NOVARTIS

COSENTYX® 150 mg/mL solution for injection

(Solution for injection in a pre-filled syringe or pre-filled pen)

COSENTYX® 300 mg/2 mL solution for injection

(Solution for injection in a pre-filled syringe or pre-filled pen)

Professional Information

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SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

COSENTYX® 150 mg/mL SOLUTION FOR INJECTION

COSENTYX® 300 mg/2 mL SOLUTION FOR INJECTION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

COSENTYX® 150 mg/mL solution for Injection:

Each 1,0 mL pre-filled syringe / pre-filled pen contains 150 mg secukinumab.

Sugar free

COSENTYX® 300 mg/2 mL solution for injection:

Each 2,0 mL pre-filled syringe or pre-filled pen contains 300 mg secukinumab.

Sugar free

Secukinumab is a recombinant fully human monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Solution for injection in a single dose pre-filled syringe:

The solution is clear and colourless to slightly yellow.

Solution for injection in a pre-filled pen:

The solution is clear and colourless to slightly yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Plaque psoriasis

COSENTYX® is indicated for the treatment of moderate to severe plaque psoriasis in patients 6 years and older who are candidates for systemic therapy or phototherapy.

Psoriatic arthritis

COSENTYX® is indicated for the treatment of adult patients with active psoriatic arthritis. COSENTYX® can be used alone or in combination with methotrexate.

Axial spondyloarthritis (axSpA) with or without radiographic damage

Ankylosing spondylitis (AS)/axSpA with radiographic damage

COSENTYX® is indicated for the treatment of adult patients with active ankylosing spondylitis.

Non-radiographic axial spondyloarthritis (nr-axSpA) / axSpA without radiographic damage

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

Hidradenitis Suppurativa (HS)

COSENTYX® is indicated for the treatment of adult patients with moderate to severe hidradenitis suppurativa (acne inversa).

4.2 Posology and method of administration

COSENTYX® is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which COSENTYX® is indicated.

Posology

Adult plaque psoriasis

The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Some patients may derive an additional benefit from receiving 300 mg every 2 weeks.

Each 300 mg dose is given as one subcutaneous injection of 300 mg or as two subcutaneous injections of 150 mg.

Paediatric plaque psoriasis (adolescents and children from the age of 6 years)

The recommended dose is based on body weight (Table 1) and administered by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3, and 4 followed by monthly maintenance dosing (every 4 weeks). Each 150 mg dose is given as one subcutaneous injection of 150 mg. Each 300 mg dose is given as one subcutaneous injection of 300 mg or as two subcutaneous injections of 150 mg.

Table 1: Recommended dose of COSENTYX® for paediatric plaque psoriasis

Body weight at time of dosing	Recommended Dose
≥ 50 kg	150 mg (*may be increased to 300 mg)
***Some patients may derive additional benefit from the higher dose.**	

The 150 mg solution for injection in pre-filled syringe or pen is not indicated for administration to paediatric patients with a weight < 50 kg.

Psoriatic arthritis

For patients with concomitant moderate to severe plaque psoriasis or who are anti-TNFα inadequate responders (IR), the recommended dose is 300 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Each 300 mg dose is given as one subcutaneous injection of 300 mg or as two subcutaneous injections of 150 mg.

For other patients, the recommended dose is 150 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Based on clinical response, the dose can be increased to 300 mg.

Axial spondyloarthritis (axSpA)

Ankylosing spondylitis (AS)

The recommended dose is 150 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Based on clinical response, the dose can be increased to 300 mg.

Each 300 mg dose is given as one subcutaneous injection of 300 mg or as two subcutaneous injections of 150 mg.

Non-radiographic axial spondyloarthritis (nr-axSpA)

The recommended dose is 150 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3, and 4 followed by monthly maintenance dosing.

For all of the above indications, available data suggest that a clinical response is usually achieved within 16 weeks of treatment. Consideration should be given to discontinuing treatment in patients who have shown no response by 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks.

Hidradenitis Suppurativa

The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by a maintenance dose of 300 mg every 2 weeks.

Each 300 mg dose is given as one subcutaneous injection of 300 mg or as two subcutaneous injections of 150 mg.

Special populations

Elderly patients (aged 65 years and over)

No dose adjustment is required (see **section 5.2**).

Renal impairment / hepatic impairment

COSENTYX® has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population

The safety and efficacy of COSENTYX® in children with plaque psoriasis below the age of 6 years have not been established.

The safety and efficacy of COSENTYX® in children below the age of 18 years in other indications have not yet been established. No data are available.

Method of administration

Pre-filled syringe and pre-filled pen:

COSENTYX® is to be administered by subcutaneous injection. If possible, areas of the skin that show psoriasis should be avoided as injection sites. The solution/the syringe/the pen must not be shaken.

After proper training in subcutaneous injection technique, patients may self-inject COSENTYX® or be injected by a caregiver if a physician determines that this is appropriate. However, the physician should ensure appropriate follow up of patients. Patients and/or caregivers should be instructed to inject the full amount of COSENTYX® according to the instructions provided in the patient information leaflet. Comprehensive instructions for administration are given in the patient information leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in **section 6.1**.

Clinically important, active infection, e.g., active tuberculosis (see **section 4.4**).

Live vaccines should not be given concurrently with COSENTYX® (see **section 4.5**).

Pregnancy and lactation.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicines, the name and the batch number of the administered product should be clearly recorded.

Infections

Secukinumab has the potential to increase the risk of infections. Serious infections have been observed in patients receiving secukinumab in the post-marketing setting. Caution should be exercised when considering the use of secukinumab in patients with a chronic infection or a history of recurrent infection.

Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and secukinumab should not be administered until the infection resolves.

In clinical studies, infections have been observed in patients receiving secukinumab (see **section 4.8**). Most of these were mild or moderate upper respiratory tract infections such as nasopharyngitis and did not require treatment discontinuation.

Related to the mechanism of action of secukinumab, non-serious mucocutaneous candida infections were more frequently reported for secukinumab than placebo in the psoriasis clinical studies (3,55 per 100 patient years for secukinumab 300 mg versus 1,00 per 100 patient years for placebo) (see **section 4.8**).

Pre-treatment evaluation for tuberculosis

Tuberculosis (active and/or latent reactivation) can occur in patients with secukinumab. Patients should be evaluated for tuberculosis infection prior to initiating treatment with secukinumab. Secukinumab should not be given to patients with active tuberculosis. Initiation of treatment for latent tuberculosis should be considered prior to administering secukinumab. Anti-tuberculosis therapy should be considered prior to initiation of secukinumab in patients with a past history of latent or active tuberculosis or in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving secukinumab should be closely monitored for signs and symptoms of active tuberculosis during and after treatment.

Hepatitis B reactivation

Hepatitis B virus reactivation can occur in patients treated with Cosentyx. In accordance with clinical guidelines for immunosuppressants, testing patients for HBV infection is to be considered before initiating treatment with Cosentyx. Cosentyx should not be given to patients with active hepatitis B. Patients with evidence of positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation during Cosentyx treatment. If reactivation of HBV occurs while on Cosentyx, discontinuation of the treatment should be considered, and patients should be treated according to clinical guidelines.

Inflammatory bowel disease (IBD)

Cases of new or exacerbations of Crohn's disease and ulcerative colitis have been reported (see **section 4.8**). Caution should be exercised when prescribing secukinumab to patients with inflammatory bowel disease, including Crohn's disease and ulcerative colitis.

In addition, cases of new onset IBD have been reported with post-marketing use.

Patients should be closely monitored.

Hypersensitivity reactions

In clinical studies, rare cases of anaphylactic reactions and angioedema have been observed in patients receiving secukinumab. Angioedema cases have also been reported in the post-marketing setting. If an anaphylactic or other serious allergic reactions occur, administration of secukinumab should be discontinued immediately and appropriate therapy initiated.

Eczematous eruptions

In post-marketing reports, cases of severe eczematous eruptions, including dermatitis-like eruptions, dyshidrotic eczema, and erythroderma (exfoliative dermatitis), were reported in patients receiving COSENTYX®; some cases resulted in hospitalization (see **section 4.8**). The onset of eczematous eruptions was variable, ranging from days to months after the first dose of COSENTYX®.

Treatment with COSENTYX® may need to be discontinued to resolve the eczematous eruption. Some patients were successfully treated for eczematous eruptions while continuing COSENTYX®.

Latex sensitive individuals – 1 mL pre-filled-syringe/pen

The removable needle caps of the COSENTYX® 1 mL pre-filled syringe/pen contain a derivative of natural rubber latex. No natural rubber latex has to date been detected in the removable needle cap. Nevertheless, the use of COSENTYX® pre-filled syringes/pens in latex sensitive individuals has not been studied and there is therefore a potential risk of hypersensitivity reactions which cannot be completely ruled out.

Vaccinations

Live vaccines should not be given concurrently with secukinumab (see **section 4.5**).

Patients receiving secukinumab may receive concurrent inactivated or non-live vaccinations. In a study, after *meningococcal* and inactivated *influenza* vaccinations, a similar proportion of healthy volunteers treated with 150 mg of secukinumab and those treated with placebo were able to mount an adequate immune response of at least a 4-fold increase in antibody titres to *meningococcal* and *influenza* vaccines. The data suggests that secukinumab does not suppress the humoral immune response to the *meningococcal* or *influenza* vaccines.

Prior to initiating therapy with COSENTYX®, it is recommended that paediatric patients receive all age-appropriate immunisations as per current immunisation guidelines.

Concomitant immunosuppressive therapy

In psoriasis studies, the safety and efficacy of secukinumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. Secukinumab was administered concomitantly with methotrexate (MTX), sulfasalazine and/or corticosteroids in arthritis studies (including in patients with psoriatic arthritis and ankylosing spondylitis). Caution should be exercised when considering concomitant use of other immunosuppressants and secukinumab (see also **section 4.5**).

4.5 Interaction with other medicines and other forms of interaction

Live vaccines should not be given concurrently with secukinumab (see also **section 4.4**).

In a study in adult subjects with plaque psoriasis, no interaction was observed between secukinumab and midazolam (CYP3A4 substrate).

No interaction was seen when secukinumab was administered concomitantly with methotrexate (MTX) and/or corticosteroids in arthritis studies (including in patients with psoriatic arthritis and ankylosing spondyloarthritis).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use an effective method of contraception during treatment and for at least 20 weeks after treatment.

Pregnancy

COSENTYX® is contraindicated in pregnant women (see **section 4.3**).

Breast-feeding

Because immunoglobulins are excreted in milk, secukinumab should not be administered to a woman who is breastfeeding.

Fertility

The effect of secukinumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines:

COSENTYX® has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

a) Summary of the Safety Profile

The most frequently reported adverse drug reactions (ADRs) are upper respiratory tract infections (most frequently nasopharyngitis, rhinitis).

b) Tabulated list of adverse reactions

ADRs from clinical studies and post-marketing reports (Table 2) are listed by MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from the available data).

Over 20,000 patients have been treated with secukinumab in blinded and open-label clinical studies in various indications (plaque psoriasis and other autoimmune conditions), representing 34,908 patient years of exposure. Of these, over 14,000 patients were exposed to secukinumab for at least one year. The safety profile of secukinumab is consistent across all indications.

Table 2: List of adverse reactions in clinical studies[1] and post-marketing experience

System Organ Class	**Frequency**	**Adverse reaction**
Infections and infestations	Very common	Upper respiratory tract infections
	Common	Oral herpes
		Tinea pedis
	Uncommon	Oral candidiasis

		Otitis externa
		Lower respiratory tract infections
	Not known	Mucosal and cutaneous candidiasis (including oesophageal candidiasis)
Blood and lymphatic system disorders	Uncommon	Neutropenia
Immune system disorders	Rare	Anaphylactic reactions
Nervous system disorders	Common	Headache
Eye disorders	Uncommon	Conjunctivitis
Respiratory, thoracic and mediastinal disorders	Common	Rhinorrhoea
Gastrointestinal disorders	Common	Diarrhoea Nausea
	Uncommon	Inflammatory bowel disease (including Crohn's disease and ulcerative colitis).[3]
Skin and subcutaneous tissue disorders	Common	Urticaria, Dermatitis (including eczema)[3,4]
	Uncommon	Dyshidrotic eczema
	Rare	Exfoliative dermatitis[2]
	Not known	Pyoderma gangrenosum, Dermatitis exfoliative generalized, angioedema, hypersensitivity vasculitis

General disorders and administration site conditions	Common	Fatigue
[1)] Placebo-controlled clinical studies (phase III) in plaque psoriasis, PsA, AS and nr-axSpA patients exposed to 300 mg, 150 mg or placebo up to 12 weeks (psoriasis) or 16 weeks (PsA, AS and nr-axSpA) treatment duration [2)] Cases were reported in patients with psoriasis diagnosis [3)] Adverse Drug Reactions added based on post marketing reports. Frequency determined based on placebo-controlled clinical studies (phase III) in plaque psoriasis patients. [4)] These events are related to Eczematous eruptions		

c) Description of selected adverse reactions

Infections

In the placebo-controlled period of clinical studies in plaque psoriasis (a total of 1,382 patients treated with secukinumab and 694 patients treated with placebo for up to 12 weeks), infections were reported in 28,7 % of patients treated with secukinumab compared with 18,9 % of patients treated with placebo. The majority of infections consisted of non-serious and mild to moderate upper respiratory tract infections, such as nasopharyngitis, which did not necessitate treatment discontinuation. There was an increase in mucosal or cutaneous candidiasis, consistent with the mechanism of action, but the cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in 0,14 % of patients treated with secukinumab and in 0,3 % of patients treated with placebo (see **section 4.4**).

Over the entire treatment period (a total of 3,430 patients treated with secukinumab for up to 52 weeks for the majority of patients), infections were reported in 47,5 % of patients treated with secukinumab (0,9

per patient-year of follow-up). Serious infections were reported in 1,2 % of patients treated with secukinumab (0,015 per patient-year of follow-up).

Infection rates observed in psoriatic arthritis and ankylosing spondylitis clinical studies were similar to those observed in the psoriasis studies.

Due to the nature of the lesions, patients with hidradenitis suppurativa are more susceptible to infections. In the placebo-controlled period of clinical studies in hidradenitis suppurativa (a total of 721 patients treated with secukinumab and 363 patients treated with placebo for up to 16 weeks), infections were numerically higher to those observed in the psoriasis studies (30.7 % of patients treated with secukinumab compared with 31.7 % in patients treated with placebo). Most of these were non-serious, mild or moderate in severity and did not require treatment discontinuation or interruption.

Neutropenia

In psoriasis phase 3 clinical studies, neutropenia was more frequently observed with secukinumab than with placebo, but most cases were mild, transient and reversible. Neutropenia < 1,0 - 0,5 x 10^9 /l (CTCAE grade 3) was reported in 18 out of 3,430 (0,5 %) patients on secukinumab, with no dose dependence and no temporal relationship to infections in 15 out of 18 cases. There were no reported cases of more severe neutropenia. Non-serious infections with usual response to standard care and not requiring discontinuation of secukinumab were reported in the remaining 3 cases.

The frequency of neutropenia in psoriatic arthritis and ankylosing spondylitis is similar to psoriasis.

Rare cases of neutropenia < 0,5 x 10^9 /l (CTCAE grade 4) were reported.

Hypersensitivity reactions

In clinical studies, urticaria, rare cases of anaphylactic reactions and angioedema have been observed in patients receiving COSENTYX®. Angioedema cases have also been reported in the post-marketing setting. (see also **section 4.4**).

Immunogenicity

In psoriasis, psoriatic arthritis, axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis), and hidradenitis suppurativa clinical studies, less than 1 % of patients treated with secukinumab developed antibodies to secukinumab up to 52 weeks of treatment. About half of the treatment-emergent anti-drug antibodies were neutralising, but this was not associated with loss of efficacy or pharmacokinetic abnormalities.

Adverse reactions in hidradenitis suppurativa

COSENTYX® was studied in two placebo-controlled hidradenitis suppurativa trials with 1,084 patients (721 patients on COSENTYX® and 363 on placebo) with a total exposure of 825 patient years of study exposure (median duration of exposure for secukinumab-treated patients: 307 days). The safety profile observed in patients with HS treated with COSENTYX® was consistent with the known safety profile observed in psoriasis.

d) Paediatric population

The safety of secukinumab was assessed in two phase III studies in paediatric patients with plaque psoriasis. The first study (paediatric study 1) was a double-blind, placebo-controlled study of 162 patients from 6 to less than 18 years of age with severe plaque psoriasis. The second study (paediatric study 2) is an open-label study of 84 patients from 6 to less than 18 years of age with moderate to severe

plaque psoriasis. The safety profile reported in these two studies was consistent with the safety profile reported in adult plaque psoriasis patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Doses up to 30 mg/kg (approximately 2000 to 3000 mg) have been administered intravenously in clinical studies without dose-limiting toxicity. In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC10

Mechanism of action

Secukinumab is a fully human IgG1/κ monoclonal antibody that selectively binds to and neutralises 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. 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. Clinically relevant levels of secukinumab reach the skin and reduce local inflammatory markers. As a direct consequence treatment with secukinumab reduces erythema, induration and desquamation present in plaque psoriasis lesions.

IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. IL-17A plays a key role in the pathogenesis of plaque psoriasis, hidradenitis suppurativa, psoriatic arthritis and axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis) and is up-regulated in lesional skin in contrast to non-lesional skin of plaque psoriasis patients, and a higher frequency of IL-17-producing cells are detected in the synovial fluid of patients with psoriatic arthritis. IL-17A is considerably upregulated in hidradenitis suppurativa lesions compared to psoriasis patients and healthy controls, and significantly increased IL-17A serum levels have been observed in affected patients. The frequency of IL-17-producing cells is also significantly higher in the subchondral bone marrow of facet joints from patients with axial spondyloarthritis.

Inhibition of IL-17A was shown to be effective in the treatment of AS, thus establishing the key role of this cytokine in axial spondyloarthritis.

Pharmacodynamic effects

Serum levels of total IL-17A (free and secukinumab-bound IL-17A) are initially increased in patients receiving secukinumab. This is followed by a slow decrease due to reduced clearance of secukinumab-bound IL-17A, indicating that secukinumab selectively captures free IL-17A, which plays a key role in the pathogenesis of plaque psoriasis.

In a study with secukinumab, infiltrating epidermal neutrophils and various neutrophil-associated markers that are increased in lesional skin of plaque psoriasis patients were significantly reduced after one to two weeks of treatment.

Secukinumab has been shown to lower (within 1 to 2 weeks of treatment) levels of C-reactive protein, which is a marker of inflammation.

Clinical efficacy and safety

Plaque psoriasis

Adult patients

The safety and efficacy of secukinumab were assessed in four randomised, double-blind, placebo-controlled phase III studies in patients with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy [ERASURE, FIXTURE, FEATURE, JUNCTURE]. The efficacy and safety of secukinumab 150 mg and 300 mg were evaluated versus either placebo or etanercept. In addition, one study assessed a chronic treatment regimen versus a “retreatment as needed” regimen [SCULPTURE]. In these studies, each 300 mg dose was given as two subcutaneous injections of 150 mg.

Of the 2,403 patients who were included in the placebo-controlled studies, 79 % were biologic-naive, 45 % were non-biologic failures and 8 % were biologic failures (6 % were anti-TNF failures, and 2 % were anti-p40 failures). Approximately 15 to 25 % of patients in phase III studies had psoriatic arthritis (PsA) at baseline.

Psoriasis study 1 (ERASURE) evaluated 738 patients. Patients randomised to secukinumab received 150 mg or 300 mg doses at weeks 0, 1, 2, 3 and 4, followed by the same dose every month. Psoriasis study 2 (FIXTURE) evaluated 1,306 patients. Patients randomised to secukinumab received 150 mg or 300 mg doses at weeks 0, 1, 2, 3 and 4, followed by the same dose every month. Patients randomised to etanercept received 50 mg doses twice per week for 12 weeks followed by 50 mg every week. In both study 1 and study 2, patients randomised to receive placebo who were non-responders at week 12 then crossed over to receive secukinumab (either 150 mg or 300 mg) at weeks 12, 13, 14, and 15, followed by the same dose every month starting at week 16. All patients were followed for up to 52 weeks following first administration of study treatment.

Psoriasis study 3 (FEATURE) evaluated 177 patients using a pre-filled syringe compared with placebo after 12 weeks of treatment to assess the safety, tolerability, and usability of secukinumab self-administration via the pre-filled syringe. Psoriasis study 4 (JUNCTURE) evaluated 182 patients using a pre-filled pen compared with placebo after 12 weeks of treatment to assess the safety, tolerability, and usability of secukinumab self-administration via the pre-filled pen. In both study 3 and study 4, patients randomised to secukinumab received 150 mg or 300 mg doses at weeks 0, 1, 2, 3 and 4, followed by the same dose every month. Patients were also randomised to receive placebo at weeks 0, 1, 2, 3 and 4, followed by the same dose every month.

Psoriasis study 5 (SCULPTURE) evaluated 966 patients. All patients received secukinumab 150 mg or 300 mg doses at weeks 0, 1, 2, 3, 4, 8 and 12 and then were randomised to receive either a maintenance regimen of the same dose every month starting at week 12 or a “retreatment as needed” regimen of the

same dose. Patients randomised to “retreatment as needed” did not achieve adequate maintenance of response and therefore a fixed monthly maintenance regimen is recommended.

The co-primary endpoints in the placebo and active-controlled studies were the proportion of patients who achieved a PASI 75 response and IGA mod 2011 “clear” or “almost clear” response versus placebo at week 12 (see Tables 3 and 4). The 300 mg dose provided improved skin clearance particularly for “clear” or “almost clear” skin across the efficacy endpoints of PASI 90, PASI 100, and IGA mod 2011 0 or 1 response across all studies with peak effects seen at week 16, therefore this dose is recommended.

Table 3: Summary of PASI 50/75/90/100 & IGA* mod 2011 “clear” or “almost clear” clinical response in psoriasis studies 1, 3 and 4 (ERASURE, FEATURE and JUNCTURE)

	Week 12			**Week 16**		**Week 52**	
	Placebo	**150 mg**	**300 mg**	**150 mg**	**300 mg**	**150 mg**	**300 mg**
Study 1							
Number of patients	246	244	245	244	245	244	245
PASI 50 response n (%)	22 (8.9 %)	203 (83.5 %)	222 (90.6 %)	212 (87.2 %)	224 (91.4 %)	187 (77 %)	207 (84.5 %)
PASI 75 response n (%)	11 (4.5 %)	174 (71.6 %)**	200 (81.6 %)**	188 (77.4 %)	211 (86.1 %)	146 (60.1 %)	182 (74.3 %)
PASI 90 response n (%)	3 (1.2 %)	95 (39.1 %)**	145 (59.2 %)**	130 (53.5 %)	171 (69.8 %)	88 (36.2 %)	147 (60.0 %)

	Week 12			Week 16		Week 52	
	Placebo	**150 mg**	**300 mg**	**150 mg**	**300 mg**	**150 mg**	**300 mg**
PASI 100 response n (%)	2 (0.8 %)	31 (12.8 %)	70 (28.6 %)	51 (21.0 %)	102 (41.6 %)	49 (20.2 %)	96 (39.2 %)
IGA mod 2011 “clear” or “almost clear” response n (%)	6 (2.40 %)	125 (51.2 %)**	160 (65.3 %)**	142 (58.2 %)	180 (73.5 %)	101 (41.4 %)	148 (60.4 %)
Study 3							
Number of patients	59	59	58	-	-	-	-
PASI 50 response n (%)	3 (5.1 %)	51 (86.4 %)	51 (87.9 %)	-	-	-	-
PASI 75 response n (%)	0 (0.0 %)	41 (69.5 %)**	44 (75.9 %)**	-	-	-	-
PASI 90 response n (%)	0 (0.0 %)	27 (45.8 %)	35 (60.3 %)	-	-	-	-
PASI 100 response n (%)	0 (0.0 %)	5 (8.5 %)	25 (43.1 %)	-	-	-	-
IGA mod 2011 “clear” or “almost clear” response n (%)	0 (0.0 %)	31 (52.5 %)**	40 (69.0 %)**	-	-	-	-
Study 4							
Number of patients	61	60	60	-	-	-	-
PASI 50 response n (%)	5 (8.2 %)	48 (80.0 %)	58 (96.7 %)	-	-	-	-

	Week 12			Week 16		Week 52	
	Placebo	**150 mg**	**300 mg**	**150 mg**	**300 mg**	**150 mg**	**300 mg**
PASI 75 response n (%)	2 (3.3 %)	43 (71.7 %)**	52 (86.7 %)**	-	-	-	-
PASI 90 response n (%)	0 (0.0 %)	24 (40.0 %)	33 (55.0 %)	-	-	-	-
PASI 100 response n (%)	0 (0.0 %)	10 (16.7 %)	16 (26.7 %)	-	-	-	-
IGA mod 2011 "clear" or "almost clear" response n (%)	0 (0.0 %)	32 (53.3 %)**	44 (73.3 %)**	-	-	-	-

**The IGA mod 2011 is a 5-category scale including "0 = clear", "1 = almost clear", "2 = mild", "3 = moderate" or "4 = severe", indicating the physician's overall assessment of the psoriasis severity focusing on induration, erythema and scaling. Treatment success of "clear" or "almost clear" consisted of no signs of psoriasis or normal to pink coloration of lesions, no thickening of the plaque and none to minimal focal scaling.*

*** p values versus placebo and adjusted for multiplicity: p < 0.0001*

Table 4: Summary of clinical response on Psoriasis Study 2 (FIXTURE)

	Week 12				Week 16			Week 52		
	Placebo	**150 mg**	**300 mg**	**Etanercept**	**150 mg**	**300 mg**	**Etanercept**	**150 mg**	**300 mg**	**Etanercept**
Number of patients	324	327	323	323	327	323	323	327	323	323

	Week 12				**Week 16**			**Week 52**		
	Placebo	**150 mg**	**300 mg**	**Etanercept**	**150 mg**	**300 mg**	**Etanercept**	**150 mg**	**300 mg**	**Etanercept**
PASI 50 response n (%)	49 (15.1%)	266 (81.3%)	296 (91.6%)	226 (70.0%)	290 (88.7%)	302 (93.5%)	257 (79.6%)	249 (76.1%)	274 (84.8%)	234 (72.4%)
PASI 75 response n (%)	16 (4.9%)	219 (67.0%)**	249 (77.1%)**	142 (44.0%)	247 (75.5%)	280 (86.7%)	189 (58.5%)	215 (65.7%)	254 (78.6%)	179 (55.4%)
PASI 90 response n (%)	5 (1.5%)	137 (41.9%)	175 (54.2%)	67 (20.7%)	176 (53.8%)	234 (72.4%)	101 (31.3%)	147 (45.0%)	210 (65.0%)	108 (33.4%)
PASI 100 response n (%)	0 (0%)	47 (14.4%)	78 (24.1%)	14 (4.3%)	84 (25.7%)	119 (36.8%)	24 (7.4%)	65 (19.9%)	117 (36.2%)	32 (9.9%)
IGA mod 2011 “clear” or “almost clear” response n (%)	9 (2.8%)	167 (51.1%)**	202 (62.5%)**	88 (27.2%)	200 (61.2%)	244 (75.5%)	127 (39.3%)	168 (51.4%)	219 (67.8%)	120 (37.2%)

*** p values versus etanercept: p = 0.0250*

In an additional psoriasis study (CLEAR) 676 patients were evaluated. Secukinumab 300 mg met the primary and secondary endpoints by showing superiority to ustekinumab based on PASI 90 response at week 16 (primary endpoint), speed of onset of PASI 75 response at week 4, and long-term PASI 90 response at week 52. Greater efficacy of secukinumab compared to ustekinumab for the endpoints PASI 75/90/100 and IGA mod 2011 0 or 1 response ("clear" or "almost clear") was observed early and continued through to week 52. In this study, each 300 mg dose was administered as two injections of 150 mg.

Table 5: Summary of clinical response on CLEAR Study

	Week 4		**Week 16**		**Week 52**	
	Secukinumab 300 mg	**Ustekinumab***	**Secukinumab 300 mg**	**Ustekinumab***	**Secukinumab 300 mg**	**Ustekinumab***
Number of patients	334	335	334	335	334	335
PASI 75 response n (%)	166 (49.7 %)**	69 (20.6 %)	311 (93.1 %)	276 (82.4 %)	306 (91.6 %)	262 (78.2 %)
PASI 90 response n (%)	70 (21.0 %)	18 (5.4 %)	264 (79.0 %)**	192 (57.3 %)	250 (74.9 %)***	203 (60.6 %)
PASI 100 response n (%)	14 (4.2 %)	3 (0.9 %)	148 (44.3 %)	95 (28.4 %)	150 (44.9 %)	123 (36.7 %)

IGA mod 2011 “clear” or “almost clear” response n (%)	128 (38.3 %)	41 (12.2 %)	278 (83.2 %)	226 (67.5 %)	261 (78.1 %)	213 (63.6 %)

*Patients treated with secukinumab received 300 mg doses at Weeks 0, 1, 2, 3, and 4 followed by the same dose every 4 weeks until Week 52. Patients treated with ustekinumab received 45 mg or 90 mg at Weeks 0 and 4, then every 12 weeks until Week 52 (dosed by weight as per approved posology)

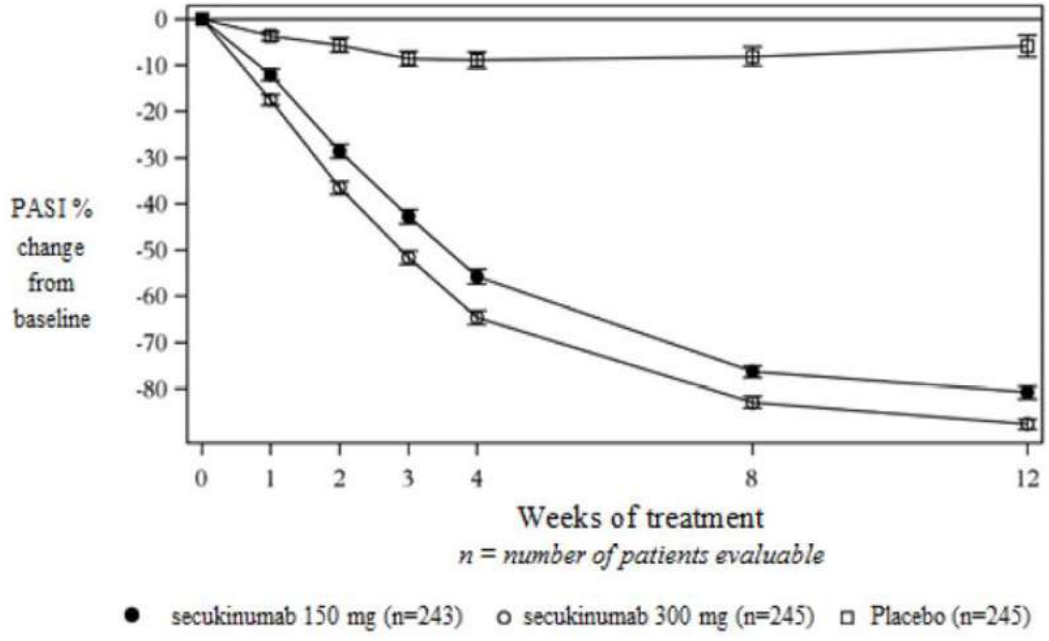
** p values versus ustekinumab: $p < 0.0001$ for primary endpoint of PASI 90 at Week 16 and secondary endpoint of PASI 75 at Week 4

*** p value versus ustekinumab: $p = 0.0001$ for secondary endpoint of PASI 90 at Week 52

Secukinumab was efficacious in systemic treatment-naive, biologic-naive, biologic/anti-TNF-exposed and biologic/anti-TNF-failure patients. Improvements in PASI 75 in patients with concurrent psoriatic arthritis at baseline were similar to those in the overall plaque psoriasis population.

Secukinumab was associated with a fast onset of efficacy with a 50 % reduction in mean PASI by week 3 for the 300 mg dose.

Figure 1: Time course of percentage change from baseline of mean PASI score in Study 1 (ERASURE)



Specific locations/forms of plaque psoriasis

In two additional placebo-controlled studies, improvement was seen in both nail psoriasis (TRANSFIGURE, 198 patients) and palmoplantar plaque psoriasis (GESTURE, 205 patients). In the TRANSFIGURE study, secukinumab was superior to placebo at week 16 (46,1 % for 300 mg, 38,4 % for 150 mg and 11,7 % for placebo) as assessed by significant improvement from baseline in the Nail Psoriasis Severity Index (NAPSI %) for patients with moderate to severe plaque psoriasis with nail involvement. In the GESTURE study, secukinumab was superior to placebo at week 16 (33,3 % for 300 mg, 22,1 % for 150 mg, and 1,5 % for placebo) as assessed by significant improvement of ppIGA 0 or 1 response (“clear” or “almost clear”) for patients with moderate to severe palmoplantar plaque psoriasis. In these studies, each 300 mg dose was given as two subcutaneous injections of 150 mg.

A placebo-controlled study evaluated 102 patients with moderate to severe scalp psoriasis, defined as having a Psoriasis Scalp Severity Index (PSSI) score of ≥ 12, an IGA mod 2011 scalp only score of 3 or greater and at least 30 % of the scalp surface area affected. Secukinumab 300 mg was superior to

placebo at week 12 as assessed by significant improvement from baseline in both the PSSI 90 response (52,9 % versus 2,0 %) and IGA mod 2011 0 or 1 scalp only response (56,9 % versus 5,9 %). Improvement in both endpoints was sustained for secukinumab patients who continued treatment through to week 24. In this study, each 300 mg dose was administered as two injections of 150 mg.

Quality of life/Patient-reported outcomes

Statistically significant improvements at week 12 (Studies 1-4) from baseline compared to placebo were demonstrated in the DLQI (Dermatology Life Quality Index). Mean decreases (improvements) in DLQI from baseline ranged from -10,4 to -11,6 with secukinumab 300 mg, from -7,7 to -10,1 with secukinumab 150 mg, versus -1,1 to -1,9 for placebo at week 12. These improvements were maintained for 52 weeks (Studies 1 and 2).

Forty percent of the participants in studies 1 and 2 completed the Psoriasis Symptom Diary©. For the participants completing the diary in each of these studies, statistically significant improvements at week 12 from baseline compared to placebo in patient-reported signs and symptoms of itching, pain and scaling were demonstrated.

Statistically significant improvements at week 4 from baseline in patients treated with secukinumab compared to patients treated with ustekinumab (CLEAR) were demonstrated in the DLQI and these improvements were maintained for up to 52 weeks.

Statistically significant improvements in patient-reported signs and symptoms of itching, pain and scaling at week 16 and week 52 (CLEAR) were demonstrated in the Psoriasis Symptom Diary© in patients treated with secukinumab compared to patients treated with ustekinumab.

Statistically significant improvements (decreases) at week 12 from baseline in the scalp psoriasis study were demonstrated in patient reported signs and symptoms of scalp itching, pain and scaling compared to placebo.

300 mg/2 mL pre-filled syringe and 300 mg/2 mL pre-filled pen.

Two randomized, double-blind, placebo-controlled studies in patients with plaque psoriasis were conducted to evaluate the safety and efficacy of secukinumab 300 mg when administered subcutaneously as a single 2 mL pre-filled syringe (ALLURE, 214 patients) or as a single 2 mL pre-filled pen (MATURE, 122 patients) compared to secukinumab 300 mg when administered as two subcutaneous injections in a 150 mg/1 mL pre-filled syringe. The co-primary endpoints were the proportion of patients who achieved a PASI 75 response and IGA mod 2011 'clear' or 'almost clear' response versus placebo at Week 12.

In the ALLURE study, the proportion of subjects achieving a PASI 75 and an IGA mod 2011 0 or 1 responses at Week 12 were 88.9 % and 76.4 % for the secukinumab 300 mg/2 mL pre-filled syringe group compared to 1.7 % and 1.4 % in the placebo group. In the MATURE study, the proportion of subjects achieving a PASI 75 and an IGA mod 2011 0 or 1 responses at Week 12 were 95.1 % and 75.6 % for the secukinumab 300 mg/2 mL pre-filled pen group compared to 10 % and 7.6 % in the placebo group. PASI 90 response at Week 12 was achieved with secukinumab 300 mg/2 mL pre-filled syringe (ALLURE study) and secukinumab 300 mg/2 mL pre-filled pen (MATURE study) compared to placebo in 66.7 % versus 1.6 % of subjects, respectively (ALLURE study) and 75.6 % versus 5 % of subjects, respectively (MATURE study).

The overall patient experience with subcutaneous self-injection with the 300 mg/2 mL pre-filled syringe and the 300 mg/2 mL pre-filled pen was measured using the Self-Injection Assessment Questionnaire (SIAQ). In the ALLURE study, the proportion of "very satisfied" and "satisfied" patients reached 89.5 %

at Week 28. In the MATURE study, the proportion of “very satisfied” and “satisfied” patients reached 91.8 % at Week 12.

With continued treatment over 52 weeks, the proportion of PASI 75/90/100 and IGA mod 2011 0 or 1 responders in the ALLURE study increased up to Week 28 and the responses were then maintained through Week 52. At Week 52, the PASI 75/90/100 and IGA mod 2011 0 or 1 response rates for the secukinumab 300 mg/2 mL pre-filled syringe group were 88.2 %, 75.6 %, 55.2 %, and 76.5 %, respectively, and 87.2 %, 81.7 %, 52.5 %, and 76.8 %, respectively for the secukinumab 2 × 150 mg/1 mL pre-filled syringe group.

Paediatric patients

Severe plaque psoriasis

A 52-week, randomized, double-blind, placebo and etanercept-controlled phase III study enrolled 162 paediatric patients 6 to less than 18 years of age, with severe plaque psoriasis (as defined by a PASI score ≥ 20, an IGA mod 2011 score of 4, and involving ≥ 10 % of the body surface area) who were candidates for systemic therapy. Approximately 43 % had prior exposure to phototherapy, 53 % to conventional systemic therapy, 3 % to biologics, and 9% had concomitant psoriatic arthritis.

Patients were randomized to receive one of the following four treatments:

- low dose secukinumab (150 mg for body weight ≥ 50 kg) at Weeks 0, 1, 2, 3, and 4 followed by the same dose every 4 weeks,
- high dose secukinumab (150 mg for body weight ≥ 25 kg and < 50 kg, or 300 mg for body weight ≥ 50 kg) at Weeks 0, 1, 2, 3, and 4 followed by the same dose every 4 weeks,
- placebo at Weeks 0, 1, 2, 3, and 4 followed by the same dose every 4 weeks
- etanercept (0.8 mg/kg) weekly (up to a maximum of 50 mg)

Patients randomized to receive placebo who were non-responders at Week 12 were switched to either the secukinumab low or high dose group (dose based on body weight group) and received study drug at Weeks 12, 13, 14, and 15, followed by the same dose every 4 weeks starting at Week 16.

The co-primary endpoints were the proportion of patients who achieved a reduction in PASI score of at least 75 % (PASI 75) and IGA mod 2011 ‘clear’ or ‘almost clear’ (0 or 1) with at least a 2 point improvement from baseline to Week 12. The key secondary endpoint was the proportion of patients who achieved a reduction in PASI score of at least 90 % (PASI 90) from baseline to Week 12. Other secondary endpoints included PASI 50, 100 responder rates at Week 12, PASI 50, 75, 90, 100 and IGA 0/1 responder rates at Week 16 and over time up to and including Week 52, change in PASI score over time up to and including Week 52 and IGA score over time up to and including Week 52, the proportion of patients with a Children’s Dermatology Life Quality Index (CDLQI) score of 0 or 1 at Week 12 and over time up to and including Week 52, and change from baseline in CDLQI compared to placebo at Week 12 and over time up to and including Week 52.

During the 12 week placebo-controlled period, the efficacy of both the low and the high dose of secukinumab was comparable for the co-primary endpoints. The odds ratio estimates in favour of both secukinumab doses were clinically relevant and statistically significant for both the PASI 75 and IGA mod 2011 ‘clear’ or ‘almost clear’ (0 or 1) responses.

All patients were followed for efficacy and safety during the 52 weeks following the first dose. The proportion of patients achieving PASI 75 and IGA mod 2011 ‘clear’ or ‘almost clear’ (0 or 1) responses showed separation between secukinumab treatment groups and placebo at the first post-baseline visit at Week 4, the difference becoming more prominent at Week 12. The response was maintained throughout the 52 week time period. Improvement in PASI 50, 90, 100 responder rates and CDLQI 0 or 1 scores were also maintained throughout the 52 week time period.

In addition, PASI 75, IGA 0 or 1, PASI 90 response rates at Weeks 12 and 52 for both secukinumab low and high dose groups were higher than the rates for patients treated with etanercept.

Beyond Week 12, efficacy of both the low and the high dose of secukinumab was comparable although the efficacy of the high dose was higher for patients ≥ 50 kg. The safety profiles of the low dose and the high dose were comparable.

The efficacy results at Weeks 12 and 52 are presented in Table 6.

Table 6: Summary of clinical response in severe paediatric psoriasis at Weeks 12* and 52*

Response criterion	Treatment comparison 'test' vs. 'control'	'test' n/m** (%)	'control' n/m** (%)	odds ratio estimate (95% CI)	p-value
		At Week 12* **			
PASI 75	secukinumab low dose vs. placebo	32/40 (80.0)	6/41 (14.6)	25.78 (7.08,114.66)	<0.0001
	secukinumab high dose vs. placebo	31/40 (77.5)	6/41 (14.6)	22.65 (6.31,98.93)	<0.0001
	secukinumab low dose vs. etanercept	32/40 (80.0)	26/41 (63.4)	2.25 (0.73,7.38)	
	secukinumab high dose vs. etanercept	31/40 (77.5)	26/41 (63.4)	1.92 (0.64,6.07)	
IGA 0/1	secukinumab low dose vs. placebo	28/40 (70.0)	2/41 (4.9)	51.77 (10.02,538.64)	<0.0001
	secukinumab high dose vs. placebo	24/40 (60.0)	2/41 (4.9)	32.52 (6.48,329.52)	<0.0001
	secukinumab low dose vs. etanercept	28/40 (70.0)	14/41 (34.1)	4.49 (1.60,13.42)	
	secukinumab high dose vs. etanercept	24/40 (60.0)	14/41 (34.1)	2.86 (1.05,8.13)	
PASI 90	secukinumab low dose vs. placebo	29/40 (72.5)	1/41 (2.4)	133.67 (16.83,6395.22)	<0.0001
	secukinumab high dose vs. placebo	27/40 (67.5)	1/41 (2.4)	102.86 (13.22,4850.13)	<0.0001
	secukinumab low dose vs. etanercept	29/40 (72.5)	12/41 (29.3)	7.03 (2.34,23.19)	
	secukinumab high dose vs. etanercept	27/40 (67.5)	12/41 (29.3)	5.32 (1.82,16.75)	
		At Week 52			
PASI 75	secukinumab low dose vs. etanercept	35/40 (87.5)	28/41 (68.3)	3.12 (0.91,12.52)	
	secukinumab high dose vs. etanercept	35/40 (87.5)	28/41 (68.3)	3.09 (0.90,12.39)	
IGA 0/1	secukinumab low dose vs. etanercept	29/40 (72.5)	23/41 (56.1)	2.02 (0.73,5.77)	
	secukinumab high dose vs. etanercept	30/40 (75.0)	23/41 (56.1)	2.26 (0.81,6.62)	
PASI 90	secukinumab low dose vs. etanercept	30/40 (75.0)	21/41 (51.2)	2.85 (1.02,8.38)	
	secukinumab high dose vs. etanercept	32/40 (80.0)	21/41 (51.2)	3.69 (1.27,11.61)	

** non-responder imputation was used to handle missing values*

*** n is the number of responders, m = number of patients evaluable*

**** extended visit-window at week 12*

Odds ratio, 95% confidence interval, and p-value are from an exact logistic regression model with treatment group, baseline body-weight category and age category as factors

A higher proportion of paediatric patients treated with secukinumab reported improvement in health-related quality of life as measured by a CDLQI score of 0 or 1 compared to placebo at Week 12 (low dose 44.7 %, high dose 50 %, placebo 15 %). From Week 12 through Week 52, the proportion of paediatric patients in both secukinumab dose groups with a CDLQI score of 0 or 1 was numerically higher than for the etanercept group (low dose 60.6 %, high dose 66.7 %, etanercept 44.4 %).

Moderate to severe plaque psoriasis

An open label, two-arm, parallel group, multicentre phase III study enrolled 84 paediatric patients 6 to less than 18 years of age with moderate to severe plaque psoriasis (as defined by a PASI score ≥ 12, an IGA mod 2011 score of ≥ 3, and involving ≥ 10 % of the body surface area) who were candidates for systemic therapy.

Patients were randomized to receive secukinumab at Weeks 0, 1, 2, 3, and 4 followed by the same dose every 4 weeks as follows:

- low dose secukinumab (150 mg for body weight ≥ 50 kg),
- high dose secukinumab (150 mg for body weight between ≥ 25 kg and < 50 kg, or 300 mg for body weight ≥ 50 kg).

The co-primary endpoints were the proportion of patients who achieved a reduction in PASI score of at least 75 % (PASI 75) and IGA mod 2011 ‘clear’ or ‘almost clear’ (0 or 1) with at least a 2 point improvement from baseline to Week 12. Secondary and additional endpoints included PASI 90 response at Week 12, PASI 75, 90, 100, and IGA mod 2011 ‘clear’ or ‘almost clear’ (0 or 1), and CDLQI responses over time up to end of treatment.

The efficacy of both the low and the high dose of secukinumab was comparable and showed statistically and clinically meaningful improvement compared to historical placebo for the co-primary endpoints. The

odds ratio estimates in favour of both secukinumab doses were clinically relevant and statistically significant for both the PASI 75 and IGA mod 2011 0 or 1 responses versus historical placebo. The estimated posterior probability of a positive treatment effect was 100 %.

All patients were followed for efficacy for at least 24 weeks following first administration. Efficacy (defined as PASI 75 response and IGA mod 2011 'clear' or 'almost clear' [0 or 1]) was observed as early as Week 2 and the proportion of patients who achieved a PASI 75 response and IGA mod 2011 'clear' or 'almost clear' (0 or 1) increased throughout the 24-week time period. Improvement in PASI 90 and PASI 100 were also observed at Week 12 and increased throughout the 24-week time period.

Beyond Week 12, efficacy of both the low and the high dose of secukinumab was comparable. The safety profiles of the low dose and the high dose were comparable.

The efficacy results at Weeks 12 and 24 are presented in Table 7.

Table 7: Summary of clinical response in moderate to severe paediatric psoriasis at Weeks 12* and 24* (paediatric psoriasis)

	Week 12		**Week 24**	
	Secukinumab low dose	**Secukinumab high dose**	**Secukinumab low dose**	**Secukinumab high dose**
Number of patients	42	42	42	42
PASI 75 response n (%)	39 (92.9 %)	39 (92.9 %)	40 (95.2 %)	40 (95.2 %)
IGA mod 2011 'clear' or 'almost clear' response n (%)	33 (78.6 %)	35 (83.3 %)	37 (88.1 %)	39 (92.9 %)
PASI 90 response n (%)	29 (69.0 %)	32 (76.2 %)	37 (88.1 %)	37 (88.1 %)
PASI 100 response n (%)	25 (59.5 %)	23 (54.8 %)	28 (66.7 %)	28 (66.7 %)
** non-responder imputation was used to handle missing values*				

In the low dose group, 50 % and 70.7 % of patients achieved a CDLQI 0 or 1 score at Weeks 12 and 24, respectively. In the high dose group, 61.9 % and 60.5 % achieved a CDLQI 0 or 1 score at Weeks 12 and 24, respectively.

Psoriatic arthritis

The safety and efficacy of secukinumab were assessed in 1,999 patients in three randomised, double-blind, placebo-controlled phase III studies in patients with active psoriatic arthritis (≥ 3 swollen and ≥ 3 tender joints) despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or disease-modifying anti-rheumatic drug (DMARD) therapy. Patients with each subtype of PsA were enrolled in these studies, including polyarticular arthritis with no evidence of rheumatoid nodules, spondylitis with peripheral arthritis, asymmetric peripheral arthritis, distal interphalangeal involvement and arthritis mutilans. Patients in these studies had a diagnosis of PsA of at least five years. The majority of patients also had active psoriasis skin lesions or a documented history of psoriasis. Over 61 % and 42 % of the PsA patients had enthesitis and dactylitis at baseline, respectively. For all studies, the primary endpoint was American College of Rheumatology (ACR) 20 response. For Psoriatic Arthritis study 1 (PsA study 1) and Psoriatic Arthritis study 2 (PsA study 2), the primary endpoint was at week 24. For Psoriatic Arthritis study 3 (PsA study 3), the primary endpoint was at week 16 with the key secondary endpoint, the change from baseline in modified Total Sharp Score (mTSS), at week 24.

In PsA study 1, PsA study 2 and PsA study 3, 29 %, 35 % and 30 % of patients, respectively, were previously treated with an anti-TNFα agent and discontinued the anti-TNFα agent for either lack of efficacy or intolerance (anti-TNFα-IR patients).

PsA study 1 (FUTURE 1) evaluated 606 patients, of whom 60,7 % had concomitant MTX. Patients randomised to secukinumab received 10 mg/kg intravenously at weeks 0, 2, and 4, followed by 150 mg subcutaneously every month starting at week 8. Patients randomised to placebo who were non-

responders at week 16 (early rescue) and other placebo patients at week 24 were crossed over to receive secukinumab (150 mg subcutaneously) followed by the same dose every month.

PsA study 2 (FUTURE 2) evaluated 397 patients, of whom 46,6 % had concomitant MTX. Patients randomised to secukinumab received 150 mg or 300 mg subcutaneously at weeks 0, 1, 2, 3 and 4, followed by the same dose every month. Patients randomised to receive placebo who were non-responders at week 16 (early rescue) were crossed over to receive secukinumab (either 150 mg or 300 mg subcutaneously) at week 16 followed by the same dose every month. Patients randomised to receive placebo who were responders at week 16 were crossed over to receive secukinumab (either 150 mg or 300 mg subcutaneously) at week 24 followed by the same dose every month.

PsA study 3 (FUTURE 5) evaluated 996 patients, of whom 50,1 % had concomitant MTX. Patients were randomised to receive secukinumab 150 mg, 300 mg or placebo subcutaneously at weeks 0, 1, 2, 3 and 4, followed by the same dose every month, or a once monthly injection of secukinumab 150 mg (without loading). Patients randomised to receive placebo who were non-responders at week 16 (early rescue) were then crossed over to receive secukinumab (either 150 mg or 300 mg subcutaneously) at week 16 followed by the same dose every month. Patients randomised to receive placebo who were responders at week 16 were crossed over to receive secukinumab (either 150 mg or 300 mg subcutaneously) at week 24 followed by the same dose every month.

Signs and symptoms

Treatment with secukinumab resulted in significant improvement in measures of disease activity compared to placebo at weeks 16, 24 and 52 (see Table 8).

Table 8 : Clinical response in PsA2 and PsA3 Studies at Week 16, Week 24, and Week 52

	PsA2			PsA3		
	Placebo	**150 mg[1]**	**300 mg[1]**	**Placebo**	**150 mg[1]**	**300 mg[1]**
Number of patients randomized	98	100	100	332	220	222
ACR 20 response n (%)						
Week 16	18 (18.4 %)	60 (60.0 %***)	57 (57.0 %***)	91◊ (27.4 %)	122◊ (55.5 %***)	139◊ (62.6 %***)
Week 24	15◊ (15.3%)	51◊ (51.0 %***)	54◊ (54.0 %***)	78 (23.5 %)	117 (53.2 %***)	141 (63.5 %***)
Week 52	-	64 (64.0 %)	64 (64.0 %)	NA	NA	NA
ACR 50 response n (%)						
Week 16	6 (6.1 %)	37 (37.0 %***)	35 (35.0 %***)	27 (8.1 %)	79 (35.9 %***)	88 (39.6 %***)
Week 24	7 (7.1 %)	35 (35.0 %***)	35 (35.0 %***)	29 (8.7 %)	86 (39.1 %***)	97 (43.7 %***)
Week 52	-	39 (39.0 %)	44 (44.0 %)	NA	NA	NA
ACR 70 response n (%)						
Week 16	2 (2.0 %)	17 (17.0 %**)	15 (15.0 %**)	14 (4.2 %)	40 (18.2 %***)	45 (20.3 %***)
Week 24	1 (1.0%)	21 (21.0 %**)	20 (20.0 %**)	13 (3.9 %)	53 (24.1 %***)	57 (25.7 %***)
Week 52	-	20 (20.0 %)	24 (24.0 %)	NA	NA	NA
DAS28-CRP						
Week 16	-0.50	-1.45***	-1.51***	-0.63	-1.29***	-1.49***
Week 24	-0.96	-1.58***	-1.61***	-0.84	-1.57***	-1.68***
Week 52	-	-1.69	-1.78	NA	NA	NA
Number of patients with ≥ 3 % BSA psoriasis skin involvement at baseline	43 (43.9 %)	58 (58.0 %)	41 (41.0 %)	162 (48.8 %)	125 (56.8 %)	110 (49.5 %)
PASI 75 response n (%)						
Week 16	3 (7. 0 %)	33 (56.9 %***)	27 (65.9 %***)	20 (12.3 %)	75 (60.0 %***)	77 (70.0 %***)
Week 24	7 (16.3 %)	28 (48.3 %***)	26 (63.4 %***)	29 (17.9 %)	80 (64.0 %***)	78 (70.9 %***)

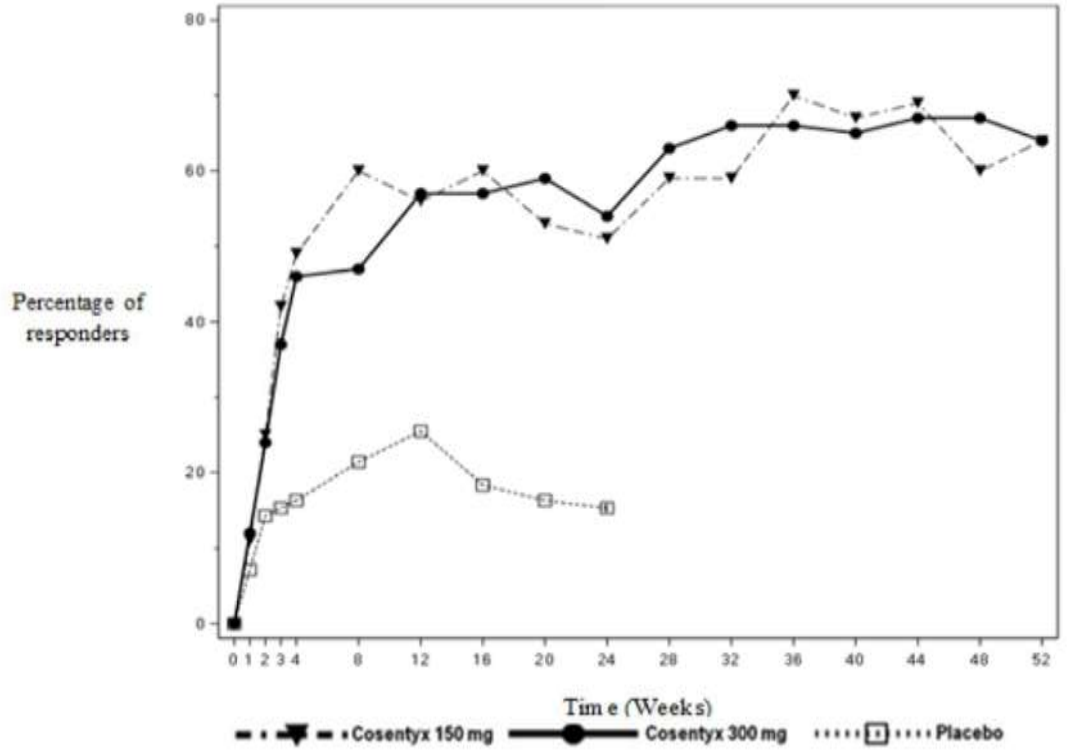
Week 52	-	33 (56.9 %)	30 (73.2 %)	NA	NA	NA
PASI 90 response n (%)						
Week 16	3 (7.0 %)	22 (37.9 %***)	18 (43.9 %***)	15 (9.3 %)	46 (36.8 %***)	59 (53.6 %***)
Week 24	4 (9.3 %)	19 (32.8 %**)	20 (48.8 %***)	19 (11.7 %)	51 (40.8 %***)	60 (54.5 %***)
Week 52	-	25 (43.1 %)	23 (56.1 %)	NA	NA	NA
Dactylitis Resolution n (%) †						
Week 16	10 (37 %)	21 (65.6 %*)	26 (56.5 %)	40 (32.3 %)	46 (57.5 %***)	54 (65.9 %***)
Week 24	4 (14.8 %)	16 (50.0 %**)	26 (56.5 %**)	42 (33.9 %)	51 (63.8 %***)	52 (63.4 %***)
Week 52	-	21 (65.6%)	32 (69.6%)	NA	NA	NA
Enthesitis Resolution n (%) ‡						
Week 16	17 (26.2 %)	32 (50.0 %**)	32 (57.1 %***)	68 (35.4 %)	77 (54.6 %***)	78 (55.7 %***)
Week 24	14 (21.5 %)	27 (42.2 %*)	27 (48.2 %**)	66 (34.4 %)	77 (54.6 %***)	86 (61.4 %***)
Week 52	-	31 (48.4 %)	30 (53.6 %)	NA	NA	NA

** p < 0.05, ** p < 0.01, *** p < 0.001; versus placebo*
All p-values are non-adjusted.
Non-responder imputation used for missing binary endpoint.
NA: Not Available; ACR: American College of Rheumatology; PASI: Psoriasis Area and Severity Index; DAS: Disease Activity Score; BSA: Body Surface Area
◊*Primary Endpoint*
[1]*Secukinumab 150 mg or 300 mg s.c. at Weeks 0, 1, 2, 3, and 4 followed by the same dose every month*
†In patients with dactylitis at baseline (n = 27, 32, 46 respectively for PsA2 and n = 124, 80, 82 respectively for PsA3)
‡In patients with enthesitis at baseline (n = 65, 64, 56 respectively for PsA2 and n = 192, 141, 140, respectively for PsA3)

The onset of action of secukinumab occurred as early as week 2. Statistically significant difference in ACR 20 versus placebo was reached at week 3.

The percentage of patients achieving ACR 20 response by visit is shown in Figure 2.

Figure 2: ACR20 response in PsA study 2 over time up to week 52



Similar responses for primary and key secondary endpoints were seen in PsA patients regardless of whether they were on concomitant MTX treatment or not. In PsA study 2, at week 24, secukinumab-treated patients with concomitant MTX use had a higher ACR 20 response (47,7 % and 54,4 % for 150 mg and 300 mg, respectively, compared to placebo 20,0 %) and ACR 50 response (31,8 % and 38,6 % for 150 mg and 300 mg, respectively, compared to placebo 8,0 %). Secukinumab-treated patients without concomitant MTX use had a higher ACR 20 response (53,6 % and 53,6 % for 150 mg and 300 mg, respectively, compared to placebo 10,4 %) and ACR 50 response (37,5 % and 32,1 % for 150 mg and 300 mg, respectively, compared to placebo 6,3 %).

In PsA study 2, both anti-TNFα-naive and anti-TNFα-IR secukinumab-treated patients had a significantly higher ACR 20 response compared to placebo at week 24, with a slightly higher response in the anti-TNFα-naive group (anti-TNFα-naive: 64 % and 58 % for 150 mg and 300 mg, respectively, compared to placebo 15,9 %; anti-TNFα-IR: 30 % and 46 % for 150 mg and 300 mg, respectively, compared to placebo 14,3 %). In the anti-TNFα-IR patients subgroup, only the 300 mg dose showed significantly higher response rate for ACR 20 compared to placebo ($p < 0.05$) and demonstrated clinical meaningful benefit over 150 mg on multiple secondary endpoints. Improvements in the PASI 75 response were seen in both subgroups and the 300 mg dose showed statistically significant benefit in the anti-TNFα-IR patients.

The number of PsA patients with axial involvement was too small to allow meaningful assessment.

Improvements were shown in all components of the ACR scores, including patient assessment of pain. In PsA study 2, the proportion of patients achieving a modified PsA Response Criteria (PsARC) response was greater in the secukinumab-treated patients (59,0 % and 61,0 % for 150 mg and 300 mg, respectively) compared to placebo (26,5 %) at week 24.

In PsA study 1 and PsA study 2, efficacy was maintained up to week 104. In PsA study 2, among 200 patients initially randomised to secukinumab 150 mg and 300 mg, 178 (89 %) patients were still on treatment at week 52. Of the 100 patients randomised to secukinumab 150 mg, 64, 39 and 20 had an ACR 20/50/70 response, respectively. Of the 100 patients randomised to secukinumab 300 mg, 64, 44 and 24 had an ACR 20/50/70 response, respectively.

Radiographic response

In PsA study 3, inhibition of progression of structural damage was assessed radiographically and expressed by the modified Total Sharp Score (mTSS) and its components, the Erosion Score (ES) and the Joint Space Narrowing Score (JSN). Radiographs of hands, wrists, and feet were obtained at baseline, week 16 and/or week 24 and scored independently by at least two readers who were blinded to treatment group and visit number. Secukinumab 150 mg and 300 mg treatment significantly inhibited the rate of progression of peripheral joint damage compared with placebo treatment as measured by change from baseline in mTSS at week 24 (Table 9).

Inhibition of progression of structural damage was also assessed in PsA study 1 at weeks 24 and 52, compared to baseline. Week 24 data are presented in Table 9.

Table 9: Change in modified Total Sharp Score in psoriatic arthritis

	PsA Study 3			**PsA Study 1**	
	Placebo n = 296	**150 mg[1] n = 213**	**300 mg[1] n = 217**	**Placebo n = 179**	**150 mg[2] n = 185**
Total Score					
Baseline (SD)	15.0 (38.2)	13.6 (25.9)	12.9 (23.7)	28.4 (63.5)	22.3 (48.0)
Mean Change at Week 24	0.5	0.13*	0.02*	0.57	0.13*

** p < 0.05 based on nominal, but not adjusted, p-value*
[1] Secukinumab 150 mg or 300 mg s.c. at Weeks 0, 1, 2, 3, and 4 followed by the same dose every month
[2]10 mg/kg at Weeks 0, 2 and 4 followed s.c. doses of 150 mg

In PsA study 1, inhibition of structural damage was maintained with secukinumab treatment up to week 52.

In PsA study 3, the percentage of patients with no disease progression (defined as a change from baseline in mTSS of ≤ 0.5) from randomisation to week 24 was 80,3 %, 88,5 % and 73,6 % for secukinumab 150 mg, 300 mg and placebo, respectively. An effect of inhibition of structural damage

was observed in anti-TNFα-naïve and anti-TNFα-IR patients and in patients treated with and without concomitant MTX.

Axial manifestations in PsA

A randomized, double-blind, placebo-controlled study (MAXIMISE) assessed the efficacy of secukinumab in 485 PsA patients with axial manifestations who were naive to biologic treatment and responded inadequately to NSAIDs. The primary variable was at least a 20% improvement in Assessment of Spondyloarthritis International Society (ASAS 20) criteria at Week 12. Treatment with secukinumab 300 mg and 150 mg compared to placebo resulted in significant improvement in signs and symptoms (including greater decreases from baseline in spinal pain) and improvement in physical function (see Table 10).

Table 10: Clinical response on MAXIMISE Study at Week 12

	Placebo (n=164)	**150 mg (n=157)**	**300 mg (n=164)**
ASAS 20 response, %	31.2	66.3*	62.9*
ASAS 40 response, %	12.2	39.5*	43.6*
BASDAI 50, %	9.8	32.7*	37.4*
Spinal pain, VAS	-13.6	-28.5*	-26.5*
Physical function, HAQDI	-0.155	-0.330**	-0.389*

** p<0.0001; ** p<0.0005; versus placebo*
ASAS: Assessment of SpondyloArthritis International Society Criteria; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; VAS: Visual Analog Scale; HAQDI: Health Assessment Questionnaire – Disability Index

Improvement in ASAS 20 and ASAS 40 for both secukinumab doses were observed by Week 4 and were maintained up to 52 weeks.

Physical function and health-related quality of life

In PsA study 2 and PsA study 3, patients treated with secukinumab 150 mg ($p = 0.0555$ and $p < 0.0001$) and 300 mg ($p = 0.0040$ and $p < 0.0001$) showed improvement in physical function compared to patients treated with placebo as assessed by Health Assessment Questionnaire-Disability Index (HAQ-DI) at week 24 and week 16, respectively. Improvements in HAQ-DI scores were seen regardless of previous anti-TNFα exposure. Similar responses were seen in PsA study 1.

Secukinumab-treated patients reported significant improvements in health-related quality of life as measured by the Short Form-36 Health Survey Physical Component Summary (SF-36 PCS) score ($p < 0.001$). There were also statistically significant improvements demonstrated in exploratory endpoints assessed by the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scores for 150 mg and 300 mg compared to placebo (7,97, 5,97 versus 1,63, respectively) and these improvements were maintained up to week 104 in PsA study 2.

Similar responses were seen in PsA study 1 and efficacy was maintained up to week 52.

Axial spondyloarthritis (axSpA) with or without radiographic damage

Ankylosing spondylitis

The safety and efficacy of secukinumab were assessed in 816 patients in three randomised, double-blind, placebo-controlled phase III studies in patients with active ankylosing spondylitis (AS) with a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or disease-modifying anti-rheumatic drug (DMARD) therapy. Patients in Ankylosing Spondylitis study 1 (AS study 1) and Ankylosing Spondylitis study 2 (AS study 2) had a diagnosis of AS for a median of 2,7 to 5,8 years. For both studies, the primary endpoint was at least a 20 % improvement in Assessment of Spondyloarthritis International Society (ASAS 20) criteria at week 16.

In Ankylosing Spondylitis study 1 (AS study 1), Ankylosing Spondylitis study 2 (AS study 2), and Ankylosing Spondylitis study 3 (AS study 3), 27,0 %, 38,8 %, and 23,5 % of patients, respectively, were previously treated with an anti-TNFα agent and discontinued the anti-TNFα agent for either lack of efficacy or intolerance (anti-TNFα-IR patients).

AS study 1 (MEASURE 1) evaluated 371 patients, of whom 14,8 % and 33,4 % used concomitant MTX or sulfasalazine, respectively. Patients randomised to secukinumab received 10 mg/kg intravenously at weeks 0, 2, and 4, followed by 150 mg subcutaneously every month starting at week 8. Patients randomised to placebo who were non-responders at week 16 (early rescue) and all other placebo patients at week 24 were crossed over to receive secukinumab (150 mg subcutaneously), followed by the same dose every month.

AS study 2 (MEASURE 2) evaluated 219 patients, of whom 11,9 % and 14,2 % used concomitant MTX or sulfasalazine, respectively. Patients randomised to secukinumab 150 mg subcutaneously at weeks 0, 1, 2, 3 and 4, followed by the same dose every month. At week 16, patients who were randomised to placebo at baseline were re-randomised to receive secukinumab (150 mg subcutaneously) every month.

AS study 3 (MEASURE 3) evaluated 226 patients, of whom 13,3 % and 23,5 % used concomitant MTX or sulfasalazine, respectively. Patients randomised to secukinumab received 10 mg/kg intravenously at weeks 0, 2, and 4, followed by either 150 mg or 300 mg subcutaneously every month. At week 16, patients who were randomised to placebo at baseline were re-randomised to receive secukinumab (either 150 mg or 300 mg subcutaneously) every month. The primary endpoint was ASAS 20 at week 16. Patients were blinded to the treatment regimen up to week 52, and the study continued to week 156.

Signs and symptoms

In AS study 2, treatment with secukinumab 150 mg resulted in greater improvement in measures of disease activity compared with placebo at week 16 (see Table 11).

Table 11: Clinical response in AS2 Study at Week 16

Outcome (p-value vs placebo)	**Placebo (n = 74)**	**150 mg (n = 72)**
Efficacy at Week 16		
ASAS 2 0 response, %	28.4	61.1***
ASAS 40 response, %	10.8	36.1***
hsCRP, (post-BSL/BSL ratio)	1.13	0.55***
ASAS 5/6, %	8.1	43.1***
ASAS partial remission, %	4.1	13.9
BASDAI 50, %	10.8	30.6**
ASDAS-CRP major improvement	4.1	25.0***

* p < 0.05, ** p < 0.01, *** p < 0.001; versus placebo
All p-values adjusted for multiplicity of testing based on pre-defined hierarchy, except BASDAI 50 and ASDAS-CRP
Non-responder imputation used for missing binary endpoint
ASAS: Assessment of SpondyloArthritis International Society Criteria; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; hsCRP: high-sensitivity C-reactive protein; ASDAS: Ankylosing Spondylitis Disease Activity Score; BSL: baseline

The onset of action of secukinumab 150 mg occurred as early as week 1 for ASAS 20 and week 2 for ASAS 40 (superior to placebo) in AS study 2.

ASAS 20 responses were improved at week 16 in both anti-TNFα-naïve patients (68,2 % versus 31,1 %; p < 0.05) and anti-TNFα-IR patients (50,0 % versus 24,1 %; p < 0.05) for secukinumab 150 mg compared with placebo, respectively.

In AS study 1 and AS study 2, secukinumab-treated patients (150 mg in AS study 2 and both regimens in AS study 1) demonstrated significantly improved signs and symptoms at week 16, with comparable magnitude of response and efficacy maintained up to week 52 in both anti-TNFα-naive and anti-TNFα-IR patients. In AS study 2, among 72 patients initially randomised to secukinumab 150 mg, 61 (84,7 %) patients were still on treatment at week 52. Of the 72 patients randomised to secukinumab 150 mg, 45 and 35 had an ASAS 20/40 response, respectively.

In AS study 3, patients treated with secukinumab (150 mg and 300 mg) demonstrated improved signs and symptoms and had comparable efficacy responses regardless of dose that were superior to placebo at week 16 for the primary endpoint (ASAS 20). Overall, the efficacy response rates for the 300 mg group were consistently greater compared to the 150 mg group for the secondary endpoints. During the blinded period, the ASAS 20 and ASAS 40 responses were 69,7 % and 47,6 % for 150 mg and 74,3 % and 57,4 % for 300 mg at week 52, respectively. The ASAS 20 and ASAS 40 responses were maintained up to week 156 (69,5 % and 47,6 % for 150 mg versus 74,8 % and 55,6 % for 300 mg). Greater response rates favouring 300 mg were also observed for ASAS partial remission (ASAS PR) response at week 16 and were maintained up to week 156. Larger differences in response rates, favouring 300 mg over 150 mg, were observed in anti-TNFα-IR patients (n = 36) compared to anti-TNFα-naïve patients (n = 114).

Spinal mobility

Patients treated with secukinumab 150 mg showed improvements in spinal mobility as measured by change from baseline in BASMI at week 16 for both AS study 1 (-0,40 versus -0,12 for placebo; p = 0.0114) and AS study 2 (-0,51 versus -0,22 for placebo; p=0,0533). These improvements were sustained up to week 52.

Physical function and health-related quality of life

In AS study 1 and study 2, patients treated with secukinumab 150 mg showed improvements in health-related quality of life as measured by AS Quality of Life Questionnaire (ASQoL) ($p = 0.001$) and SF-36 Physical Component Summary (SF-36PCS) ($p < 0.001$). Patients treated with secukinumab 150 mg also showed statistically significant improvements on exploratory endpoints in physical function as assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI) compared to placebo (-2,15 versus -0,68), and in fatigue as assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale compared to placebo (8,10 versus 3,30). These improvements were sustained up to week 52.

Non-radiographic axial spondyloarthritis (nr-axSpA) / axSpA without radiographic damage

The safety and efficacy of COSENTYX® were assessed in 555 patients in one randomized, double-blind, placebo-controlled phase III study in patients with active non-radiographic axial spondyloarthritis (nr-axSpA) fulfilling the Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axial spondyloarthritis (axSpA) with no radiographic evidence of changes in the sacroiliac joints that would meet the modified New York criteria for ankylosing spondylitis (AS). Patients enrolled had active disease, defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4, a Visual Analogue Scale (VAS) for total back pain of ≥ 40 (on a scale of 0 to 100 mm), despite current or previous non-steroidal anti-inflammatory drug (NSAID) therapy and increased C-reactive protein (CRP) and/or evidence of sacroiliitis on Magnetic Resonance Imaging (MRI). Patients in this study had a diagnosis of axSpA for a mean of 2,1 to 3,0 years and 54 % of the study participants were female.

In nr-axSpA 1 Study, 57,6 % of patients had increased CRP, 72,2 % had evidence of sacroiliitis on MRI and 29,9 % had both increased CRP and evidence of sacroiliitis on MRI. In addition, 9,7 % of patients were previously treated with an anti-TNF-alpha agent and discontinued the anti-TNF-alpha agent for either lack of efficacy or intolerance (anti-TNF-alpha-IR patients).

Nr-axSpA 1 Study (PREVENT) evaluated 555 patients, of whom 9,9 % and 14,8 % used concomitant MTX or sulfasalazine, respectively. In the double-blind period, patients received either placebo or COSENTYX® for 52 weeks. Patients randomized to COSENTYX® received 150 mg s.c. at Weeks 0, 1, 2, 3 and 4 followed by the same dose every month, or a once monthly injection of COSENTYX® 150 mg. The primary endpoint was at least 40 % improvement in ASAS 40 at Week 16 in TNF-naive patients.

Clinical response

Signs and symptoms

In nr-axSpA1 Study, treatment with COSENTYX® 150 mg resulted in significant improvements in the measures of disease activity compared to placebo at Week 16. These measures include ASAS 40, ASAS 5/6, BASDAI score, BASDAI 50, high-sensitivity CRP (hsCRP), ASAS 20 and ASAS partial remission response compared to placebo at Week 16 (Table 12).

Table 12: Clinical response in nr-axSpA1 Study at Week 16

Outcome (p-value vs placebo)	**Placebo**	**150 mg[1]**
Number of TNF-naive patients randomized	**171**	**164**
ASAS 40 response, %	29.2 %	41.5 %*
Total number of patients randomized	**186**	**185**
ASAS 40 response, %	28.0 %	40.0 %*
ASAS 5/6, %	23.7 %	40.0 %**
BASDAI, LS mean change from baseline score	-1.46	-2.35**
BASDAI 50, %	21.0 %	37.3 %**
hsCRP, (post-BSL/BSL ratio)	0.91	0.64**
ASAS 20 response, %	45.7 %	56.8 %*
ASAS partial remission, %	7.0 %	21.6 %**
**p < 0.05; **p < 0.001 vs. placebo* *All p-values adjusted for multiplicity of testing based on pre-defined hierarchy* *Non-responder imputation used for missing binary endpoint* [1]*COSENTYX® 150 mg s.c. at Weeks 0, 1, 2, 3, and 4 followed by the same dose every month* *ASAS: Assessment of SpondyloArthritis International Society Criteria; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; hsCRP: high-sensitivity C-reactive protein; BSL: baseline; LS: least square*		

The results of the main components of the ASAS40 response criteria are shown in Table 13.

Table 13: Main components of the ASAS40 response criteria and other measures of disease activity in nr-axSpA patients at baseline and Week 16 in nr-axSpA1 Study

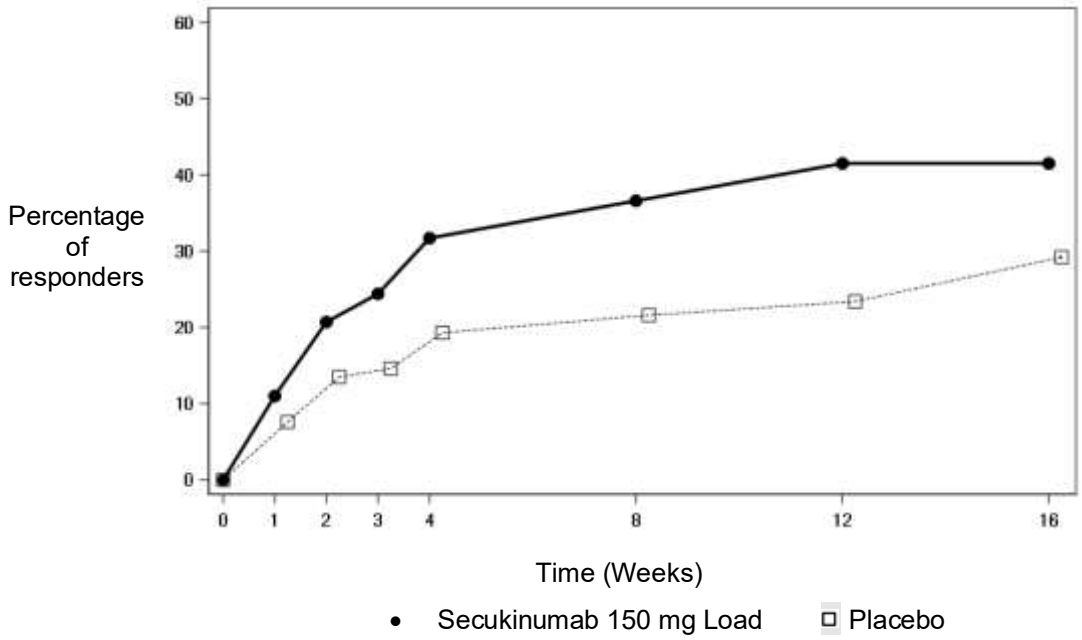
	Placebo (N = 186)		**150 mg Load** (N = 185)		**150 mg No Load** (N = 184)	
	Baseline	Week 16 change from baseline	Baseline	Week 16 change from baseline	Baseline	Week 16 change from baseline

ASAS40 Response criteria						
-Patient global assessment of Disease Activity (0 to 100 mm)	68.8	-13.78	72.6	-24.10	71.0	-26.17
-Total back pain (0 to 100 mm)	70.9	-15.64	73.3	-24.96	72.0	-25.52
-BASFI (0 to 10)	5.893	-1.01	6.244	-1.75	5.922	-1.64
-Inflammation (0 to 10)	6.588	-1.71	7.206	-2.76	6.827	-2.84
hsCRP (mg/L) Mean Change at Week 16	10.76	-2.42	13.17	-7.90	9.67	-4.67
BASDAI (0 to 10)	6.760	-1.46	7.082	-2.35	6.931	-2.43
- Spinal pain	7.52	-2.03	7.76	-3.00	7.62	-2.98
- Peripheral pain and swelling (0 to 10)	6.13	-1.60	6.29	-2.26	6.55	-2.42
BASMI	2.765	-0.13	2.923	-0.26	2.772	-0.27

The onset of action of COSENTYX® 150 mg occurred as early as Week 3 for ASAS 40 in anti-TNF-alpha naive patients (superior to placebo) in nr-axSpA1 Study. The percentage of patients achieving an ASAS

40 response in anti-TNF-alpha naive patients by visit is shown in Figure 3. Patients treated with COSENTYX® maintained their response compared to placebo up to Week 52.

Figure 3: ASAS 40 responses in anti-TNF-alpha naive patients in nr-axSpA1 Study over time up to Week 16



ASAS 40 responses were also improved at Week 16 in anti-TNF-alpha-IR patients (28,6 % vs. 13,3 %) for COSENTYX® 150 mg compared with placebo. The magnitude of response (treatment difference versus placebo) with respect to signs and symptoms at Week 16 was similar in anti-TNF-alpha-naïve and anti-TNF-alpha-IR patients, with higher absolute response rates in anti-TNF-alpha-naïve patients. Efficacy versus placebo was maintained in anti-TNF-alpha-naïve and anti-TNF-alpha-IR patients up to Week 52.

Physical function and health-related quality of life

Patients treated with COSENTYX® 150 mg showed statistically significant improvements by Week 16 compared to placebo-treated patients in physical function as assessed by the BASFI (Week 16: -1,75

vs -1.01, p < 0.01). Patients treated with COSENTYX® reported significant improvements compared to placebo-treated patients by Week 16 in health-related quality of life as measured by ASQoL (LS mean change: Week 16: -3,45 vs -1,84, p < 0.001) and SF-36 Physical Component Summary (SF-36 PCS) (LS mean change: Week 16: 5,71 vs 2,93, p < 0.001). These improvements were sustained up to Week 52.

Spinal mobility

Spinal mobility was assessed by BASMI up to Week 16. Numerically greater improvements were demonstrated in patients treated with COSENTYX® compared with placebo-treated patients at Weeks 4, 8, 12 and 16.

Inhibition of inflammation in magnetic resonance imaging (MRI)

Signs of inflammation were assessed by MRI at baseline and Week 16 and expressed as change from baseline in Berlin SI-joint oedema score for sacroiliac joints and ASspiMRI-a score and Berlin spine score for the spine. Inhibition of inflammatory signs in both sacroiliac joints and the spine was observed in patients treated with secukinumab. Mean change from baseline in Berlin SI-joint oedema score was -1,68 for patients treated with COSENTYX® 150 mg (n=180) versus -0,39 for the placebo-treated patients (n = 174) (p < 0.0001).

Hidradenitis Suppurativa

The safety and efficacy of secukinumab were assessed in 1,084 patients in two randomized, double-blind, placebo-controlled phase III studies in adult patients with moderate to severe hidradenitis suppurativa (HS) who were candidates for systemic biologic therapy. Patients enrolled in HS study 1 (SUNSHINE) and HS study 2 (SUNRISE) had Hurley stage I (4.6 % and 2.8 %, respectively), II (61.4 % and 56.7 %, respectively) or III (34.0 % and 40.5 %, respectively) disease at baseline with at least five inflammatory lesions affecting two anatomical areas. The proportion of patients weighing ≥ 90 kg was

54.7 % in HS study 1 and 50.8 % in HS study 2. Patients in these studies had a diagnosis of moderate to severe HS for a mean of 7.3 years and 56.3 % of the study participants were female.

In HS study 1 and HS study 2, 23.8 % and 23.2 % of patients, respectively, were previously treated with a biologic and discontinued the biologic agent for either lack of efficacy or intolerance (bio-exposed patients).

HS study 1 evaluated 541 patients and HS study 2 evaluated 543 patients, of whom 12.8 % and 10.7 %, respectively, received concomitant stable dose of antibiotics. In both studies, patients randomized to secukinumab received 300 mg subcutaneously at Weeks 0, 1, 2, 3 and 4, followed by 300 mg every 2 weeks (Q2W) or every 4 weeks (Q4W). At Week 16, patients who were randomized to placebo were reassigned to receive secukinumab 300 mg at Weeks 16, 17, 18, 19 and 20 followed by either secukinumab 300 mg Q2W or secukinumab 300 mg Q4W.

The primary endpoint in both studies (HS study 1 and HS study 2) was the proportion of patients achieving a Hidradenitis Suppurativa Clinical Response defined as at least a 50 % decrease in abscesses and inflammatory nodules count with no increase in the number of abscesses and/or in the number of draining fistulae relative to baseline (HiSCR50) at Week 16. Reduction in HS-related skin pain was assessed as a secondary endpoint on the pooled data of HS study 1 and HS study 2 using a Numerical Rating Scale (NRS) in patients who entered the studies with an initial baseline score of 3 or greater.

In HS study 1 and HS study 2, a significantly higher proportion of patients treated with secukinumab 300 mg Q2W achieved a HiSCR50 response with a significant decrease in abscesses and inflammatory nodules (AN) count compared to placebo at Week 16. In HS study 1, a significantly lower rate of patients experienced flares up to Week 16 with secukinumab 300 mg Q2W. A significantly higher proportion of patients treated with secukinumab 300 mg Q2W (pooled data) experienced a clinically relevant decrease in HS-related skin pain compared to placebo at Week 16.

Table 14 Clinical response in HS study 1 and HS study 2 at Week 16

	HS study 1			HS study 2		
	Placebo	**300 mg Q4W**	**300 mg Q2W**	**Placebo**	**300 mg Q4W**	**300 mg Q2W**
Number of patients randomized	180	180	181	183	180	180
HiSCR50, %	33.7	41.8	45.0*	31.2	46.1*	42.3*
AN count, LS mean change from baseline	- 24.3	-4 2.4	- 46.8*	- 22.4	- 45.5*	- 39.3*
Flares, %	29.0	23.2	15.4*	27.0	15.6*	20.1
	Pooled data (HS study 1 and HS study 2)					
	Placebo		**300 mg Q4W**		**300 mg Q2W**	
Number of patients with NRS ≥ 3 at baseline	251		252		266	
NRS30 response, %	23.0		33.5		36.6*	

[1] Multiple imputation was implemented for missing data
* Statistically significant versus placebo based on the pre-defined hierarchy with overall alpha = 0.05
AN: Abcesses and inflammatory Nodules; HiSCR: Hidradenitis Suppurativa Clinical Response; NRS: Numerical Rating Scale

In both studies, the onset of action of secukinumab occurred as early as Week 2, the efficacy progressively increased to Week 16 and was maintained up to Week 52.

Improvements were seen for the primary and key secondary endpoints in HS patients regardless of previous or concomitant antibiotic treatment.

HiSCR50 responses were improved at Week 16 in both biologic-naive and biologic-exposed patients (pooled data; biologic-naive: 45.6 % and 45.4 % for 300 mg Q2W and 300 mg Q4W, respectively, compared to placebo 34.2 %; biologic-exposed: 37.0 % and 38.8 % for 300 mg Q2W and 300 mg Q4W, respectively, compared to placebo 27.3 %).

Greater improvements at Week 16 from baseline compared to placebo were demonstrated in health-related quality of life as measured by the Dermatology Life Quality Index (DLQI response; HS study 1: 47.8 % and 48.4 % for 300 mg Q2W and 300 mg Q4W, respectively, compared to placebo 28.9 %; HS study 2: 37.5 % and 47.2 % for 300 mg Q2W and 300 mg Q4W, respectively, compared to placebo

31.7 %) and the Euro-QoL 5-Dimension 3-Level Health Status Questionnaire (EQ-5D-3L mean absolute change from baseline; HS study 1: 4.5 and 2.8 for 300 mg Q2W and 300 mg Q4W, respectively, compared to placebo 0.8; HS study 2: 9.9 and 3.3 for 300 mg Q2W and 300 mg Q4W, respectively, compared to placebo 0.3). Greater improvements at Week 16 from baseline compared to placebo were also demonstrated in Patient Global Impression of change and Patient Global Impression of severity.

5.2 Pharmacokinetic properties

Most pharmacokinetics properties observed in patients with plaque psoriasis, psoriatic arthritis and ankylosing spondylitis were similar.

Absorption

Following a single subcutaneous dose of 300 mg as a liquid formulation in healthy volunteers, secukinumab reached peak serum concentrations of 13,7 ± 4,8 µg/mL or 27.3 ± 9.5 µg/mL, respectively, between 5 and 6 days post dose.

Based on population pharmacokinetic analysis, following a single subcutaneous dose of either 150 mg or 300 mg in plaque psoriasis patients, secukinumab reached peak serum concentrations of 13,7 ± 4,8 µg/mL or 27,3 ± 9,5 µg/mL, respectively, between 5- and 6-days post dose.

After initial weekly dosing during the first month, time to reach the maximum concentration was between 31 and 34 days based on population pharmacokinetic analysis.

On the basis of simulated data, peak concentrations at steady-state ($C_{max,ss}$) following subcutaneous administration of 150 mg or 300 mg were 27,6 µg/mL and 55,2 µg/mL, respectively. Population

pharmacokinetic analysis suggests that steady-state is reached after 20 weeks with monthly dosing regimens.

Compared with exposure after a single dose, the population pharmacokinetic analysis showed that patients exhibited a 2-fold increase in peak serum concentrations and area under the curve (AUC) following repeated monthly dosing during maintenance.

Population pharmacokinetic analysis showed that secukinumab was absorbed with an average absolute bioavailability of 73 % in patients with plaque psoriasis. Across studies, absolute bioavailabilities in the range between 60 and 77 % were calculated.

The bioavailability of secukinumab in PsA patients was 85 % on the basis of the population pharmacokinetic model.

Following multiple subcutaneous doses of 300 mg administered via the 300 mg/2 mL pen in plaque psoriasis patients, the mean serum trough concentrations of secukinumab were consistent with those observed in the previous 150 mg/1 mL studies used to deliver 300 mg.

Following subcutaneous administrations of 300 mg at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 2 weeks, the mean ± SD steady-state secukinumab trough concentration at Week 16 was approximately 55.1±26.7 µg/mL and 58.1±30.1 µg/mL in HS study 1 and HS study 2, respectively.

Distribution

The mean volume of distribution during the terminal phase (V_z) following single intravenous administration ranged from 7,10 to 8,60 litres in plaque psoriasis patients, suggesting that secukinumab undergoes limited distribution to peripheral compartments.

Biotransformation

The majority of IgG elimination occurs via intracellular catabolism, following fluid-phase or receptor mediated endocytosis.

Elimination

Mean systemic clearance (CL) following a single intravenous administration to patients with plaque psoriasis ranged from 0,13 to 0,36 L/day. In a population pharmacokinetic analysis, the mean systemic clearance (CL) was 0,19 L/day in plaque psoriasis patients. The CL was not impacted by gender. Clearance was dose- and time-independent.

The mean elimination half-life, as estimated from population pharmacokinetic analysis, was 27 days in plaque psoriasis patients, ranging from 18 to 46 days across psoriasis studies with intravenous administration.

In a population pharmacokinetic analysis, the mean systemic CL following subcutaneous administrations of 300 mg at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 2 weeks to patients with hidradenitis suppurativa was 0.26 L/day.

The mean elimination half-life, as estimated from population pharmacokinetic analysis, was 23 days in hidradenitis suppurativa patients.

Linearity/non-linearity

The single and multiple dose pharmacokinetics of secukinumab in plaque psoriasis patients were determined in several studies with intravenous doses ranging from 1 x 0,3 mg/kg to 3 x 10 mg/kg and with subcutaneous doses ranging from 1 x 25 mg to multiple doses of 300 mg. Exposure was dose proportional across all dosing regimens.

Special populations

Elderly patients

Of the 721 hidradenitis suppurativa patients exposed to secukinumab in clinical studies, a total of 11 patients were 65 years of age or older and 0 patients were 75 years of age or older.

Based on population pharmacokinetic analysis with a limited number of elderly patients (n = 71 for age ≥ 65 years and n = 7 for age ≥ 75 years), clearance in elderly patients and patients less than 65 years of age was similar.

Patients with renal or hepatic impairment

No pharmacokinetic data are available in patients with renal or hepatic impairment. The renal elimination of intact secukinumab, an IgG monoclonal antibody, is expected to be low and of minor importance. IgGs are mainly eliminated via catabolism and hepatic impairment is not expected to influence clearance of secukinumab.

Effect of weight on pharmacokinetics

Secukinumab clearance and volume of distribution increase as body weight increases.

Paediatric patients

Plaque psoriasis

In a pool of the two paediatric studies, patients with moderate to severe plaque psoriasis (6 to less than 18 years of age) were administered secukinumab at the recommended paediatric dosing regimen. At Week 24, patients weighing ≥ 50 kg had a mean ± SD steady-state trough concentration of 27.3 ± 10.1 microgram/mL (n = 36) after 150 mg of secukinumab.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose and reproductive toxicity, or tissue cross-reactivity.

Animal studies have not been conducted to evaluate the carcinogenic potential of secukinumab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Solution for Injection (pre-filled syringe and pre-filled pen):

Trehalose dihydrate

Histidine/Histidine hydrochloride monohydrate

L-Methionine

Polysorbate 80

Water for injection

6.2 Incompatibilities

Solution for Injection (pre-filled syringe and pre-filled pen):

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

COSENTYX® 150 mg/mL Solution for Injection:

24 months

If necessary, COSENTYX® may be stored unrefrigerated for a single period of up to 4 days at room temperature, not above 30 °C.

COSENTYX® 300 mg/2 mL Solution for injection in a pre-filled syringe or pre-filled pen:

24 months

If necessary, COSENTYX® may be stored unrefrigerated for a single period of up to 4 days at room temperature, not above 30 °C.

6.4 Special precautions for storage

COSENTYX® 150 mg/mL and 300 mg/2 mL Solution for Injection:

Store refrigerated at 2 °C – 8 °C. Do not freeze.

Store in the original carton until required for use and protect from light.

6.5 Nature and contents of container

COSENTYX® 150 mg solution for injection in pre-filled syringe

Immediate container:

The immediate container of the pre-filled syringe consists of a sterile, colourless, non-pyrogenic, borosilicate glass syringe, with a stacked 27 gauge ½ inch needle, closed by a grey, bromobutyl rubber stopper and rigid needle shield.

Outer Container:

Carton containing 1 or 2 colourless pre-filled syringe/s (1 mL) with a safety device attached.

COSENTYX® 300 mg solution for injection in pre-filled syringe

Immediate container:

COSENTYX® 300 mg solution for injection in pre-filled syringe is supplied in a pre-filled 2.25 mL glass syringe with a silicone-coated bromobutyl rubber plunger stopper, staked 27G x ½″ needle and rigid needle shield of synthetic polyisoprene rubber assembled in an automatic needle guard of polycarbonate.

Outer container:

COSENTYX® 300 mg solution for injection in pre-filled syringe is available in unit packs containing 1 pre-filled syringe and in multipacks containing 3 (3 packs of 1) pre-filled syringes.

COSENTYX® 150 mg solution for injection in pre-filled pen

Immediate container:

The immediate container of the autoinjector pen, consists of a sterile, colourless, non-pyrogenic, borosilicate glass syringe, with a stacked 27 gauge ½ inch needle, closed by a grey, bromobutyl rubber stopper and rigid needle shield.

Outer Container:

Carton containing 1 or 2 pre-filled fixed dose disposable autoinjector pens.

COSENTYX® 300 mg solution for injection in pre-filled pen

Immediate container:

COSENTYX® 300 mg solution for injection in pre-filled pen is supplied in a single-use pre-filled syringe assembled into a squared-shaped pen with transparent window and label. The pre-filled syringe inside

the pen is a 2.25 mL glass syringe with a silicone-coated bromobutyl rubber plunger stopper, staked 27G x ½″ needle and rigid needle shield of synthetic polyisoprene rubber.

Outer container:

COSENTYX® 300 mg solution for injection in pre-filled pen is available in unit packs containing 1 pre-filled pen and in multipacks containing 3 (3 packs of 1) pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

COSENTYX® 150 mg solution for injection in pre-filled syringe

COSENTYX® 150 mg solution for injection is supplied in a single-use pre-filled syringe for individual use. The syringe should be taken out of the refrigerator 15 - 30 minutes before injecting to allow it to reach room temperature.

COSENTYX® 300 mg solution for injection in pre-filled syringe

COSENTYX® 300 mg solution for injection is supplied in a single-use pre-filled syringe for individual use. The syringe should be taken out of the refrigerator 30 - 45 minutes before injecting to allow it to reach room temperature.

COSENTYX® 150 mg solution for injection in pre-filled pen

COSENTYX® 150 mg solution for injection is supplied in a single-use pre-filled pen for individual use. The pen should be taken out of the refrigerator 15 - 30 minutes before injecting to allow it to reach room temperature.

COSENTYX® 300 mg solution for injection in pre-filled pen

COSENTYX® 300 mg solution for injection is supplied in a single-use pre-filled pen for individual use. The pen should be taken out of the refrigerator 30 - 45 minutes before injecting to allow it to reach room temperature.

Prior to use, a visual inspection of the pre-filled syringe or pre-filled pen is recommended. The liquid should be clear. Its colour may vary from colourless to slightly yellow. You may see a small air bubble, which is normal. Do not use if the liquid contains easily visible particles, is cloudy or is distinctly brown.

Detailed instructions for use are provided in the patient information leaflet.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd.

Magwa Crescent West

Waterfall City, Jukskei View

Johannesburg, 2090

South Africa

(011) 347 6600

8. REGISTRATION NUMBER(S)

COSENTYX® 150 mg/mL Solution for Injection: 49/30.1/0233

COSENTYX® 300 mg/2mL Solution for Injection: 56/30.1/0242

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

COSENTYX® 150 mg/mL solution for injection: 25 September 2018

COSENTYX® 300 mg/2 mL solution for injection: 06 September 2022

10. DATE OF REVISION OF THE TEXT

30 April 2026

Namibia	
COSENTYX® 150 mg/mL Solution for Injection: 19/30.1/0059	NS2
Manufacturers: *Novartis Pharma Stein AG Schaffhauserstrasse 4332 Stein, Switzerland* *Novartis Pharmaceutical Manufacturing GmbH,Biochemiestraße 10 6336 Langkampfen, Austria*	

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