission) resulting from attenuated live vaccines.
Reversibility	No	No data available
Risk factors	No	No data available
Preventability	No	Patients receiving live vaccines are excluded from secukinumab clinical trials. The ‘Warnings and precautions’ section of Core Data Sheet suggests that live vaccines should not be given concurrently with secukinumab.
Strength of evidence	No	Current evidence is based on a clinical data, literature, and post marketing experience.
Impact on the individual patient	No	Primary infectious manifestations in the recipient of live attenuated vaccines.
Impact on public health	No	Secondary transmission of infection from microbial strains in live attenuated vaccines from the recipient to others

Parameter	Updated	Detailed information
Impact on the benefit-risk balance	No	The new information received in the reporting interval does not change the benefit-risk profile of Cosentyx

Sources: Risk Management Plan version 7.1, Core Data Sheet version 3.4

Actions taken or proposed

Based on the results of the risk evaluation performed in Section 16.3 and unchanged risk profile, no special actions have been taken during the reporting period. Provided that interaction with live vaccines has been removed from the list of safety concerns on 06 Apr 2021, RMP v.8.1, that no change on secukinumab risk-benefit balance has been identified, nor implications for public health are deemed due to this risk; and that it is well characterized; the MAH proposes to consider this potential risk as not categorized as important and to no longer review in subsequent PSURs unless a validated signal arises.

16.4.3 Missing information

16.4.3.1 Patients with CCI [redacted]

The review of the data did not reveal any new trends/patterns, and the safety profile in this sub-group of patients was found to be similar to the existing safety profile established for secukinumab. There was no new safety information from ICSRs, no new relevant safety information from CTs, and no new relevant literature or epidemiology data.

Actions taken or proposed

Based on the results of the update of the missing information presented in Section 16.3, no special actions have been taken or are being proposed. The current CDS of Cosentyx is deemed adequate and warrants no change. Therefore, it is proposed to no longer review this topic in subsequent PSURs unless a new signal arises in relation to these events.

16.5 Effectiveness of risk minimization

Routine risk minimization activities are in place and evaluated on an ongoing basis by signal detection and periodically in PSURs by evaluating the frequency and severity of all risks as per the RMP. The findings from the safety review performed in this PSUR do not warrant additional risk minimization activities; the current risk activities are considered appropriate and effective.

17 Benefit evaluation

17.1 Important baseline efficacy and effectiveness information

Information on both efficacy and effectiveness of product at the beginning of the reporting interval is provided in the following. This information forms the basis for the benefit-evaluation.

Psoriasis

Efficacy for psoriasis was demonstrated in the phase III pivotal studies that have been described in previous PSURs. Additional data have been generated demonstrating superiority of the

secukinumab 300 mg Q2W dose over the 300 mg Q4W dose, as well as efficacy in pediatric population.

The CAIN457A2324 study demonstrated superiority of the secukinumab 300 mg Q2W dose regimen over the currently used and approved 300 mg Q4W dose regimen in the treatment of moderate to severe chronic plaque-type psoriasis in patients weighing 90 kg or more. The efficacy response was shown to be clinically meaningful and statistically significant in favor of the Q2W regimen at week 16, but also higher and sustained beyond Week 16 up to one year of treatment. Moreover, the efficacy responses also improved in patients who started to be treated with the Q4W regimen but did not achieve a satisfactory clinical response at Week 16 and were therefore up-titrated to the Q2W regimen for the rest of the trial. Finally, the safety profile in the study was comparable between the 2 dosing regimens and consistent with the known safety profile of secukinumab, showing no new or unexpected safety signals despite the higher exposure of the Q2W regimen.

The 52-week data from two studies (CAIN457A2310 and the CAIN457A2311) led to approval in a multitude of countries including EU/EEA in Jul 2020 for the inclusion of the pediatric psoriasis population (children and adolescents from the age of six years who are candidates for systemic therapy) as a new therapeutic indication. CAIN457A2310 study achieved the primary and key secondary objectives, demonstrating superior efficacy over placebo in pediatric patients with severe psoriasis. As shown in the recent final analysis efficacy was sustained for over 4.5 years of secukinumab treatment (Section 17.2). Similarly, study CAIN457A2311 met primary and key secondary objectives showing superior efficacy of secukinumab versus historical placebo in patients with moderate to severe psoriasis in adults. There were no new or unexpected safety signals for secukinumab in the pediatric population. The safety profile for secukinumab treatment in both phase 3 pediatric studies was consistent with the extensive experience in adult psoriasis and other approved indications. The benefit-risk balance is positive for secukinumab in the indication of moderate to severe plaque psoriasis in pediatric population.

Psoriatic arthritis

Efficacy for psoriatic arthritis were demonstrated in the phase III studies and have been described in the previous PSURs

Axial spondyloarthritis (Ankylosing spondylitis and non-radiographic axial spondyloarthritis)

Efficacy for ankylosing spondylitis were demonstrated in the pivotal phase III studies that have been described in the previous PSURs. New data have been generated to demonstrate efficacy for non-radiographic axial spondyloarthritis (nr-axSpA).

The placebo-controlled study CAIN457H2315 led to approval for the treatment of adult patients with active non-radiographic axial spondyloarthritis (nr-axSpA). This study demonstrated secukinumab to be very effective in treating patients with non-radiographic axSpA, a disease within the spectrum of axSpA which is considered an early form of AS. A dose of 150 mg, with or without loading regimen, delivered both statistically significant and clinically meaningful benefit to both biologically naive patients who had never received prior biologic therapy, as well as those with inadequate response to anti-TNF biologic therapy. Secukinumab demonstrated rapid onset of response and superior efficacy over placebo across measures of clinical response, QoL and markers of inflammation with overall efficacy seen similar to

efficacy observed in AS trials. Safety data from this trial did not reveal any new safety concern, and no concerning pattern of events.

17.2 Newly identified information on efficacy and effectiveness

This section includes the following new information: final analysis (from Week-52 to Week-236) of the pediatric study CAIN457A2310, weight-based intravenous administration of secukinumab for PsA and axSpA, and the studies leading to newly approved indications (JIA and HS).

Pediatric plaque psoriasis

During the reporting period the final analysis of pediatric study CAIN457A2310 was performed providing results of long term (236 weeks) secukinumab treatment. In both secukinumab dose groups (low dose and high dose), IGA mod 2011 0/1 and the PASI 75/90/100 responses remained overall sustained from Week 52 until the end of the 236 weeks treatment. While over this period IGA mod 2011 0/1, PASI 75 and PASI 90 responses were mostly similar between the low and high dose, consistently numerically higher results for PASI 100 (clear skin) response were observed for the high dose. Between Week 52 and end of treatment the mean PASI score remained consistently low (less than 3) for both the low and high dose treatment groups.

Psoriatic arthritis

Intravenous administration of secukinumab for PsA was investigated in study CAIN457P12302 leading to approval in the United States. The dose regimen under clinical development includes weight-based dosing with a loading dose of 6 mg/kg i.v. at Baseline, followed by secukinumab 3mg/kg i.v. every four weeks (compared to placebo).

At Week 16, the study met the primary endpoint of ACR50 along with all hierarchical secondary endpoints including ACR20 response, MDA 5/7 response, PASI90 response, PASDAS score, HAQ-DI score, SF36-PCS score, FACIT-Fatigue score, mNAPSI score, resolution of dactylitis and enthesitis. Treatment response was maintained up to Week 52. No new or unexpected safety signals were detected in this study, and the safety profile in this patient population was consistent with the safety profile observed in other indications.

The results of the study CAIN457P12302 supported the registration of secukinumab formulation for i.v. use for the treatment of adult patients with psoriatic arthritis.

Axial spondyloarthritis (Ankylosing spondylitis and non-radiographic axial spondyloarthritis)

Intravenous administration of secukinumab was also investigated in study CAIN457P12301 leading to approval for the indications of AS and nr-axSpA. . The dose regimen under clinical development includes a loading dose of 6 mg/kg i.v. at Baseline, followed by secukinumab 3 mg/kg i.v. every four weeks (compared to placebo).

At Week 16, the study met the primary endpoint of ASAS40 along with all hierarchical secondary endpoints including ASDAS-CRP major improvement, BASDAI change from Baseline, ASAS5/6 response, BASFI change from Baseline; SF-36 physical component score (PCS) change from Baseline; ASQoL change from Baseline; hsCRP change from Baseline;

ASAS20 response; ASDAS-CRP ID; ASAS-PR; PSQI change from Baseline. Treatment response was maintained up to Week 52. No new or unexpected safety signals were detected in this study, and the safety profile in this patient population was consistent with the safety profile observed in other indications.

The results of the study CAIN457P12301 supported the registration of secukinumab formulation for i.v. use for the treatment of adult patients with active ankylosing spondylitis and non-radiographic axial spondyloarthritis.

Juvenile idiopathic arthritis subtypes of psoriatic and enthesitis-related arthritis

A double-blind, randomized, placebo controlled, event-driven treatment withdrawal phase 3 study (AIN457F2304) demonstrated that the time to JIA disease flare was statistically longer in patients treated with secukinumab compared with placebo-treated patients from week 12 up to week 104.

Improvements in JIA American College of Rheumatology (ACR) responses, JIA ACR inactive disease, JIA ACR core set components, Juvenile Arthritis Disease Activity Score were reported in patients treated with secukinumab up to 12 weeks.

No new safety signals were reported with secukinumab for up to two years.

The results of the study AIN457F2304 supported the registration of secukinumab for the treatment of JPsA and ERA subtypes of JIA in children and adolescents.

Hidradenitis suppurativa

In two identical phase III placebo-controlled registration studies (CAIN457M2301 and CAIN457M2302), efficacy of secukinumab was demonstrated in treating moderate-to-severe HS patients. Achieving a rapid onset of action and a clinically meaningful improvements sustained over an extended period of time in the most critical disease domains (clinical signs, i.e. Hidradenitis Suppurativa Clinical Response (HiSCR)50 (at least a 50% decrease in AN count with no increase in the number of abscesses and/or in the number of draining fistulae), AN count (Percentage change from baseline in abscess and inflammatory nodules lesion count), disease flare and NRS30/skin pain) for adult patients with moderate-to-severe HS, at the proposed dose regimen of 300 mg s.c. administered every two weeks after a weekly loading dose at Weeks 0, 1, 2, 3, and 4.

The efficacy of the secukinumab at Weeks 16 and 52 was generally consistent across subgroups evaluated, including age, body weight, current antibiotic use, previous exposure to biologics, disease duration and Hurley stage. Improvement in inflammatory markers levels (hsCRP and ESR) and PROs (QoL scales and patient global assessment), as well as the pooled data of the two identical studies, further supported the clinical benefit of both secukinumab dose regimens (Q2W and Q4W) in this patient population.

17.3 Characterization of benefits

New relevant benefit data is available with secukinumab being approved in multiple countries, including EU/EEA, for the treatment of juvenile idiopathic arthritis subtypes of psoriatic and enthesitis-related arthritis and hidradenitis suppurativa. Data from CAIN457F3302 (MAXIMISE), a completed trial reported in the prior PSUR, formed the basis of EU approval

to include psoriatic arthritis (PsA) patients with axial manifestations within the currently approved indication of PsA. A new flexible dosing recommendation for plaque psoriasis and psoriatic arthritis in adult patients is also now available in the EU for patients who may derive additional benefit from secukinumab 300 mg every two weeks (Q2W). While secukinumab has been previously approved for pediatric moderate to severe PsO ex-US, the approval in the US was received during this reporting period. Intravenous formulation of secukinumab was also approved in the US for adults with active psoriatic arthritis, active ankylosing spondylitis, and active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation. There is no significant change in risk profile, refer to Section 17.1 for baseline benefit information.

18 Integrated benefit/risk analysis for authorized indications

An overall appraisal of the benefit and risk of Cosentyx as used in clinical practice is provided in the following sub-sections.

18.1 Benefit-risk context – Medical need and important alternatives

Cosentyx (AIN457 / secukinumab) is a fully human immunoglobulin G1 (IgG1) antibody that selectively binds to and neutralizes the proinflammatory cytokine IL-17A. Cosentyx works by targeting IL-17A and inhibiting its interaction with the IL-17 receptor, which is expressed on various cell types including keratinocytes and synoviocytes. As a result, Cosentyx inhibits the release of pro-inflammatory cytokines, chemokines and mediators of tissue damage and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases. The rationale for targeting IL-17A in autoimmune diseases is based on both animal models of autoimmune disease as well as increased expression of IL-17 mRNA or IL-17 protein cells in human autoimmune diseases. IL-17A mRNA and/or protein are upregulated in several pathological inflammatory and autoimmune conditions, including psoriasis, psoriatic arthritis, and AS[26, 79, 80].

Moderate to severe plaque psoriasis

Psoriasis is one of the most common human skin diseases affecting 2 to 3% of the general population[81, 82]. It is a complex disorder, characterized by inflammation, increased keratinocyte proliferation, and altered epidermal differentiation[83]. Approximately 80-90% of psoriasis patients have chronic plaque psoriasis, characterized by recurrent exacerbations and remissions of thickened, erythematous, scaly patches of skin that can occur anywhere on the body[84, 85]. Psoriatic arthritis is an important co-morbidity in up to 40% of psoriasis patients, which causes pain, stiffness and swelling in and around the joints, and which may lead to long term structural damage[84-86].

Moderate to severe disease affects 15% to 25% of plaque psoriasis patients and generally require systemic therapy, as outlined in several international and regional treatment guidelines. Several non-biologic systemic drugs (e.g. acitretin, cyclosporine, MTX, and apremilast), and several biologics, including TNF-α antagonists (adalimumab, etanercept, infliximab), anti-IL-12/IL-23 (ustekinumab, guselkumab), and anti-IL17 (ixekizumab, brodalumab) have been approved for the treatment of psoriasis. Most of these approved agents have safety limitations, including organ toxicity, infection, malignancy, and teratogenicity, that limit their usefulness in

the long-term management of psoriasis. Tumor necrosis factor-α antagonists have been approved for the treatment of psoriasis, but none achieved the goal of clear/almost clear skin for a majority of patients. Additionally, most of these products are also accompanied by drug-specific safety concerns like infections (including TB), malignancies (including lymphoma), immunogenicity and demyelinating neurologic events[82, 87].

Alike in the adult population, plaque type psoriasis is also the most common variant of the disease in pediatric patients. Disease prevalence in children varies depending on study population and age, with 1% as a commonly quoted and increasing with the age. Most children manifest with plaque psoriasis in patterns similar to adult patients and associated with significant co-morbidities. In these patients, it is fundamental to achieve psychological comfort and to prevent the appearance of comorbidities.

Other four biologics are also approved for the treatment of psoriasis in children (etanercept, adalimumab, ustekinumab, and ixekizumab) and all of these have limitations both with regard to the population for which they are indicated and the benefit risk-profile in individual patients. As both treatment options and available controlled studies are limited in this population, there is still an unmet medical need for additional options for the treatment of plaque psoriasis in pediatric patients.

Thus, secukinumab addresses a significant unmet need with rapid onset of effect, improved symptom clearance, sustained efficacy, accompanied by a safety profile that allows for chronic use.

Psoriatic arthritis and Axial spondyloarthritis (ankylosing spondylitis and non-radiographic spondyloarthritis)

Psoriatic arthritis and axial spondyloarthritis (including ankylosing spondylitis and non-radiographic axial spondyloarthritis) are autoimmune-mediated chronic inflammatory diseases belonging to the same spectrum of conditions commonly referred to as spondyloarthritis (SpA).

Psoriatic arthritis is a chronic immune-mediated debilitating disease encompassing a spectrum of overlapping clinical entities afflicting peripheral, synovial, axial, and entheseal structures, and is associated with skin psoriasis and nail involvement[88]. PsA is associated with impaired physical function and poor quality of life[89, 90] imposing significant morbidity and disability thus constituting a major socioeconomic burden.

Psoriatic arthritis has been conventionally managed with the hierarchical use of NSAIDs and csDMARDs. Pathogenesis-based interventions have improved outcomes in patients with PsA. Clinical trials demonstrated efficacy of T cell targeted therapy in PsA (cyclosporine A, CTLA4 Ig, alefacept). TNF-blocking therapy was successfully introduced to the treatment of patients with PsA[85]. Additional biologic therapies have also been included in the treatment armamentarium with variable efficacy on the different domains of PsA disease. The interleukin 12/23 inhibitor ustekinumab has also shown some clinical benefit with inhibition of radiographic progression mainly in anti-TNF naïve patients[91] [92].

Spondyloarthritis usually starts at young-adult age, affect males more often than females and family recurrence depends partly on inheritance of human leukocyte antigen (HLA)-B27 gene. The prevalence of AS in the US, based on data from the National Health and Nutrition Examination Survey, is 0.5%; the prevalence for axial SpA is 1.4% (Reveille et al 2013)[93]. The

first lines of treatment involve non-steroidal anti-inflammatory drugs and locally injected steroids. For patients who do not respond to these treatments, systemic steroids and Disease-Modifying Anti-Rheumatic Drugs (DMARDs) can be considered. However, DMARDs have limited benefits and come with extensive side effects. Tumor necrosis factor-α antagonists (e.g. etanercept, infliximab, adalimumab) have been approved for the treatment of SpA. These treatments present safety concerns, including an increased risk for malignancies, serious infections, reactivation of latent TB (Lemos et al 2014)[94, 95].

While biologic treatments have been successfully introduced for the treatment of patients with SpA, an unmet clinical need exists for a better disease control, fewer adverse effects and long-term prevention of structural damage beyond mere abrogation of inflammatory processes.

Juvenile Idiopathic arthritis subtypes of psoriatic and enthesitis-related arthritis

Juvenile Idiopathic arthritis is a broad term that describes a clinically heterogeneous group of arthritides of unknown cause, which begin before 16 years of age. The JIA categories ERA and JPsA are chronic, debilitating conditions with decreased health related quality of life and risk of permanent joint damage. Long-term complications in ERA and JPsA include joint erosions and deformities, growth retardation, reduced bone and muscle mass, metabolic complications, and osteoporosis. ERA and JPsA, as defined by the ILAR classification, represent pediatric correlates of the adult conditions for which secukinumab is approved, i.e., AS, nr-axSpA, and PsA.

NSAIDs are the first-line of treatment in ERA and JPsA. They provide symptomatic relief, but are not disease-modifying and do not alter disease progression; in addition, some patients respond poorly to NSAIDs. Intra-articular corticosteroid injections are widely used to induce rapid relief of inflammatory symptoms and for functional improvement, and they play an important part in the prevention of deformities secondary to joint contractures; however, corticosteroids should not be used long-term. Methotrexate, which is the most widely used synthetic DMARD in JIA, does not improve axial disease, and the ACR JIA guidelines advise against methotrexate monotherapy in children with sacroiliitis and enthesitis[96].

Tumor necrosis factor inhibitors are recommended for patients with enthesitis and/or sacroiliitis who do not achieve disease control on NSAIDs. However, many children, including patients with ERA and JPsA, do not respond to TNF therapy[97] reported that 31% of patients with ERA or JPsA treated at the Cincinnati Children's Hospital Medical Center and 55% of those in the CARRA registry continued to experience chronically uncontrolled disease, despite having received two or more biologic agents. In one study, only 24% of children with ERA and 60% of children with JPsA achieved inactive disease during the initial 12 months of anti-TNF treatment[98]. In addition, while other classes of biologic agents (abatacept, tocilizumab, anakinra, canakinumab) including JAK inhibitor (tofacitinib) have now become available for certain types of JIA, none of them are labeled for use in both ERA and JPsA.

Hence, secukinumab provides not only a valuable additional treatment option for patients with ERA and JPsA, it also addresses an unmet medical need for patients with an inadequate response to the limited treatment options currently available.

Hidradenitis suppurativa

Hidradenitis suppurativa is a chronic, recurrent, disabling skin condition that manifests with deep, painful, inflammatory skin lesions that may be associated with malodorous discharge, and can be complicated by sinus tract formation and fistulization, with a profound impact on the QoL of affected patients. Over time, the consequence of chronic, recurrent, inadequately treated inflammation is irreversible fibrosis, which limits functionality and does not respond to medical therapy, necessitating surgery which can be repetitive and extensive in some cases.

The disease starts after puberty, and women are more frequently affected than men in a ratio of 3:1. Risk factors include obesity and smoking. Although epidemiological prevalence estimates vary widely (0.03% to 4.0%) and geographical differences exist, a prevalence of approximately 0.1% to 1% is accepted by the scientific community[99-101]. The first lines of treatment involve topical and systemic antibiotics, hormonal therapies, retinoids, systemic immunomodulators and biologics[102, 103]. Recurrent combination therapy using multiple antimicrobials represents the first step to control the symptoms in patients with HS [103-105]. However, it is widely recognized that HS is not an infectious disease, but rather a chronic inflammatory condition, with elevated systemic levels of inflammatory markers[104]. Therefore, systemic anti-inflammatory agents are 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 fibrotic lesion is surgery[106].

Adalimumab (Humira®), an anti-TNF-α antibody, is also approved for the treatment of adults with moderate to severe HS (approval granted in 2015 in the US and EU). Two similarly designed Phase 3 studies demonstrated the superiority of weekly adalimumab over placebo with respect to Hidradenitis Suppurativa Clinical Response (HiSCR) 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 a numerical decline over time(107). Besides the known immunogenicity of adalimumab, the mechanisms underlying the progressive loss of response are not known[108, 109]. As captured in the product label, adalimumab is associated with an increased risk of 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[37, 110]..

Hence, there is an unmet need for systemic therapies that effectively reduce inflammation over an extended period of time while having a favorable safety profile. Cosentyx was approved for HS on 26 May 2023 in the EU and on 31 Oct 2023 in the US.

18.2 Benefit-risk analysis evaluation

Each safety data set was reviewed to identify any new (i.e. not considered in the current CDS) or changing safety signal (i.e. altered specificity, severity, frequency or outcome of an ADR already described in the CDS). Overall, the review of the cumulative safety data showed a consistent safety profile of secukinumab across indications. Newly identified signals during the reporting period that led to CDS update (eczematous eruptions [including dyshidrotic eczema, atopic dermatitis-like eruptions and dermatitis exfoliative generalized], pyoderma gangrenosum and angioedema) have not altered the benefit/risk profile for secukinumab, since these reactions

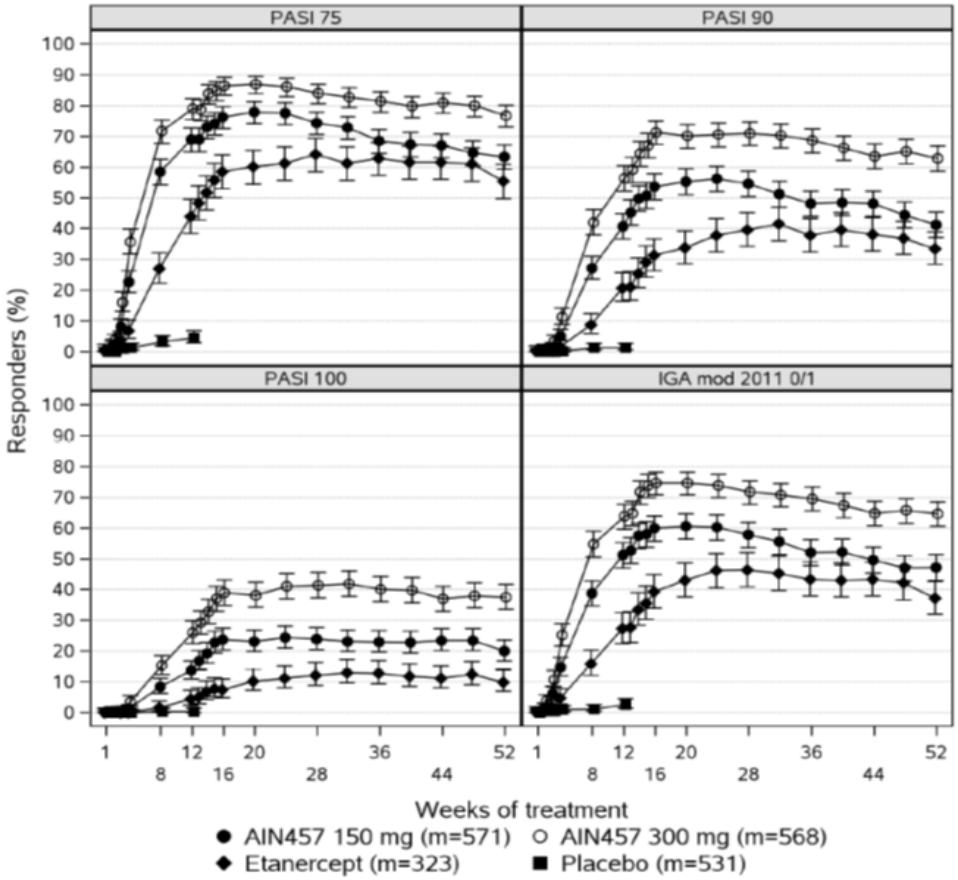
are detectable, mainly of mild-moderate intensity and manageable with standard of care. The review of data of the reporting period has not revealed a change for the safety concerns (important identified and potential risks and missing information). Long-term use of secukinumab in PsO, PsA and AS have consolidated the benefit in these indications, plus extended indications for pediatric population have been confirmed. Lastly secukinumab has demonstrated to benefit patients with moderate to severe HS.

An overall appraisal of the benefit and risk of Cosentyx as used in clinical practice is provided in the following sub-sections.

Moderate to severe plaque psoriasis

Efficacy of secukinumab to treat plaque psoriasis was initially demonstrated in four phase III studies. The majority of treated patients achieved clear to almost clear skin, as shown by PASI 90 response and IGA mod 2011 0 or 1 response (Figure 18-1).

Figure 18-1 PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response over 52 weeks of treatment (estimate + 95% CI) – Induction and Maintenance periods (non-responder imputation) (FAS) (studies CAIN457A2302 and CAIN457A2303)



Since the initial approval of secukinumab based on the phase III data, efficacy of secukinumab has been consistently demonstrated in the following additional studies described below.

Two long term extension studies, CAIN457A2302E1 (core studies were CAIN457A2302 and A2303) and CAIN457A2304E1 (core study was CAIN457A2304) with treatment duration up to four years beyond their core studies further demonstrated the long-term benefit of secukinumab therapy. In CAIN457A2302E1 study, treatment withdrawal was mostly followed by loss of response that was rapidly regained with re-start of secukinumab. Overall, in both extension studies the efficacy observed in the core studies appeared to be sustained during long term treatment. The safety profile was consistent over the years without an increase in AE rate or severity or any new safety signal. The long-term secukinumab treatment resulted in favorable benefit-risk relationship similar to the one year treatment period of their respective core studies.

Efficacy for sub-type psoriasis was demonstrated in three placebo-controlled studies. In study CAIN457A2312 in palmoplantar psoriasis and CAIN457A2313 in nail psoriasis, secukinumab was also superior to placebo at Week 16 as assessed by significant improvement of palmoplantar IGA 0 or 1 response (“clear” or “almost clear”) for patients with moderate to severe palmoplantar PsO, and as assessed by significant improvement from Baseline in the Nail Psoriasis Severity Index (NAPSI %) for patients with moderate to severe PsO with nail involvement. In study CAIN457AUS01 in patients with moderate to severe scalp psoriasis, secukinumab 300 mg was superior to placebo at Week 12 as assessed by significant improvement from Baseline in both the Psoriasis Scalp Severity Index (PSSI) 90 response IGA mod 2011 0 or 1 scalp only response.

Clinical trials CAIN457A2323 and CAIN457A2325, the latter completed during the reporting period, demonstrated the superior efficacy of secukinumab 300 mg when administered as 2 mL PFS or as 2 ml Autoinjector respectively, in subjects with plaque-type psoriasis with respect to both PASI 75 and IGA mod 2011 0 or 1 response (coprimary endpoint) at Week 12, compared to placebo. Efficacy was further sustained up to Week 52. The use of the 2 mL PFS or auto-injector in these studies did not result in any specific findings (injection site reactions were very rare) and the safety profile was consistent with the known safety profile of secukinumab and showed no new or unexpected safety signals.

Superiority of secukinumab 300 mg q2w over secukinumab 300 mg q4w was demonstrated in study CAIN457A2324 (which completed during the reporting period) in heavier patients (≥90 kg) with moderate to severe chronic plaque-type psoriasis. The q2w regimen resulted in higher PASI 90 response rate at Week-16 and higher sustained PASI 90 response rate at Week 52. The safety was comparable between the two dosing regimens; no dose-dependent increase in the incidence of AEs or risks were observed. The safety profile in this study was consistent with the known safety profile of secukinumab and showed no new or unexpected safety signals.

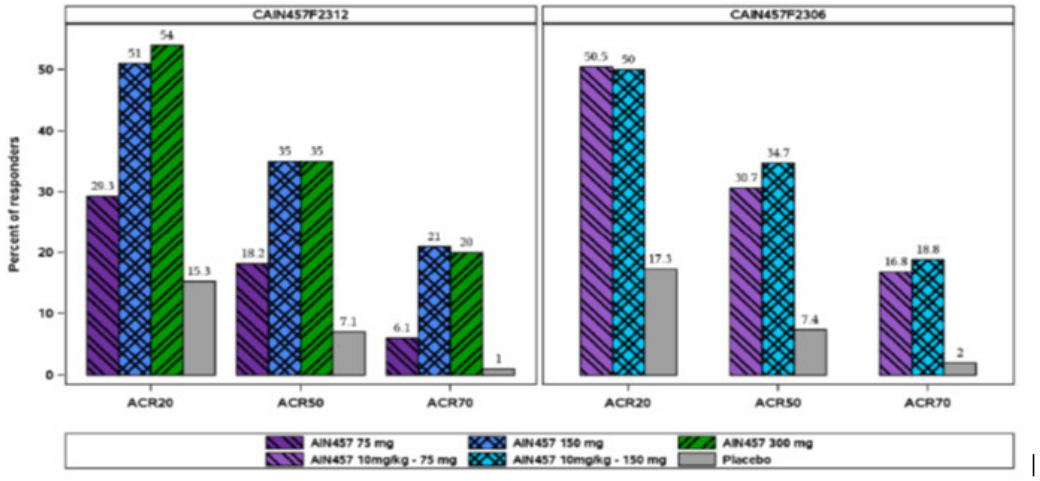
Favorable benefit/risk profiles of secukinumab in pediatric PsO patients were demonstrated in two studies. In study CAIN457A2310 which completed during the reporting period was a randomized, double-blind, placebo and active controlled multicenter trial to demonstrate efficacy of s.c. secukinumab compared to placebo and etanercept (in a single-blinded arm) after twelve weeks of treatment, and to assess the safety, tolerability, and long-term efficacy in subjects from six to less than 18 years of age with severe chronic plaque psoriasis. The study met its co-primary endpoints. Both secukinumab doses (low and high) were superior to placebo

with respect to the co-primary efficacy endpoints of PASI 75 and IGA mod 2011 0 or 1 responses at Week 12 ($p<0.0001$ for all comparisons). The study also met the key secondary endpoint since both secukinumab doses (low and high dose) were superior to placebo with respect to PASI 90 response at Week 12 $p<0.0001$ for both comparisons). In both secukinumab dose groups, the PASI 50/75/90/100 and IGA mod 2011 0 or 1 responses further improved after Week 12 peaking before or at Week 24 and were thereafter maintained up to Week 52 and further until the end of the long-term treatment of 236 weeks. The other pediatric study (CAIN457A2311) is an ongoing open-label, multicenter trial to assess the efficacy of s.c. secukinumab after 12 weeks of treatment, and to assess the long-term safety, tolerability and efficacy in subjects from six to less than 18 years of age with moderate to severe chronic plaque psoriasis. The study met its co-primary objective as secukinumab doses (both low and high) were superior at week 12 compared to placebo (historical control) with respect to PASI 75 and IGA mod 2011 0 or 1 responses. High efficacy responses were sustained at the last analysis at Week 52. In both pediatric studies CAIN457A2310 and CAIN457A2311, low and high secukinumab dose doses were safe, well tolerated and the safety profile was consistent with that of the psoriasis Phase 3 trials in adults, with no new or unexpected safety signals.

Psoriatic arthritis

Secukinumab demonstrated clinically meaningful sustained and statistically significant efficacy for the treatment of patients with active PsA through all components of joint and skin disease, physical function, health-related quality of life and structural damage. Pre-specified endpoints adjusted for multiple testing demonstrated the superiority of secukinumab 150 mg and 300 mg regimens compared with placebo. ACR20 achieved at 24 weeks with 150 mg s.c. regimen was comparable to the responses with 300 mg s.c. regimen (Figure 18-2). As in the psoriasis program, secukinumab 150 mg s.c. and 300 mg s.c. provided greater improvements in plaque psoriasis than placebo in PsA patients with concomitant psoriasis. Overall, secukinumab is efficacious and demonstrated a rapid onset of response in achieving clinically meaningful improvements in key clinical domains of PsA disease. These domains include signs and symptoms, skin disease, structural damage, physical function and quality of life. The 150 mg s.c. regimen provides rapid, superior efficacy for most patients, and the 300 mg s.c. regimen offers increased benefit for TNF-IR patients and in patients with moderate to severe plaque psoriasis. Efficacy results were sustained with time in all studies.

Figure 18-2 ACR20, ACR50 and ACR70 responses at Week 24 by pivotal study (full analysis set; Study CAIN457F2312 and Study CAIN457F2306)



The original PsA registration dossier was based on two Phase 3 studies (F2306 and F2312). The PsA indication was originally approved by the EMA on 19 Nov 2015 (EMEA/H/C/003729/II/0001/G).

Subsequently, in all large placebo-controlled Phase III studies (CAIN457F2306, CAIN457F2306E1, CAIN457F2312, CAIN457F2318, CAIN457F2336 and CAIN457F2342), secukinumab consistently demonstrated both statistically significant and clinically meaningful differences compared to placebo in adult patients with active psoriatic arthritis. The majority of patients treated with the recommended 150 mg and 300 mg regimens achieved an American College of Rheumatology (ACR)20 response in joint-related signs and symptoms, achieved benefit in skin endpoints (as shown by PASI75, PASI 90 response rates and IGA mod 2011 0 or 1 response), improvement in physical function, inhibition of radiographic structural progression and improvement in QoL.

Intravenous administration of secukinumab for PsA was investigated in a phase III placebo-controlled trial (CAIN457P12302) leading to approval in the United States. The initial dose was 6mg/kg at BSL followed by 3 mg/kg q4w thereafter. Secukinumab demonstrated superiority over placebo for the primary endpoint of ACR50 response at Week 16 (60/191 (31.41%) vs. 12/190 (6.32%); p<0.0001). At Week 16, secukinumab 6 mg/kg-3 mg/kg group also demonstrated superiority over placebo for all secondary efficacy endpoints including ACR20 response, MDA 5/7 response, PASI90 response, PASDAS score, HAQ-DI score, SF36-PCS score, FACIT-Fatigue score, mNAPSI score, resolution of dactylitis and enthesitis. The efficacy demonstrated by secukinumab at Week 16 was sustained up to Week 52. The safety profile of secukinumab in this study showed no new or unexpected safety signals from what is currently known.

Overall, the efficacy results across all studies in PsA are consistent with the efficacy data demonstrated in the original MAA. The safety profile of secukinumab showed no new or unexpected safety signals in PsA patients.

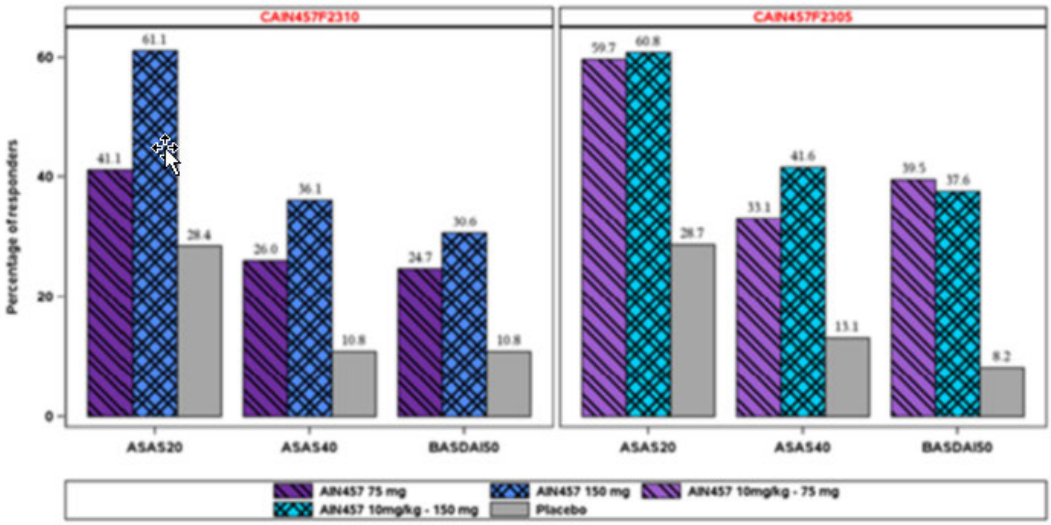
Axial spondyloarthritis (Ankylosing spondylitis and non-radiographic spondyloarthritis)

In multiple large phase 3 placebo controlled double blind trials (CAIN457F2305, CAIN457F2305E1 CAIN457F2310 and CAIN457F2320), secukinumab 150 mg s.c. demonstrated clinically meaningful sustained and statistically significant efficacy for the treatment of patients with active AS through all key measures of efficacy, including disease signs and symptoms, objective measures of inflammation, physical function and mobility, and health-related quality of life. Secukinumab demonstrated clinically meaningful and statistically significant improvements compared to placebo in all key measures of active AS at Week 16. Patients treated with secukinumab demonstrated greater improvements in ASAS20, ASAS40 and BASDAI 50 responses compared to placebo at Week 16 (Figure 18-3). Responses were similar in patients regardless of concomitant therapies and the onset of responses was rapid, appearing as early as one week after s.c. loading. Results for exploratory variables related to signs and symptoms, functional assessments, and health-related QoL all further support the clinical benefit of the secukinumab 150 mg s.c. regimen.

In a large phase 3 placebo-controlled trial (CAIN457H2315) in patients with nr-axSpA secukinumab 150 mg demonstrated a rapid onset of response and superior efficacy over placebo across measures of clinical response, quality of life and markers of inflammation, including the higher hurdle endpoints of ASAS40, BASDAI50, ASAS partial remission, and ASDAS-CRP inactive disease which are considered to be clinically meaningful treatment outcomes for nr-axSpA patients. The safety profile of secukinumab 150 mg showed no new or unexpected safety signals and was consistent with the overall safety profile of secukinumab.

Intravenous administration of secukinumab for axSpA was investigated in two phase III placebo-controlled studies leading to approval in the United States. Study CAIN457P12301 was to evaluate an intravenous, weight-based dosing regimen of secukinumab starting with a loading dose of 6 mg/kg i.v. at baseline, followed by secukinumab 3 mg/kg i.v. every 4 weeks in axSpA patients, including both, AS and nr-axSpA. Secukinumab 6 mg/kg - 3 mg/kg demonstrated superiority over placebo at Week 16 across measures of clinical response, quality of life and markers of inflammation, including the higher hurdle endpoints of ASAS40 (primary endpoint) ASDAS-CRP ID and ASAS-PR. Treatment response was maintained up to Week 52. No new or unexpected safety signals were detected in this study, and the safety profile in this patient population was consistent with the safety profile observed in other indications. In another study (CAIN457F2314), secukinumab iv-150 mg and iv-300 demonstrated a rapid onset of response and efficacy over placebo in subjects with moderate to severe active AS, as assessed by measures of clinical response, quality of life and markers of inflammation. These responses continued over 156 weeks of treatment, with a consistent trend for a greater response in the iv-300 mg group particularly for higher hurdle outcomes including ASAS partial remission and ASDAS inactive disease. The safety profile of secukinumab iv-150 mg and iv-300 mg dose regimens showed no clinically meaningful differences between treatments through Week 156 with no new or unexpected safety findings. Efficacy results were sustained over time in all studies.

Figure 18-3 ASAS 20, ASAS 40 and BASDAI 50 response rates at Week 16 (full analysis set, Study CAIN457F2310 and Study CAIN457F2305)



Juvenile Idiopathic arthritis subtypes of psoriatic and enthesitis-related arthritis

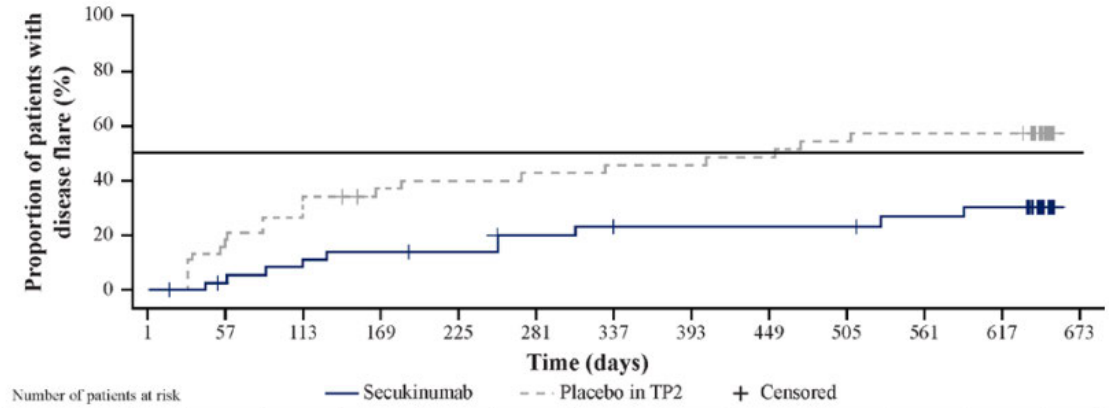
The efficacy and safety of secukinumab treatment (150 mg for subjects ≥50 kg and 75 mg for subjects <50 kg) in patients with JPsA and ERA subtypes of JIA was assessed in a 2-year, double-blind, randomized, placebo-controlled, event-driven treatment withdrawal phase 3 study. The study consisted of three treatment periods (TPs): open-label (OL) secukinumab TP1 (up to 8 weeks); a randomized, double-blind, placebo-controlled, withdrawal period (up to week 104) TP2; OL secukinumab TP3 and a post-treatment follow-up period

Efficacy with secukinumab treatment was demonstrated for the primary endpoint of significantly ($p<0.001$) longer time to flare in the active group vs. placebo as well as in higher JIA ACR30 response rates and improved signs and symptoms with secukinumab treatment vs. placebo (Figure 18-4).

Secukinumab treatment resulted in rapid and clinically relevant benefits based on key measures of disease, including fewer sites of enthesitis and joints with active disease, improvement (or complete resolution) of sacroiliitis and inflammatory back pain (assessed in ERA), improvement in skin disease (assessed in JPsA), less disability, and improved overall well-being.

The safety profile of secukinumab in this study of pediatric patients showed no new or unexpected safety signals.

Figure 18-4 Time to flare in Treatment Period 2 is significantly longer with AIN457 for combined ERA and JPsA than with Placebo



Number of patients at risk													
Secukinumab	37	34	32	30	29	25	24	23	23	23	21	20	0
Placebo in TP2	38	32	28	22	21	20	19	19	18	16	15	15	0

Treatment	Number of patients (n)	Number of events (m)	m/n	Kaplan-Meier estimate (days)		Hazard ratio to placebo		*P*-value
				Median	95% CI	Estimate	95% CI	
Secukinumab	37	10	0.27	NC	(NC, NC)	0.28	(0.13, 0.63)	<0.001
Placebo in TP2	38	21	0.55	453.0	(114.0, NC)			

- AIN457: all subjects who did not take any placebo. Placebo in TP2: all subjects who took placebo in TP2 and AIN457 in other period/s.
- Day 1 = date of randomization. Disease flare was derived relative to the end of Treatment Period 1 (Week 12 visit).
- Subjects who did not experience a flare in TP2, were censored at the date of their last non-missing flare evaluation in TP2.
- Subjects at risk = subjects in TP2 who did not have flare and were not censored before or at the start of the specified day.

The use of secukinumab for these juvenile forms of arthritis has been approved in the US, EU and other countries.

An extension study (c) of secukinumab to evaluate the long--term efficacy, safety and tolerability up to four years in patients with JPsA and ERA is currently ongoing.

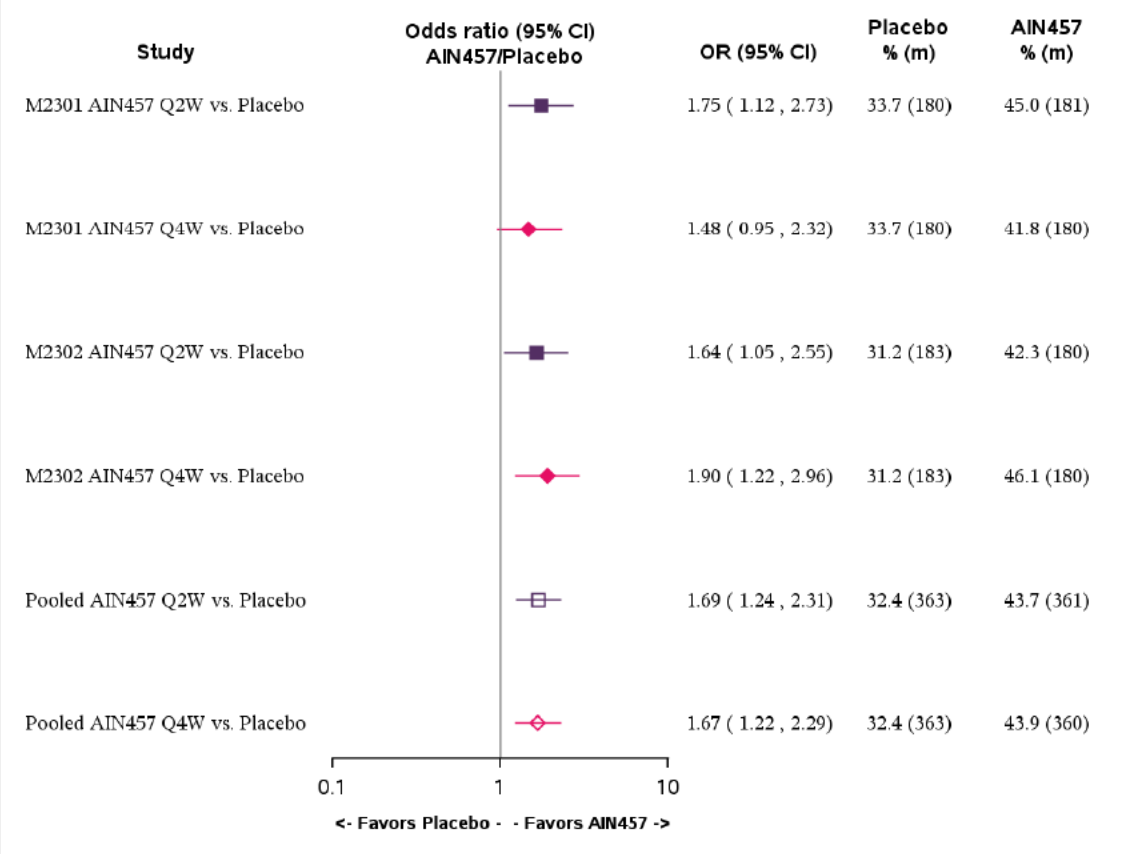
Hidradenitis suppurativa

The efficacy of Cosentyx in patients with moderate-to-severe HS was assessed in a phase III program, involving two core large, identical, ongoing, multi-center, randomized, double-blind, placebo-controlled, parallel group Phase 3 studies (CAIN457M2301 and CAIN457M2302) conducted to assess the short (16 weeks) and long-term (up to 52 weeks) efficacy and safety of two secukinumab 300 mg dose regimens (Q2W or Q4W) compared to placebo in adult subjects with moderate to severe HS, with achievement of HiSCR50 at Week 16 as the primary endpoint. The HS indication was approved in the EU on 26 May 2023 and in the US on 31 Oct 2023.

In each study, both secukinumab dose regimens demonstrated higher HiSCR50 response rates than placebo at Week 16. The estimated odds ratio of secukinumab compared to placebo for the HiSCR50 response rate at Week 16 was clinically relevant and statistically significant for the

secukinumab Q2W dose regimen in both studies and for the secukinumab Q4W dose regimen only in Study M2302. Pooled data further supported the beneficial treatment effect of both secukinumab dose regimens (Figure 18-5).

Figure 18-5 Forest plot of the treatment effect (95% CI) for HiSCR50 response at Week 16 (primary estimand, multiple imputation) (M2301, M2302 and pooled data) (Full analysis set)

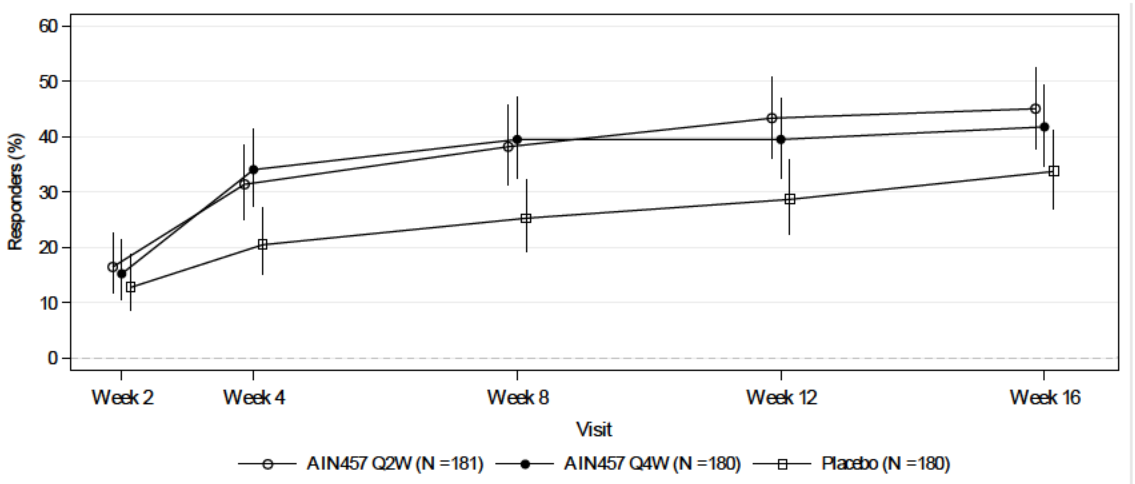


- m=number of subjects evaluable.
- Covariates included in the model: treatment group, Hurley stage, baseline AN count, geographical region, use of antibiotic, baseline body weight and study.

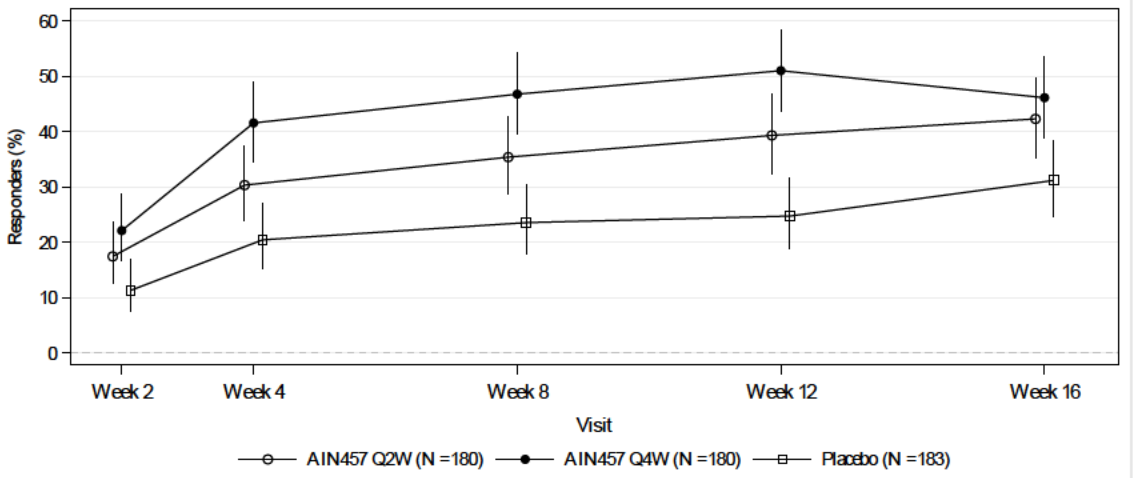
Source: [AIN457M SCE-Figure 3-1]

Figure 18-6 HiSCR50 responders up to Week 16 (mean response rate with 95% CI) (primary estimand, multiple imputation) (M2301, M2302 and pooled data) (Full analysis set)

M2301



M2302



Efficacy of secukinumab over placebo was observed as early as Week 2, with progressive improvement through to Week 16 which continued to increase up to Week 52 across the variables associated with the primary and secondary endpoints. The greater benefits of secukinumab compared to placebo were generally consistent across subgroups evaluated, including subjects with more severe disease (Hurley stage III and long disease duration), higher body weight (≥90 kg), concurrent antibiotic use and previous exposure to biologics. Improvement in inflammatory marker levels (hsCRP and ESR) and PROs (QoL scales and patient global assessments) further supported the clinical benefits of secukinumab in this patient population.

Safety profile for all indications

Safety data have been generated following substantial exposure to secukinumab. In pooled clinical trials, a total of 25,110 secukinumab-treated patients accumulated to a total of 39,527.14 PTY exposure. Safety data from the secukinumab-treated patients may be compared to the placebo group with a total of 5,445 patients, with accumulated 1,805.73 PTY follow-up period. Of the total patients enrolled in clinical trials, 284 were pediatric patients with 798.44 PTY exposure and 41 placebo pediatric patients with 10.33 PTY follow up period.

In the post-marketing experience, patient exposure has been accumulated to more than 1.8 million PTY. In the PsO registry (CorEvitas), enrollments included 3,297 secukinumab-treated patients, 9,210 treated with non-IL-17 biologic therapies and 986 PsO patients receiving non-biologic systemic therapies.

In clinical trials, secukinumab has been well-tolerated. AEs are mostly non-serious. To account for the fact that not all groups were observed for an equally long time, exposure adjusted incidence rates (EAIR per 100 subject-years) were also computed. However, treatment comparisons of secukinumab to placebo for the Entire Study Period must still be interpreted with caution, given that AE rates may not be constant over time.

EAIR of the TEAEs in clinical trials remained stable since the last PSUR and were generally comparable with placebo (acknowledging small sample size and shorter exposure of placebo, and the fact that in general patients on placebo switch to active treatment arms). Dose-dependency was not of evidence except for infection and hypersensitivity reactions. The dose-dependent infection rate has already been described in the CDS. EAIR for the important identified and potential risks is summarized by dose for all indications in Table 18-1.

Post-marketing reports also remains stable over years (with a trend of decrease). Infections have been the most common AEs related to the important identified risk. Nasopharyngitis has been the most common infection and pneumonia or lower respiratory infection has been the most commonly reported serious infection. Candidiasis is the most commonly reported fungal infection and is mainly non-serious and non-invasive.

Hypersensitivity reactions mainly concern skin/cutaneous reactions (e.g. eczema). Anaphylactic reaction and serious angioedema (newly proposed ADR within this PSUR) may also occur; however, these events remain as rarely reported It is notable that the hypersensitivity events that were retrieved by the search criteria and not all of them (e.g., circulatory collapse) were automatically deemed to be a hypersensitivity reaction.

Additionally, rare paradoxical skin reactions of eczematous eruptions (including atopic-dermatitis-like reactions and exfoliative dermatitis generalized), dyshidrotic eczema, pyoderma gangrenosum are the new ADRs added to the CDS during the reporting period.

The clinical characteristics of the listed ADRs including IBD and neutropenia remain unchanged. Regarding IBD, it is notable that in pooled clinical trials for secukinumab, 77% of the patients with a history of IBD did not experience IBD flare[25]

Malignancy remains as an important potential risk. In pooled clinical trials, the overall incidence rates of malignancies are comparable with the general population in the United States as captured in SEER for all malignancies CCI [redacted]; however, CCI [redacted]

CCI [redacted] Moreover, in post-marketing reports, more than ¼ cases had a history of malignancies, and approximately 9% of the malignancies were reported with six months (even though time to onset can only be assessed in 40% of the cases) after initiating secukinumab treatment suggesting unlikely causality. Lastly, real world data from CorEvitas registry, shows similar malignancy incidence rate (including CCI [redacted]) among secukinumab, non-IL-17 biologics and non-biologic systemic therapies. Overall, no evidence of causal association with any malignancy is identified and the characteristics for this potential risk remain unchanged.

MACE has been monitored as an important potential risk. Pre-existing risks for cardiovascular diseases are commonly identified in these MACE reports. Real world data form CorEvitas registry, shows similar malignancy incidence rate among secukinumab, non-IL-17 biologics and non-biologic systemic therapies. Overall, no evidence of causal association with MACE is identified and the characteristics for this potential risk remain unchanged.

No increased risk was recognized hepatitis B reaction or suicidal ideation and behavior, and no evidence of causal association with these two potential risks was identified therefore, characteristics for these potential risks remain unchanged. No pediatric-specific safety signal was identified.

Characterization of the key risks is summarized in Table 18-4. The benefit-risk profile of Cosentyx in the approved indications remains favorable and unchanged.

Table 18-1 Incidence rates per 100 PTY for important identified and potential risks in pooled clinical trials (data cut-off 25 Dec 2023)

Treatment Groups	Incidence rate per 100 PTY (95% CI)					
Important identified risks						
	Any infections		**Fatal infection**		**Fungal infection**	
Any AIN457 75mg Q4W	53.60	(49.91, 57.50)	0.07	(0.01, 0.25)	3.64	(3.32, 3.97)
Any AIN457 150mg Q4W	61.45	(59.66, 63.28)	0.05	(0.02, 0.10)	6.69	(6.31, 7.09)
Any AIN457 300 Q4W	75.24	(73.54, 76.96)	0.01	(0.00, 0.04)	11.73	(9.39, 14.47)
Any AIN457 300 Q2W	90.13	(82.19, 98.63)	0.00	(0.00, 0.47)	5.08	(4.85, 5.31)
Any AIN457 dose	68.94	(67.80, 70.10)	0.03	(0.02, 0.05)	4.20	(3.30, 5.26)
Placebo	96.07	(91.14, 101.19)	0.06	(0.00, 0.31)	2.10	(1.20, 3.41)
Any AIN457 dose (pediatric)	70.51	(61.03, 81.05)	0.00	(0.00, 0.46)	9.92	(0.25, 55.26)

Treatment Groups	Incidence rate per 100 PTY (95% CI)					
Placebo (pediatric)	212.12	(121.25, 344.48)	0.00	(0.00, 35.70)	3.64	(3.32, 3.97)
	Herpes viral infection		**Mycobacterial infection**		**Opportunistic infection**	
Any AIN457 75mg Q4W	2.00	(1.51, 2.60)	0.10	(0.02, 0.30)	0.17	(0.06, 0.40)
Any AIN457 150mg Q4W	2.31	(2.07, 2.58)	0.07	(0.03, 0.13)	0.16	(0.10, 0.24)
Any AIN457 300 Q4W	3.02	(2.77, 3.28)	0.03	(0.01, 0.07)	0.18	(0.12, 0.25)
Any AIN457 300 Q2W	2.33	(1.38, 3.68)	0.26	(0.03, 0.92)	0.51	(0.14, 1.31)
Any AIN457 dose	2.65	(2.49, 2.82)	0.06	(0.03, 0.08)	0.16	(0.13, 0.21)
Placebo	3.91	(3.05, 4.94)	0.11	(0.01, 0.40)	0.06	(0.00, 0.31)
Any AIN457 dose (pediatric)	2.08	(1.19, 3.38)	0.00	(0.00, 0.46)	0.00	(0.00, 0.46)
Placebo (pediatric)	9.76	(0.25, 54.37)	0.00	(0.00, 35.70)	0.00	(0.00, 35.70)
	Staphylococcal infection		**CNS infection**			
Any AIN457 75mg Q4W	0.28	(0.12, 0.55)	0.10	(0.02, 0.30)	-	-
Any AIN457 150mg Q4W	0.57	(0.45, 0.71)	0.04	(0.02, 0.09)	-	-
Any AIN457 300 Q4W	0.66	(0.55, 0.79)	0.06	(0.03, 0.11)	-	-
Any AIN457 300 Q2W	1.29	(0.62, 2.36)	0.26	(0.03, 0.92)	-	-
Any AIN457 dose	0.63	(0.56, 0.72)	0.06	(0.04, 0.09)	-	-
Placebo	0.39	(0.16, 0.80)	0.11	(0.01, 0.40)	-	-
Any AIN457 dose (pediatric)	0.38	(0.08, 1.11)	0.13	(0.00, 0.70)	-	-
Placebo (pediatric)	0.00	(0.00, 35.70)	0.00	(0.00, 35.70)	-	-
	Hypersensitivity					
Any AIN457 75mg Q4W	4.83	(4.04, 5.74)	-	-	-	-
Any AIN457 150mg Q4W	6.58	(6.15, 7.04)	-	-	-	-
Any AIN457 300 Q4W	7.98	(7.56, 8.42)	-	-	-	-
Any AIN457 300 Q2W	12.26	(9.86, 15.07)	-	-	-	-
Any AIN457 dose	7.32	(7.05, 7.61)	-	-	-	-
Placebo	9.75	(8.35, 11.33)	-	-	-	-

Treatment Groups	Incidence rate per 100 PTY (95% CI)					
Any AIN457 dose (pediatric)	6.35	(4.61, 8.53)	-	-	-	-
Placebo (pediatric)	9.90	(0.25, 55.17)	-	-	-	-
Important potential risks						
	Malignancy		**SIB**		**Hepatitis B reactivation**	
Any AIN457 75mg Q4W	0.45	(0.24, 0.77)	0.00	(0.00, 0.13)	0.00	(0.00, 0.13)
Any AIN457 150mg Q4W	0.83	(0.68, 0.99)	0.08	(0.04, 0.14)	0.03	(0.01, 0.07)
Any AIN457 300 Q4W	0.82	(0.69, 0.96)	0.07	(0.04, 0.12)	0.01	(0.00, 0.04)
Any AIN457 300 Q2W	0.38	(0.08, 1.12)	0.26	(0.03, 0.92)	0.00	(0.00, 0.47)
Any AIN457 dose	0.81	(0.72, 0.90)	0.08	(0.05, 0.11)	0.02	(0.01, 0.03)
Placebo	1.11	(0.68, 1.71)	0.17	(0.03, 0.49)	0.06	(0.00, 0.31)
Any AIN457 dose (pediatric)	0.00	(0.00, 0.46)	0.38	(0.08, 1.10)	0.00	(0.00, 0.46)
Placebo (pediatric)	0.00	(0.00, 35.70)	0.00	(0.00, 35.70)	0.00	(0.00, 35.70)
	MACE (composite)		**MACE (MI)**		**MACE (Stroke)**	
Any AIN457 75mg Q4W	0.70	(0.43, 1.08)	0.35	(0.17, 0.64)	-	(0.10, 0.50)
Any AIN457 150mg Q4W	0.41	(0.31, 0.53)	0.20	(0.13, 0.29)	0.16	(0.10, 0.24)
Any AIN457 300 Q4W	0.38	(0.30, 0.48)	0.19	(0.13, 0.26)	0.14	(0.09, 0.20)
Any AIN457 300 Q2W	0.13	(0.00, 0.71)	0.00	(0.00, 0.47)	0.13	(0.00, 0.71)
Any AIN457 dose	0.41	(0.35, 0.48)	0.21	(0.17, 0.26)	0.14	(0.11, 0.118)
Placebo	0.67	(0.34, 1.16)	0.28	(0.09, 0.65)	0.33	(0.12, 0.72)
Any AIN457 dose (pediatric)	0.13	(0.00, 0.70)	0.00	(0.00, 0.46)	0.13	(0.00, 0.70)
Placebo (pediatric)	0.00	(0.00, 35.70)	0.00	(0.00, 35.70)	0.00	(0.00, 35.70)
	MACE (Cardiovascuklar death)					
Any AIN457 75mg Q4W	0.31	(0.14, 0.59)	-	-	-	-
Any AIN457 150mg Q4W	0.12	(0.07, 0.19)	-	-	-	-
Any AIN457 300 Q4W	0.09	(0.05, 0.14)	-	-	-	-

Treatment Groups	Incidence rate per 100 PTY (95% CI)					
Any AIN457 300 Q2W	0.00	(0.00, 0.47)	-	-	-	-
Any AIN457 dose	0.11	(0.08, 0.15)	-	-	-	-
Placebo	0.22	(0.06, 0.57)	-	-	-	-
Any AIN457 dose (pediatric)	0.00	(0.00, 0.46)	-	-	-	-
Placebo (pediatric)	0.00	(0.00, 35.70)	-	-	-	-

Source: PSUR 9 outputs Table 18 Change in the incidence rates relative to the last review period of treatment emergent adverse events of special interest by PSUR risks, by treatment group Entire treatment group Safety.

Table below describes the key benefits (i.e. those which contribute importantly to the overall benefit-risk evaluation) and the rationale for the choice of each benefit as key; Table 18-2 provides a summary of the characterization of key benefits as presented in Section 17.

Table 18-2 Key benefits and rationale

Indication	Key benefit	Rationale
Psoriasis	PASI response	PASI score is a standard and validated measurement in psoriasis. Although > 50% and > 75% improvements, compared to baseline, have been considered as clinically meaningful, new psoriasis therapies have demonstrated higher levels of efficacy by achieving PASI 90 (90% reduction) or PASI 100 (100% clearance). Currently, the best evidence of efficacy is the percentage of patients who achieve the result of “clear or almost clear” (PASI>90%) on treatment.
Psoriatic arthritis	ACR20 response	ACR20 response is a key benefit because this composite score represents a minimum 20% improvement in key components of psoriatic arthritis including the number of swollen and tender joints, physician and patient assessment of overall disease activity, patient assessment of pain due to psoriatic arthritis and patient reported outcome measure of disability. It is recommended as an important endpoint in clinical guidelines for the disease.
Axial spondyloarthritis	ASAS 20 or 40	The ASAS 20 response is defined as an improvement of ≥20% and ≥1 unit on a scale of 10 in at least three of the four main domains and no worsening of ≥20% and ≥1 unit on a scale of 10 in the remaining domain. The ASAS 40 response is defined as an improvement of ≥40% and ≥2 units on a scale of 10 in at least three of the four main domains and no worsening at all in the remaining domain.
	BASDAI 50	BASDAI 50, the proportion of patients who achieved at least a 50% improvement from baseline in total BASDAI score, was included as an exploratory efficacy variable that supports the clinical relevance of the improvement in BASDAI score. BASDAI 50 is a clinically meaningful, higher hurdle efficacy endpoint that has been identified by

Indication	Key benefit	Rationale
		the Assessment in Spondyloarthritis International Society (ASAS) as a key indicator in determining the adequacy of therapeutic response to treatment in AS.
Juvenile idiopathic arthritis	Time to flare (JIA)	Time to disease flare (JIA)is a clinically significant outcome defined in the registrational study as ≥30% worsening in at least three of the six JIA ACR response variables Physician global assessment of overall disease activity Parent or patient global assessment of overall well-being Functional ability (CHAQ) Number of joints with active arthritis Number of joints with limited range of motion Index of inflammation: CRP and ≥ 30% improvement in not more than one of the six JIA ACR response variables and a minimum of two active joints.
Hidradenitis suppurativa	HiSCR50	The HiSCR is defined by the status of three types of lesions: abscesses (fluctuant, with or without pus, tender or painful), inflammatory nodules (tender, erythematous, pyogenicgranulomatous lesions), and draining fistulae (sinus tracts, with communications to skin surface, d draining purulent discharge) (Kimball et al 2016(111)). The definition of response to treatment (HiSCR achievement) is: at least a 50% reduction in abscesses and inflammatory nodules (AN), no increase in the number of abscesses, and no increase in the number of draining fistulae from baseline.HiSCR75, HiSCR90, and HiSCR100 were defined by increasing the threshold on percentage reduction in AN count to 75%, 90% and 100%, respectively.

ACR: American College of Rheumatology; AS: Ankylosing Spondylitis; ASAS: Assessment in Spondyloarthritis International Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; HiSCR50: Hidradenitis Suppurativa Clinical Response, 50% reduction; JIA: Juvenile Idiopathic Arthritis; PASI: Psoriasis Area and Severity Index

The table below provides a summary of the characterization of key benefits as presented in Section 17.

Table 18-3 Summary of characterization of key benefits

Indications	Key benefit	Data source	Data	Conclusion
Psoriasis[1]	PASI response	Clinical trial data	In the pooled assessment of studies CAIN457A2302, CAIN457A2303, CAIN457A2308, CAIN457A2309, at Week 12 showed: A significantly higher proportion of patients achieved PASI 75 in the secukinumab 300 mg	Secukinumab demonstrated superior efficacy over placebo in the treatment of patients with moderate to severe; efficacy was dose-dependent, with higher response rates observed with the 300 mg dose

Indications	Key benefit	Data source	Data	Conclusion
			(79.4%) and 150 mg (69.2%) vs. placebo (4.2%). A significantly higher proportion of patients achieved PASI 90 in the secukinumab 300 mg (56.6%) and 150 mg (41.1%) vs. placebo (1.2%). A significantly higher proportion of patients achieved PASI 100 (i.e. clear skin) in the 300 mg (27.6%) and 150 mg (13.5%) vs. placebo (0.3%) achieved PASI 100. CAIN457A2310 week 12 data showed: A significantly higher proportion of patients achieved PASI 75 in the secukinumab low dose group (80.2%) and high dose group (80.1%) compared to placebo (14.9%). A significantly higher proportion of patients achieved IGA 0/1 in the secukinumab low dose group (69.8%) and high dose group (62.6%) compared to placebo (6.3%). A significantly higher proportion of patients achieved PASI 90 in the secukinumab low dose group (71.1%) and high dose group (69.3%) compared to placebo (2.5%). CAIN457A2311 week 12 data showed: A significantly higher proportion of patients achieved PASI 75 in both secukinumab low dose	group (compared to the 150 mg dose group) at all time-points in terms of PASI response The pediatric studies demonstrated the superiority of both secukinumab Low and High dose regimens compared to placebo (A2310) and historical placebo (A2311). Comparison of efficacy response rates at Week 12 between pediatric and adult pool showed a numerically higher efficacy response in pediatric patients vs. adult patients with same disease severity (moderate and severe) and same dose level (Low/150 mg and High/300 mg)

Indications	Key benefit	Data source	Data	Conclusion
			and high dose groups (92.9%) compared to historical placebo. A significantly higher proportion of patients achieved IGA 0/1 in the secukinumab low dose group (78.6%) and high dose group (83.3%) compared to historical placebo. A significantly higher proportion of patients achieved PASI 90 in the secukinumab low dose group (69.0%) and high dose group (76.2%) compared to historical placebo. CAIN457A2324 week 16 data showed: A significantly higher proportion of patients achieved PASI 90 in the secukinumab 300 mg Q2W group (73.2%) compared to the 300 mg Q4W group (55.5). A numerically higher proportion of patients achieved IGA 0/1 in the secukinumab 300 mg Q2W group (74.2%) compared to the 300 mg Q4W group (65.9).	The secukinumab 300 mg Q2W dose regimen demonstrated superiority over the secukinumab 300 mg Q4W dose regimen in heavier body weight patients (>=90 kg).
Psoriatic arthritis[1]	Proportion of patients with ACR20 response at Week 16 Proportion of patients with PASI90 at Week 16 in PsA trials	Clinical trial data	Significantly higher proportion of patients in the 300mg (51.2%) and 150mg (47.4%) vs placebo (18.1%) achieved an ACR20 response at Week 16 Significantly higher proportion of patients in the 300mg (46.8%) and 150mg (34.9%) vs placebo (5.8%) achieved a PASI90 response at Week 16.	The majority of patients treated with the recommended 150 mg and 300 mg regimens achieved an ACR20 response in joint-related signs and symptoms and achieved benefit in skin clinically meaningful endpoint PASI90. This data is consistent with the CDS information. The I.V. regimen (secukinumab 6

Indications	Key benefit	Data source	Data	Conclusion
	Proportion of patients achieving ACR 50 at Week 16	Clinical trial data	In study P12302, secukinumab 6 mg/kg - 3 mg/kg demonstrated superiority over placebo for ACR50 response using non-responder imputation with a rapid onset of action as early as Week 4 that was sustained at all subsequent visits until and including at Week 16 (60/191 (31.41%) vs. 12/190 (6.32%); p<0.0001).	mg/kg - 3 mg/kg) demonstrated efficacy in adult patients of active PsA. The efficacy demonstrated by secukinumab at Week 16 was sustained up to Week 52
Axial spondyloarthritis[1]	Proportion of patients with ASAS 20 response at Week 16	Clinical trial data	Study CAIN457F2305 produced significantly higher ASAS 20 response rates compared with placebo at Week 16: 60.8% for iv-150 mg and 59.7% for iv-75 mg vs 28.7% for placebo (p<0.0001 for both comparisons vs placebo). Study CAIN457F2310 demonstrated significantly higher ASAS 20 response rates for secukinumab 150 mg s.c. vs placebo at Week 16, in contrast to the 75 mg s.c. dose, with a clinically meaningful lower absolute response rate of 20% compared to the 150 mg s.c. dose at Week 16: 61.1% for 150 mg s.c. (p=0.0001 vs placebo); 41.1% for 75 mg s.c. (p=0.0967 vs placebo); 28.4% for placebo.	The 150 mg s.c. regimen produced significantly higher ASAS 20 response rates than placebo, with clinically meaningful dose separation from the 75 mg s.c. regimen through Week 16.
	Proportion of patients with ASAS 40	Clinical trial data	In Study CAIN457F2305, both secukinumab regimens (iv-150 mg and iv-75 mg) produced	The higher response rates observed with all secukinumab doses compared to

Indications	Key benefit	Data source	Data	Conclusion
	response at Week 16		significantly higher ASAS 40 response rates compared with placebo at Week 16 (iv-150 mg: 41.6%, p<0.0001 vs placebo, iv-75 mg: 33.1%, p=0.0006 vs placebo; 13.1% for placebo. In Study CAIN457F2310, ASAS 40 response rates were significantly higher for secukinumab 150 mg s.c. vs placebo at Week 16, with secukinumab 75 mg s.c. shown to be ineffective as tested in the hierarchy (150 mg s.c.: 36.1%, p=0.0008 vs placebo, 75 mg s.c.: 26.0%, p=0.0967 vs placebo; 10.8% for placebo. In study CAIN457H2315 ASAS 40 response in overall population using non-responder imputation at Week 16 (FAS) was statistically significantly higher in the secukinumab 150 mg Load and No Load groups compared to the placebo group (40.0% and 40.8% vs. 28.0%; p=0.0108 and p=0.0087). In study CAIN457P12301 ASAS 40 response in overall population using non-responder imputation at Week 16 was statistically significantly higher in the secukinumab 6 mg/kg-3 mg/kg group compared to the placebo group (108/264 (40.91%) vs. 60/262 (22.90%); p<0.0001).	placebo were evident at all-time points up to Week 16, with a rapid onset of action at Week 1 and minimal dose separation between the secukinumab 150 mg and 75 mg regimens till Week 16. The I.V. regimen (secukinumab 6 mg/kg - 3 mg/kg) demonstrated efficacy in adult patients with axSpA. The responses were sustained up to Week 52
	Proportion of patients with	Clinical trial data	At Week 16 in Study CAIN457F2305, the	All studies demonstrated a

Indications	Key benefit	Data source	Data	Conclusion
	BASDAI 50 response at Week 16		percentage of BASDAI 50 responders was 37.6% for iv-150 mg and 39.5% for iv-75 mg vs 8.2% for placebo. At Week 16 in Study CAIN457F2310, the percentage of BASDAI 50 responders was 30.6% for the 150 mg s.c. group and 24.7% for the 75 mg s.c. group vs 10.8% for the placebo group. In Study CAIN457H2315 BASDAI 50 response using non-responder imputation at Week 16 was statistically significantly higher for secukinumab 150 mg Load and No Load compared to placebo (37.3% and 37.5% vs. 21.0%; p=0.0001 and p=0.0002).	rapid onset of action for secukinumab by Weeks 1-2, with greater response rates compared with placebo up to Week 16.
Juvenile idiopathic arthritis[2]	Time to disease flare (JIA)	Clinical trial data	The time to flare in TP2 was statistically significantly longer with secukinumab for combined ERA and JPsA groups than with placebo (HR, 0.28 (95% CI 0.13 to 0.63), p<0.001).This corresponds to a 72% relative reduction in the risk of disease flare for patients randomized to continue secukinumab treatment compared to those randomized to placebo in TP2. A total of 31 JIA flares had occurred. The flare events occurred in 10/37 (27%) in the secukinumab group versus 21/38 (55%) in the placebo group. The median time to flare was not reached for the secukinumab group and	Secukinumab (150 mg for subjects ≥50 kg and 75 mg for subjects <50 kg) demonstrated efficacy for ERA and JPsA categories of JIA based on the significantly longer time to disease flare in TP2 and improvement in disease activity

Indications	Key benefit	Data source	Data	Conclusion
			was 453 days for the placebo group.	
Hidradenitis suppurativa[3]	Proportion of patients with HiSCR50 response at Week 16	Clinical Trial	At Week 16, in study CAIN457M2301, HiSCR50 response was achieved by 45.0% of subjects in the secukinumab Q2W group and 41.8% of subjects in the secukinumab Q4W group compared to 33.7% of subjects in the placebo group. The estimated odds ratios favoring both secukinumab dose regimens compared to placebo, were clinically relevant but statistical significance was achieved only for the secukinumab Q2W dose regimen (one-sided p=0.0070) and not for the secukinumab Q4W dose regimen (one-sided p=0.0418) based on the pre-defined testing hierarchy. In study CAIN457M2302, HiSCR50 response at Week 16 was achieved by 42.3% of subjects in the secukinumab Q2W group and 46.1% of subjects in the secukinumab Q4W group compared to 31.2% of subjects in the placebo group. The estimated odds ratios favoring both secukinumab dose regimens compared to placebo, were clinically relevant and statistically significant.	The two Phase 3 studies, M2301 and M2302, demonstrated that secukinumab was efficacious across multiple, clinically meaningful endpoints, with responses with the Q2W dose regimen being numerically better than the Q4W regimen. Importantly, these beneficial effects of secukinumab, including its effect on skin pain, translated into improvements in patient-reported QoL outcomes. Based on available long-term data, the beneficial treatment effects were rapid, maintained and progressively increasing up to Week 52, supporting the sustained efficacy of secukinumab in HS.

Source: Summary of Clinical Efficacy, Brunner, et. al. 2022,(97) Week 16 Clinical Study Report

ACR: American College of Rheumatology; AIN457: secukinumab; ASAS: Assessment in Spondyloarthritis International Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CDS: Core Data sheet; CI: Confidence Interval; ERA: Enthesitis-Related Arthritis; HiSCR50:

Hidradenitis Suppurativa Clinical Response, 50% reduction; HS: Hidradenitis suppurativa; i.v: intravenous; JIA: Juvenile Idiopathic Arthritis; JPsA: Juvenile Psoriatic Arthritis; kg: kilogram; mg: milligram; PASI: Psoriasis Area and Severity Index; q2w: every 2 weeks; q4w: every 4 weeks; QoL: Quality of Life; s.c: subcutaneous; TP: Treatment Period

Table below describes the key risks (i.e. those which contribute importantly to the overall benefit-risk evaluation) and the rationale for the choice of each risk as key.

Table 18-4 Key risks and rationale

Key risk	Rationale
Infections and infestations	Cytokine inhibition leads to a diminished inflammatory response, especially adaptive immunity, against pathogens. IL-17 is involved in host immunity against extracellular bacteria and fungi, which may explain the higher incidence of infections and candidiasis[112]. Autoimmune diseases themselves are a risk factor for infection. 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. This is replicated for other authorized indications, where the concomitant use of other immunosuppressants is an additional risk. Serious infections may lead to treatment discontinuation, therefore impact for treatment continuation in continuously monitored.
Hypersensitivity	Administration of proteins such as immunoglobulin (Ig) can lead to hypersensitivity reactions. Mechanism involved can be varied (type I hypersensitivity, or cytokine imbalance syndromes [paradoxical reaction]), while acute hypersensitivity reactions are recognizable, occurrence of long latency reactions require of continuous monitoring. Serious hypersensitivity reactions require immediate medical attention and lead to treatment discontinuation; therefore, impact for safety and treatment continuation will be monitored.
Malignant or unspecified tumors	Immune cells and cytokines dysregulated in autoimmune conditions may play a role in the development of cancer[113]. IL-17 has a controversial role in tumor immunity as it is hypothesized to play a role in both tumor suppression as well as proliferation[114]. Pooled data from clinical trials and post-marketing studies showed the low and infrequent incidence of malignancy in the secukinumab-treated patient population over a 5-year follow-up period[115]. Long term data from ongoing trials and newly approved indications will continue to be monitored for the occurrence of malignancies.
Major adverse cardiovascular events	Cardiovascular comorbidities have been linked to autoimmune diseases. Psoriasis is identified as an independent factor for myocardial infarction (MI), especially in the younger population[116]. Additionally, a meta-analysis assessing observational studies indicates that patients with ankylosing spondylitis are at a 1.41-fold risk of having CAD[117]. Psoriatic arthritis also increases the risk of clinical and subclinical cardiovascular disease, thus attributing to hastened atherosclerosis[118]. The role of biologics in directly precipitating cardiac adverse events is controversial. as controlling inflammation could potentially prevent cardiovascular events. Long term data from ongoing trials and newly approved indications will continue to be monitored for the occurrence of MACE events.

Key risk	Rationale
Suicidal ideation and behavior	Concern about suicidal tendencies with autoimmune diseases per se exist. Patients with autoimmune diseases often lead a poor quality of life and face social stigma. It is seen that inflammation may be associated with depression[119], and cytokine levels in the blood may correlate with depression[120]. Additionally, high levels of IL-17 have been seen in anxious patients with rheumatoid arthritis[121]. However, in a pooled safety analysis, secukinumab posed no risk of suicidal tendency in 3,430 patients followed for 52 weeks[122]. Although the overall incidence of SIB related adverse events is low (which may or may not exceed the background incidence of SIB in PsO, PsA and AS patients) and causality has not been established, this risk may potentially result in death of the patient; therefore, long term data from ongoing trials and newly approved indications will continue to be monitored for the occurrence of SIB events.
Hepatitis B reactivation	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. Long term data from ongoing trials and newly approved indications will continue to be monitored for the occurrence of hepatitis B reactivation.

NMSC: Non-Melanoma Skin Cancer; MACE: Major Adverse Cardiovascular Events; SIB: Suicidal ideation and behavior

Table below provides a summary of the characterization of the key risks.

Table 18-5 Summary of characterization of key risks

Key risks	Data source	Data	Conclusion
Important identified risks			
Infections	Pooled clinical trials	EAIR for Any secukinumab dose for all indications was 68.9/100 (95% CI 67.8, 70.1) PTY as compared to 96.1/100 (95% CI 91.1, 101.2) PTY for placebo. EAIR by indication was similar. Dose-dependence has been observed for fungal infections. The EAIR of fungal infection for 300mg (both Q4W and Q2W) is statistically higher than the lower dose groups and placebo with the highest EAIR reported for the 300mg Q2W as 11.7/100 PTY 95% CI 9.39, 14.47). In pediatric patients, the overall EAIR for infections was in the range in adults receiving 300mg Q4W or lower dose; and EAIR for fungal infection was in the lowest range (2.1/100 PTY, 95%CI 1.2 – 3.4)	Infections are the most common AEs related to the known safety risk for secukinumab. In clinical trials, The EAIR for overall infections is similar to placebo. Dose-dependence has been recognized for fundal infections. In real-world data (CorEvitas) serious IR for serious infections is similar to non-IL-17 biologics. Post-marketing reporting rate has been stable over years with a trend of decrease.
	Post-marketing reports	Cumulative reporting rates per 100 PTY were CCI for all infections and CCI for serious infections. Both reporting rates have remained stable over years with a decreasing trend. Upper respiratory infection (per MedDRA HLT) was reported in CCI (30%) infections cases (CCI /100 PTY), mainly nasopharyngitis (N= CCI CCI /100 PTY). Of the serious infections, pneumonia (N=CCI CCI /100 PTY) and lower respiratory tract infection (N=CCI CCI /100 PTY) were the most common serious infections. Fungal infections (per MedDRA HLGT) were reported in CCI cases (CCI /100 PTY) with candia infections (per MedDRA HLT) being most common (N=CCI CCI /100 PTY)	

Key risks	Data source	Data	Conclusion
	CorEvitas	IR per 100 PTY for overall serious infections and pneumonia, respectively: Secukinumab CCI) and CCI Non-IL-17 biologics: CCI) and CCI) Non-biologic systemic therapies: CCI) and CCI)	
Hypersensitivity	Pooled clinical trials	EAIR per 100 PTY for overall hypersensitivity events in all indications: Any secukinumab dose: 7.32 (7.05, 7.61) Placebo: 9.75 (8.35, 11.33) In patients receiving 300mg Q2W, the EAIR was 12.26 (9.86, 15.07) EAIR in pediatric patients were in the similar range	The nature of the search criteria inevitably includes the events that are not necessarily a hypersensitivity reaction, such as "rash" which may be an underlying condition. In clinical trials, CCI . Per available real-world data, there is no difference in the incidence between secukinumab and other therapies.
	Post-marketing reports	Reporting rate: CCI /100 PTY. Stable over years with a trend of decrease. Rash was reported in CCI (40%) of the hypersensitivity cases. Serious reactions included anaphylactic reaction and angioedema	
	CorEvitas	IR per 100 PTY for severe and anaphylactic reactions: Secukinumab: CCI (CCI) Non-IL-17 biologics: CCI (CCI) Non-biologic systemic therapies: CCI (CCI)	

Key risks	Data source	Data	Conclusion
Important potential risks:			
Malignancy (overall and the top 5 malignancies :skin, breast, CCI [redacted])	Pooled clinical trials	EAIR per 100 PTY for overall malignancy events in all indications: Any secukinumab dose: 0.81 (0.72, 0.90) Placebo: 1.11 (0.68, 1.71) After excluding NMSC, when compared the CT data with general population in the US (SEER registry) the SIR was 1.13 (0.97 – 1.30). When examining the top 5 malignancies (excluding NMSC) as compared to SEER, incidence for skin melanoma was found to be higher for Any 150mg Q4W (SIR 2.89, [1.32 – 5.48]) and 300mg Q4W (SIR 2.79, [1.48 – 4.77]). However, when comparing with PsO and PsA subjects (with / without exposure to other Il-17 inhibitors and biologics), no increased risk has been identified in patients treated with secukinumab, therefore, baseline indication risk cannot be ruled out. No increased risk for secukinumab exposed patients over the suspected risk for the correlation between PsO and PsA patients with skin melanoma is observed	Incidence of overall malignancies (excluding NMSC) in CT are similar to the US general population as registered in SEER registry. CCI [redacted]. Post-marketing reporting rate has been stable with a trend of decrease. Pre-existing malignancies are common in post-marketing reports
	Post-marketing reports	Reporting rate CCI /100 PTY, stable over years with a trend of decrease. Pre-existing malignancies were common (at least CCI given a history of prior cancer diagnosesor/and chemo- or/and radiation therapies. At least 9% cases occurred with 6 months after the first dose of secukinumab	

Key risks	Data source	Data	Conclusion
	CorEvitas	IR per 100 PTY for malignancies (excluding NMSC): Secukinumab: CCI) Non-IL-17 biologics: CCI) Non-biologic systemic therapies: CCI) EAIR per 100 PTY for skin melanoma: Secukinumab: CCI (CCI) Non-IL-17 biologics: CCI (CCI) Non-biologic systemic therapies: < CCI (CCI)	
MACE	Pooled clinical trials	EAIR per 100 PTY for MACE (composite) for all indications: Any secukinumab dose: 0.41 (0.35, 0.48) Placebo: 0.67 (0.34, 1.16)	No increased risk for MACE is identified
	Post-marketing reports	Post-marketing reporting rate for composite MACE was CCI /100 PTY. Pre-existing cardiovascular risks were common	
	CorEvitas	Baseline comorbidities were reported in more than 70% of the enrolled patients, mainly cardiovascular risks. IR per 100 PTY for MACE (composite): Secukinumab: CCI (CCI) Non-IL-17 biologics: CCI (CCI) Non-biologic systemic therapies: CCI (CCI	
SIB	Pooled clinical trials	EAIR per 100 PTY for SIB for all indications: Any secukinumab dose: 0.08 (0.05, 0.11) Placebo: 0.17 (0.03, 0.49) Completed suicide was reported for 2 patients (both in PsO studies)	No increased risk for SIB is identified.
	Post-marketing reports	Reporting rate for overall SIB was CCI /100 PTY (stable over years). Completed suicide was reported for 16 patients (CCI /100 PTY)	

Key risks	Data source	Data	Conclusion
	CorEvitas	IR per 100 PTY for SIB: Secukinuman: CCI) Non-IL-17 biologics: CCI Non-biologic systemic therapies: CCI) No completed suicide reported	
Hepatitis B reactivation	Pooled clinical trials	EAIR per 100 PTY for SIB for all indications: Any secukinumab dose: 0.02 (0.01, 0.03) Placebo: 0.06 (0.00, 0.31)	The incidence rate in clinical trials are calculated based on all events as identified by the search criteria. Each of these cases need to be reviewed for evidence of HBV reactivation. Cumulatively there are only CCI confirmed cases (all in postmarketing reports.
	Post-marketing reports	Upon medical review, HBV reactivation was demonstrated in CCI cases (CCI /100 PTY).	
	CorEvitas	N/A	

AE: Adverse event; EAIR: CI: Confidence interval; Exposure adjusted incidence rate; GI: Gastrointestinal; HLT: High level term; HLGT: High level group term; IR: Incidence ratio; MACE: Major adverse cardiovascular events; MedDRA: Medical Dictionary for Regulatory Activities; NMSC: on Melanoma Skin Cancer; PsA: Psoriatic arthritis; PsO: Psoriasis; PTY: Patient treatment years; SEER: Surveillance, Epidemiology; SIB: Suicidal ideation and behavior; US: United States

Overall, the benefit-risk balance of Cosentyx for the approved indications is considered to remain favorable.

19 Conclusions and actions

Overall, review of the cumulative safety data showed a consistent safety profile of secukinumab across indications. Newly identified signals during the reporting period that led to CDS update (eczematous eruptions [including dyshidrotic eczema, atopic dermatitis-like eruptions and dermatitis exfoliative generalized], and pyoderma gangrenosum) have not altered the benefit/risk profile for secukinumab, since these reactions are detectable, mainly of mild-moderate intensity and manageable with standard of care. It is considered that the label update is enough for risk minimization, and no change in the RMP is deemed necessary.

Per PRAC request the MAH has reviewed cases of angioedema reported in clinical trials and post-marketing experience; though the number of cases is very limited causal association with secukinumab cannot be ruled out for 36% of the reported cases, this summed-up to the listed allergic reactions for which a common mechanism is shared (urticaria and anaphylaxis) has been considered sufficient evidence to confirm angioedema as a new ADR for secukinumab; therefore the MAH is updating the CDS to include angioedema in sections warning and precautions and ADR. Similar to the above described new ADRs, no change in the benefit/risk profile for secukinumab due to the inclusion of angioedema, since these reactions are clinically detectable, mainly of mild-moderate intensity and manageable with standard of care; thus, no need for additional risk minimization measures and no update to the risk management plan is warranted.

Likewise, per PRAC request, review of data of CCI has been done for second consecutive time, this comprehensive analysis did not provide evidence of any direct or indirect effect of secukinumab treatment on CCI. Therefore, the MAH concludes this signal is refuted, based on lack of evidence supporting a causal association between CCI and secukinumab exposure. An update to the CDS/SmPC is not currently warranted and no updates to the RMP are deemed necessary. Novartis will continue to monitor CCI under routine pharmacovigilance procedures, and proposes this topic not to be presented in future PSURs unless a validated signal is identified.

The review of information from all available sources revealed no clinically relevant increase in the frequency or severity of any of the identified risks, and no change in the characteristics for the safety concerns (important identified and potential risks and missing information) has been identified. The safety data remain in accord with the previous cumulative (i.e. CT and post-marketing) experience and with ongoing standard pharmacovigilance and risk minimization activities (labeling).

Long-term use of secukinumab in PsO, PsA and SpA have consolidated the benefit in these indications, plus extended indications for pediatric population have been confirmed. Lastly secukinumab has demonstrated to benefit patients with moderate to severe HS.

In conclusion, the benefit/risk assessment is considered favorable (and unchanged) in the approved indications (psoriasis including pediatric psoriasis, PsA, SpA, JIA and HS).

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