1. NAME OF THE MEDICINAL PRODUCT

Cosentyx® 150 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe or pre-filled pen contains 150 mg secukinumab in 1ml.

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 pre-filled syringe
Solution for injection in pre-filled pen (SensoReady® 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 adults who are candidates for systemic therapy.

Psoriatic arthritis

Cosentyx, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate (see section 5.1).

Axial spondyloarthritis (axSpA)

Ankylosing spondylitis (AS, radiographic axial spondyloarthritis)

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

Non-radiographic axial spondyloarthritis (nr-axSpA)
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 magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs).

Juvenile idiopathic arthritis (JIA)

Enthesitis-related arthritis (ERA)

Cosentyx, alone or in combination with methotrexate (MTX), is indicated for the treatment of active enthesitis-related arthritis in patients 6 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy (see section 5.1).

Juvenile psoriatic arthritis (JPsA)
Cosentyx, alone or in combination with methotrexate (MTX), is indicated for the treatment of active juvenile psoriatic arthritis in patients 6 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy (see section 5.1).

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

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

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 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, radiographic axial spondyloarthritis)
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 two subcutaneous injections of 150 mg.

Non-radiographic axial spondyloarthritis (nr-axSpA)
Administer Cosentyx with or without a loading dosage by subcutaneous injection (see section 5.1). The recommended dosage:
• With a loading dosage is 150 mg at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter
• Without a loading dosage is 150 mg every 4 weeks.

Juvenile idiopathic arthritis (JIA)

Enthesitis-related arthritis (ERA) and juvenile psoriatic arthritis (JPsA)
The recommended dose is based on body weight (Table 1) and administered by subcutaneous injection at weeks 0, 1, 2, 3, and 4, followed by monthly maintenance dosing. Each 75 mg dose is given as one subcutaneous injection of 75 mg. Each 150 mg dose is given as one subcutaneous injection of 150 mg.

Table 1 Recommended dose for juvenile idiopathic arthritis

Body weight at time of dosing	Recommended dose
<50 kg	75 mg
≥50 kg	150 mg

The 150 mg solution for injection in pre-filled syringe and in pre-filled pen are not indicated for administration to paediatric patients with a weight <50 kg. Cosentyx may be available in other strengths and/or presentations depending on the individual treatment needs.

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.

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 the juvenile idiopathic arthritis (JIA) categories of ERA and JPsA 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
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 if a physician determines that this is appropriate. However, the physician should ensure appropriate follow-up of patients. Patients should be instructed to inject the full amount of Cosentyx according to the instructions provided in the package leaflet. Comprehensive instructions for administration are given in the package 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).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, 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).

No increased susceptibility to tuberculosis was reported from clinical studies. However, secukinumab should not be given to patients with active tuberculosis. Anti-tuberculosis therapy should be considered prior to initiation of secukinumab in patients with latent tuberculosis.

Inflammatory bowel disease (including Crohn's disease and ulcerative colitis)

Cases of new or exacerbations of inflammatory bowel disease have been reported with secukinumab (see section 4.8). Secukinumab is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated.

Hypersensitivity reactions

In clinical studies, rare cases of anaphylactic reactions have been observed in patients receiving secukinumab. If an anaphylactic or other serious allergic reactions occur, administration of secukinumab should be discontinued immediately and appropriate therapy initiated.

Latex-sensitive individuals

The removable needle cap of the Cosentyx pre-filled syringe/pre-filled pen contains 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/pre-filled 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.
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 suggest that secukinumab does not suppress the humoral immune response to the *meningococcal* or *influenza* vaccines.

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 medicinal products and other forms of interaction

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

In a study in 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 axial 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
There are no adequate data from the use of secukinumab in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Cosentyx during pregnancy.

Breast-feeding
It is not known whether secukinumab is excreted in human milk. Immunoglobulins are excreted in human milk and it is not known if secukinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from secukinumab, a decision on whether to discontinue breast-feeding during treatment and up to 20 weeks after treatment or to discontinue therapy with Cosentyx must be made taking into account the benefit of breast-feeding to the child and the benefit of therapy to the woman.

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

Summary of the safety profile

The most frequently reported adverse drug reactions (ADRs) are upper respiratory tract infections (17.7%) (most frequently nasopharyngitis, rhinitis).

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 18,000 patients have been treated with secukinumab in blinded and open-label clinical studies in various indications (plaque psoriasis, psoriatic arthritis, axial spondyloarthritis and other autoimmune conditions), representing 30,565 patient years of exposure. Of these, over 11,700 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
	Common	Nausea
	Uncommon	Inflammatory bowel disease
Skin and subcutaneous tissue disorders	Uncommon	Urticaria
		Dyshidrotic eczema
	Rare	Exfoliative dermatitis[2)]
		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, 75 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

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 axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis) clinical studies were similar to those observed in the psoriasis studies.

Neutropenia
In psoriasis phase III clinical studies, neutropenia was more frequently observed with secukinumab than with placebo, but most cases were mild, transient and reversible. Neutropenia <1.0-0.5x10^9/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 axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis) was similar to psoriasis.

Rare cases of neutropenia <0.5x10^9/l (CTCAE grade 4) were reported.

Hypersensitivity reactions
In clinical studies, urticaria and rare cases of anaphylactic reaction to secukinumab were observed (see also section 4.4).

Immunogenicity
In psoriasis, psoriatic arthritis and axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis) 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.

Undesirable effects in paediatric patients with JIA
The safety of secukinumab was also assessed in a phase III study in 86 juvenile idiopathic arthritis patients with ERA and JPsA from 2 to less than 18 years of age. The safety profile reported in this study was consistent with the safety profile reported in adult patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

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, 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 in synovial tissue of psoriatic arthritis patients. The frequency of IL-17-producing cells was also significantly higher in the subchondral bone marrow of facet joints from patients with ankylosing spondylitis.
Increased numbers of IL-17A producing lymphocytes have also been found in patients with non-radiographic axial spondyloarthritis. Inhibition of IL-17A was shown to be effective in the treatment of ankylosing spondylitis, 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
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].

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 Table 3 and Table **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%)
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%)	-	-	-	-
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 colouration 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
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.

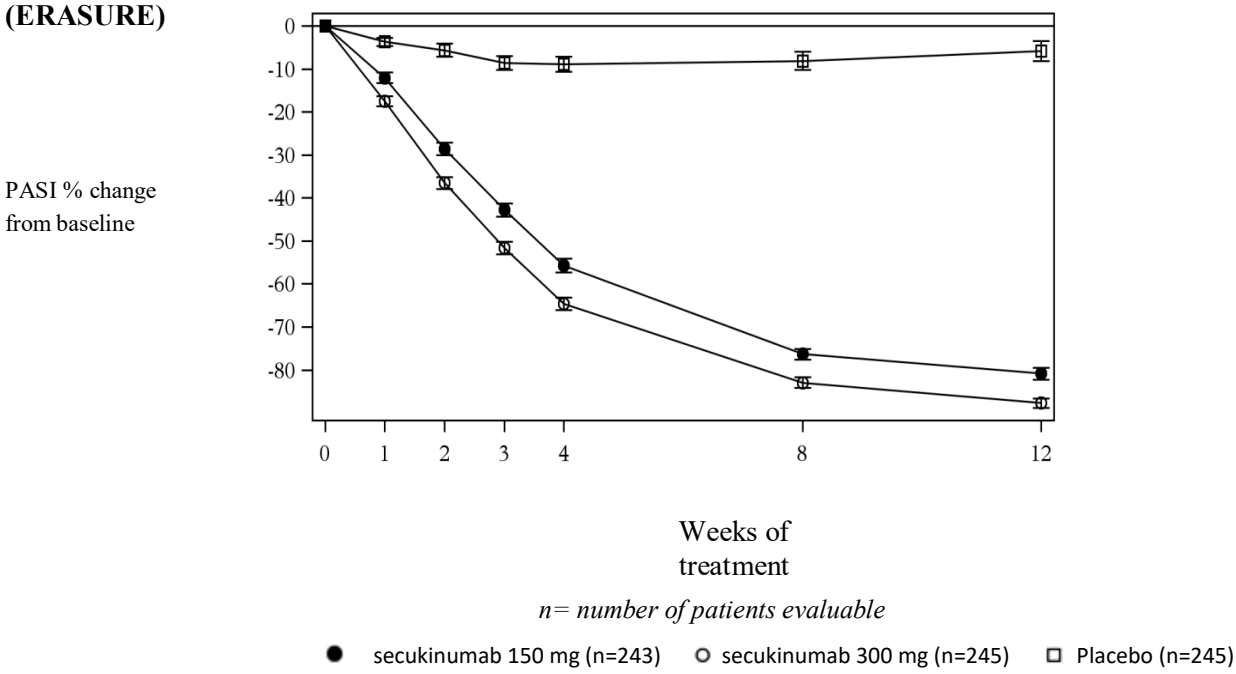
Table 5 Summary of clinical response on CLEAR study

	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 values 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 (ERASURE) **Time course of percentage change from baseline of mean PASI score in study 1**



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.

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.

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.

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 either 75 mg or 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 (either 75 mg or 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 75 mg, 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 and 24 (see Table 6).

Table 6 Clinical response in PsA study 2 and PsA study 3 at week 16 and week 24

	PsA study 2			**PsA study 3**		
	Placebo	150 mg[1]	300 mg[1]	Placebo	150 mg[1]	300 mg[1]
Number of patients randomised	98	100	100	332	220	222
ACR20 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%***)
ACR50 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%***)
ACR70 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%***)
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***
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%***)
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%***)

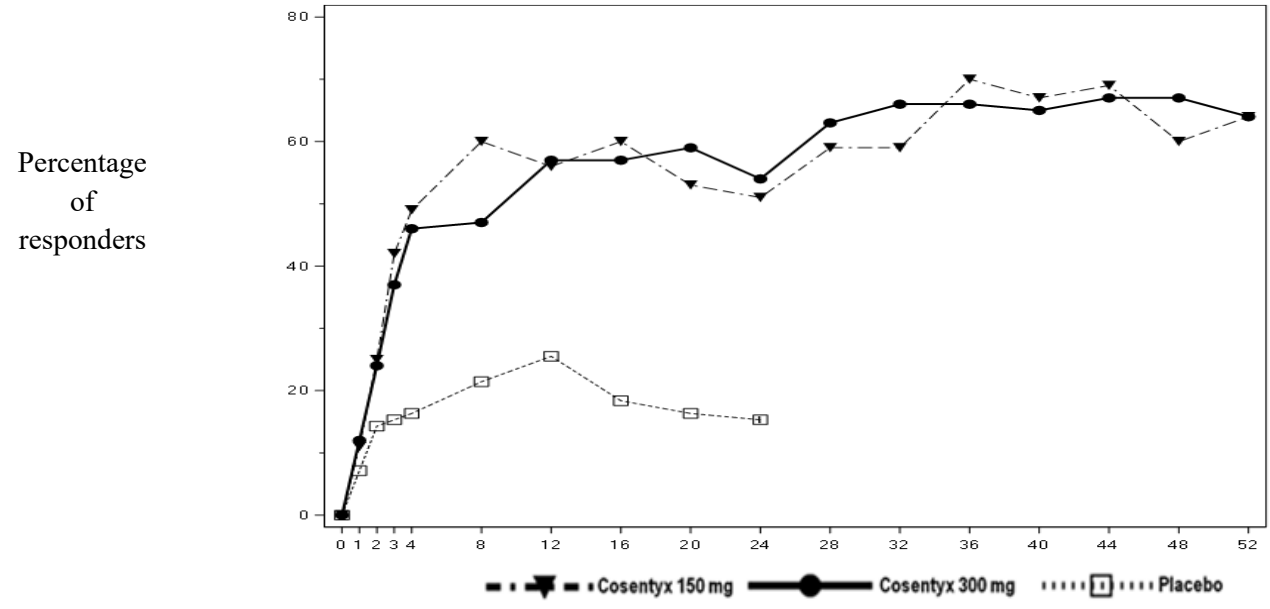
Dactylitis resolution n (%) †						
Week 16	10 (37%)	21 (65.6%*)	26 (56.5%)	40 (32.3%)	46 (57.5%*)	54 (65.9%*)
Week 24	4 (14.8%)	16 (50.0%**)	26 (56.5%**)	42 (33.9%)	51 (63.8%***)	52 (63.4%***)
Enthesitis resolution n (%) ‡						
Week 16	17 (26.2%)	32 (50.0%**)	32 (57.1%***)	68 (35.4%)	77 (54.6%*)	78 (55.7%*)
Week 24	14 (21.5%)	27 (42.2%*)	27 (48.2%**)	66 (34.4%)	77 (54.6%***)	86 (61.4%***)

* p<0.05, ** p<0.01, *** p<0.001; versus placebo
All p-values are adjusted for multiplicity of testing based on pre-defined hierarchy at week 24 for PsA study 2, except for ACR70, Dactylitis and Enthesitis, which were exploratory endpoints and all endpoints at week 16.
All p-values are adjusted for multiplicity of testing based on pre-defined hierarchy at week 16 for PsA study 3, except for ACR70 which was an exploratory endpoint and all endpoints at week 24.
Non-responder imputation used for missing binary endpoint.
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 PsA study 2 and n=124, 80, 82, respectively for PsA study 3)
‡In patients with enthesitis at baseline (n=65, 64, 56, respectively for PsA study 2 and n=192, 141, 140, respectively for PsA study 3)

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.

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 7).

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 7.

Table 7 Change in modified Total Sharp Score in psoriatic arthritis

	PsA study 3			PsA study 1	
	Placebo n=296	**secukinumab 150 mg[1] n=213**	**secukinumab 300 mg[1] n=217**	**Placebo n=179**	**secukinumab 150 mg[2] n=185**
Total score					
Baseline (SD)	15.0 (38.2)	13.5 (25.6)	12.9 (23.8)	28.4 (63.5)	22.3 (48.0)
Mean change at Week 24	0.50	0.13*	0.02*	0.57	0.13*

*p<0.05 based on nominal, but non 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 by subcutaneous doses of 75 mg or 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.

In PsA study 1, 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 82.3% in secukinumab 10 mg/kg intravenous load – 150 mg subcutaneous maintenance and 75.7% in placebo. The percentage of patients with no disease progression from week 24 to Week 52 for secukinumab 10 mg/kg intravenous load – followed by 150 mg subcutaneous maintenance and for placebo patients who switched to 75 mg or 150 mg subcutaneous every 4 weeks at week 16 or week 24 was 85.7% and 86.8%, respectively.

Axial manifestations in PsA
A randomised, 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 of at least a 20% improvement in Assessment of SpondyloArthritis International Society (ASAS 20) criteria at week 12 was met. Treatment with secukinumab 300 mg and 150 mg compared to placebo also resulted in greater improvement in signs and symptoms (including decreases from baseline in spinal pain) and improvement in physical function (see Table 8).

Table 8 Clinical response on MAXIMISE study at week 12

	Placebo (n=164)	150 mg (n=157)	300 mg (n=164)
ASAS 20 response, % (95% CI)	31.2 (24.6, 38.7)	66.3 (58.4, 73.3)*	62.9 (55.2, 70.0)*
ASAS 40 response, % (95% CI)	12.2 (7.8, 18.4)	39.5 (32.1, 47.4)**	43.6 (36.2, 51.3)**
BASDAI 50, % (95% CI)	9.8 (5.9, 15.6)	32.7 (25.8, 40.5)**	37.4 (30.1, 45.4)**
Spinal pain, VAS (95% CI)	-13.6 (-17.2, -10.0)	-28.5 (-32.2, -24.8)**	-26.5 (-30.1, -22.9)**
Physical function, HAQ-DI (95% CI)	-0.155 (-0.224, -0.086)	-0.330 (-0.401, -0.259)**	-0.389 (-0.458, -0.320)**
* p<0.0001; versus placebo using multiple imputation. ** Comparison versus placebo was not adjusted for multiplicity. ASAS: Assessment of SpondyloArthritis International Society Criteria; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; VAS: Visual Analog Scale; HAQ-DI: 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)

Ankylosing spondylitis (AS) / Radiographic axial spondyloarthritis
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 either 75 mg or 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 (either 75 mg or 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 received 75 mg or 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 (either 75 mg or 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 9).

Table 9 Clinical response in AS study 2 at week 16

Outcome (p-value versus placebo)	**Placebo (n = 74)**	**75 mg (n = 73)**	**150 mg (n = 72)**
ASAS 20 response, %	28.4	41.1	61.1***
ASAS 40 response, %	10.8	26.0	36.1***
hsCRP, (post-BSL/BSL ratio)	1.13	0.61	0.55***
ASAS 5/6, %	8.1	34.2	43.1***
ASAS partial remission, %	4.1	15.1	13.9
BASDAI 50, %	10.8	24.7*	30.6**
ASDAS-CRP major improvement	4.1	15.1*	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)
The safety and efficacy of secukinumab were assessed in 555 patients in one randomised, double-blind, placebo-controlled phase III study (PREVENT), consisting of a 2-year core phase and a 2-year extension phase, 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 0-100 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 the PREVENT study, 9.7% of patients 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).

In the PREVENT study, 9.9% and 14.8% of patients used concomitant MTX or sulfasalazine, respectively. In the double-blind period, patients received either placebo or secukinumab for 52 weeks. Patients randomised to secukinumab received 150 mg 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. The primary endpoint was at least 40% improvement in Assessment of Spondyloarthritis International Society (ASAS 40) at Week 16 in anti-TNFα-naive patients.

Signs and symptoms:
In the PREVENT study, treatment with secukinumab 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 (Table 10). Responses were maintained up to week 52.

Table 10 Clinical response in the PREVENT study at week 16

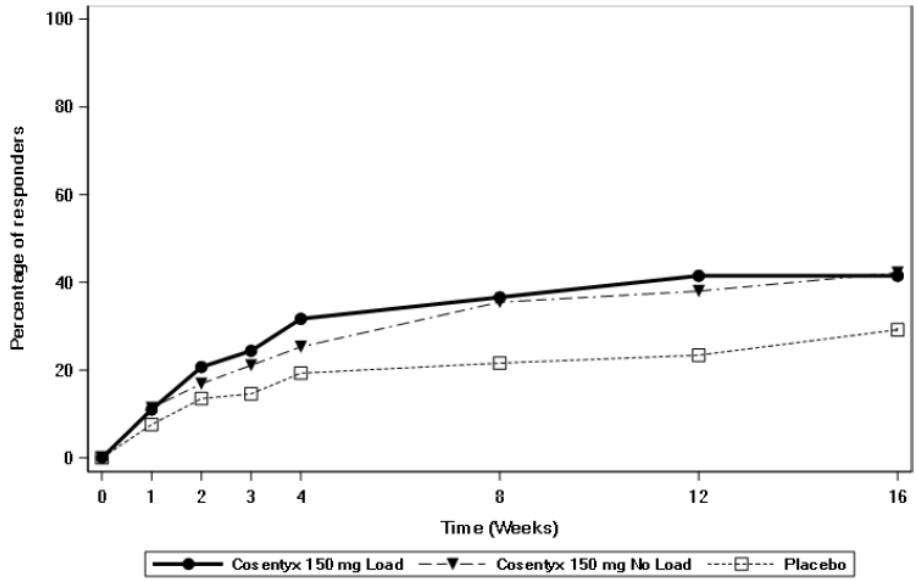
Outcome (p-value versus placebo)	**Placebo**	**150 mg[1]**
Number of anti-TNFα-naive patients randomised	**171**	**164**
ASAS 40 response, %	29.2	41.5*
Total number of patients randomised	**186**	**185**
ASAS 40 response, %	28.0	40.0*
ASAS 5/6, %	23.7	40.0*
BASDAI, LS mean change from baseline score	-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 versus placebo
All p-values adjusted for multiplicity of testing based on pre-defined hierarchy
Non-responder imputation used for missing binary endpoint
[1]secukinumab 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 onset of action of secukinumab 150 mg occurred as early as week 3 with the Load regimen and week 8 with the No Load regimen for ASAS 40 in anti-TNFα naive patients (superior to placebo) in the PREVENT study. The percentage of patients achieving an ASAS 40 response in the PREVENT study by visit is shown in Figure 3.

Figure 3 ASAS 40 responses in the PREVENT Study Over Time up to week 16



ASAS 40 responses were also improved at week 16 in anti-TNFα-IR patients for secukinumab 150 mg compared with placebo.

Physical function and health-related quality of life:
Patients treated with secukinumab 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 versus -1.01, $p<0.05$). Patients treated with secukinumab 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 versus -1.84, $p<0.05$) and SF-36 Physical Component Summary (SF-36 PCS) (LS mean change: week 16: 5.71 versus 2.93, $p<0.05$). 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 secukinumab 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 secukinumab 150 mg (n=180) versus -0.39 for the placebo-treated patients (n=174) ($p<0.05$).

Paediatric population

Juvenile idiopathic arthritis (JIA)

Enthesitis-related arthritis (ERA) and juvenile psoriatic arthritis (JPsA)

The efficacy and safety of secukinumab were assessed in 86 patients in a 3-part, double-blind, placebo-controlled, event-driven, randomised, phase III study in patients 2 to <18 years of age with active ERA or JPsA as diagnosed based on a modified International League of Associations for Rheumatology (ILAR) JIA classification criteria. The study consisted of an open-label portion (Part 1) where all patients received

secukinumab until week 12. Patients demonstrating a JIA ACR 30 response at week 12 entered into the Part 2 double-blind phase and were randomised 1:1 to continue treatment with secukinumab or to begin treatment with placebo (randomised withdrawal) until week 104 or until a flare occured. Patients who flared then entered open-label secukinumab treatment until week 104 (Part 3).

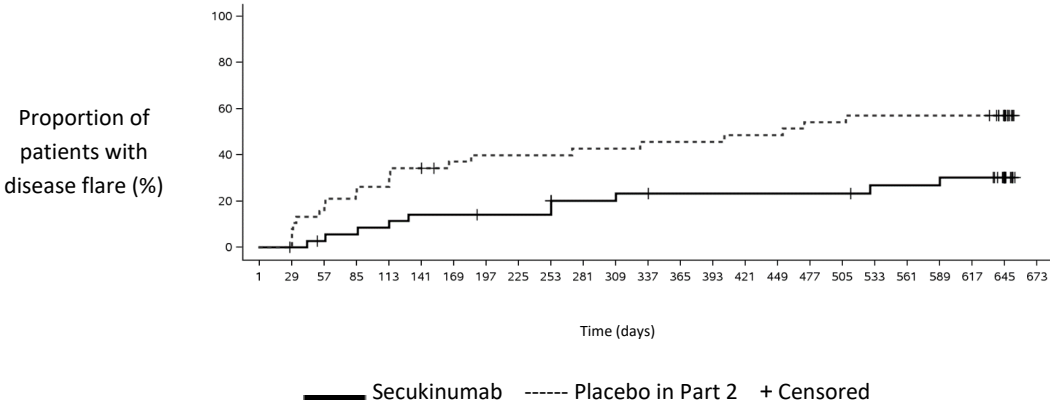
The JIA patient subtypes at study entry were: 60.5% ERA and 39.5% JPsA, who either had inadequate response or were intolerant to ≥1 disease-modifying antirheumatic drugs (DMARDs) and ≥1 non-steroidal anti-inflammatory drugs (NSAIDs). At baseline, MTX use was reported for 65.1% of patients; (63.5% [33/52] of ERA patients and 67.6% [23/34] of JPsA patients). There were 12 out of 52 ERA patients concomitantly treated with sulfasalazine (23.1%). Patients with a body weight at baseline <50 kg (n=30) were given a dose of 75 mg and patients with a body weight ≥50 kg (n=56) were given a dose of 150 mg. Age at baseline ranged from 2 to 17 years, with 3 patients between 2 to <6 years, 22 patients 6 to <12 years and 61 patients 12 to <18 years. At baseline the Juvenile Arthritis Disease Activity Score (JADAS)-27 was 15.1 (SD:7.1).

The primary endpoint was time to flare in the randomised withdrawal period (Part 2). Disease flare was defined as a ≥30% worsening in at least three of the six JIA ACR response criteria and ≥30% improvement in not more than one of the six JIA ACR response criteria and a minimum of two active joints.

At the end of Part 1, 75 out of 86 (87.2%) patients demonstrated a JIA ACR 30 response and entered into Part 2.

The study met its primary endpoint by demonstrating a statistically significant prolongation in the time to disease flare in patients treated with secukinumab compared to placebo in Part 2. The risk of flare was reduced by 72% for patients on secukinumab compared with patients on placebo in Part 2 (Hazard ratio=0.28, 95% CI: 0.13 to 0.63, p<0.001) (Figure 4 and Table 10). During Part 2, a total of 21 patients in the placebo group experienced a flare event (11 JPsA and 10 ERA) compared with 10 patients in the secukinumab group (4 JPsA and 6 ERA).

Figure 4 Kaplan-Meier estimates of the time to disease flare in Part 2



Number of patients at risk

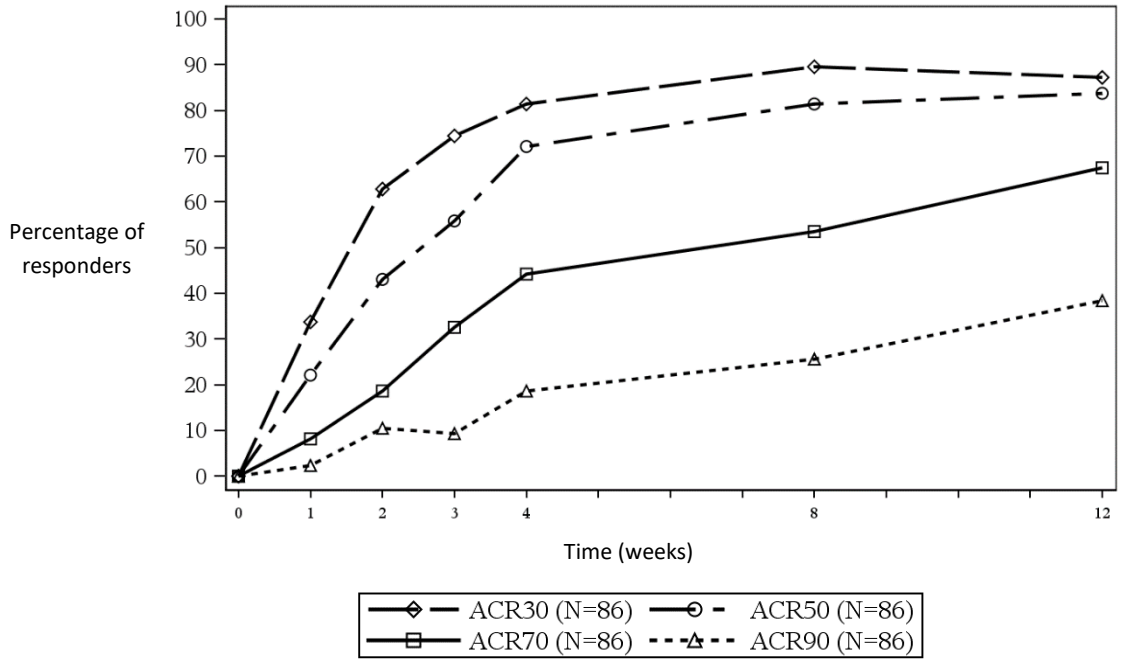
Secukinumab	37	36	34	33	32	30	30	29	29	29	25	25	24	23	23	23	23	23	23	21	21	21	20	14	0
Placebo in Part 2	38	38	32	29	28	25	22	21	21	21	20	20	19	19	19	18	18	16	16	15	15	15	15	10	0

Table 10 Survival analysis of time to disease flare – Part 2

	Secukinumab (N=37)	**Placebo in Part 2** (N=38)
Number of flare events at the end of Part 2, n (%)	10 (27.0)	21 (55.3)
Kaplan-Meier estimates:		
Median, in days (95% CI)	NC (NC, NC)	453.0 (114.0, NC)
Flare-free rate at 6 months (95% CI)	85.8 (69.2, 93.8)	60.1 (42.7, 73.7)
Flare-free rate at 12 months (95% CI)	76.7 (58.7, 87.6)	54.3 (37.1, 68.7)
Flare-free rate at 18 months (95% CI)	73.2 (54.6, 85.1)	42.9 (26.7, 58.1)
Hazard ratio to placebo: Estimate (95% CI)	0.28 (0.13, 0.63)	
Stratified log-rank test p-value	<0.001**	
Analysis was conducted on all randomised patients who received at least one dose of study drug in Part 2. Secukinumab: all patients who did not take any placebo. Placebo in Part 2: all patients who took placebo in Part 2 and secukinumab in other period/s. NC = Not calculable. ** = Statistically significant on one-sided significance level 0.025.		

In open-label Part 1, all patients received secukinumab until week 12. At week 12, 83.7%, 67.4%, and 38.4% of children were JIA ACR 50, 70 and 90 responders, respectively (Figure 5). The onset of action of secukinumab occurred as early as week 1. At week 12 the JADAS-27 score was 4.64 (SD:4.73) and the mean decrease from baseline in JADAS-27 was -10.487 (SD:7.23).

Figure 5 JIA ACR 30/50/70/90 response for subjects up to week 12 in Part 1*



*non-responder imputation was used to handle missing values

The data in the 2 to <6 age group were inconclusive due to the low number of patients below 6 years of age enrolled in the study.

5.2 Pharmacokinetic properties

Most pharmacokinetics properties observed in patients with plaque psoriasis, psoraitic 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 43.2±10.4 µg/ml between 2 and 14 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.

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.

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 1x 0.3 mg/kg to 3x 10 mg/kg and with

subcutaneous doses ranging from 1x 25 mg to multiple doses of 300 mg. Exposure was dose proportional across all dosing regimens.

Special populations

Elderly patients

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 population
Juvenile idiopathic arthritis
In a paediatric study, ERA and JPsA patients (2 to less than 18 years of age) were administered secukinumab at the recommended paediatric dosing regimen. At week 24, patients weighing <50 kg, and weighing ≥50 kg had a mean ± SD steady-state trough concentration of 25.2±5.45 µg/ml (n=10) and 27.9±9.57 µg/ml (n=19), respectively.

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

Water for injections
Trehalose dihydrate
L-histidine/histidine hydrochloride monohydrate
L-methionine
Polysorbate 80, low peroxide quality

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is printed on the package materials.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).. If necessary, Cosentyx may be stored unrefrigerated for a single period of up to 4 days at room temperature, not above 30°C. Do not freeze
Store the syringes and pens in the original package in order to protect from light.

6.5 Nature and contents of container

Cosentyx 150 mg solution for injection in pre-filled syringe

Cosentyx150 mg solution for injection is supplied in a pre-filled 1 ml long glass syringe with a rubber plunger stopper, staked needle and rigid needle shield

Cosentyx is available in unit packs containing 1 or 2 pre-filled syringes.
Not all pack sizes may be marketed.

Cosentyx 150 mg solution for injection in pre-filled pen (SensoReady pen)
Cosentyx 150 mg solution for injection is supplied in a single-use pre-filled syringe assembled into a auto-injector (SensoReady pen). The pre-filled syringe inside the pen is a 1 ml glass syringe with a rubber plunger stopper, staked needle and rigid needle shield.

Cosentyx is available in unit pack containing 1 or 2 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 and pre-filled pen

Cosentyx 150 mg solution for injection is supplied in a single-use pre-filled syringe/pen for individual use. The syringe or the pen should be taken out of the refrigerator 20 minutes before injecting to allow it to reach room temperature.

Prior to use a visual inspection of the pre-filled syringe/ 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 package leaflet.

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

8. REGISTRATION HOLDER and IMPORTER:

Novartis Israel Ltd.
P.O.B 7126, Tel Aviv

9. REGISTRATION NUMBER: 154-20-34342

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