SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cosentyx 75 mg solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 75 mg secukinumab in 0.5 ml.

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 (injection)

The solution is clear and colourless to slightly yellow.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Paediatric plaque psoriasis

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

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

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. 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. 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 for paediatric plaque psoriasis

Body weight at time of dosing	**Recommended dose**
<25 kg	75 mg
25 to <50 kg	75 mg
≥50 kg	150 mg (*may be increased to 300 mg)

*Some patients may derive additional benefit from the higher dose.

Juvenile idiopathic arthritis (JIA)

Enthesitis-related arthritis (ERA) and juvenile psoriatic arthritis (JPsA)
The recommended dose is based on body weight (Table 2) 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 2 Recommended dose for juvenile idiopathic arthritis

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

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.

The safety and efficacy of Cosentyx in children with plaque psoriasis and 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.

Special populations

Renal impairment / hepatic impairment
Cosentyx has not been studied in these patient populations. No dose recommendations can be made.

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 syringe 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 or caregivers 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).

Tuberculosis

Tuberculosis (active and/or latent reactivation) has been reported in patients treated 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 (see section 4.3). In patients with latent tuberculosis, anti-tuberculosis therapy should be considered prior to initiation of secukinumab as per clinical guidelines. Patients receiving secukinumab should be monitored for signs and symptoms of active 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

Rare cases of anaphylactic reactions and angioedema have been observed in patients receiving secukinumab. If an anaphylactic reaction, angioedema 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 Cosentyx 75 mg solution for injection in pre-filled syringe 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 75 mg solution for injection in pre-filled syringe 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.

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).

Hepatitis B reactivation

Hepatitis B virus reactivation can occur in patients treated with secukinumab. In accordance with clinical guidelines for immunosuppresants, testing patients for HBV infection is to be considered before initiating treatment with secukinumab. Patients with evidence of positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation during secukinumab treatment. If reactivation of HBV occurs while on secukinumab, discontinuation of the treatment should be considered, and patients should be treated according to clinical guidelines.

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 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 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 reactions are upper respiratory tract infections (17.1%) (most frequently nasopharyngitis, rhinitis).

Tabulated list of adverse reactions

Adverse reactions from clinical studies and post-marketing reports (Table 3) are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse 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, psoriatic arthritis, axial spondyloarthritis, hidradenitis suppurativa [HS] 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 3 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
	Uncommon	Oral candidiasis
		Otitis externa
		Lower respiratory tract infections
		Tinea pedis
	Not known	Mucosal and cutaneous candidiasis (including oesophageal candidiasis)
Blood and lymphatic system disorders	Uncommon	Neutropenia
Immune system disorders	Rare	Anaphylactic reactions
		Angioedema
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
Skin and subcutaneous tissue disorders	Common	Eczema
	Uncommon	Urticaria
		Dyshidrotic eczema
	Rare	Exfoliative dermatitis[2)]
		Hypersensitivity vasculitis
	Not known	Pyoderma gangrenosum
General disorders and administration site conditions	Common	Fatigue

[1)] Placebo-controlled clinical studies (phase III) in plaque psoriasis, PsA, AS, nr-axSpA and HS patients exposed to 300 mg, 150 mg, 75 mg or placebo up to 12 weeks (psoriasis) or 16 weeks (PsA, AS, nr-axSpA and HS) 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.

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 compared 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 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, axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis) and hidradenitis suppurativa was similar to psoriasis.

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

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.

Paediatric population

Undesirable effects in paediatric patients from the age of 6 years with plaque psoriasis
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.

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

Adult 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 Tables 4 and 5). 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 4 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 5 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 6).

Table 6 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

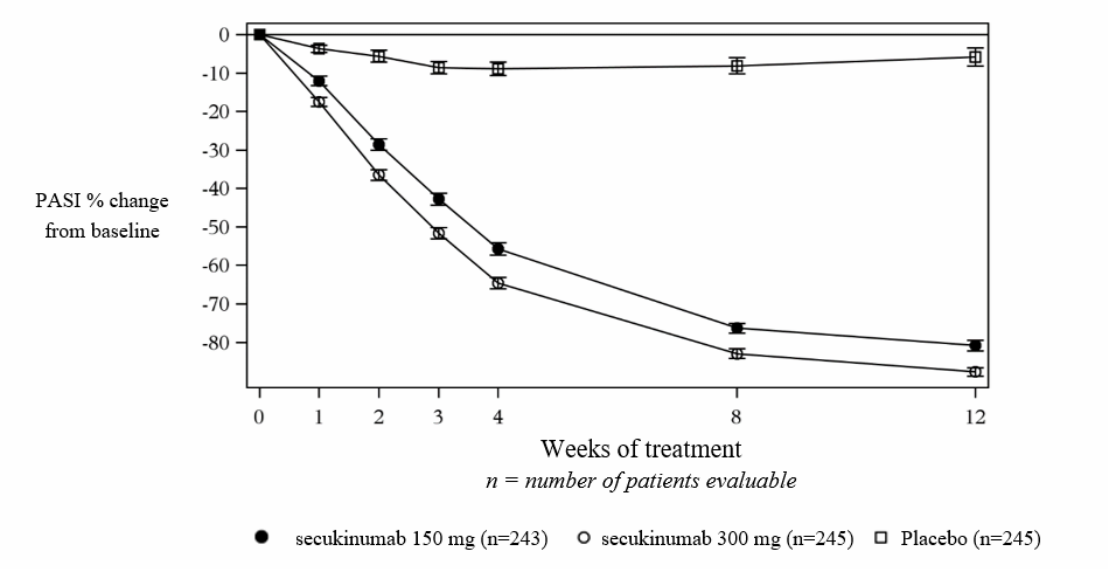
*** p-values versus ustekinumab: p=0.0001 for secondary endpoint of PASI 90 at week 52

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 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.

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.

Paediatric population

Paediatric plaque psoriasis
Secukinumab has been shown to improve signs and symptoms, and health-related quality of life in paediatric patients 6 years and older with plaque psoriasis (see Tables 8 and 10).

Severe plaque psoriasis
The safety and efficacy of secukinumab were assessed in a randomised, double-blind, placebo and etanercept-controlled phase III study in paediatric patients from 6 to <18 years of age with severe plaque psoriasis, as defined by a PASI score ≥20, an IGA mod 2011 score of 4, and BSA involvement of ≥10%, who were candidates for systemic therapy. Approximately 43% of the patients had prior exposure to phototherapy, 53% to conventional systemic therapy, 3% to biologics, and 9% had concomitant psoriatic arthritis.

The paediatric psoriasis study 1 evaluated 162 patients who were randomised to receive low dose secukinumab (75 mg for body weight <50 kg or 150 mg for body weight ≥50 kg), high dose secukinumab (75 mg for body weight <25 kg, 150 mg for body weight between ≥25 kg and <50 kg, or 300 mg for body weight ≥50 kg), or placebo at weeks 0, 1, 2, 3, and 4 followed by the same dose every 4 weeks, or etanercept. Patients randomised to etanercept received 0.8 mg/kg weekly (up to a maximum of 50 mg). Patient distribution by weight and age at randomisation is described in Table 7.

Table 7 Patient distribution by weight and age for paediatric psoriasis study 1

Randomisation strata	**Description**	**Secukinumab low dose n=40**	**Secukinumab high dose n=40**	**Placebo n=41**	**Etanercept n=41**	**Total N=162**
Age	6-<12 years	8	9	10	10	37
	≥12-<18 years	32	31	31	31	125
Weight	<25 kg	2	3	3	4	12
	≥25-<50 kg	17	15	17	16	65
	≥50 kg	21	22	21	21	85

Patients randomised 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 PASI 75 response and IGA mod 2011 ‘clear’ or ‘almost clear’ (0 or 1) response at week 12.

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 statistically significant for both the PASI 75 and IGA mod 2011 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 (see Table 8). Improvement in PASI 50, 90, 100 responder rates and Children's Dermatology Life Quality Index (CDLQI) scores of 0 or 1 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 (see Table 8).

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 and consistent with the safety profile in adults.

Table 8 Summary of clinical response in severe paediatric psoriasis at weeks 12 and 52 (paediatric psoriasis study 1)*

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%). Over time up to and including week 52 both secukinumab dose groups were numerically higher than the etanercept group (low dose 60.6%, high dose 66.7%, etanercept 44.4%).

Moderate to severe plaque psoriasis
Secukinumab was predicted to be effective for the treatment of paediatric patients with moderate plaque psoriasis based on the demonstrated efficacy and exposure response relationship in adult patients with moderate to severe plaque psoriasis, and the similarity of the disease course, pathophysiology, and drug effect in adult and paediatric patients at the same exposure levels.

Moreover, the safety and efficacy of secukinumab was assessed in an open-label, two-arm, parallel-group, multicentre phase III study in paediatric patients from 6 to <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 BSA involvement of ≥10%, who were candidates for systemic therapy.

The paediatric psoriasis study 2 evaluated 84 patients who were randomised to receive low dose secukinumab (75 mg for body weight <50 kg or 150 mg for body weight ≥50 kg) or high dose secukinumab (75 mg for body weight <25 kg, 150 mg for body weight between ≥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. Patient distribution by weight and age at randomisation is described in Table 9.

Table 9 Patient distribution by weight and age for paediatric psoriasis study 2

Sub-groups	**Description**	**Secukinumab low dose n=42**	**Secukinumab high dose n=42**	**Total N=84**
Age	6-<12 years	17	16	33
	≥12-<18 years	25	26	51
Weight	<25 kg	4	4	8
	≥25-<50 kg	13	12	25
	≥50 kg	25	26	51

The co-primary endpoints were the proportion of patients who achieved a PASI 75 response and IGA mod 2011 ‘clear’ or ‘almost clear’ (0 or 1) response at week 12.

The efficacy of both the low and the high dose of secukinumab was comparable and showed statistically significant improvement compared to historical placebo for the co-primary endpoints. The estimated posterior probability of a positive treatment effect was 100%.

Patients were followed for efficacy over a 52 week period after first administration. Efficacy (defined as PASI 75 response and IGA mod 2011 ‘clear’ or ‘almost clear’ [0 or 1]) was observed as early as the first post-baseline visit at 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 up to week 24 and were sustained until week 52. Improvement in PASI 90 and PASI 100 were also observed at week 12, increased up to week 24, and were sustained until week 52 (see Table 10).

The safety profiles of the low dose and the high dose were comparable and consistent with the safety profile in adults.

Table 10 Summary of clinical response in moderate to severe paediatric psoriasis at weeks 12 and 52 (paediatric psoriasis study 2)*

	Week 12		Week 52	
	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%)	37 (88.1%)	38 (90.5%)
IGA mod 2011 'clear' or 'almost clear' response n (%)	33 (78.6%)	35 (83.3%)	36 (85.7%)	35 (83.3%)
PASI 90 response n (%)	29 (69%)	32 (76.2%)	32 (76.2%)	35 (83.3%)
PASI 100 response n (%)	25 (59.5%)	23 (54.8%)	22 (52.4%)	29 (69.0%)
* non-responder imputation was used to handle missing values				

These outcomes in the paediatric moderate to severe plaque psoriasis population confirmed the predictive assumptions based on the efficacy and exposure response relationship in adult patients, mentioned above.

In the low dose group, 50% and 70.7% of patients achieved a CDLQI 0 or 1 score at weeks 12 and 52, respectively. In the high dose group, 61.9% and 70.3% achieved a CDLQI 0 or 1 score at weeks 12 and 52, respectively.

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 2 and Table 11). 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 2 Kaplan-Meier estimates of the time to disease flare in Part 2

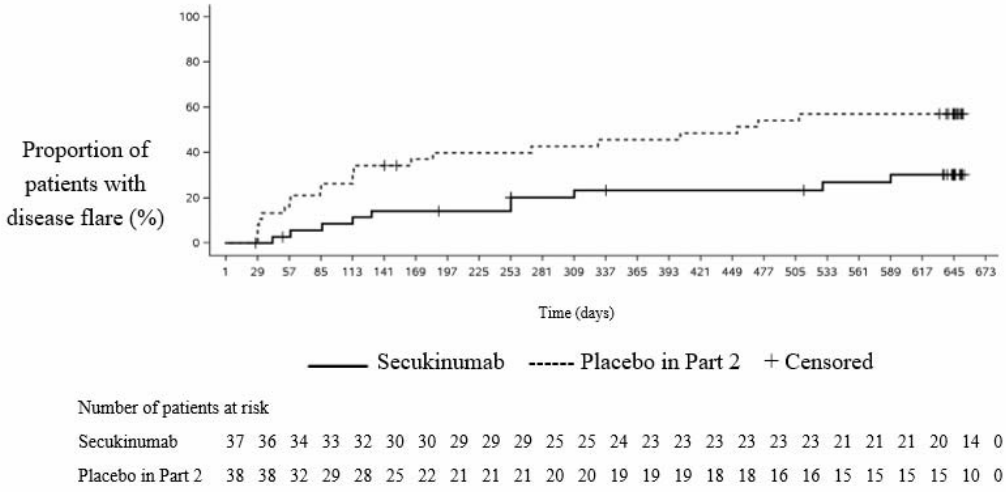
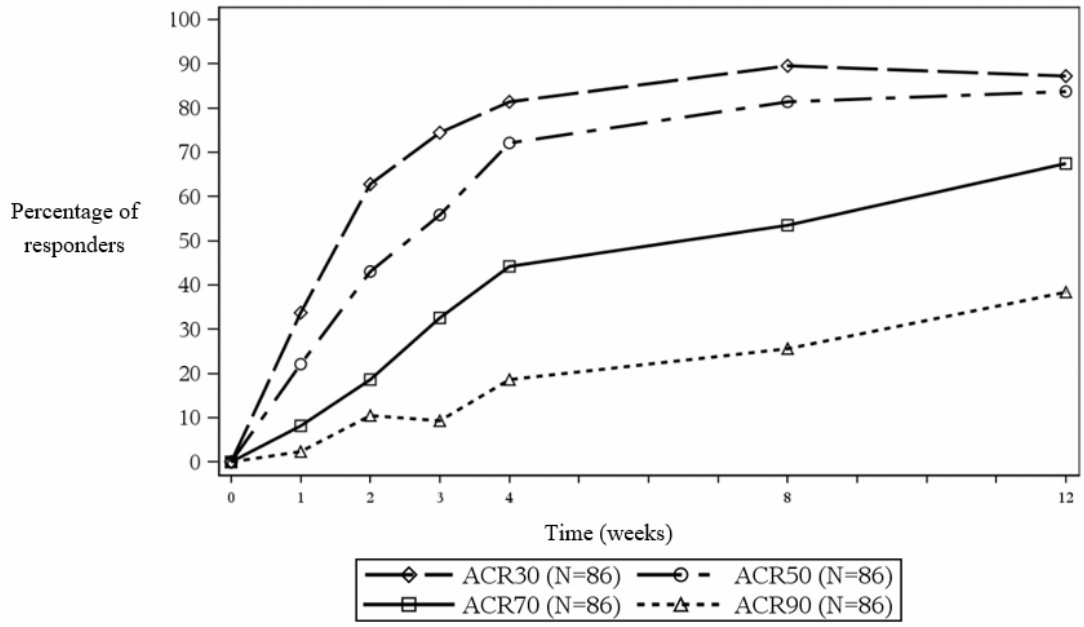


Table 11 Survival analysis of time to disease flare – Part 2

	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 3). 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 3 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.

The licensing authority has waived the obligation to submit the results of studies with Cosentyx in plaque psoriasis in paediatric patients aged from birth to less than 6 years and in chronic idiopathic arthritis for paediatric patients aged from birth to less than 2 years (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Paediatric population

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 ≥25 and <50 kg had a mean ± SD steady-state trough concentration of 19.8±6.96 µg/ml (n=24) after 75 mg of secukinumab and patients weighing ≥50 kg had mean ±SD trough concentration of 27.3±10.1 µg/ml (n=36) after 150 mg of secukinumab. The mean ± SD steady-state trough concentration in patients weighing <25 kg (n=8) was 32.6±10.8 µg/ml at week 24 after 75 mg dose.

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.

Adult population

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.

Following a single subcutaneous injection of 300 mg solution for injection in pre-filled syringe in plaque psoriasis patients, secukinumab systemic exposure was similar to what was observed previously with two injections of 150 mg.

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

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.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans (adult or paediatric) 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

Trehalose dihydrate
Histidine
Histidine hydrochloride monohydrate
Methionine
Polysorbate 80
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Cosentyx 75 mg solution for injection in pre-filled syringe is supplied in a pre-filled 0.5 ml glass syringe with a silicone-coated bromobutyl rubber plunger stopper, staked 27G x ½″ needle and rigid needle shield of styrene butadiene rubber assembled in an automatic needle guard of polycarbonate.

Cosentyx 75 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.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Cosentyx 75 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 20 minutes before injecting to allow it to reach room temperature.

Prior to use, a visual inspection of the pre-filled syringe 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.

7 MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals UK Limited
2nd Floor, The WestWorks Building, White City Place
195 Wood Lane,
London,
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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00101/1205

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/07/2021

10 DATE OF REVISION OF THE TEXT

05/08/2025