

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Taltz 80 mg solution for injection in pre-filled syringe

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 80 mg ixekizumab in 1 ml.

Ixekizumab is produced in CHO cells by recombinant DNA technology.

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

#### Plaque psoriasis

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

#### Paediatric plaque psoriasis

Taltz is indicated for the treatment of moderate to severe plaque psoriasis in children from the age of 6 years and with a body weight of at least 25 kg and adolescents who are candidates for systemic therapy.

#### Psoriatic arthritis

Taltz, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drug (DMARD) therapies (see section 5.1).

#### Axial spondyloarthritis

##### *Ankylosing spondylitis (radiographic axial spondyloarthritis)*

Taltz is indicated for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy.

##### *Non-radiographic axial spondyloarthritis*

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

## 4.2 Posology and method of administration

This medicinal product is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which it is indicated.

### Posology

#### *Plaque psoriasis in adults*

The recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) at weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks (Q4W).

#### *Paediatric plaque psoriasis (age 6 years and above)*

Efficacy and safety data is not available in children below the age of 6 years (see section 5.1).

Available data do not support a posology below a body weight of 25 kg.

The recommended dose given by subcutaneous injection in children is based on the following weight categories:

<b>Children's body weight</b>	<b>Recommended starting dose (week 0)</b>	<b>Recommended dose every 4 weeks (Q4W) thereafter</b>
Greater than 50 kg	160 mg (two 80 mg injections)	80 mg
25 to 50 kg	80 mg	40 mg

For children prescribed 80 mg, Taltz can be used directly from the pre-filled syringe.

For instructions on preparation of Taltz 40 mg, see section 6.6. Doses less than 80 mg must be prepared by a healthcare professional.

Taltz is not recommended for use in children with a body weight below 25 kg. Paediatric body weights must be recorded and regularly re-checked prior to dosing.

#### *Psoriatic arthritis*

The recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) every 4 weeks thereafter. For psoriatic arthritis patients with concomitant moderate to severe plaque psoriasis, the recommended dosing regimen is the same as for plaque psoriasis.

#### *Axial spondyloarthritis (radiographic and non-radiographic)*

The recommended dose is 160 mg (two 80 mg injections) by subcutaneous injection at week 0, followed by 80 mg every 4 weeks (see section 5.1 for further information).

For all indications (plaque psoriasis in adults and children, psoriatic arthritis, axial spondyloarthritis) consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks.

### Special populations

#### *Elderly ( $\geq 65$ years)*

No dose adjustment is required (see section 5.2).

There is limited information in subjects aged  $\geq 75$  years.

#### *Renal or hepatic impairment*

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

### Paediatric population

#### *Paediatric plaque psoriasis (below a body weight of 25 kg and below the age of 6 years)*

There is no relevant use of Taltz in children below a body weight of 25 kg and below the age of 6 years in the treatment of moderate to severe plaque psoriasis.

#### *Paediatric psoriatic arthritis*

The safety and efficacy of Taltz in children and adolescents aged 2 to less than 18 years in the treatment of psoriatic arthritis (a category of juvenile idiopathic arthritis) have not yet been established. No data are available.

There is no relevant use of Taltz in children below 2 years for the indication of psoriatic arthritis.

### Method of administration

Subcutaneous use.

Taltz is for subcutaneous injection. Injection sites may be alternated. If possible, areas of the skin that show psoriasis should be avoided as injection sites. The solution/the syringe must not be shaken.

After proper training in subcutaneous injection technique, patients may self-inject Taltz if a healthcare professional determines that it is appropriate. However, the physician should ensure appropriate follow-up of patients. Comprehensive instructions for administration are given in the package leaflet and the user manual.

Doses less than 80 mg which require dose preparation should only be administered by a healthcare professional.

For instructions on preparation of the medicinal product before administration, see section 6.6.

### **4.3 Contraindications**

Serious hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically important active infections (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

Treatment with Taltz is associated with an increased rate of infections such as upper respiratory tract infection, oral candidiasis, conjunctivitis, and tinea infections (see section 4.8).

Taltz should be used with caution in patients with clinically important 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 an infection develops, patients should be carefully monitored and Taltz discontinued if the patient is not responding to standard therapy or if the infection becomes serious. Taltz should not be resumed until the infection resolves.

Taltz must not be given to patients with active tuberculosis (TB). Anti-TB therapy prior to initiation of Taltz in patients with latent TB should be considered.

## Hypersensitivity

Serious hypersensitivity reactions, including some cases of anaphylaxis, angioedema, urticaria and, rarely, late (10-14 days following injection) serious hypersensitivity reactions including widespread urticaria, dyspnea and high antibody titres have been reported. If a serious hypersensitivity reaction occurs, administration of Taltz should be discontinued immediately and appropriate therapy initiated.

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

Cases of new or exacerbations of inflammatory bowel disease have been reported with ixekizumab (see section 4.8). Ixekizumab 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, ixekizumab should be discontinued and appropriate medical management should be initiated.

## Immunisations

Taltz should not be used with live vaccines. No data are available on the response to live vaccines; there are insufficient data on response to inactive vaccines (see section 5.1).

## Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per 80 mg dose, that is to say essentially “sodium-free”.

## **4.5 Interaction with other medicinal products and other forms of interaction**

In plaque psoriasis studies, the safety of Taltz in combination with other immunomodulatory agents or phototherapy has not been evaluated.

In population pharmacokinetic analyses, clearance of ixekizumab was not affected by concomitant administration of oral corticosteroids, NSAIDs, sulfasalazine, or methotrexate.

## Cytochrome P450 substrates

Results from an interaction study in patients with moderate-to-severe psoriasis determined that 12 weeks of administration of ixekizumab with substances metabolised by CYP3A4 (i.e., midazolam), CYP2C9 (i.e., warfarin), CYP2C19 (i.e., omeprazole), CYP1A2 (i.e., caffeine) or CYP2D6 (i.e., dextromethorphan) does not have a clinically significant impact on the pharmacokinetics of these substances.

## **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 10 weeks after treatment.

### Pregnancy

There is a limited amount of data from the use of ixekizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or post-natal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Taltz during pregnancy.

## Breast-feeding

It is not known whether ixekizumab is excreted in human milk or absorbed systemically after ingestion. However, ixekizumab is excreted at low levels in the milk of cynomolgus monkeys. A decision should be made whether to discontinue breast-feeding or to discontinue Taltz taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

## Fertility

The effect of ixekizumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

### **4.7 Effects on ability to drive and use machines**

Taltz 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 were injection site reactions (15.5 %) and upper respiratory tract infections (16.4 %) (most frequently nasopharyngitis).

#### Tabulated list of adverse reactions

Adverse reactions from clinical studies and postmarketing reports (Table 1) 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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

A total of 8,956 patients have been treated with Taltz in blinded and open-label clinical studies in plaque psoriasis, psoriatic arthritis, axial spondyloarthritis, and other autoimmune conditions. Of these, 6,385 patients were exposed to Taltz for at least one year, cumulatively representing 19,833 adult patient years of exposure and 196 children cumulatively representing 207 patient years of exposure.

**Table 1. List of adverse reactions in clinical studies and postmarketing reports**

<b>System organ class</b>	<b>Frequency</b>	<b>Adverse reaction</b>
Infections and infestations	Very common	Upper respiratory tract infection
	Common	Tinea infection, Herpes simplex (mucocutaneous)
	Uncommon	Influenza, Rhinitis, Oral candidiasis, Conjunctivitis, Cellulitis
	Rare	Oesophageal candidiasis
Blood and lymphatic system disorders	Uncommon	Neutropenia, Thrombocytopenia
Immune system disorders	Uncommon	Angioedema
	Rare	Anaphylaxis
Respiratory, thoracic and mediastinal disorders	Common	Oropharyngeal pain
Gastrointestinal disorders	Common	Nausea
	Uncommon	Inflammatory bowel disease
Skin and subcutaneous disorders	Uncommon	Urticaria, Rash, Eczema
General disorders and administration site conditions	Very common	Injection site reactions <sup>a</sup>

<sup>a</sup> See section description of selected adverse reactions

#### Description of selected adverse reactions

##### *Injection site reactions*

The most frequent injection site reactions observed were erythema and pain. These reactions were predominantly mild to moderate in severity and did not lead to discontinuation of Taltz.

In the adult plaque psoriasis studies, injection site reactions were more common in subjects with a body weight < 60 kg compared with the group with a body weight ≥ 60 kg (25 % vs. 14 % for the combined Q2W and Q4W groups). In the psoriatic arthritis studies, injection site reactions were more common in subjects with a body weight < 100 kg compared with the group with a body weight ≥ 100 kg (24 % vs. 13 % for the combined Q2W and Q4W groups). In the axial spondyloarthritis studies, injection site reactions were similar in subjects with a body weight < 100 kg compared with the group with a body weight ≥ 100 kg (14 % vs. 9 % for the combined Q2W and Q4W groups). The increased frequency of injection site reactions in the combined Q2W and Q4W groups did not result in an increase in discontinuations in either the plaque psoriasis, the psoriatic arthritis or the axial spondyloarthritis studies.

The results described above are obtained with the original formulation of Taltz. In a single-blinded, randomized cross-over study in 45 healthy subjects comparing the original formulation with the revised, citrate-free formulation, statistically significantly lower VAS pain scores were obtained with the citrate-free vs. the original formulation during injection (difference in LS Mean VAS score -21.69) and 10 min after injection (difference in LS Mean VAS score -4.47).

##### *Infections*

In the placebo-controlled period of the phase III clinical studies in plaque psoriasis in adults, infections were reported in 27.2 % of patients treated with Taltz for up to 12 weeks compared with 22.9 % of patients treated with placebo.

The majority of infections were non-serious and mild to moderate in severity, most of which did not necessitate treatment discontinuation. Serious infections occurred in 13 (0.6 %) of patients treated with Taltz and in 3 (0.4 %) of patients treated with placebo (see section 4.4). Over the entire treatment period infections were reported in 52.8 % of patients treated with Taltz (46.9 per 100 patient years). Serious infections were reported in 1.6 % of patients treated with Taltz (1.5 per 100 patient years).

Infection rates observed in psoriatic arthritis and axial spondyloarthritis clinical studies were similar to those observed in the plaque psoriasis studies with the exception of the frequencies of the adverse reactions of influenza and conjunctivitis which were common in patients with psoriatic arthritis.

#### *Laboratory assessment of neutropenia and thrombocytopenia*

In plaque psoriasis studies, 9% of patients receiving Taltz developed neutropenia. In most cases, the blood neutrophil count was  $\geq 1,000$  cells/mm<sup>3</sup>. Such levels of neutropenia may persist, fluctuate or be transient. 0.1% of patients receiving Taltz developed a neutrophil count  $< 1,000$  cells/mm<sup>3</sup>. In general, neutropenia did not require discontinuation of Taltz. 3% of patients exposed to Taltz had a shift from a normal baseline platelet value to  $< 150,000$  platelet cells/mm<sup>3</sup> to  $\geq 75,000$  cells/mm<sup>3</sup>. Thrombocytopenia may persist, fluctuate or be transient.

The frequency of neutropenia and thrombocytopenia in psoriatic arthritis and axial spondyloarthritis clinical studies is similar to that observed in the plaque psoriasis studies.

#### *Immunogenicity*

Approximately 9-17% of adult plaque psoriasis patients treated with Taltz at the recommended dosing regimen developed anti-drug antibodies, the majority of which were low titres and not associated with reduced clinical response up to 60 weeks of treatment. However, approximately 1% of patients treated with Taltz had confirmed neutralising antibodies associated with low drug concentrations and reduced clinical response.

In psoriatic arthritis patients treated with Taltz at the recommended dosing regimen up to 52 weeks, approximately 11% developed anti-drug antibodies, the majority of which were low titre, and approximately 8% had confirmed neutralising antibodies. No apparent association between the presence of neutralising antibodies and impact on drug concentration or efficacy was observed.

In paediatric psoriasis patients treated with Taltz at the recommended dosing regimen up to 12 weeks, 21 patients (18%) developed anti-drug antibodies, approximately half were low titer and 5 patients (4%) had confirmed neutralizing antibodies associated with low drug concentrations. There was no association with clinical response or adverse events.

In radiographic axial spondyloarthritis patients treated with Taltz at the recommended dosing regimen up to 16 weeks, 5.2% developed anti-drug antibodies, the majority of which were low titer, and 1.5% (3 patients) had neutralising antibodies (NAb). In these 3 patients, NAb-positive samples had low ixekizumab concentrations and none of these patients achieved an ASAS40 response. In non-radiographic axial spondyloarthritis patients treated with Taltz at the recommended dosing regimen for up to 52 weeks, 8.9% developed anti-drug antibodies, all of which were low titer; no patient had neutralising antibodies; and no apparent association between the presence of anti-drug antibodies and drug concentration, efficacy, or safety was observed.

Across all indications, an association between immunogenicity and treatment emergent adverse events has not been clearly established.

#### Paediatric population

The safety profile observed in children with plaque psoriasis treated with Taltz every 4 weeks is consistent with the safety profile in adult patients with plaque psoriasis with the exception of the frequencies of conjunctivitis, influenza, and urticaria which were common. Inflammatory bowel disease was also more frequent in paediatric patients, although it was still uncommon. In the paediatric clinical study, Crohn's disease occurred in 0.9% of patients in the Taltz group and 0% of patients in



the placebo group during the 12-week, placebo-controlled period. Crohn's disease occurred in a total of 4 Taltz treated subjects (2.0%) during the combined placebo-controlled and maintenance periods of the paediatric clinical study.

#### 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 national reporting system listed in Appendix V.

#### **4.9 Overdose**

Doses up to 180 mg have been administered subcutaneously in clinical trials without dose-limiting toxicity. Overdoses up to 240 mg, subcutaneously, as a single administration in clinical trials, have been reported without any serious adverse events.

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: L04AC13

#### Mechanism of action

Ixekizumab is an IgG4 monoclonal antibody that binds with high affinity (< 3 pM) and specificity to interleukin 17A (both IL-17A and IL-17A/F). Elevated concentrations of IL-17A have been implicated in the pathogenesis of psoriasis by promoting keratinocyte proliferation and activation, as well as in the pathogenesis of psoriatic arthritis and axial spondyloarthritis by driving inflammation leading to erosive bone damage and pathological new bone formation. Neutralisation of IL-17A by ixekizumab inhibits these actions. Ixekizumab does not bind to ligands IL-17B, IL-17C, IL-17D, IL-17E or IL-17F.

In vitro binding assays confirmed that ixekizumab does not bind to human Fcγ receptors I, IIa, and IIIa or to complement component C1q.

#### Pharmacodynamic effects

Ixekizumab modulates biological responses that are induced or regulated by IL-17A. Based on psoriatic skin biopsy data from a phase I study, there was a dose-related trend towards decreased epidermal thickness, number of proliferating keratinocytes, T cells, and dendritic cells, as well as reductions in local inflammatory markers from baseline to day 43. As a direct consequence treatment with ixekizumab reduces erythema, induration and desquamation present in plaque psoriasis lesions.

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

#### Clinical efficacy and safety

##### *Adult plaque psoriasis*

The efficacy and safety of Taltz were assessed in three randomised, double-blind, placebo-controlled phase III studies in adult patients (N=3,866) with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy (UNCOVER-1, UNCOVER-2, and UNCOVER-3). The efficacy and safety of Taltz were also evaluated versus etanercept (UNCOVER-2 and

UNCOVER-3). Patients randomised to Taltz who were sPGA (0,1) responders (static Physicians Global Assessment) at week 12 were re-randomised to receive placebo or Taltz for an additional 48 weeks (UNCOVER-1 and UNCOVER-2); patients randomised to placebo, etanercept or Taltz who were sPGA (0,1) non-responders received Taltz for up to 48 weeks. In addition, long-term efficacy and safety were evaluated in all three studies for up to a total of 5 years in patients who participated through the entire study.

64 % of patients had received prior systemic therapy (biologic, conventional systemic or psoralen and ultraviolet A (PUVA)), 43.5 % prior phototherapy, 49.3 % prior conventional systemic therapy, and 26.4 % prior biologic therapy. 14.9 % had received at least one anti-TNF alpha agent, and 8.7 % an anti-IL-12/IL-23. 23.4 % of patients had a history of psoriatic arthritis at baseline.

In all three studies, the co-primary endpoints were the proportion of patients who achieved a PASI 75 response (Psoriasis Area and Severity Index) and an sPGA of “0” (“clear”) or 1 (“minimal”) response at week 12 versus placebo. The median baseline PASI score ranged from 17.4 to 18.3; 48.3 % to 51.2 % of patients had a baseline sPGA score of severe or very severe, and mean baseline itch Numeric Rating Scale (itch NRS) ranged from 6.3 to 7.1.

#### *Clinical response at 12 weeks*

UNCOVER-1 randomised 1,296 patients (1:1:1) to receive either placebo or Taltz (80 mg every two or four weeks [Q2W or Q4W] following a 160 mg starting dose) for 12 weeks.

**Table 2. Efficacy results at week 12 in UNCOVER-1**

Endpoints	Number of patients (%)			Difference from placebo in response rate (95% CI)	
	Placebo (N = 431)	Taltz 80 mg Q4W (N = 432)	Taltz 80 mg Q2W (N = 433)	Taltz 80 mg Q4W	Taltz 80 mg Q2W
sPGA of “0” (clear) or “1” (minimal)	14 (3.2)	330 (76.4) <sup>a</sup>	354 (81.8) <sup>a</sup>	73.1 (68.8, 77.5)	78.5 (74.5, 82.5)
sPGA of “0” (clear)	0	149 (34.5) <sup>a</sup>	160 (37.0) <sup>a</sup>	34.5 (30.0, 39.0)	37.0 (32.4, 41.5)
PASI 75	17 (3.9)	357 (82.6) <sup>a</sup>	386 (89.1) <sup>a</sup>	78.7 (74.7, 82.7)	85.2 (81.7, 88.7)
PASI 90	2 (0.5)	279 (64.6) <sup>a</sup>	307 (70.9) <sup>a</sup>	64.1 (59.6, 68.7)	70.4 (66.1, 74.8)
PASI 100	0	145 (33.6) <sup>a</sup>	153 (35.3) <sup>a</sup>	33.6 (29.1, 38.0)	35.3 (30.8, 39.8)
Itch NRS reduction $\geq 4$ <sup>b</sup>	58 (15.5)	305 (80.5) <sup>a</sup>	336 (85.9) <sup>a</sup>	65.0 (59.5, 70.4)	70.4 (65.4, 75.5)

*Abbreviations: N = number of patients in the intent-to-treat population*

*Note: patients with missing data were counted as non-responders*

<sup>a</sup> *p < 0.001 compared with placebo*

<sup>b</sup> *Patients with Itch NRS  $\geq 4$  at baseline: placebo N = 374, Taltz 80 mg Q4W N = 379, Taltz 80 mg Q2W N = 391*

UNCOVER-2 randomised 1,224 patients (1:2:2:2) to receive either placebo, or Taltz (80 mg every two or four weeks [Q2W or Q4W] following a 160 mg starting dose) or etanercept 50 mg twice weekly for 12 weeks.

**Table 3. Efficacy results at week 12 in UNCOVER-2**

Endpoints	Number of patients (%)				Difference from placebo in response rate (95% CI)	
	Placebo (N = 168)	Taltz 80 mg Q4W (N = 347)	Taltz 80 mg Q2W (N = 351)	Etanercept 50 mg twice weekly (N = 358)	Taltz 80 mg Q4W	Taltz 80 mg Q2W
sPGA of “0” (clear) or “1” (minimal)	4 (2.4)	253 (72.9) <sup>a,b</sup>	292 (83.2) <sup>a,b</sup>	129 (36.0) <sup>a</sup>	70.5 (65.3, 75.7)	80.8 (76.3, 85.4)
sPGA of “0” (clear)	1 (0.6)	112 (32.3) <sup>a,b</sup>	147 (41.9) <sup>a,b</sup>	21 (5.9) <sup>c</sup>	31.7 (26.6, 36.7)	41.3 (36.0, 46.6)
PASI 75	4 (2.4)	269 (77.5) <sup>a,b</sup>	315 (89.7) <sup>a,b</sup>	149 (41.6) <sup>a</sup>	75.1 (70.2, 80.1)	87.4 (83.4, 91.3)
PASI 90	1 (0.6)	207 (59.7) <sup>a,b</sup>	248 (70.7) <sup>a,b</sup>	67 (18.7) <sup>a</sup>	59.1 (53.8, 64.4)	70.1 (65.2, 75.0)
PASI 100	1 (0.6)	107 (30.8) <sup>a,b</sup>	142 (40.5) <sup>a,b</sup>	19 (5.3) <sup>c</sup>	30.2 (25.2, 35.2)	39.9 (34.6, 45.1)
Itch NRS reduction $\geq 4$ <sup>d</sup>	19 (14.1)	225 (76.8) <sup>a,b</sup>	258 (85.1) <sup>a,b</sup>	177 (57.8) <sup>a</sup>	62.7 (55.1, 70.3)	71.1 (64.0, 78.2)

Abbreviations: N = number of patients in the intent-to-treat population

Note: patients with missing data were counted as non-responders.

<sup>a</sup>  $p < 0.001$  compared with placebo; <sup>b</sup>  $p < 0.001$  compared with etanercept;

<sup>c</sup>  $p < 0.01$  compared with placebo

<sup>d</sup> Patients with Itch NRS  $\geq 4$  at baseline: placebo N = 135, Taltz 80 mg Q4W N = 293, Taltz 80 mg Q2W N = 303, etanercept N = 306

UNCOVER-3 randomised 1,346 patients (1:2:2:2) to receive either placebo, or Taltz (80 mg every two or four weeks [Q2W or Q4W] following a 160 mg starting dose) or etanercept 50 mg twice weekly for 12 weeks.

**Table 4. Efficacy results at week 12 in UNCOVER-3**

Endpoints	Number of patients (%)				Difference from placebo in response rate (95% CI)	
	Placebo (N = 193)	Taltz 80 mg Q4W (N = 386)	Taltz 80 mg Q2W (N = 385)	Etanercept 50 mg twice weekly (N = 382)	Taltz 80 mg Q4W	Taltz 80 mg Q2W
sPGA of “0” (clear) or “1” (minimal)	13 (6.7)	291 (75.4) <sup>a,b</sup>	310 (80.5) <sup>a,b</sup>	159 (41.6) <sup>a</sup>	68.7 (63.1, 74.2)	73.8 (68.5, 79.1)
sPGA of “0” (clear)	0	139 (36.0) <sup>a,b</sup>	155 (40.3) <sup>a,b</sup>	33 (8.6) <sup>a</sup>	36.0 (31.2, 40.8)	40.3 (35.4, 45.2)
PASI 75	14 (7.3)	325 (84.2) <sup>a,b</sup>	336 (87.3) <sup>a,b</sup>	204 (53.4) <sup>a</sup>	76.9 (71.8, 82.1)	80.0 (75.1, 85.0)
PASI 90	6 (3.1)	252 (65.3) <sup>a,b</sup>	262 (68.1) <sup>a,b</sup>	98 (25.7) <sup>a</sup>	62.2 (56.8, 67.5)	64.9 (59.7, 70.2)
PASI 100	0	135 (35.0) <sup>a,b</sup>	145 (37.7) <sup>a,b</sup>	28 (7.3) <sup>a</sup>	35 (30.2, 39.7)	37.7 (32.8, 42.5)
Itch NRS reduction $\geq 4^c$	33 (20.9)	250 (79.9) <sup>a,b</sup>	264 (82.5) <sup>a,b</sup>	200 (64.1) <sup>a</sup>	59.0 (51.2, 66.7)	61.6 (54.0, 69.2)

Abbreviations: N = number of patients in the intent-to-treat population

Note: patients with missing data were counted as non-responders

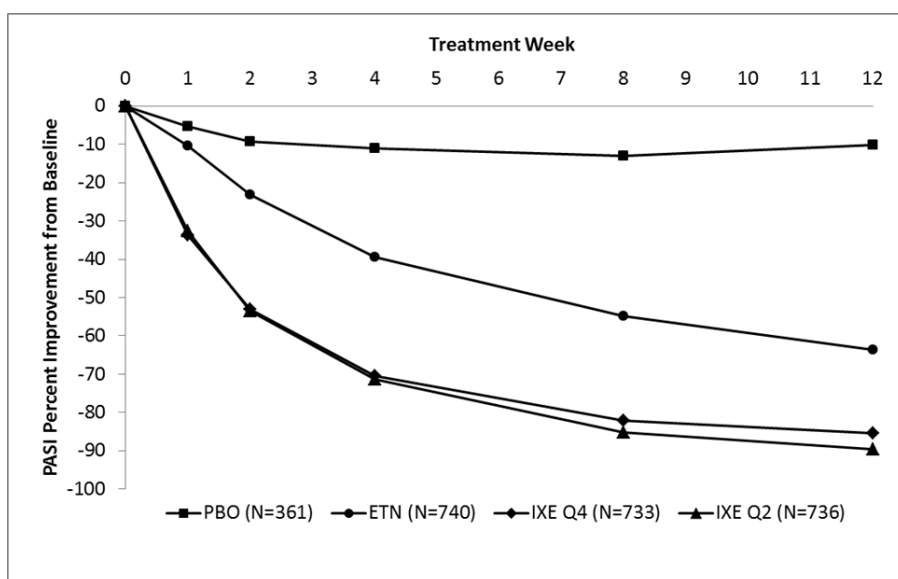
<sup>a</sup>  $p < 0.001$  compared with placebo

<sup>b</sup>  $p < 0.001$  compared with etanercept

<sup>c</sup> Patients with Itch NRS  $\geq 4$  at baseline: placebo N = 158, Taltz 80 mg Q4W N = 313, Taltz 80 mg Q2W N = 320, etanercept N = 312

Taltz was associated with a fast onset of efficacy with > 50 % reduction in mean PASI by week 2 (Figure 1). The percentage of patients achieving PASI 75 was significantly greater for Taltz compared with placebo and etanercept as early as week 1. Approximately 25 % of patients treated with Taltz achieved a PASI score < 5 by week 2, more than 55 % achieved the PASI score < 5 by week 4, and increased to 85 % by week 12 (compared to 3 %, 14 % and 50 % for etanercept). Significant improvements in itch severity were seen at week 1 in patients treated with Taltz.

**Figure 1. PASI score, percent improvement at each post baseline visit (mBOCF) in the intent-to-treat population during the induction dosing period - UNCOVER-2 and UNCOVER-3**



The efficacy and safety of Taltz was demonstrated regardless of age, gender, race, body weight, PASI baseline severity, plaques location, concurrent psoriatic arthritis, and previous treatment with a biologic. Taltz was efficacious in systemic treatment-naïve, biologic-naïve, biologic/anti-TNF-exposed and biologic/anti-TNF-failure patients.

For patients identified as an sPGA (0,1) non-responder to etanercept at week 12 in UNCOVER-2 (N = 200) and who were switched to Taltz 80 mg Q4W after a 4 week washout period, 73 % and 83.5 % of patients achieved sPGA (0,1) and PASI 75, respectively, after 12 weeks of treatment with Taltz.

In the 2 clinical studies that included an active comparator (UNCOVER-2 and UNCOVER-3), the rate of serious adverse events was 1.9 % for both etanercept and for Taltz, and the rate of discontinuation due to adverse events was 1.2 % for etanercept and 2.0 % for Taltz. The rate of infections was 21.5 % for etanercept and 26.0 % for Taltz, with 0.4 % being serious for etanercept and 0.5 % for Taltz.

#### *Maintenance of response at week 60 and up to 5 years*

Patients originally randomised to Taltz and who were responders at week 12 (i.e., sPGA score of 0,1) in UNCOVER-1 and UNCOVER-2 were re-randomised to an additional 48 weeks of treatment with placebo or Taltz (80 mg every four or twelve weeks [Q4W or Q12W]).

For sPGA (0,1) responders at week 12 re-randomised to treatment withdrawal (i.e., placebo), the median time to relapse (sPGA  $\geq$  3) was 164 days in integrated UNCOVER-1 and UNCOVER-2 studies. Among these patients, 71.5 % regained at least an sPGA (0,1) response within 12 weeks of restarting treatment with Taltz 80 mg Q4W.

**Table 5. Maintenance of response and efficacy at week 60 (Studies UNCOVER-1 and UNCOVER-2)**

Endpoints	Number of patients (%)				Difference from placebo in response rate (95% CI)	
	80 mg Q4W (induction) / Placebo (maintenance) (N = 191)	80 mg Q2W (induction) / Placebo (maintenance) (N = 211)	80 mg Q4W (induction) / 80 mg Q4W (maintenance) (N = 195)	80 mg Q2W (induction) / 80 mg Q4W (maintenance) (N = 221)	80 mg Q4W (induction) / 80 mg Q4W (maintenance)	80 mg Q2W (induction) / 80 mg Q4W (maintenance)
Maintained sPGA of “0” (clear) or “1” (minimal)	12 (6.3)	16 (7.6)	134 (68.7) <sup>a</sup>	173 (78.3) <sup>a</sup>	62.4 (55.1, 69.8)	70.7 (64.2, 77.2)
Maintained or achieved sPGA 0 (clear)	3 (1.6)	6 (2.8)	96 (49.2) <sup>a</sup>	130 (58.8) <sup>a</sup>	47.7 (40.4, 54.9)	56.0 (49.1, 62.8)
Maintained or achieved PASI 75	15 (7.9)	19 (9.0)	145 (74.4) <sup>a</sup>	184 (83.3) <sup>a</sup>	66.5 (59.3, 73.7)	74.3 (68.0, 80.5)
Maintained or achieved PASI 90	9 (4.7)	10 (4.7)	130 (66.7) <sup>a</sup>	169 (76.5) <sup>a</sup>	62.0 (54.7, 69.2)	71.7 (65.4, 78.0)
Maintained or achieved PASI 100	3 (1.6)	6 (2.8)	97 (49.7) <sup>a</sup>	127 (57.5) <sup>a</sup>	48.2 (40.9, 55.4)	54.6 (47.7, 61.5)

Abbreviations: N = number of patients in the analysis population

Note: patients with missing data were counted as non-responders

<sup>a</sup> p < 0.001 compared with placebo

Taltz was efficacious in the maintenance of response in systemic treatment-naïve, biologic-naïve, biologic/anti-TNF-exposed and biologic/anti-TNF-failure patients.

Significantly greater improvements at week 12 from baseline compared to placebo and etanercept were demonstrated in nail psoriasis (as measured by the Nail Psoriasis Severity Index [NAPSI]), in scalp psoriasis (as measured by Psoriasis Scalp Severity Index [PSSI]) and in palmoplantar psoriasis (as measured by Psoriasis Palmoplantar Severity Index [PPASI]) and were maintained at week 60 in patients treated with Taltz who were sPGA (0,1) responders at week 12.

Of 591 subjects who received Taltz Q2W during the Induction Period then Q4W afterward in study UNCOVER-1, UNCOVER-2, and UNCOVER-3, 427 subjects completed 5 years of Taltz treatment, among those 101 patients required a dose escalation. Among the patients who completed the week 264 assessment (N=427), 295 patients (69%), 289 patients (68%) and 205 patients (48%) were observed to have sPGA (0,1), PASI 90 and PASI 100 response, respectively, at week 264. DLQI were collected after Induction Period in UNCOVER-1 and UNCOVER-2, 113 patients (66%) were observed to have DLQI (0,1) response.

#### *Quality of life/patient-reported outcomes*

At week 12 and across studies, Taltz was associated with statistically significant improvement in Health-related Quality of Life as assessed by mean decrease ranges from baseline in the Dermatology Life Quality Index (DLQI) (Taltz 80 mg Q2W from -10.2 to -11.1, Taltz 80 mg Q4W from -9.4 to -10.7, etanercept from -7.7 to -8.0 and placebo -1.0 to -2.0). A significantly greater proportion of patients treated with Taltz achieved a DLQI 0 or 1. Across studies a significantly greater proportion of patients treated with Taltz achieved a reduction of Itch NRS ≥ 4 points at week 12 (84.6% for Taltz Q2W, 79.2% for Taltz Q4W and 16.5% for placebo) and the benefit was sustained over time up to week 60 in patients treated with Taltz who were sPGA (0 or 1) responders at week 12. There was not

any evidence of worsening of depression up to 60 weeks treatment with Taltz as assessed by the Quick Inventory of Depressive Symptomatology Self Report.

*Postmarketing direct comparative studies*

IXORA-S: In a double-blind study Taltz was superior against ustekinumab on the primary study objective PASI 90 response at week 12 (Table 6). Onset of response was superior on PASI 75 as early as week 2 ( $p < 0.001$ ) and on PASI 90 and PASI 100 by week 4 ( $p < 0.001$ ). Superiority of Taltz versus ustekinumab was also demonstrated in the subgroups stratified by weight.

**Table 6. PASI-response rates from comparative study ixekizumab versus ustekinumab**

	week 12		week 24		week 52	
	Taltz*	Ustekinumab**	Taltz*	Ustekinumab**	Taltz*	Ustekinumab**
Patients (n)	136	166	136	166	136	166
PASI 75, n (%)	120 (88.2 %)	114 (68.7 %)	124 (91.2 %)	136 (81.9%)	120 (88.2%)	126 (75.9 %)
PASI 90, n (%)	99 (72.8%) <sup>§</sup>	70 (42.2 %)	113 (83.1 %)	98 (59.0 %)	104 (76.5%)	98 (59.0 %)
PASI 100, n (%)	49 (36.0 %)	24 (14.5 %)	67 (49.3%)	39 (23.5 %)	71 (52.2%)	59 (35.5 %)

\* Ixekizumab 160 mg given as a loading dose followed by 80 mg at week 2,4,6,8,10 and 12, and 80 mg Q4W thereafter

\*\* Weight based dosing: 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)

<sup>§</sup> $p < 0.001$  versus ustekinumab ( $p$  value only provided for primary endpoint)

IXORA-R: Efficacy and safety of Taltz was also investigated in a 24-week randomized, double-blind, parallel-group study comparing Taltz to guselkumab, with Taltz being superior as early as week 4 in achieving complete skin clearance and on the primary study objective (PASI 100 at week 12) and non-inferior on PASI 100 at week 24 (Table 7).

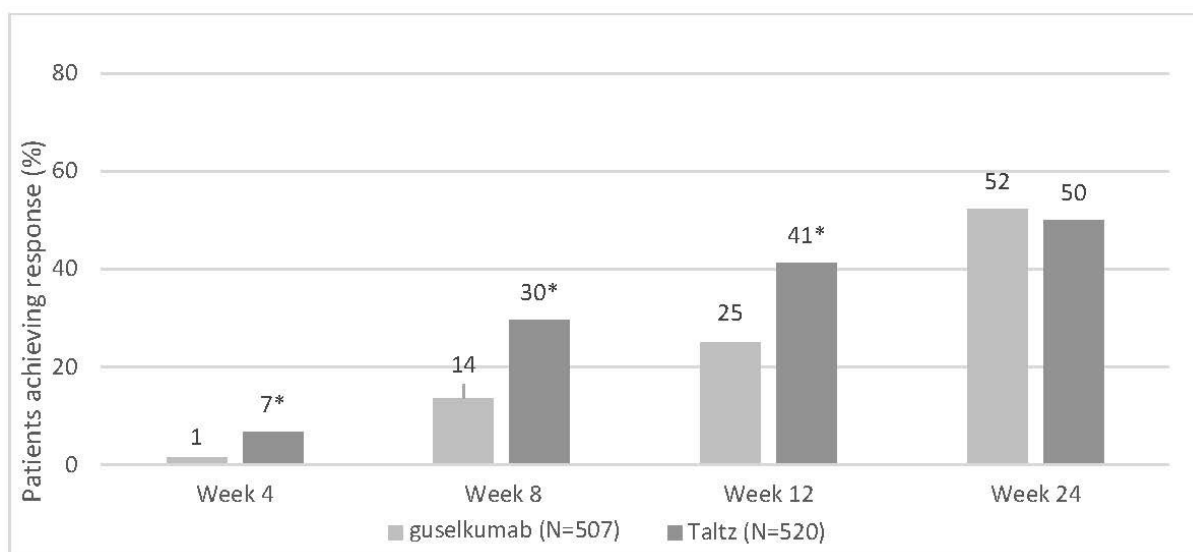
**Table 7. Efficacy Responses from comparative study ixekizumab versus guselkumab, Intent-to-Treat Population<sup>a</sup>**

Endpoint	Time point	Guselkumab (N=507) response, n (%)	Ixekizumab (N=520) response, n (%)	Difference (IXE - GUS), % (CI)	p-value
<b>Primary Objective</b>					
PASI 100	Week 12	126 (24.9)	215 (41.3)	16.5 (10.8, 22.2)	<0.001
<b>Major Secondary Objectives</b>					
PASI 75	Week 2	26 (5.1)	119 (22.9)	17.8 (13.7, 21.8)	<0.001
PASI 90	Week 4	40 (7.9)	109 (21.0)	13.1 (8.9, 17.3)	<0.001
PASI 100	Week 4	7 (1.4)	35 (6.7)	5.4 (3.0, 7.7)	<0.001
PASI 90	Week 8	182 (35.9)	304 (58.5)	22.6 (16.6, 28.5)	<0.001
sPGA (0)	Week 12	128 (25.2)	218 (41.9)	16.7 (11.0, 22.4)	<0.001
PASI 50	Week 1	47 (9.3)	143 (27.5)	18.2 (13.6, 22.8)	<0.001
PASI 100	Week 8	69 (13.6)	154 (29.6)	16.0 (11.1, 20.9)	<0.001
PASI 100	Week 24	265 (52.3)	260 (50.0)	-2.3 (-8.4, 3.8)	0.414

Abbreviations: CI = confidence interval; GUS = guselkumab; IXE = ixekizumab; N = number of patients in the analysis population; n = number of patients in the specified category; PASI = psoriasis area and severity index; sPGA = static physician global assessment.

<sup>a</sup> Endpoints were gated in this order

**Figure 2: PASI 100 at weeks 4, 8, 12 and 24, NRI**



\*p<0.001 vs guselkumab at weeks 4, 8, and 12

NRI = Non-Responder Imputation

#### *Efficacy in genital psoriasis*

A randomised, double-blind, placebo-controlled study (IXORA-Q) was conducted in 149 adult subjects (24% females) with moderate to severe genital psoriasis (sPGA of Genitalia score of  $\geq 3$ ), a minimum body surface area (BSA) involvement of 1% (60.4% had a BSA  $\geq 10\%$ ) and previous failure of or intolerance to at least one topical therapy for genital psoriasis. Patients had at least moderate plaque psoriasis (defined as sPGA score of  $\geq 3$  and being candidates for phototherapy and/or systemic therapy) for at least 6 months.

Subjects randomised to Taltz received an initial dose of 160 mg followed by 80 mg every 2 weeks for 12 weeks. The primary endpoint was the proportion of patients who achieved at least a "0" (clear) or "1" (minimal) response on the sPGA of Genitalia (sPGA of Genitalia 0/1). At week 12, significantly more subjects in the Taltz group than placebo group achieved a sPGA of Genitalia 0/1 and a sPGA 0/1 independent of baseline BSA (baseline BSA 1% - <10% resp.  $\geq 10\%$ : sPGA of Genitalia "0" or "1": Taltz 71%, resp. 75%; placebo: 0%, resp. 13%). A significantly greater proportion of patients treated with Taltz achieved a reduction in the PROs of severity of genital pain, genital itch, impact of genital psoriasis on sexual activity, and Dermatology Quality of Life Index (DLQI).

**Table 8. Efficacy results at week 12 in Adults with genital psoriasis in trial IXORA-Q; NRI <sup>a</sup>**

Endpoints	Taltz	Placebo	Difference from placebo (95% CI)
<b>Number of patients (N) randomised</b>	<b>N=75</b>	<b>N=74</b>	
sPGA of Genitalia "0" or "1"	73%	8%	65% (53%, 77%)
sPGA "0" or "1"	73%	3%	71% (60%, 81%)
DLQI 0,1 <sup>b</sup>	45%	3%	43% (31%, 55%)
<b>N with baseline GPSS Itch NRS Score <math>\geq 3</math></b>	<b>N=62</b>	<b>N=60</b>	
GPSS Genital Itch ( $\geq 3$ point improvement)	60%	8%	51% (37%, 65%)
<b>N with baseline SFQ Item 2 Score <math>\geq 2</math></b>	<b>N=37</b>	<b>N=42</b>	
SFQ-item 2 score, "0" (never limited) or "1" (rarely limited)	78%	21%	57% (39%, 75%)

<sup>a</sup> Abbreviations: NRI = Non-Responder Imputation; sPGA = static Physician Global Assessment; GPSS = Genital Psoriasis Symptom Scale; SFQ = Sexual Frequency Questionnaire; DLQI = Dermatology Quality of Life Index; <sup>b</sup> Total DLQI score of 0,1 indicates skin condition has no effect at



all on patient's life. sPGA of "0" or "1" is equivalent to "clear" or "minimal"; NRS = Numeric Rating Scale

### Paediatric plaque psoriasis

A randomised, double-blind, multicenter, placebo-controlled trial (IXORA-Peds) enrolled 201 children 6 to less than 18 years of age, with moderate to severe plaque psoriasis (as defined by a sPGA score  $\geq 3$ , involving  $\geq 10\%$  of the body surface area, and a PASI score  $\geq 12$ ) who were candidates for phototherapy or systemic therapy, or were inadequately controlled on topical therapy. Patients were randomised to placebo (n=56), etanercept (n=30) or Taltz (n=115) with dosing stratified by weight:

- <25 kg: 40 mg at week 0 followed by 20 mg Q4W (n=4)
- 25 kg to 50 kg: 80 mg at week 0 followed by 40 mg Q4W (n=50)
- >50 kg: 160 mg at week 0 followed by 80 mg Q4W (n=147)

Patients randomised to etanercept (patients with severe psoriasis) received 0.8 mg/kg, not exceeding 50 mg per dose, every week from week 0 through week 11.

Response to treatment was assessed after 12 weeks and defined by the proportion of patients who achieved the co-primary endpoint of an sPGA score of "0" (clear) or "1" (almost clear) with at least a 2 point improvement from baseline and the proportion of patients that achieved a reduction in PASI score of at least 75% (PASI 75) from baseline.

Other evaluated outcomes at week 12 included the proportion of patients who achieved PASI 90, PASI 100, sPGA of "0" and an improvement of itch severity as measured by a reduction of at least 4 points on an 11-point itch Numeric Rating Scale.

Patients had a median baseline PASI of 17 score ranging from 12-49. Baseline sPGA score was severe or very severe in 49%. Of all patients, 22% had received prior phototherapy and 32% had received prior conventional systemic therapy for the treatment of psoriasis. 25% of patients (n=43) were below 12 years (14% of patients [n=24] were 6-9 years and 11% of patients [n=19] were 10-11 years); 75% (n=128) were 12 years or above.

The clinical response data are presented in Table 9.

**Table 9. Efficacy results in pediatric patients with plaque psoriasis, NRI**

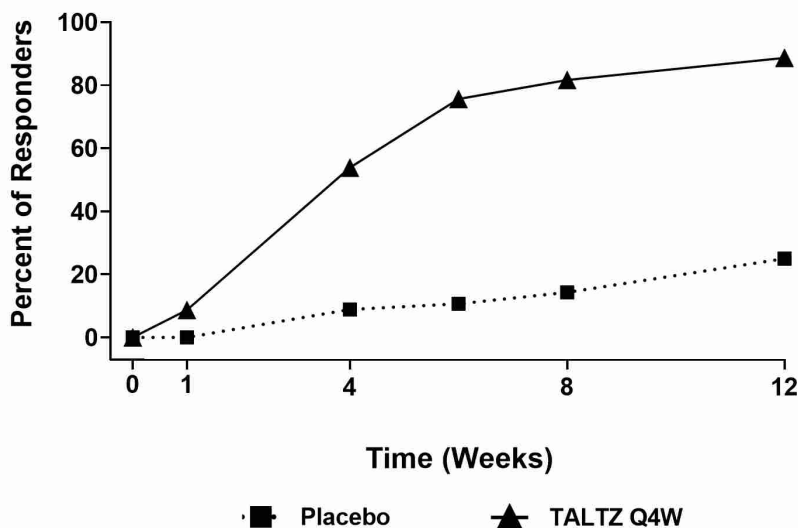
Endpoints	Taltz <sup>a</sup> (N=115) n (%)	Placebo (N=56) n (%)	Difference vs placebo (95% CI)	Etanercept <sup>b</sup> (N=30) n (%)	Difference vs etanercept (95% CI) <sup>b</sup>
sPGA "0" (clear) or "1" (almost clear) <sup>c</sup>					
week 4	55 (48)	4 (7)	40.7 (29.3, 52.0) <sup>f</sup>	0(0)	36.8 (21.5, 52.2)
week 12 <sup>c</sup>	93 (81)	6 (11)	70.2 (59.3, 81.0) <sup>f</sup>	16 (53)	23.0 (0.6, 45.4)
sPGA "0" (clear) <sup>d</sup>	60 (52)	1 (2)	50.4 (40.6, 60.2) <sup>f</sup>	5 (17)	46.5 (26.2, 66.8)
PASI 75					
week 4	62 (54)	5 (9)	45.0 (33.2, 56.8) <sup>f</sup>	3 (10)	34.7 (15.6, 53.8)
week 12 <sup>c</sup>	102 (89)	14 (25)	63.7 (51.0, 76.4) <sup>f</sup>	19 (63)	20.9 (0.1, 41.7)
PASI 90 <sup>d</sup>	90 (78)	3 (5)	72.9 (63.3, 82.5) <sup>f</sup>	12 (40)	36.3 (14.2, 58.5)
PASI 100 <sup>d</sup>	57 (50)	1 (2)	47.8 (38.0, 57.6) <sup>f</sup>	5 (17)	43.9 (23.4, 64.3)
Itch NRS ( $\geq 4$ point improvement) <sup>d, e</sup>	59 (71)	8 (20)	51.1 (35.3, 66.9) <sup>f</sup>	Not evaluated	---

Abbreviations: N = Number of patients in the intent-to-treat population; NRI = Non-Responder Imputation.

<sup>a</sup> At week 0, subjects received 160 mg, 80 mg, or 40 mg of Taltz, followed by 80 mg, 40 mg, or 20 mg every 4 weeks, depending on weight category, for 12 weeks.

- <sup>b</sup> Comparisons to etanercept were performed within the sub-population of patients outside of US and Canada with severe Ps (N for Taltz = 38).
- <sup>c</sup> Co-primary endpoints.
- <sup>d</sup> Results at week 12.
- <sup>e</sup> Itch NRS ( $\geq 4$  improvement) in patients with baseline Itch NRS  $\geq 4$ . The number of ITT patients with baseline Itch NRS Score  $\geq 4$  are as follows: Taltz, n = 83; PBO, n = 40.
- <sup>f</sup> p<0.001

**Figure 3. Percent of patients achieving PASI 75 in pediatric psoriasis through week 12**



Patients in the ixekizumab treatment group had clinically meaningful higher CDLQI/DLQI (0,1) responses at week 12 (NRI) compared with placebo. The difference between treatment groups was apparent from as early as week 4.

There were greater improvements at week 12 from baseline compared to placebo in nail psoriasis (as measured by the Nail Psoriasis Severity Index [NAPSI=0: Taltz 18% (6/34), placebo 0% (0/12)]), in scalp psoriasis (as measured by Psoriasis Scalp Severity Index [PSSI=0: Taltz 69% (70/102), placebo 16% (8/50)]) and in palmoplantar psoriasis (as measured by Psoriasis Palmoplantar Severity Index [PPASI 75: Taltz 53% (9/17), placebo 11% (1/9)]).

### Psoriatic arthritis

Taltz was assessed in two randomised, double-blind, placebo-controlled phase III studies in 780 patients with active psoriatic arthritis ( $\geq 3$  swollen and  $\geq 3$  tender joints). Patients had a diagnosis of psoriatic arthritis (Classification Criteria for Psoriatic Arthritis [CASPAR] criteria) for a median of 5.33 years and had current plaque psoriasis skin lesions (94.0%) or a documented history of plaque psoriasis, with 12.1% of patients with moderate to severe plaque psoriasis at baseline. Over 58.9% and 22.3% of the psoriatic arthritis patients had enthesitis and dactylitis at baseline, respectively. Primary endpoint of both studies was American College of Rheumatology (ACR) 20 response at week 24, followed by a long-term extension period from week 24 to week 156 (3 years).

In Psoriatic Arthritis Study 1 (SPIRIT-P1), patients naive to biologic therapy with active psoriatic arthritis were randomised to placebo, adalimumab 40 mg once every 2 weeks (active control reference arm), Taltz 80 mg once every 2 weeks (Q2W), or 80 mg once every 4 weeks (Q4W). Both Taltz regimens included a 160 mg starting dose. 85.3% of patients in this study had received prior treatment with  $\geq 1$  cDMARD. 53% of patients had concomitant use of MTX at a mean weekly dose of 15.8 mg. 67% of patients who had concomitant use of MTX had a dose of 15 mg or greater. Patients with an inadequate response at week 16 received rescue therapy (modification to background therapy). Patients on Taltz Q2W or Q4W remained on their originally assigned dose of Taltz. Patients receiving

adalimumab or placebo were re-randomised 1:1 to Taltz Q2W or Q4W at week 16 or 24 based on responder status. 243 patients completed the extension period of 3 years on Taltz.

Psoriatic Arthritis Study 2 (SPIRIT-P2) enrolled patients who were previously treated with an anti-TNF agent and discontinued the anti-TNF agent for either lack of efficacy or intolerance (anti-TNF-IR patients). Patients were randomised to placebo, Taltz 80 mg once every 2 weeks (Q2W), or 80 mg once every 4 weeks (Q4W). Both Taltz regimens included a 160 mg starting dose. 56% and 35% of patients were inadequate responders to 1 anti-TNF or 2 anti-TNF, respectively. SPIRIT-P2 evaluated 363 patients, of whom 41% had concomitant use of MTX at a mean weekly dose of 16.1 mg. 73.2% of patients who had concomitant use of MTX had a dose of 15 mg or greater. Patients with an inadequate response at week 16 received rescue therapy (modification to background therapy). Patients in Taltz Q2W or Q4W remained on their originally assigned dose of Taltz. Patients receiving placebo were re-randomised 1:1 to Taltz Q2W or Q4W at week 16 or 24 based on responder status. 168 patients completed the extension period of 3 years on Taltz.

### Signs and symptoms

Treatment with Taltz resulted in significant improvement in measures of disease activity compared to placebo at week 24 (see Table 10).

**Table 10. Efficacy results in SPIRIT-P1 and SPIRIT-P2 at week 24**

Endpoints	SPIRIT-P1					SPIRIT-P2						
	PBO (N = 106)	Taltz Q4W (N = 107)	Taltz Q2W (N = 103)	ADA (N = 101)	Difference from placebo in response rate (95% CI)	Taltz Q4W	Taltz Q2W	PBO (N = 118)	Taltz Q4W (N = 122)	Taltz Q2W (N = 123)	Taltz Q4W	Taltz Q2W
<b>ACR 20 response, n (%)</b>												
week 24	32 (30.2)	62 (57.9)	64 (62.1)	58 (57.4)	27.8 (15.0, 40.6) <sup>c</sup>	31.9 (19.1, 44.8) <sup>c</sup>	23 (19.5)	65 (53.3)	59 (48.0)	33.8 (22.4, 45.2) <sup>c</sup>	28.5 (17.1, 39.8) <sup>c</sup>	
<b>ACR 50 response, n (%)</b>												
week 24	16 (15.1)	43 (40.2)	48 (46.6)	39 (38.6)	25.1 (13.6, 36.6) <sup>c</sup>	31.5 (19.7, 43.3) <sup>c</sup>	6 (5.1)	43 (35.2)	41 (33.3)	30.2 (20.8, 39.5) <sup>c</sup>	28.3 (19.0, 37.5) <sup>c</sup>	
<b>ACR 70 response, n (%)</b>												
week 24	6 (5.7)	25 (23.4)	35 (34.0)	26 (25.7)	17.7 (8.6, 26.8) <sup>c</sup>	28.3 (18.2, 38.5) <sup>c</sup>	0	27 (22.1)	15 (12.2)	22.1 (14.8, 29.5) <sup>c</sup>	12.2 (6.4, 18.0) <sup>c</sup>	
<b>Minimal disease activity (MDA) n (%)</b>												
week 24	16 (15.1)	32 (29.9)	42 (40.8)	32 (31.7)	14.8 (3.8, 25.8) <sup>a</sup>	25.7 (14.0, 37.4) <sup>c</sup>	4 (3.4)	34 (27.9)	29 (23.6)	24.5 (15.9, 33.1) <sup>c</sup>	20.2 (12.0, 28.4) <sup>c</sup>	
<b>ACR 50 and PASI 100 in patients with <math>\geq 3\%</math> BSA psoriasis skin involvement at baseline, n (%)</b>												
week 24	1 (1.5)	21 (28.8)	19 (32.2)	9 (13.2)	27.3 (16.5, 38.1) <sup>c</sup>	30.7 (18.4, 43.0) <sup>b</sup>	0 (0.0)	12 (17.6)	10 (14.7)	17.6 (8.6, 26.7) <sup>c</sup>	14.7 (6.3, 23.1) <sup>c</sup>	

Abbreviations: ACR 20/50/70 = American College of Rheumatology 20%/50%/70% response rate; ADA = adalimumab; BSA = body surface area; CI = confidence interval; Q4W = Taltz 80 mg every 4 weeks; Q2W = Taltz 80 mg every 2 weeks; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = non-responder imputation; PASI

100 = psoriasis area and severity index 100% improvement; PBO = placebo.

Note: patients who were rescued at week 16 or discontinued or with missing data were imputed as non-responders for week 24 analyses.

Concomitant cDMARDs included MTX, leflunomide and sulfasalazine.

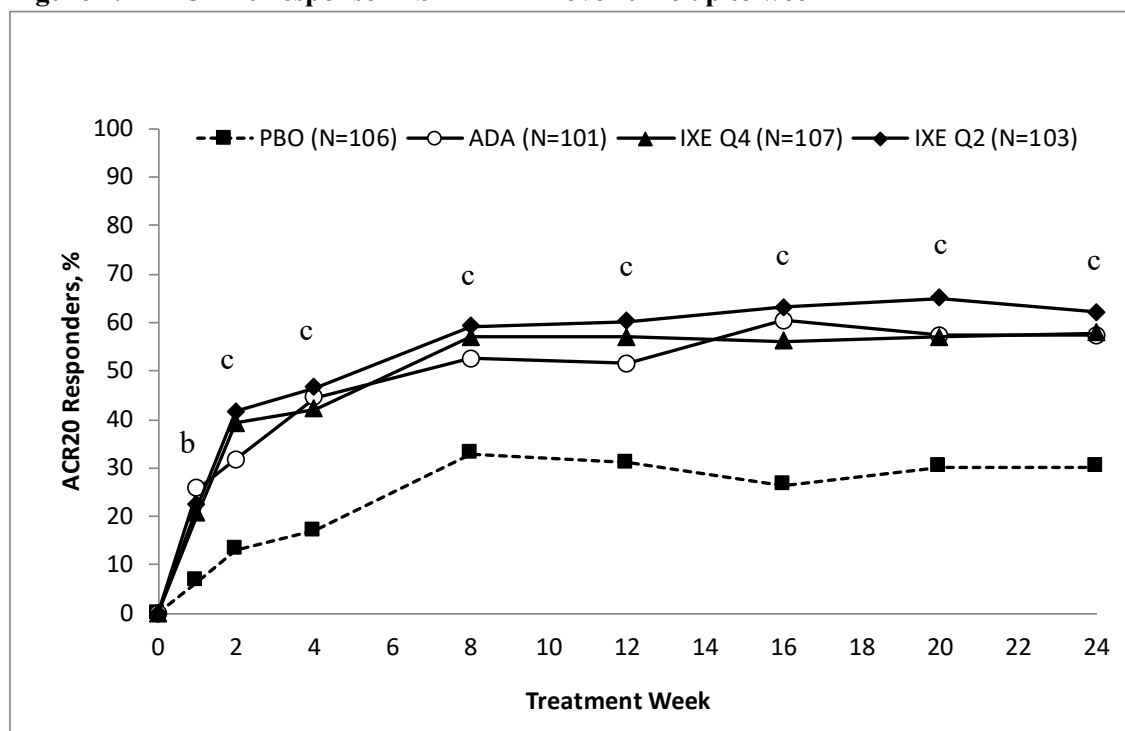
a  $p < 0.05$ ; b  $p < 0.01$ ; c  $p < 0.001$  compared with placebo.

In patients with pre-existing dactylitis or enthesitis, treatment with Taltz Q4W resulted in improvement in dactylitis and enthesitis at week 24 compared to placebo (resolution: 78% vs. 24%;  $p < 0.001$ , and 39% vs. 21%;  $p < 0.01$ , respectively).

In patients with  $\geq 3\%$  BSA, the improvement in skin clearance at week 12 as measured by 75% improvement in Psoriasis Area Severity Index (PASI 75), was 67% (94/141) for those treated with the Q4W dosing regimen, and 9% (12/134) for those treated with placebo ( $p < 0.001$ ). The proportion of patients achieving a PASI 75, PASI 90, and PASI 100 response at week 24 was greater with Taltz Q4W compared to placebo ( $p < 0.001$ ). In patients with concomitant moderate to severe psoriasis and psoriatic arthritis, Taltz Q2W dose regimen showed significantly higher response rate for PASI75, PASI 90 and PASI 100 compared to placebo ( $p < 0.001$ ) and demonstrated clinically meaningful benefit over the Q4W dose regimen.

Treatment responses on Taltz were significantly greater than those on placebo as early as week 1 for ACR 20, week 4 for ACR 50 and week 8 for ACR 70 and persisted through week 24; effects were maintained through 3 years for patients who remained in the study.

**Figure 4. ACR 20 response in SPIRIT-P1 over time up to week 24**



For both Taltz Q2W and Q4W: b  $p < 0.01$  and c  $p < 0.001$  compared with placebo.

In SPIRIT-P1 and SPIRIT-P2, similar responses for ACR 20/50/70 were seen in patients with psoriatic arthritis regardless of whether they were on concomitant cDMARDs, including MTX treatment, or not.

In SPIRIT-P1 and SPIRIT-P2, improvements were shown in all components of the ACR scores including patient assessment of pain. At week 24 the proportion of patients achieving a modified Psoriatic Arthritis Response Criteria (PsARC) response was greater in the Taltz-treated patients compared to placebo.

In SPIRIT-P1, efficacy was maintained up to week 52 as assessed by ACR 20/50/70, MDA, enthesitis resolution, dactylitis resolution, and PASI 75/90/100 response rates.

The efficacy and safety of Taltz was demonstrated regardless of age, gender, race, disease duration, baseline body weight, baseline psoriasis involvement, baseline CRP, baseline DAS28-CRP, concomitant corticosteroid use, and previous treatment with a biologic. Taltz was efficacious in biologic-naive, biologic-exposed and biologic-failure patients.

In SPIRIT-P1, 63 patients completed 3 years of Q4W ixekizumab treatment. Among the 107 patients who were randomized to ixekizumab Q4W (NRI analysis in ITT population), 54 patients (50%), 41 patients (38%), 29 patients (27%), and 36 patients (34%) were observed to have ACR20, ACR50, ACR70, and MDA response, respectively, at week 156.

In SPIRIT-P2, 70 patients completed 3 years of Q4W ixekizumab treatment. Among the 122 patients who were randomized to ixekizumab Q4W (NRI analysis in ITT population), 56 patients (46%), 39 patients (32%), 24 patients (20%) and 33 (27%) were observed to have ACR20, ACR50, ACR70, and MDA response, respectively, at week 156.

#### *Radiographic response*

In SPIRIT-P1, inhibition of progression of structural damage was assessed radiographically and expressed as the change in modified total Sharp Score (mTSS) and its components, the Erosion Score (ES) and the Joint Space Narrowing score (JSN) at weeks 24 and 52, compared to baseline. week 24 data are presented in Table 11.

**Table 11. Change in modified Total Sharp Score in SPIRIT-P1**

					Difference from placebo (95% CI)	
	PBO (N = 106)	Taltz Q4W (N = 107)	Taltz Q2W (N = 103)	ADA (N = 101)	Taltz Q4W	Taltz Q2W
Baseline score, mean (SD)	17.6 (28.62)	19.2 (32.68)	15.2 (28.86)	15.9 (27.37)	NA	NA
Change from baseline at week 24, LSM (SE)	0.51 (0.092)	0.18 (0.090)	0.09 (0.091)	0.13 (0.093)	-0.33 (-0.57,-0.09) <sup>b</sup>	-0.42 (-0.66,-0.19) <sup>c</sup>

*Abbreviations: ADA = adalimumab; CI = confidence interval; Q4W = Taltz 80 mg every 4 weeks; Q2W = Taltz 80 mg every 2 weeks; LSM = least squares mean; N = number of patients in the analysis population; PBO = placebo; SE = standard error; SD = standard deviation.*

*<sup>b</sup> p<0.01; <sup>c</sup> p<0.001 compared with placebo.*

Radiographic joint damage progression was inhibited by Taltz (Table 11) at week 24, and the percentage of patients with no radiographic joint damage progression (defined as a change from baseline in mTSS of  $\leq 0.5$ ) from randomisation to week 24 was 94.8% for Taltz Q2W ( $p<0.001$ ), 89.0% for Taltz Q4W ( $p=0.026$ ), 95.8% for adalimumab ( $p<0.001$ ), all compared to 77.4% for placebo. At week 52, the mean change from baseline in mTSS was 0.27 for placebo/Taltz Q4W, 0.54 for Taltz Q4W/Taltz Q4W, and 0.32 for adalimumab/Taltz Q4W. The percentage of patients with no radiographic joint damage progression from randomisation to week 52 was 90.9% for placebo/Taltz Q4W, 85.6% for Taltz Q4W/Taltz Q4W, and 89.4% for adalimumab/Taltz Q4W. Patients had no structural progression from baseline (defined as  $mTSS \leq 0.5$ ) in the treatment arms as follows: Placebo/Taltz Q4W 81.5% (N=22/27), Taltz Q4W/Taltz Q4W 73.6% (N=53/72), and adalimumab/Taltz Q4W 88.2% (N=30/34).

#### *Physical function and health-related quality of life*

In both SPIRIT-P1 and SPIRIT-P2, patients treated with Taltz Q2W ( $p<0.001$ ) and Q4W ( $p<0.001$ ) showed significant improvement in physical function compared to patients treated with placebo as assessed by Health Assessment Questionnaire-Disability Index (HAQ-DI) at week 24, and maintained at week 52 in SPIRIT-P1.

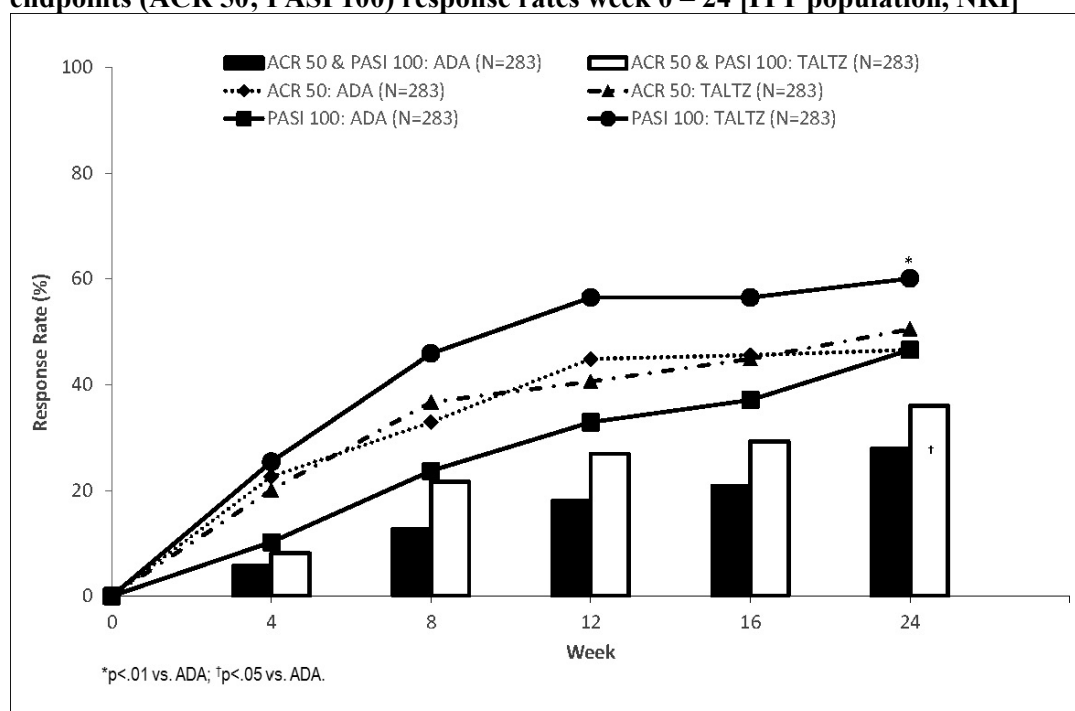
Taltz-treated patients reported improvements in health-related quality of life as measured by the Physical Component Summary of the Short Form-36 Health Survey (SF-36 PCS) score ( $p < 0.001$ ). There were also improvements demonstrated in fatigue as assessed by Fatigue severity NRS scores ( $p < 0.001$ ).

#### Postmarketing phase 4, direct comparative study

Efficacy and safety of Taltz was investigated in a multicenter, randomised, open-label, rater-blinded, parallel-group study (SPIRIT-H2H) compared to adalimumab (ADA) in 566 patients with PsA who were naïve to biologic disease-modifying anti-rheumatic drugs (bDMARD). Patients were stratified at baseline based on concomitant cDMARD use and presence of moderate-to-severe psoriasis ( $\text{PASI} \geq 12$ ,  $\text{BSA} \geq 10$  and  $\text{sPGA} \geq 3$ ).

Taltz was superior to ADA on the primary study objective: simultaneous achievement of ACR 50 and PASI 100 response at week 24 (Taltz 36.0% vs ADA 27.9%;  $p = 0.036$ ; 95% confidence interval [0.5%, 15.8%]). Taltz also showed non-inferiority (pre-specified margin of -12%) to ADA on ACR 50 (ITT analysis: Taltz 50.5% vs ADA 46.6%; 3.9% difference vs. ADA; 95% confidence interval [-4.3%; 12.1%]; PPS analysis Taltz: 52.3%, ADA: 53.1%, difference: -0.8% [CI: -10.3%; 8.7%]) and superiority on PASI 100 at week 24 (60.1% with Taltz vs 46.6% with ADA,  $p = 0.001$ ), which were the major secondary endpoints in the study. At week 52 a higher proportion of patients treated with Taltz versus ADA simultaneously achieved ACR50 and PASI 100 [39% (111/283) versus 26% (74/283)] and PASI 100 [64% (182/283) versus 41% (117/283)]. Taltz and ADA treatment resulted in similar responses for ACR50 [49.8% (141/283) versus 49.8% (141/283)]. Responses to Taltz were consistent when used as monotherapy or with concomitant use of methotrexate.

**Figure 5. Primary endpoint (simultaneous ACR 50 & PASI 100) and major secondary endpoints (ACR 50; PASI 100) response rates week 0 – 24 [ITT population, NRI]\*\***



\*\* Taltz 160 mg week 0, then 80 mg every 2 weeks to week 12 and every 4 weeks thereafter for patients with moderate to severe plaque psoriasis or 160 mg week 0, then 80 mg every 4 week for other patients, ADA 80 mg week 0, then 40 mg every 2 weeks from week 1 for patients with moderate to severe plaque psoriasis or 40 mg week 0, then 40 mg every 2 weeks for other patients. Significance level only provided for endpoint that was pre-defined and multiplicity tested.

#### Axial spondyloarthritis

Taltz was assessed in a total of 960 adult patients with axial spondyloarthritis in three randomised placebo-controlled studies (two in radiographic and one in non-radiographic axial spondyloarthritis).

## Radiographic axial spondyloarthritis

Taltz was assessed in a total of 657 patients in two randomised, double-blind, placebo-controlled studies (COAST-V and COAST-W) in adult patients who had active disease as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)  $\geq 4$  and total back pain  $\geq 4$  on a numeric rating scale despite non-steroidal anti-inflammatory drug (NSAID) therapy. Across both studies at baseline, patients had symptoms for a mean of 17 years (median of 16 years). At baseline, approximately 32% of the patients were on a concomitant cDMARD.

COAST-V evaluated 341 biologic-naive patients treated with either Taltz 80 mg or 160 mg at week 0 followed by 80 mg every 2 weeks (Q2W) or 4 weeks (Q4W), adalimumab 40 mg every 2 weeks, or with placebo. Patients receiving placebo were re-randomised at week 16 to receive Taltz (160 mg starting dose, followed by 80 mg Q2W or Q4W). Patients receiving adalimumab were re-randomised at week 16 to receive Taltz (80 mg Q2W or Q4W).

COAST-W evaluated 316 patients who had prior experience with 1 or 2 TNF-inhibitors (90% were inadequate responders and 10% were intolerant to TNF inhibitors). All patients were treated with Taltz 80 or 160 mg at week 0 followed by 80 mg Q2W or Q4W, or with placebo. Patients receiving placebo were re-randomised at week 16 to receive Taltz (160 mg initial dose, followed by 80 mg Q2W or Q4W).

The primary endpoint in both studies was the percentage of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response at week 16.

### *Clinical response*

In both studies, patients treated with Taltz 80 mg Q2W or 80 mg Q4W demonstrated greater improvements in ASAS40 and ASAS20 responses compared to placebo at week 16 (Table 12). Responses were similar in patients regardless of concomitant therapies. In COAST-W, responses were seen regardless of the number of prior TNF inhibitors.

**Table 12. Efficacy results in COAST-V and COAST-W at week 16**

	COAST-V, biologic-naive				COAST-W, TNF-inhibitor experienced		
	Taltz 80 mg Q4W <sup>a</sup> (N=81)	Placebo (N=87)	Difference from placebo <sup>g</sup>	Adalimumab 40 mg Q2W (N=90)	Taltz 80 mg Q4W <sup>c</sup> (N=114)	Placebo (N=104)	Difference from placebo <sup>g</sup>
ASAS20 response <sup>b</sup> , n (%), NRI	52 (64.2%)	35 (40.2%)	24.0 (9.3, 38.6)**	53 (58.9%)	55 (48.2%)	31 (29.8%)	18.4 (5.7, 31.1)**
ASAS40 response <sup>b,c</sup> , n (%), NRI	39 (48.1%)	16 (18.4%)	29.8 (16.2, 43.3)***	32 (35.6%)	29 (25.4%)	13 (12.5%)	12.9 (2.7, 23.2)*
ASDAS							
Change from baseline	-1.4	-0.5	-1.0 (-1.3, -0.7)	-1.3***	-1.2	-0.1	-1.1 (-1.3, -0.8)
Baseline	3.7	3.9	***	3.7	4.2	4.1	***
BASDAI Score							
Change from baseline	-2.9	-1.4	-1.5 (-2.1, -0.9)	-2.5***	-2.2	-0.9	-1.2 (-1.8, -0.7)
Baseline	6.8 <sup>i</sup>	6.8 <sup>i</sup>	***	6.7 <sup>i</sup>	7.5	7.3	***
MRI Spine SPARCC <sup>d</sup>							
Change from baseline	-11.0	-7.5	-9.5 (-12.6, -6.4)***	-11.6***	-3.0	3.3	-6.3 (-10.0, -2.5)**
Baseline	14.5	15.8	***	20.0	8.3	6.4	***
BASDAI50 <sup>e</sup> n (%), NRI	34 (42.0%)	15 (17.2%)	24.7 (11.4, 38.1)***	29 (32.2%)*	25 (21.9%) <sup>i</sup>	10 (9.6%) <sup>i</sup>	12.3 (2.8, 21.8)*
ASDAS <2.1, n (%) (low disease activity), NRI	35 (43.2%) <sup>h</sup>	11 (12.6%) <sup>h</sup>	30.6 (17.7, 43.4)***	34 (37.8%)*** <sup>h</sup>	20 (17.5%)	5 (4.8%)	12.7 (4.6, 20.8)**
ASDAS <1.3, n (%) (inactive disease), NRI	13 (16.0%)	2 (2.3%)	13.8 (5.2, 22.3)**	14 (15.6%)**	4 (3.5%) <sup>i</sup>	1 (1.0%) <sup>i</sup>	2.5 (-1.3, 6.4)
ASAS HI <sup>f</sup>							
Change from baseline	-2.4	-1.3	-1.1 (-2.0, -0.3)	-2.3*	-1.9	-0.9	-1.0 (-1.9, -0.1)
Baseline	7.5	8.1	*	8.2	10.0	9.0	*
SF-36 PCS							

Change from baseline	7.7	3.6	4.1 (1.9, 6.2)	6.9**	6.6	1.4	5.2 (3.0, 7.4)
Baseline	34.0	32.0	***	33.5	27.5	30.6	***

Abbreviations: N = number of patients in the intent-to-treat population; NRI = Non-responder Imputation; patients with missing data were counted as non-responders.

ASAS HI = Assessment of SpondyloArthritis International Society Health Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CFB = least square mean change from baseline at week 16; MRI Spine SPARCC = Spondyloarthritis Research Consortium of Canada Magnetic Resonance Imaging Scoring of the Spine (23 discovertebral unit scale)

<sup>a</sup> At week 0, patients received 80 mg or 160 mg of Taltz.

<sup>b</sup> An ASAS20 response is defined as a  $\geq 20\%$  improvement and an absolute improvement from baseline of  $\geq 1$  unit (range 0 to 10) in  $\geq 3$  of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation), and no worsening of  $\geq 20\%$  and  $\geq 1$  unit (range 0 to 10) in the remaining domain. An ASAS40 response is defined as a  $\geq 40\%$  improvement and an absolute improvement from baseline of  $\geq 2$  units in  $\geq 3$  of 4 domains without any worsening in the remaining domain.

<sup>c</sup> Primary endpoint.

<sup>d</sup> The numbers of ITT patients with MRI data at baseline are as follows: COAST-V: Taltz, n = 81; PBO, n = 82; ADA, n=85. COAST-W: Taltz, n = 58; PBO, n = 51.

<sup>e</sup> BASDAI50 response defined as an improvement of  $\geq 50\%$  of the BASDAI score from baseline.

<sup>f</sup> ASAS HI: Assessment of SpondyloArthritis International Society Health Index (ASAS HI) across all domains.

<sup>g</sup> The reported values are difference in % (95% CI) for categorical variables, and difference in LSM (95% CI) for continuous variables.

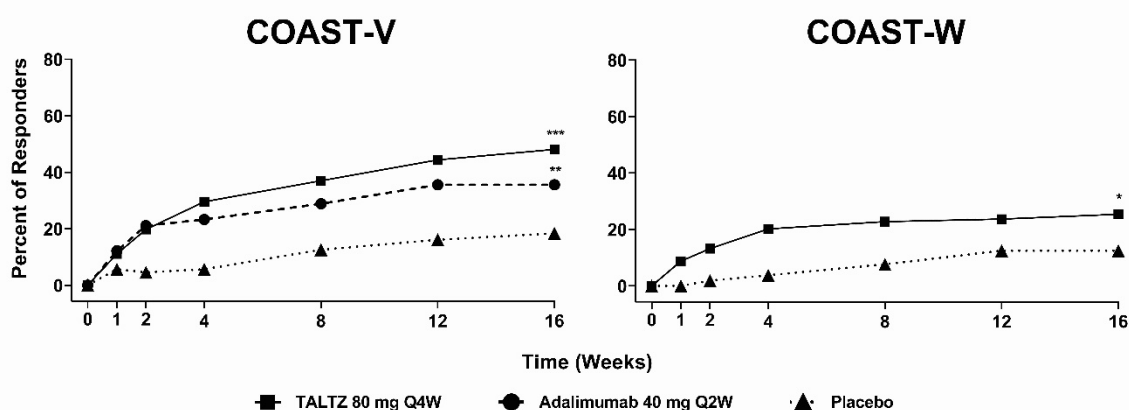
<sup>h</sup> post hoc analysis, not multiplicity corrected.

<sup>i</sup> prespecified, but not multiplicity gated.

\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$  compared with placebo.

There were improvements in the main components of the ASAS40 response criteria (spinal pain, BASFI, patient global assessment, stiffness) and other measures of disease activity, including CRP, at week 16.

**Figure 6. Percent of ITT patients achieving ASAS40 responses in COAST-V and COAST-W through week 16, NRI<sup>a</sup>**



<sup>a</sup> Patients with missing data were counted as non-responders.

\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$  compared with placebo.

Similar response in ASAS40 was seen in patients regardless of baseline CRP levels, baseline ASDAS scores and MRI spine SPARCC scores. The ASAS40 response was demonstrated regardless of age, gender, race, disease duration, baseline body weight, baseline BASDAI score and prior biologic treatment.



In COAST-V and COAST-W efficacy was maintained up to week 52 as assessed by the endpoints presented in Table 12, including ASAS20, ASAS40, ASDAS, BASDAI, and ASAS HI response rates.

#### *Health-related outcomes*

Spinal pain showed improvements versus placebo as early as week 1, maintained through week 16 [Taltz vs placebo: COAST-V -3.2 vs -1.7; COAST-W -2.4 vs -1.0]; fatigue and spinal mobility showed improvements versus placebo at week 16. Improvements in spinal pain, fatigue and spinal mobility were maintained through week 52.

#### Non-radiographic axial spondyloarthritis

Taltz was assessed in a randomised, double-blind study with a 52-week placebo-controlled period (COAST-X) in 303 adult patients with active axial spondyloarthritis for at least 3 months. Patients must have had objective signs of inflammation indicated by elevated C-reactive protein (CRP) and/or sacroiliitis on magnetic resonance imaging (MRI), and no definitive radiographic evidence of structural damage on sacroiliac joints. Patients had active disease as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)  $\geq 4$ , and spinal pain  $\geq 4$  on a 0 to 10 Numerical Rating Scale (NRS), despite non-steroidal anti-inflammatory drug (NSAID) therapy. Patients were treated with either Taltz 80 mg or 160 mg at week 0, followed by 80 mg every 2 weeks (Q2W) or 80 mg every 4 weeks (Q4W) or with placebo. Dose adjustment and/or initiation of concomitant medications (NSAIDs, cDMARDs, corticosteroids, analgesics) were permitted starting at week 16.

At baseline, patients had symptoms of non-radiographic axSpA for an average of 11 years. Approximately 39% of the patients were on a concomitant cDMARD.

The primary endpoint was the percentage of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response at week 16.

#### *Clinical response*

Higher proportions of patients treated with Taltz 80 mg Q4W achieved ASAS40 response compared to placebo at week 16 (Table 13). Responses were similar regardless of concomitant therapies.

**Table 13. Efficacy results at week 16 in COAST-X, NRI <sup>a,b</sup>**

	<b>Taltz 80 mg Q4W<sup>c</sup> (N=96)</b>	<b>Placebo (N=105)</b>	<b>Difference from placebo <sup>h</sup></b>
ASAS20 response <sup>d</sup> , n (%), NRI	52 (54.2%)	41 (39.0%)	15.1 (1.5, 28.8)*
ASAS40 response <sup>d,e</sup> , n (%), NRI	34 (35.4%)	20 (19.0%)	16.4 (4.2, 28.5)**
<b>ASDAS</b>			
Change from baseline	-1.1	-0.6	-0.5 (-0.8, -0.3) ***
<i>Baseline</i>	3.8	3.8	
<b>BASDAI Score</b>			
Change from baseline	-2.2	-1.5	-0.7 (-1.3, -0.1) *
<i>Baseline</i>	7.0	7.2	
<b>MRI SIJ SPARCC<sup>f</sup></b>			
Change from baseline	-3.4	-0.3	-3.1 (-4.6, -1.6) ***
<i>Baseline</i>	5.1	6.3	
ASDAS <2.1, n (%) (low disease activity), NRI <sup>g</sup>	26 (27.7%)	13 (12.4%)	15.3 (4.3, 26.3) **
<b>SF-36 PCS</b>			
Change from baseline	8.1	5.2	2.9 (0.6, 5.1) *
<i>Baseline</i>	33.5	32.6	

<sup>a</sup> Abbreviations: N = number of patients in the intent-to-treat population; NRI = Non-responder Imputation. ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; Change from baseline = least square mean change from baseline

at week 16; MRI SIJ SPARCC = Spondyloarthritis Research Consortium of Canada Magnetic Resonance Imaging Scoring of the sacroiliac joint.

<sup>b</sup> Patients with missing data were counted as non-responders.

<sup>c</sup> At week 0, patients received 80 mg or 160 mg of Taltz.

<sup>d</sup> An ASAS20 response is defined as a  $\geq 20\%$  improvement and an absolute improvement from baseline of  $\geq 1$  units (range 0 to 10) in  $\geq 3$  of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation), and no worsening of  $\geq 20\%$  and  $\geq 1$  unit (range 0 to 10) in the remaining domain. An ASAS40 response is defined as a  $\geq 40\%$  improvement and an absolute improvement from baseline of  $\geq 2$  units in  $\geq 3$  of 4 domains without any worsening in the remaining domain.

<sup>e</sup> Primary endpoint at week 16.

<sup>f</sup> The numbers of ITT patients with MRI data at baseline and week 16 are as follows: Taltz,  $n = 85$ ; PBO,  $n = 90$ .

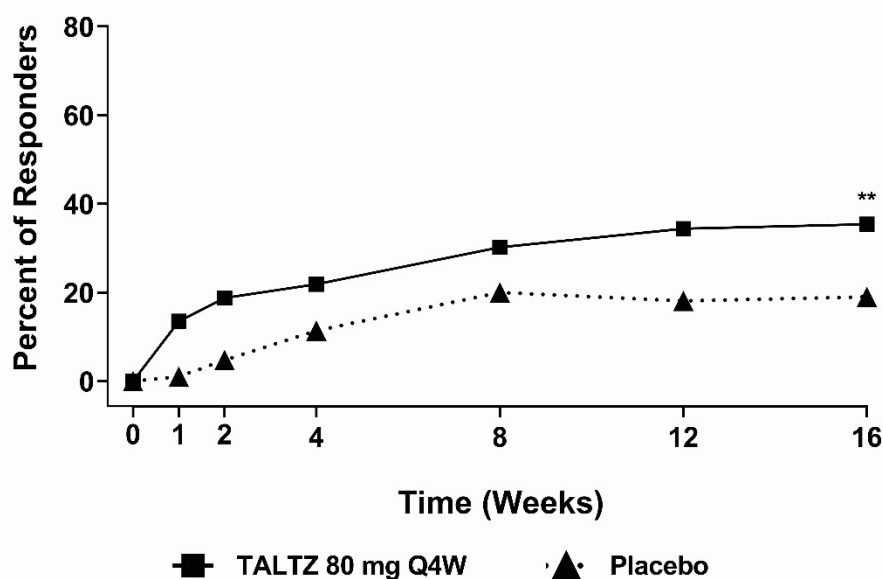
<sup>g</sup> Patients with missing data were counted as non-responders. Percentages are based on the number of patients in the ITT population with baseline ASDAS  $\geq 2.1$ .

<sup>h</sup> The reported values are difference in % (95% CI) for categorical variables, and difference in LSM (95% CI) for continuous variables.

\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$  compared with placebo.

The improvement in the main components of the ASAS40 response criteria (spinal pain, BASFI, patient global assessment, stiffness) and other measures of disease activity demonstrated significant clinical improvement at week 16.

**Figure 7. Percent of patients achieving ASAS40 response through week 16 in COAST-X, NRI<sup>a</sup>**



<sup>a</sup> Patients with missing data were counted as non-responders.

\*\*  $p < 0.01$  compared with placebo.

Efficacy was maintained up to week 52 as assessed by the endpoints presented in Table 13.

#### Health-related outcomes

Spinal pain showed improvements versus placebo as early as week 1 and was maintained through week 16 [Taltz vs placebo: COAST-X: -2.4 vs -1.5]. In addition, more patients on Taltz compared with placebo achieved good health status (ASAS HI  $\leq 5$ ) at week 16 and week 52.

#### Long-term outcomes Axial Spondyloarthritis

Patients who completed one of the three pivotal studies COAST-V/W/X (52 weeks) were offered participation in a long-term extension and randomised withdrawal study (COAST-Y, with 350 and 423 patients enrolled on Taltz Q4W and Q2W, respectively). Among those who achieved remission

157/773 (20.3%) (Ankylosing Spondylitis Disease Activity Score [ASDAS] <1.3 at least once, and no ASDAS score  $\geq$ 2.1, at weeks 16 and 20), 155 patients exposed to Taltz up to 76 weeks were randomised at week 24 of the COAST-Y study (Placebo, N=53; Taltz Q4W, N=48; and Taltz Q2W, N=54); of these, 148 (95.5%) completed the week 64 visit (Placebo, N=50; Taltz Q4W, N=47; Taltz Q2W, N=51). The primary endpoint was the proportion of patients in the randomised withdrawal population who did not experience a flare during weeks 24-64 (combined Taltz Q2W and Taltz Q4W groups versus placebo). A significantly larger proportion of patients (NRI) in the combined Taltz groups (83.3% (85/102),  $p < 0.001$ ) and Taltz Q4W (83.3 % (40/48),  $p = 0.003$ ) had no flare during weeks 24-64 compared with those who withdrew from Taltz to placebo (54.7 % (29/53)). Taltz (in both combined Taltz groups and Taltz Q4W group) significantly delayed the time to flare (Log-Rank Test  $p < 0.001$  and  $p < 0.01$ , respectively) compared to Placebo.

In patients who received Taltz Q4W continuously (N=157), the ASAS40, ASDAS <2.1 and BASDAI50 responses were maintained to week 116.

### *Immunisations*

In a study in healthy subjects, no safety concerns were identified of two inactivated vaccines (tetanus and pneumococcal), received after two doses of ixekizumab (160 mg followed by a second dose of 80 mg two weeks later). However, the data concerning immunisation were insufficient to conclude on an adequate immune response to these vaccines following administration of Taltz.

### Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Taltz in one or more subsets of the paediatric population in the treatment of plaque psoriasis and psoriatic arthritis/axial spondyloarthritis (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

### Absorption

Following a single subcutaneous dose of ixekizumab in patients with psoriasis, mean peak concentrations were achieved within 4 to 7 days, across a dose range of 5 to 160 mg. The mean (SD) maximum plasma concentration ( $C_{max}$ ) of ixekizumab, after the 160 mg starting dose, was 19.9 (8.15)  $\mu\text{g/ml}$ .

After the 160 mg starting dose, steady state was achieved by week 8 with the 80 mg Q2W dosing regimen. Mean (SD)  $C_{max,ss}$ , and  $C_{trough,ss}$  estimates are 21.5 (9.16)  $\mu\text{g/ml}$ , and 5.23 (3.19)  $\mu\text{g/ml}$ .

After switching from the 80 mg Q2W dosing regimen to the 80 mg Q4W dosing regimen at week 12, steady state would be achieved after approximately 10 weeks. Mean (SD)  $C_{max,ss}$ , and  $C_{trough,ss}$  estimates are 14.6 (6.04)  $\mu\text{g/ml}$ , and 1.87 (1.30)  $\mu\text{g/ml}$ .

The average bioavailability of ixekizumab after subcutaneous administration was 54 % to 90 % across analyses.

### Distribution

From population pharmacokinetic analyses, the mean total volume of distribution at steady state was 7.11 L.

### Biotransformation

Ixekizumab is a monoclonal antibody and is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous immunoglobulins.

### Elimination

In the population PK analysis, mean serum clearance was 0.0161 L/hr. Clearance is independent of dose. The mean elimination half-life, as estimated from population pharmacokinetic analysis, is 13 days in patients with plaque psoriasis.

### Linearity/non-linearity

Exposure (AUC) increased proportionally over a dose range of 5 to 160 mg given as a subcutaneous injection.

### Pharmacokinetic properties across indications

The pharmacokinetic properties of Taltz were similar across the plaque psoriasis, psoriatic arthritis, radiographic axial spondyloarthritis and non-radiographic axial spondyloarthritis indications.

### Elderly

Of the 4,204 plaque psoriasis patients exposed to Taltz in clinical studies, a total of 301 were 65 years of age or older and 36 patients were 75 years of age or older. Of the 1,118 psoriatic arthritis patients exposed to Taltz in clinical studies, a total of 122 patients were 65 years of age or older and 6 patients were 75 years of age or older.

Based on population pharmacokinetic analysis with a limited number of elderly patients (n = 94 for age  $\geq$  65 years and n = 12 for age  $\geq$  75 years), clearance in elderly patients and patients less than 65 years of age was similar.

### Renal or hepatic impairment

Specific clinical pharmacology studies to evaluate the effects of renal impairment and hepatic impairment on the PK of ixekizumab have not been conducted. Renal elimination of intact ixekizumab, an IgG MAb, is expected to be low and of minor importance; similarly, IgG MAbs are mainly eliminated via intracellular catabolism and hepatic impairment is not expected to influence clearance of ixekizumab.

### Paediatric population

Paediatric psoriasis patients (age 6 to less than 18 years) were administered ixekizumab at the recommended paediatric dosing regimen for 12 weeks. Patients weighing  $>50$  kg and 25 to 50 kg had a mean  $\pm$ SD steady-state trough concentration of  $3.8 \pm 2.2$   $\mu$ g/ml and  $3.9 \pm 2.4$   $\mu$ g/ml, respectively, at week 12.

## **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on repeat-dose toxicity studies, safety pharmacology evaluations, and reproductive and developmental toxicity studies.

Ixekizumab administration to cynomolgus monkeys for 39 weeks at subcutaneous doses up to 50 mg/kg weekly produced no organ toxicity or undesirable effects on immune function (e.g. T-cell dependent antibody response and NK cell activity). A weekly subcutaneous dose of 50 mg/kg to monkeys is approximately 19 times the 160 mg starting dose of Taltz and in monkeys results in exposure (AUC) that is at least 61-fold higher than the predicted mean steady-state exposure in humans administered the recommended dose regimen.

Non-clinical studies have not been conducted to evaluate the carcinogenic or mutagenic potential of ixekizumab.

No effects on reproductive organs, menstrual cycles or sperm were observed in sexually mature cynomolgus monkeys that received ixekizumab for 13 weeks at a weekly subcutaneous dose of 50 mg/kg.

In developmental toxicity studies, ixekizumab was shown to cross the placenta and was present in the blood of offspring for up to 6 months of age. A higher incidence of postnatal mortality occurred in the offspring of monkeys given ixekizumab compared to concurrent controls. This was related primarily to early delivery or maternal neglect of offspring, common findings in nonhuman primate studies, and considered clinically irrelevant.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sucrose  
Polysorbate 80  
Water for injections  
Sodium hydroxide may be used to adjust pH

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years.

### **6.4 Special precautions for storage**

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

Taltz may be stored unrefrigerated for up to 5 days at a temperature not above 30 °C.

### **6.5 Nature and contents of container**

1 ml solution in a type I clear glass syringe.  
Pack sizes of 1, 2, or 3 pre-filled syringes.  
Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

The instructions for using the syringe, included with the package leaflet, must be followed carefully.  
The pre-filled syringe is for single use only.

Taltz should not be used if particles appear or if the solution is cloudy and/or distinctly brown.

Taltz that has been frozen must not be used.

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

#### 40 mg preparation of ixekizumab for children 25-50 kg body weight

Ixekizumab doses of 40 mg must be prepared and administered by a qualified healthcare professional. Use only Taltz 80 mg solution for injection in pre-filled syringe when preparing the prescribed 40 mg paediatric doses.

1. Expel the entire contents of the pre-filled syringe into a sterile, clear glass vial. DO NOT shake or swirl the vial.
2. Use a 0.5 mL or 1 mL disposable syringe and sterile needle to withdraw the prescribed dose (0.5 ml for 40 mg) from the vial.
3. Change the needle and use a 27-gauge, sterile needle to inject the patient. Discard any unused ixekizumab in the vial.

The prepared ixekizumab must be administered within 4 hours of puncturing the sterile vial at room temperature.

#### **7. MARKETING AUTHORISATION HOLDER**

Eli Lilly and Company (Ireland) Limited, Dunderrow, Kinsale, Co. Cork, Ireland.

#### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1085/004

EU/1/15/1085/005

EU/1/15/1085/006

#### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 25 April 2016

Date of latest renewal: 17 December 2020

#### **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## 1. NAME OF THE MEDICINAL PRODUCT

Taltz 80 mg solution for injection in pre-filled pen

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 80 mg ixekizumab in 1 ml.

Ixekizumab is produced in CHO cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear and colourless to slightly yellow.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

#### Plaque psoriasis

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

#### Paediatric plaque psoriasis

Taltz is indicated for the treatment of moderate to severe plaque psoriasis in children from the age of 6 years and with a body weight of at least 25 kg and adolescents who are candidates for systemic therapy.

#### Psoriatic arthritis

Taltz, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drug (DMARD) therapies (see section 5.1).

#### Axial spondyloarthritis

##### *Ankylosing spondylitis (radiographic axial spondyloarthritis)*

Taltz is indicated for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy.

##### *Non-radiographic axial spondyloarthritis*

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

## 4.2 Posology and method of administration

This medicinal product is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which it is indicated.

### Posology

#### *Plaque psoriasis in adults*

The recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) at weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks (Q4W).

#### *Paediatric plaque psoriasis (age 6 years and above)*

Efficacy and safety data is not available in children below the age of 6 years (see section 5.1).

Available data do not support a posology below a body weight of 25 kg.

The recommended dose given by subcutaneous injection in children is based on the following weight categories:

<b>Children's body weight</b>	<b>Recommended starting dose (week 0)</b>	<b>Recommended dose every 4 weeks (Q4W) thereafter</b>
Greater than 50 kg	160 mg (two 80 mg injections)	80 mg
25 to 50 kg	80 mg	40 mg

Ixekizumab doses of 40 mg must be prepared and administered by a qualified healthcare professional using the commercial Taltz 80 mg/1 ml pre-filled syringe.

Use the Taltz 80 mg pre-filled pen only in those children that require a dose of 80 mg and do not require dose preparation.

Taltz is not recommended for use in children with a body weight below 25 kg. Paediatric body weights must be recorded and regularly re-checked prior to dosing.

#### *Psoriatic arthritis*

The recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) every 4 weeks thereafter. For psoriatic arthritis patients with concomitant moderate to severe plaque psoriasis, the recommended dosing regimen is the same as for plaque psoriasis.

#### *Axial spondyloarthritis (radiographic and non-radiographic)*

The recommended dose is 160 mg (two 80 mg injections) by subcutaneous injection at week 0, followed by 80 mg every 4 weeks (see section 5.1 for further information).

For all indications (plaque psoriasis in adults and children, psoriatic arthritis, axial spondyloarthritis) consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks.

### Special populations

#### *Elderly ( $\geq 65$ years)*

No dose adjustment is required (see section 5.2).

There is limited information in subjects aged  $\geq 75$  years.

#### *Renal or hepatic impairment*

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



### Paediatric population

#### *Paediatric plaque psoriasis (below a body weight of 25 kg and below the age of 6 years)*

There is no relevant use of Taltz in children below a body weight of 25 kg and below the age of 6 years in the treatment of moderate to severe plaque psoriasis.

#### *Paediatric psoriatic arthritis*

The safety and efficacy of Taltz in children and adolescents aged 2 to less than 18 years in the treatment of psoriatic arthritis (a category of juvenile idiopathic arthritis) have not yet been established. No data are available. There is no relevant use of Taltz in children below 2 years for the indication of psoriatic arthritis.

### Method of administration

Subcutaneous use.

Taltz is for subcutaneous injection. Injection sites may be alternated. If possible, areas of the skin that show psoriasis should be avoided as injection sites. The solution/the pen must not be shaken.

After proper training in subcutaneous injection technique, patients may self-inject Taltz if a healthcare professional determines that it is appropriate. However, the physician should ensure appropriate follow-up of patients. Comprehensive instructions for administration are given in the package leaflet and the user manual.

### **4.3 Contraindications**

Serious hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically important active infections (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

Treatment with Taltz is associated with an increased rate of infections such as upper respiratory tract infection, oral candidiasis, conjunctivitis, and tinea infections (see section 4.8).

Taltz should be used with caution in patients with clinically important 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 an infection develops, patients should be carefully monitored and Taltz discontinued if the patient is not responding to standard therapy or if the infection becomes serious. Taltz should not be resumed until the infection resolves.

Taltz must not be given to patients with active tuberculosis (TB). Anti-TB therapy prior to initiation of Taltz in patients with latent TB should be considered.

#### Hypersensitivity

Serious hypersensitivity reactions, including some cases of anaphylaxis, angioedema, urticaria and, rarely, late (10-14 days following injection) serious hypersensitivity reactions including widespread

urticaria, dyspnea and high antibody titres have been reported. If a serious hypersensitivity reaction occurs, administration of Taltz should be discontinued immediately and appropriate therapy initiated.

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

Cases of new or exacerbations of inflammatory bowel disease have been reported with ixekizumab (see section 4.8). Ixekizumab 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, ixekizumab should be discontinued and appropriate medical management should be initiated.

#### Immunisations

Taltz should not be used with live vaccines. No data are available on the response to live vaccines; there are insufficient data on response to inactive vaccines (see section 5.1).

#### Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per 80 mg dose, that is to say essentially “sodium-free”.

### **4.5 Interaction with other medicinal products and other forms of interaction**

In plaque psoriasis studies, the safety of Taltz in combination with other immunomodulatory agents or phototherapy has not been evaluated.

In population pharmacokinetic analyses, clearance of ixekizumab was not affected by concomitant administration of oral corticosteroids, NSAIDs, sulfasalazine, or methotrexate.

#### Cytochrome P450 substrates

Results from an interaction study in patients with moderate-to-severe psoriasis determined that 12 weeks of administration of ixekizumab with substances metabolised by CYP3A4 (i.e., midazolam), CYP2C9 (i.e., warfarin), CYP2C19 (i.e., omeprazole), CYP1A2 (i.e., caffeine) or CYP2D6 (i.e., dextromethorphan) does not have a clinically significant impact on the pharmacokinetics of these substances.

### **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 10 weeks after treatment.

#### Pregnancy

There is a limited amount of data from the use of ixekizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or post-natal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Taltz during pregnancy.

#### Breast-feeding

It is not known whether ixekizumab is excreted in human milk or absorbed systemically after ingestion. However, ixekizumab is excreted at low levels in the milk of cynomolgus monkeys. A decision should be made whether to discontinue breast-feeding or to discontinue Taltz taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

## Fertility

The effect of ixekizumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

### **4.7 Effects on ability to drive and use machines**

Taltz 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 were injection site reactions (15.5 %) and upper respiratory tract infections (16.4 %) (most frequently nasopharyngitis).

#### Tabulated list of adverse reactions

Adverse reactions from clinical studies and postmarketing reports (Table 1) 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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

A total of 8,956 patients have been treated with Taltz in blinded and open-label clinical studies in plaque psoriasis, psoriatic arthritis, axial spondyloarthritis, and other autoimmune conditions. Of these, 6,385 patients were exposed to Taltz for at least one year, cumulatively representing 19,833 adult patient years of exposure and 196 children cumulatively representing 207 patient years of exposure.

**Table 1. List of adverse reactions in clinical studies and postmarketing reports**

<b>System organ class</b>	<b>Frequency</b>	<b>Adverse reaction</b>
Infections and infestations	Very common	Upper respiratory tract infection
	Common	Tinea infection, Herpes simplex (mucocutaneous)
	Uncommon	Influenza, Rhinitis, Oral candidiasis, Conjunctivitis, Cellulitis
	Rare	Oesophageal candidiasis
Blood and lymphatic system disorders	Uncommon	Neutropenia, Thrombocytopenia
Immune system disorders	Uncommon	Angioedema
	Rare	Anaphylaxis
Respiratory, thoracic and mediastinal disorders	Common	Oropharyngeal pain
Gastrointestinal disorders	Common	Nausea
	Uncommon	Inflammatory bowel disease
Skin and subcutaneous disorders	Uncommon	Urticaria, Rash, Eczema
General disorders and administration site conditions	Very common	Injection site reactions <sup>a</sup>

<sup>a</sup> See section description of selected adverse reactions

### Description of selected adverse reactions

#### *Injection site reactions*

The most frequent injection site reactions observed were erythema and pain. These reactions were predominantly mild to moderate in severity and did not lead to discontinuation of Taltz. In the adult plaque psoriasis studies, injection site reactions were more common in subjects with a body weight < 60 kg compared with the group with a body weight ≥ 60 kg (25 % vs. 14 % for the combined Q2W and Q4W groups). In the psoriatic arthritis studies, injection site reactions were more common in subjects with a body weight < 100 kg compared with the group with a body weight ≥ 100 kg (24 % vs. 13 % for the combined Q2W and Q4W groups). In the axial spondyloarthritis studies, injection site reactions were similar in subjects with a body weight < 100 kg compared with the group with a body weight ≥ 100 kg (14 % vs. 9 % for the combined Q2W and Q4W groups). The increased frequency of injection site reactions in the combined Q2W and Q4W groups did not result in an increase in discontinuations in either the plaque psoriasis, the psoriatic arthritis or the axial spondyloarthritis studies.

The results described above are obtained with the original formulation of Taltz. In a single-blinded, randomized cross-over study in 45 healthy subjects comparing the original formulation with the revised, citrate-free formulation, statistically significantly lower VAS pain scores were obtained with the citrate-free vs. the original formulation during injection (difference in LS Mean VAS score -21.69) and 10 min after injection (difference in LS Mean VAS score -4.47).

#### *Infections*

In the placebo-controlled period of the phase III clinical studies in plaque psoriasis in adults, infections were reported in 27.2 % of patients treated with Taltz for up to 12 weeks compared with 22.9 % of patients treated with placebo.

The majority of infections were non-serious and mild to moderate in severity, most of which did not necessitate treatment discontinuation. Serious infections occurred in 13 (0.6 %) of patients treated with Taltz and in 3 (0.4 %) of patients treated with placebo (see section 4.4). Over the entire treatment period infections were reported in 52.8 % of patients treated with Taltz (46.9 per 100 patient years). Serious infections were reported in 1.6 % of patients treated with Taltz (1.5 per 100 patient years).

Infection rates observed in psoriatic arthritis and axial spondyloarthritis clinical studies were similar to those observed in the plaque psoriasis studies with the exception of the frequencies of the adverse reactions of influenza and conjunctivitis which were common in patients with psoriatic arthritis.

#### *Laboratory assessment of neutropenia and thrombocytopenia*

In plaque psoriasis studies, 9% of patients receiving Taltz developed neutropenia. In most cases, the blood neutrophil count was  $\geq 1,000$  cells/mm<sup>3</sup>. Such levels of neutropenia may persist, fluctuate or be transient. 0.1% of patients receiving Taltz developed a neutrophil count  $< 1,000$  cells/mm<sup>3</sup>. In general, neutropenia did not require discontinuation of Taltz. 3% of patients exposed to Taltz had a shift from a normal baseline platelet value to  $< 150,000$  platelet cells/mm<sup>3</sup> to  $\geq 75,000$  cells/mm<sup>3</sup>. Thrombocytopenia may persist, fluctuate or be transient.

The frequency of neutropenia and thrombocytopenia in psoriatic arthritis and axial spondyloarthritis clinical studies is similar to that observed in the plaque psoriasis studies.

#### *Immunogenicity*

Approximately 9–17% of adult plaque psoriasis patients treated with Taltz at the recommended dosing regimen developed anti-drug antibodies, the majority of which were low titres and not associated with reduced clinical response up to 60 weeks of treatment. However, approximately 1% of patients treated with Taltz had confirmed neutralising antibodies associated with low drug concentrations and reduced clinical response.

In psoriatic arthritis patients treated with Taltz at the recommended dosing regimen up to 52 weeks, approximately 11% developed anti-drug antibodies, the majority of which were low titre, and approximately 8% had confirmed neutralising antibodies. No apparent association between the presence of neutralising antibodies and impact on drug concentration or efficacy was observed.

In paediatric psoriasis patients treated with Taltz at the recommended dosing regimen up to 12 weeks, 21 patients (18%) developed anti-drug antibodies, approximately half were low titer and 5 patients (4%) had confirmed neutralizing antibodies associated with low drug concentrations. There was no association with clinical response or adverse events.

In radiographic axial spondyloarthritis patients treated with Taltz at the recommended dosing regimen up to 16 weeks, 5.2% developed anti-drug antibodies, the majority of which were low titer, and 1.5% (3 patients) had neutralising antibodies (NAb). In these 3 patients, NAb-positive samples had low ixekizumab concentrations and none of these patients achieved an ASAS40 response. In non-radiographic axial spondyloarthritis patients treated with Taltz at the recommended dosing regimen for up to 52 weeks, 8.9% developed anti-drug antibodies, all of which were low titer; no patient had neutralising antibodies; and no apparent association between the presence of anti-drug antibodies and drug concentration, efficacy, or safety was observed.

Across all indications, an association between immunogenicity and treatment emergent adverse events has not been clearly established.

#### Paediatric population

The safety profile observed in children with plaque psoriasis treated with Taltz every 4 weeks is consistent with the safety profile in adult patients with plaque psoriasis with the exception of the frequencies of conjunctivitis, influenza, and urticaria which were common. Inflammatory bowel disease was also more frequent in paediatric patients, although it was still uncommon. In the paediatric clinical study, Crohn's disease occurred in 0.9% of patients in the Taltz group and 0% of patients in

the placebo group during the 12-week, placebo-controlled period. Crohn's disease occurred in a total of 4 Taltz treated subjects (2.0%) during the combined placebo-controlled and maintenance periods of the paediatric clinical study.

#### 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 national reporting system listed in Appendix V.

#### **4.9 Overdose**

Doses up to 180 mg have been administered subcutaneously in clinical trials without dose-limiting toxicity. Overdoses up to 240 mg, subcutaneously, as a single administration in clinical trials, have been reported without any serious adverse events. 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: L04AC13

#### Mechanism of action

Ixekizumab is an IgG4 monoclonal antibody that binds with high affinity (< 3 pM) and specificity to interleukin 17A (both IL-17A and IL-17A/F). Elevated concentrations of IL-17A have been implicated in the pathogenesis of psoriasis by promoting keratinocyte proliferation and activation, as well as in the pathogenesis of psoriatic arthritis and axial spondyloarthritis by driving inflammation leading to erosive bone damage and pathological new bone formation. Neutralisation of IL-17A by ixekizumab inhibits these actions. Ixekizumab does not bind to ligands IL-17B, IL-17C, IL-17D, IL-17E or IL-17F.

In vitro binding assays confirmed that ixekizumab does not bind to human Fcγ receptors I, IIa, and IIIa or to complement component C1q.

#### Pharmacodynamic effects

Ixekizumab modulates biological responses that are induced or regulated by IL-17A. Based on psoriatic skin biopsy data from a phase I study, there was a dose-related trend towards decreased epidermal thickness, number of proliferating keratinocytes, T cells, and dendritic cells, as well as reductions in local inflammatory markers from baseline to day 43. As a direct consequence treatment with ixekizumab reduces erythema, induration and desquamation present in plaque psoriasis lesions.

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

#### Clinical efficacy and safety

##### Adult plaque psoriasis

The efficacy and safety of Taltz were assessed in three randomised, double-blind, placebo-controlled phase III studies in adult patients (N=3,866) with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy (UNCOVER-1, UNCOVER-2, and UNCOVER-3).

The efficacy and safety of Taltz were also evaluated versus etanercept (UNCOVER-2 and UNCOVER-3). Patients randomised to Taltz who were sPGA (0,1) responders (static Physicians Global Assessment) at week 12 were re-randomised to receive placebo or Taltz for an additional 48 weeks (UNCOVER-1 and UNCOVER-2); patients randomised to placebo, etanercept or Taltz who were sPGA (0,1) non-responders received Taltz for up to 48 weeks. In addition, long-term efficacy and safety were evaluated in all three studies for up to a total of 5 years in patients who participated through the entire study.

64 % of patients had received prior systemic therapy (biologic, conventional systemic or psoralen and ultraviolet A (PUVA)), 43.5 % prior phototherapy, 49.3 % prior conventional systemic therapy, and 26.4 % prior biologic therapy. 14.9 % had received at least one anti-TNF alpha agent, and 8.7 % an anti-IL-12/IL-23. 23.4 % of patients had a history of psoriatic arthritis at baseline.

In all three studies, the co-primary endpoints were the proportion of patients who achieved a PASI 75 response (Psoriasis Area and Severity Index) and an sPGA of “0” (“clear”) or 1 (“minimal”) response at week 12 versus placebo. The median baseline PASI score ranged from 17.4 to 18.3; 48.3 % to 51.2 % of patients had a baseline sPGA score of severe or very severe, and mean baseline itch Numeric Rating Scale (itch NRS) ranged from 6.3 to 7.1.

#### *Clinical response at 12 weeks*

UNCOVER-1 randomised 1,296 patients (1:1:1) to receive either placebo or Taltz (80 mg every two or four weeks [Q2W or Q4W] following a 160 mg starting dose) for 12 weeks.

**Table 2. Efficacy results at week 12 in UNCOVER-1**

Endpoints	Number of patients (%)			Difference from placebo in response rate (95% CI)	
	Placebo (N = 431)	Taltz 80 mg Q4W (N = 432)	Taltz 80 mg Q2W (N = 433)	Taltz 80 mg Q4W	Taltz 80 mg Q2W
sPGA of “0” (clear) or “1” (minimal)	14 (3.2)	330 (76.4) <sup>a</sup>	354 (81.8) <sup>a</sup>	73.1 (68.8, 77.5)	78.5 (74.5, 82.5)
sPGA of “0” (clear)	0	149 (34.5) <sup>a</sup>	160 (37.0) <sup>a</sup>	34.5 (30.0, 39.0)	37.0 (32.4, 41.5)
PASI 75	17 (3.9)	357 (82.6) <sup>a</sup>	386 (89.1) <sup>a</sup>	78.7 (74.7, 82.7)	85.2 (81.7, 88.7)
PASI 90	2 (0.5)	279 (64.6) <sup>a</sup>	307 (70.9) <sup>a</sup>	64.1 (59.6, 68.7)	70.4 (66.1, 74.8)
PASI 100	0	145 (33.6) <sup>a</sup>	153 (35.3) <sup>a</sup>	33.6 (29.1, 38.0)	35.3 (30.8, 39.8)
Itch NRS reduction $\geq 4$ <sup>b</sup>	58 (15.5)	305 (80.5) <sup>a</sup>	336 (85.9) <sup>a</sup>	65.0 (59.5, 70.4)	70.4 (65.4, 75.5)

*Abbreviations: N = number of patients in the intent-to-treat population*

*Note: patients with missing data were counted as non-responders*

<sup>a</sup> *p < 0.001 compared with placebo*

<sup>b</sup> *Patients with Itch NRS  $\geq 4$  at baseline: placebo N = 374, Taltz 80 mg Q4W N = 379, Taltz 80 mg Q2W N = 391*

UNCOVER-2 randomised 1,224 patients (1:2:2:2) to receive either placebo, or Taltz (80 mg every two or four weeks [Q2W or Q4W] following a 160 mg starting dose) or etanercept 50 mg twice weekly for 12 weeks.

**Table 3. Efficacy results at week 12 in UNCOVER-2**

Endpoints	Number of patients (%)				Difference from placebo in response rate (95% CI)	
	Placebo (N = 168)	Taltz 80 mg Q4W (N = 347)	Taltz 80 mg Q2W (N = 351)	Etanercept 50 mg twice weekly (N = 358)	Taltz 80 mg Q4W	Taltz 80 mg Q2W
sPGA of “0” (clear) or “1” (minimal)	4 (2.4)	253 (72.9) <sup>a,b</sup>	292 (83.2) <sup>a,b</sup>	129 (36.0) <sup>a</sup>	70.5 (65.3, 75.7)	80.8 (76.3, 85.4)
sPGA of “0” (clear)	1 (0.6)	112 (32.3) <sup>a,b</sup>	147 (41.9) <sup>a,b</sup>	21 (5.9) <sup>c</sup>	31.7 (26.6, 36.7)	41.3 (36.0, 46.6)
PASI 75	4 (2.4)	269 (77.5) <sup>a,b</sup>	315 (89.7) <sup>a,b</sup>	149 (41.6) <sup>a</sup>	75.1 (70.2, 80.1)	87.4 (83.4, 91.3)
PASI 90	1 (0.6)	207 (59.7) <sup>a,b</sup>	248 (70.7) <sup>a,b</sup>	67 (18.7) <sup>a</sup>	59.1 (53.8, 64.4)	70.1 (65.2, 75.0)
PASI 100	1 (0.6)	107 (30.8) <sup>a,b</sup>	142 (40.5) <sup>a,b</sup>	19 (5.3) <sup>c</sup>	30.2 (25.2, 35.2)	39.9 (34.6, 45.1)
Itch NRS reduction $\geq 4^d$	19 (14.1)	225 (76.8) <sup>a,b</sup>	258 (85.1) <sup>a,b</sup>	177 (57.8) <sup>a</sup>	62.7 (55.1, 70.3)	71.1 (64.0, 78.2)

Abbreviations: N = number of patients in the intent-to-treat population

Note: patients with missing data were counted as non-responders.

<sup>a</sup>  $p < 0.001$  compared with placebo; <sup>b</sup>  $p < 0.001$  compared with etanercept;

<sup>c</sup>  $p < 0.01$  compared with placebo

<sup>d</sup> Patients with Itch NRS  $\geq 4$  at baseline: placebo N = 135, Taltz 80 mg Q4W N = 293, Taltz 80 mg Q2W N = 303, etanercept N = 306

UNCOVER-3 randomised 1,346 patients (1:2:2:2) to receive either placebo, or Taltz (80 mg every two or four weeks [Q2W or Q4W] following a 160 mg starting dose) or etanercept 50 mg twice weekly for 12 weeks.



**Table 4. Efficacy results at week 12 in UNCOVER-3**

Endpoints	Number of patients (%)				Difference from placebo in response rate (95% CI)	
	Placebo (N = 193)	Taltz 80 mg Q4W (N = 386)	Taltz 80 mg Q2W (N = 385)	Etanercept 50 mg twice weekly (N = 382)	Taltz 80 mg Q4W	Taltz 80 mg Q2W
sPGA of “0” (clear) or “1” (minimal)	13 (6.7)	291 (75.4) <sup>a,b</sup>	310 (80.5) <sup>a,b</sup>	159 (41.6) <sup>a</sup>	68.7 (63.1, 74.2)	73.8 (68.5, 79.1)
sPGA of “0” (clear)	0	139 (36.0) <sup>a,b</sup>	155 (40.3) <sup>a,b</sup>	33 (8.6) <sup>a</sup>	36.0 (31.2, 40.8)	40.3 (35.4, 45.2)
PASI 75	14 (7.3)	325 (84.2) <sup>a,b</sup>	336 (87.3) <sup>a,b</sup>	204 (53.4) <sup>a</sup>	76.9 (71.8, 82.1)	80.0 (75.1, 85.0)
PASI 90	6 (3.1)	252 (65.3) <sup>a,b</sup>	262 (68.1) <sup>a,b</sup>	98 (25.7) <sup>a</sup>	62.2 (56.8, 67.5)	64.9 (59.7, 70.2)
PASI 100	0	135 (35.0) <sup>a,b</sup>	145 (37.7) <sup>a,b</sup>	28 (7.3) <sup>a</sup>	35 (30.2, 39.7)	37.7 (32.8, 42.5)
Itch NRS reduction $\geq 4^c$	33 (20.9)	250 (79.9) <sup>a,b</sup>	264 (82.5) <sup>a,b</sup>	200 (64.1) <sup>a</sup>	59.0 (51.2, 66.7)	61.6 (54.0, 69.2)

Abbreviations: N = number of patients in the intent-to-treat population

Note: patients with missing data were counted as non-responders

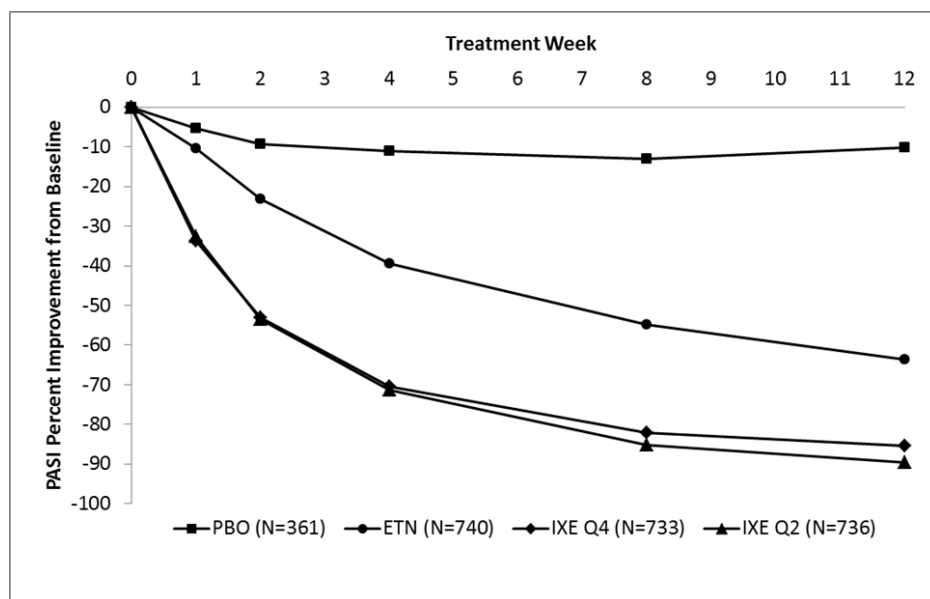
<sup>a</sup>  $p < 0.001$  compared with placebo

<sup>b</sup>  $p < 0.001$  compared with etanercept

<sup>c</sup> Patients with Itch NRS  $\geq 4$  at baseline: placebo N = 158, Taltz 80 mg Q4W N = 313, Taltz 80 mg Q2W N = 320, etanercept N = 312

Taltz was associated with a fast onset of efficacy with > 50 % reduction in mean PASI by week 2 (Figure 1). The percentage of patients achieving PASI 75 was significantly greater for Taltz compared with placebo and etanercept as early as week 1. Approximately 25 % of patients treated with Taltz achieved a PASI score < 5 by week 2, more than 55 % achieved the PASI score < 5 by week 4, and increased to 85 % by week 12 (compared to 3 %, 14 % and 50 % for etanercept). Significant improvements in itch severity were seen at week 1 in patients treated with Taltz.

**Figure 1. PASI score, percent improvement at each post baseline visit (mBOCF) in the intent-to-treat population during the induction dosing period – UNCOVER-2 and UNCOVER-3**



The efficacy and safety of Taltz was demonstrated regardless of age, gender, race, body weight, PASI baseline severity, plaques location, concurrent psoriatic arthritis, and previous treatment with a biologic. Taltz was efficacious in systemic treatment-naïve, biologic-naïve, biologic/anti-TNF-exposed and biologic/anti-TNF-failure patients.

For patients identified as an sPGA (0,1) non-responder to etanercept at week 12 in UNCOVER-2 (N = 200) and who were switched to Taltz 80 mg Q4W after a 4 week washout period, 73 % and 83.5 % of patients achieved sPGA (0,1) and PASI 75, respectively, after 12 weeks of treatment with Taltz.

In the 2 clinical studies that included an active comparator (UNCOVER-2 and UNCOVER-3), the rate of serious adverse events was 1.9 % for both etanercept and for Taltz, and the rate of discontinuation due to adverse events was 1.2 % for etanercept and 2.0 % for Taltz. The rate of infections was 21.5 % for etanercept and 26.0 % for Taltz, with 0.4 % being serious for etanercept and 0.5 % for Taltz.

#### *Maintenance of response at week 60 and up to 5 years*

Patients originally randomised to Taltz and who were responders at week 12 (i.e., sPGA score of 0,1) in UNCOVER-1 and UNCOVER-2 were re-randomised to an additional 48 weeks of treatment with placebo or Taltz (80 mg every four or twelve weeks [Q4W or Q12W]).

For sPGA (0,1) responders at week 12 re-randomised to treatment withdrawal (i.e., placebo), the median time to relapse (sPGA  $\geq$  3) was 164 days in integrated UNCOVER-1 and UNCOVER-2 studies. Among these patients, 71.5 % regained at least an sPGA (0,1) response within 12 weeks of restarting treatment with Taltz 80 mg Q4W.

**Table 5. Maintenance of response and efficacy at week 60 (Studies UNCOVER-1 and UNCOVER-2)**

Endpoints	Number of patients (%)				Difference from placebo in response rate (95% CI)	
	80 mg Q4W (induction) / Placebo (maintenance) (N = 191)	80 mg Q2W (induction) / Placebo (maintenance) (N = 211)	80 mg Q4W (induction) / 80 mg Q4W (maintenance) (N = 195)	80 mg Q2W (induction) / 80 mg Q4W (maintenance) (N = 221)	80 mg Q4W (induction) / 80 mg Q4W (maintenance)	80 mg Q2W (induction) / 80 mg Q4W (maintenance)
Maintained sPGA of “0” (clear) or “1” (minimal)	12 (6.3)	16 (7.6)	134 (68.7) <sup>a</sup>	173 (78.3) <sup>a</sup>	62.4 (55.1, 69.8)	70.7 (64.2, 77.2)
Maintained or achieved sPGA 0 (clear)	3 (1.6)	6 (2.8)	96 (49.2) <sup>a</sup>	130 (58.8) <sup>a</sup>	47.7 (40.4, 54.9)	56.0 (49.1, 62.8)
Maintained or achieved PASI 75	15 (7.9)	19 (9.0)	145 (74.4) <sup>a</sup>	184 (83.3) <sup>a</sup>	66.5 (59.3, 73.7)	74.3 (68.0, 80.5)
Maintained or achieved PASI 90	9 (4.7)	10 (4.7)	130 (66.7) <sup>a</sup>	169 (76.5) <sup>a</sup>	62.0 (54.7, 69.2)	71.7 (65.4, 78.0)
Maintained or achieved PASI 100	3 (1.6)	6 (2.8)	97 (49.7) <sup>a</sup>	127 (57.5) <sup>a</sup>	48.2 (40.9, 55.4)	54.6 (47.7, 61.5)

Abbreviations: N = number of patients in the analysis population

Note: patients with missing data were counted as non-responders

<sup>a</sup> p < 0.001 compared with placebo

Taltz was efficacious in the maintenance of response in systemic treatment-naive, biologic-naive, biologic/anti-TNF-exposed and biologic/anti-TNF-failure patients.

Significantly greater improvements at week 12 from baseline compared to placebo and etanercept were demonstrated in nail psoriasis (as measured by the Nail Psoriasis Severity Index [NAPSI]), in scalp psoriasis (as measured by Psoriasis Scalp Severity Index [PSSI]) and in palmoplantar psoriasis (as measured by Psoriasis Palmoplantar Severity Index [PPASI]) and were maintained at week 60 in patients treated with Taltz who were sPGA (0,1) responders at week 12.

Of 591 subjects who received Taltz Q2W during the Induction Period then Q4W afterward in study UNCOVER-1, UNCOVER-2, and UNCOVER-3, 427 subjects completed 5 years of Taltz treatment, among those 101 patients required a dose escalation. Among the patients who completed the week 264 assessment (N=427), 295 patients (69%), 289 patients (68%) and 205 patients (48%) were observed to have sPGA (0,1), PASI 90 and PASI 100 response, respectively, at week 264. DLQI were collected after Induction Period in UNCOVER-1 and UNCOVER-2, 113 patients (66%) were observed to have DLQI (0,1) response.

#### *Quality of life/patient-reported outcomes*

At week 12 and across studies, Taltz was associated with statistically significant improvement in Health-related Quality of Life as assessed by mean decrease ranges from baseline in the Dermatology Life Quality Index (DLQI) (Taltz 80 mg Q2W from -10.2 to -11.1, Taltz 80 mg Q4W from -9.4 to -10.7, etanercept from -7.7 to -8.0 and placebo -1.0 to -2.0). A significantly greater proportion of patients treated with Taltz achieved a DLQI 0 or 1. Across studies a significantly greater proportion of patients treated with Taltz achieved a reduction of Itch NRS ≥ 4 points at week 12 (84.6% for Taltz Q2W, 79.2% for Taltz Q4W and 16.5% for placebo) and the benefit was sustained over time up to week 60 in patients treated with Taltz who were sPGA (0 or 1) responders at week 12. There was not

any evidence of worsening of depression up to 60 weeks treatment with Taltz as assessed by the Quick Inventory of Depressive Symptomatology Self Report.

*Postmarketing direct comparative studies*

IXORA-S: In a double-blind study Taltz was superior against ustekinumab on the primary study objective PASI 90 response at week 12 (Table 6). Onset of response was superior on PASI 75 as early as week 2 ( $p < 0.001$ ) and on PASI 90 and PASI 100 by week 4 ( $p < 0.001$ ). Superiority of Taltz versus ustekinumab was also demonstrated in the subgroups stratified by weight.

**Table 6. PASI-response rates from comparative study ixekizumab versus ustekinumab**

	week 12		week 24		week 52	
	Taltz*	Ustekinumab**	Taltz*	Ustekinumab**	Taltz*	Ustekinumab**
Patients (n)	136	166	136	166	136	166
PASI 75, n (%)	120 (88.2 %)	114 (68.7 %)	124 (91.2 %)	136 (81.9%)	120 (88.2%)	126 (75.9 %)
PASI 90, n (%)	99 (72.8%) <sup>§</sup>	70 (42.2 %)	113 (83.1 %)	98 (59.0 %)	104 (76.5%)	98 (59.0 %)
PASI 100, n (%)	49 (36.0 %)	24 (14.5 %)	67 (49.3%)	39 (23.5 %)	71 (52.2%)	59 (35.5 %)

\* Ixekizumab 160 mg given as a loading dose followed by 80 mg at week 2,4,6,8,10 and 12, and 80 mg Q4W thereafter

\*\* Weight based dosing: 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)

<sup>§</sup> $p < 0.001$  versus ustekinumab ( $p$  value only provided for primary endpoint)

IXORA-R: Efficacy and safety of Taltz was also investigated in a 24-week randomized, double-blind, parallel-group study comparing Taltz to guselkumab, with Taltz being superior as early as week 4 in achieving complete skin clearance and on the primary study objective (PASI 100 at week 12) and non-inferior on PASI 100 at week 24 (Table 7).

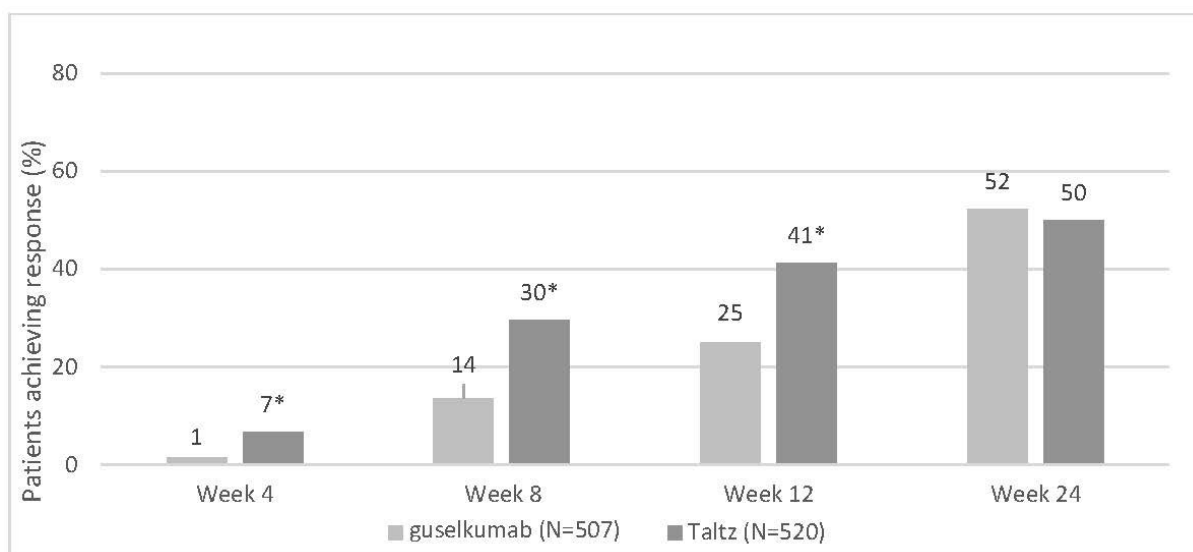
**Table 7. Efficacy Responses from comparative study ixekizumab versus guselkumab, Intent-to-Treat Population<sup>a</sup>**

Endpoint	Time point	Guselkumab (N=507) response, n (%)	Ixekizumab (N=520) response, n (%)	Difference (IXE - GUS), % (CI)	p-value
<b>Primary Objective</b>					
PASI 100	Week 12	126 (24.9)	215 (41.3)	16.5 (10.8, 22.2)	<0.001
<b>Major Secondary Objectives</b>					
PASI 75	Week 2	26 (5.1)	119 (22.9)	17.8 (13.7, 21.8)	<0.001
PASI 90	Week 4	40 (7.9)	109 (21.0)	13.1 (8.9, 17.3)	<0.001
PASI 100	Week 4	7 (1.4)	35 (6.7)	5.4 (3.0, 7.7)	<0.001
PASI 90	Week 8	182 (35.9)	304 (58.5)	22.6 (16.6, 28.5)	<0.001
sPGA (0)	Week 12	128 (25.2)	218 (41.9)	16.7 (11.0, 22.4)	<0.001
PASI 50	Week 1	47 (9.3)	143 (27.5)	18.2 (13.6, 22.8)	<0.001
PASI 100	Week 8	69 (13.6)	154 (29.6)	16.0 (11.1, 20.9)	<0.001
PASI 100	Week 24	265 (52.3)	260 (50.0)	-2.3 (-8.4, 3.8)	0.414

Abbreviations: CI = confidence interval; GUS = guselkumab; IXE = ixekizumab; N = number of patients in the analysis population; n = number of patients in the specified category; PASI = psoriasis area and severity index; sPGA = static physician global assessment.

<sup>a</sup> Endpoints were gated in this order

**Figure 2: PASI 100 at weeks 4, 8, 12 and 24, NRI**



\*p<0.001 vs guselkumab at weeks 4, 8, and 12

NRI = Non-Responder Imputation

#### *Efficacy in genital psoriasis*

A randomised, double-blind, placebo-controlled study (IXORA-Q) was conducted in 149 adult subjects (24% females) with moderate to severe genital psoriasis (sPGA of Genitalia score of  $\geq 3$ ), a minimum body surface area (BSA) involvement of 1% (60.4% had a BSA  $\geq 10\%$ ) and previous failure of or intolerance to at least one topical therapy for genital psoriasis. Patients had at least moderate plaque psoriasis (defined as sPGA score of  $\geq 3$  and being candidates for phototherapy and/or systemic therapy) for at least 6 months.

Subjects randomised to Taltz received an initial dose of 160 mg followed by 80 mg every 2 weeks for 12 weeks. The primary endpoint was the proportion of patients who achieved at least a "0" (clear) or "1" (minimal) response on the sPGA of Genitalia (sPGA of Genitalia 0/1). At week 12, significantly more subjects in the Taltz group than placebo group achieved a sPGA of Genitalia 0/1 and a sPGA 0/1 independent of baseline BSA (baseline BSA 1% - <10% resp.  $\geq 10\%$ : sPGA of Genitalia "0" or "1": Taltz 71%, resp. 75%; placebo: 0%, resp. 13%). A significantly greater proportion of patients treated with Taltz achieved a reduction in the PROs of severity of genital pain, genital itch, impact of genital psoriasis on sexual activity, and Dermatology Quality of Life Index (DLQI).

**Table 8. Efficacy results at week 12 in Adults with genital psoriasis in trial IXORA-Q; NRI <sup>a</sup>**

Endpoints	Taltz	Placebo	Difference from placebo (95% CI)
<b>Number of patients (N) randomised</b>	<b>N=75</b>	<b>N=74</b>	
sPGA of Genitalia "0" or "1"	73%	8%	65% (53%, 77%)
sPGA "0" or "1"	73%	3%	71% (60%, 81%)
DLQI 0,1 <sup>b</sup>	45%	3%	43% (31%, 55%)
<b>N with baseline GPSS Itch NRS Score <math>\geq 3</math></b>	<b>N=62</b>	<b>N=60</b>	
GPSS Genital Itch ( $\geq 3$ point improvement)	60%	8%	51% (37%, 65%)
<b>N with baseline SFQ Item 2 Score <math>\geq 2</math></b>	<b>N=37</b>	<b>N=42</b>	
SFQ-item 2 score, "0" (never limited) or "1" (rarely limited)	78%	21%	57% (39%, 75%)

<sup>a</sup> Abbreviations: NRI = Non-Responder Imputation; sPGA = static Physician Global Assessment; GPSS = Genital Psoriasis Symptom Scale; SFQ = Sexual Frequency Questionnaire; DLQI = Dermatology Quality of Life Index; <sup>b</sup> Total DLQI score of 0,1 indicates skin condition has no

effect at all on patient's life. sPGA of "0" or "1" is equivalent to "clear" or "minimal";  
NRS = Numeric Rating Scale

### Paediatric plaque psoriasis

A randomised, double-blind, multicenter, placebo-controlled trial (IXORA-Peds) enrolled 201 children 6 to less than 18 years of age, with moderate to severe plaque psoriasis (as defined by a sPGA score  $\geq 3$ , involving  $\geq 10\%$  of the body surface area, and a PASI score  $\geq 12$ ) who were candidates for phototherapy or systemic therapy, or were inadequately controlled on topical therapy. Patients were randomised to placebo (n=56), etanercept (n=30) or Taltz (n=115) with dosing stratified by weight:

- <25 kg: 40 mg at week 0 followed by 20 mg Q4W (n=4)
- 25 kg to 50 kg: 80 mg at week 0 followed by 40 mg Q4W (n=50)
- >50 kg: 160 mg at week 0 followed by 80 mg Q4W (n=147)

Patients randomised to etanercept (patients with severe psoriasis) received 0.8 mg/kg, not exceeding 50 mg per dose, every week from week 0 through week 11.

Response to treatment was assessed after 12 weeks and defined by the proportion of patients who achieved the co-primary endpoint of an sPGA score of "0" (clear) or "1" (almost clear) with at least a 2 point improvement from baseline and the proportion of patients that achieved a reduction in PASI score of at least 75% (PASI 75) from baseline.

Other evaluated outcomes at week 12 included the proportion of patients who achieved PASI 90, PASI 100, sPGA of "0" and an improvement of itch severity as measured by a reduction of at least 4 points on an 11-point itch Numeric Rating Scale.

Patients had a median baseline PASI of 17 score ranging from 12-49. Baseline sPGA score was severe or very severe in 49%. Of all patients, 22% had received prior phototherapy and 32% had received prior conventional systemic therapy for the treatment of psoriasis. 25% of patients (n=43) were below 12 years (14% of patients [n=24] were 6-9 years and 11% of patients [n=19] were 10-11 years); 75% (n=128) were 12 years or above.

The clinical response data are presented in Table 9.

**Table 9. Efficacy results in pediatric patients with plaque psoriasis, NRI**

Endpoints	Taltz <sup>a</sup> (N=115) n (%)	Placebo (N=56) n (%)	Difference vs placebo (95% CI)	Etanercept <sup>b</sup> (N=30) n (%)	Difference vs etanercept (95% CI) <sup>b</sup>
sPGA "0" (clear) or "1" (almost clear) <sup>c</sup>					
week 4	55 (48)	4 (7)	40.7 (29.3, 52.0) <sup>f</sup>	0(0)	36.8 (21.5, 52.2)
week 12 <sup>c</sup>	93 (81)	6 (11)	70.2 (59.3, 81.0) <sup>f</sup>	16 (53)	23.0 (0.6, 45.4)
sPGA "0" (clear) <sup>d</sup>	60 (52)	1 (2)	50.4 (40.6, 60.2) <sup>f</sup>	5 (17)	46.5 (26.2, 66.8)
PASI 75					
week 4	62 (54)	5 (9)	45.0 (33.2, 56.8) <sup>f</sup>	3 (10)	34.7 (15.6, 53.8)
week 12 <sup>c</sup>	102 (89)	14 (25)	63.7 (51.0, 76.4) <sup>f</sup>	19 (63)	20.9 (0.1, 41.7)
PASI 90 <sup>d</sup>	90 (78)	3 (5)	72.9 (63.3, 82.5) <sup>f</sup>	12 (40)	36.3 (14.2, 58.5)
PASI 100 <sup>d</sup>	57 (50)	1 (2)	47.8 (38.0, 57.6) <sup>f</sup>	5 (17)	43.9 (23.4, 64.3)
Itch NRS ( $\geq 4$ point improvement) <sup>d, e</sup>	59 (71)	8 (20)	51.1 (35.3, 66.9) <sup>f</sup>	Not evaluated	---

Abbreviations: N = Number of patients in the intent-to-treat population; NRI = Non-Responder Imputation.

<sup>a</sup> At week 0, subjects received 160 mg, 80 mg, or 40 mg of Taltz, followed by 80 mg, 40 mg, or 20 mg every 4 weeks, depending on weight category, for 12 weeks.

<sup>b</sup> Comparisons to etanercept were performed within the sub-population of patients outside of US and Canada with severe Ps (N for Taltz = 38).

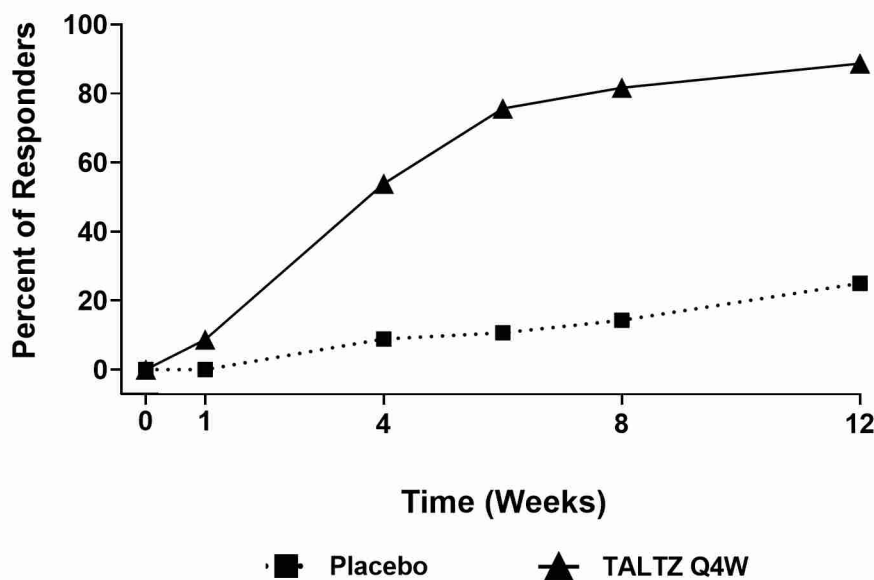
<sup>c</sup> Co-primary endpoints.

<sup>d</sup> Results at week 12.

<sup>e</sup> Itch NRS ( $\geq 4$  improvement) in patients with baseline Itch NRS  $\geq 4$ . The number of ITT patients with baseline Itch NRS Score  $\geq 4$  are as follows: Taltz, n = 83; PBO, n = 40.

<sup>f</sup> p<0.001

**Figure 3. Percent of patients achieving PASI 75 in pediatric psoriasis through week 12**



Patients in the ixekizumab treatment group had clinically meaningful higher CDLQI/DLQI (0,1) responses at week 12 (NRI) compared with placebo. The difference between treatment groups was apparent from as early as week 4.

There were greater improvements at week 12 from baseline compared to placebo in nail psoriasis (as measured by the Nail Psoriasis Severity Index [NAPSI=0: Taltz 18% (6/34), placebo 0% (0/12)]), in scalp psoriasis (as measured by Psoriasis Scalp Severity Index [PSSI=0: Taltz 69% (70/102), placebo 16% (8/50)]) and in palmoplantar psoriasis (as measured by Psoriasis Palmoplantar Severity Index [PPASI 75: Taltz 53% (9/17), placebo 11% (1/9)]).

### Psoriatic arthritis

Taltz was assessed in two randomised, double-blind, placebo-controlled phase III studies in 780 patients with active psoriatic arthritis ( $\geq 3$  swollen and  $\geq 3$  tender joints). Patients had a diagnosis of psoriatic arthritis (Classification Criteria for Psoriatic Arthritis [CASPAR] criteria) for a median of 5.33 years and had current plaque psoriasis skin lesions (94.0%) or a documented history of plaque psoriasis, with 12.1% of patients with moderate to severe plaque psoriasis at baseline. Over 58.9% and 22.3% of the psoriatic arthritis patients had enthesitis and dactylitis at baseline, respectively. Primary endpoint of both studies was American College of Rheumatology (ACR) 20 response at week 24, followed by a long-term extension period from week 24 to week 156 (3 years).

In Psoriatic Arthritis Study 1 (SPIRIT-P1), patients naive to biologic therapy with active psoriatic arthritis were randomised to placebo, adalimumab 40 mg once every 2 weeks (active control reference arm), Taltz 80 mg once every 2 weeks (Q2W), or 80 mg once every 4 weeks (Q4W). Both Taltz regimens included a 160 mg starting dose. 85.3% of patients in this study had received prior treatment with  $\geq 1$  cDMARD. 53% of patients had concomitant use of MTX at a mean weekly dose of 15.8 mg. 67% of patients who had concomitant use of MTX had a dose of 15 mg or greater. Patients with an inadequate response at week 16 received rescue therapy (modification to background therapy). Patients on Taltz Q2W or Q4W remained on their originally assigned dose of Taltz. Patients receiving

adalimumab or placebo were re-randomised 1:1 to Taltz Q2W or Q4W at week 16 or 24 based on responder status. 243 patients completed the extension period of 3 years on Taltz.

Psoriatic Arthritis Study 2 (SPIRIT-P2) enrolled patients who were previously treated with an anti-TNF agent and discontinued the anti-TNF agent for either lack of efficacy or intolerance (anti-TNF-IR patients). Patients were randomised to placebo, Taltz 80 mg once every 2 weeks (Q2W), or 80 mg once every 4 weeks (Q4W). Both Taltz regimens included a 160 mg starting dose. 56% and 35% of patients were inadequate responders to 1 anti-TNF or 2 anti-TNF, respectively. SPIRIT-P2 evaluated 363 patients, of whom 41% had concomitant use of MTX at a mean weekly dose of 16.1 mg. 73.2% of patients who had concomitant use of MTX had a dose of 15 mg or greater. Patients with an inadequate response at week 16 received rescue therapy (modification to background therapy). Patients in Taltz Q2W or Q4W remained on their originally assigned dose of Taltz. Patients receiving placebo were re-randomised 1:1 to Taltz Q2W or Q4W at week 16 or 24 based on responder status. 168 patients completed the extension period of 3 years on Taltz.

### Signs and symptoms

Treatment with Taltz resulted in significant improvement in measures of disease activity compared to placebo at week 24 (see Table 10).

**Table 10. Efficacy results in SPIRIT-P1 and SPIRIT-P2 at week 24**

Endpoints	SPIRIT-P1					SPIRIT-P2						
	PBO (N = 106)	Taltz Q4W (N = 107)	Taltz Q2W (N = 103)	ADA (N = 101)	Difference from placebo in response rate (95% CI)	Taltz Q4W	Taltz Q2W	PBO (N = 118)	Taltz Q4W (N = 122)	Taltz Q2W (N = 123)	Taltz Q4W	Taltz Q2W
<b>ACR 20 response, n (%)</b>												
week 24	32 (30.2)	62 (57.9)	64 (62.1)	58 (57.4)	27.8 (15.0, 40.6) <sup>c</sup>	31.9 (19.1, 44.8) <sup>c</sup>	23 (19.5)	65 (53.3)	59 (48.0)	33.8 (22.4, 45.2) <sup>c</sup>	28.5 (17.1, 39.8) <sup>c</sup>	
<b>ACR 50 response, n (%)</b>												
week 24	16 (15.1)	43 (40.2)	48 (46.6)	39 (38.6)	25.1 (13.6, 36.6) <sup>c</sup>	31.5 (19.7, 43.3) <sup>c</sup>	6 (5.1)	43 (35.2)	41 (33.3)	30.2 (20.8, 39.5) <sup>c</sup>	28.3 (19.0, 37.5) <sup>c</sup>	
<b>ACR 70 response, n (%)</b>												
week 24	6 (5.7)	25 (23.4)	35 (34.0)	26 (25.7)	17.7 (8.6, 26.8) <sup>c</sup>	28.3 (18.2, 38.5) <sup>c</sup>	0	27 (22.1)	15 (12.2)	22.1 (14.8, 29.5) <sup>c</sup>	12.2 (6.4, 18.0) <sup>c</sup>	
<b>Minimal disease activity (MDA) n (%)</b>												
week 24	16 (15.1)	32 (29.9)	42 (40.8)	32 (31.7)	14.8 (3.8, 25.8) <sup>a</sup>	25.7 (14.0, 37.4) <sup>c</sup>	4 (3.4)	34 (27.9)	29 (23.6)	24.5 (15.9, 33.1) <sup>c</sup>	20.2 (12.0, 28.4) <sup>c</sup>	
<b>ACR 50 and PASI 100 in patients with <math>\geq 3\%</math> BSA psoriasis skin involvement at baseline, n (%)</b>												
week 24	1 (1.5)	21 (28.8)	19 (32.2)	9 (13.2)	27.3 (16.5, 38.1) <sup>c</sup>	30.7 (18.4, 43.0) <sup>b</sup>	0 (0.0)	12 (17.6)	10 (14.7)	17.6 (8.6, 26.7) <sup>c</sup>	14.7 (6.3, 23.1) <sup>c</sup>	

Abbreviations: ACR 20/50/70 = American College of Rheumatology 20%/50%/70% response rate; ADA = adalimumab; BSA = body surface area; CI = confidence interval; Q4W = Taltz 80 mg every 4 weeks; Q2W = Taltz 80 mg every 2 weeks; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = non-responder imputation; PASI



100 = psoriasis area and severity index 100% improvement; PBO = placebo.

Note: patients who were rescued at week 16 or discontinued or with missing data were imputed as non-responders for week 24 analyses.

Concomitant cDMARDs included MTX, leflunomide and sulfasalazine.

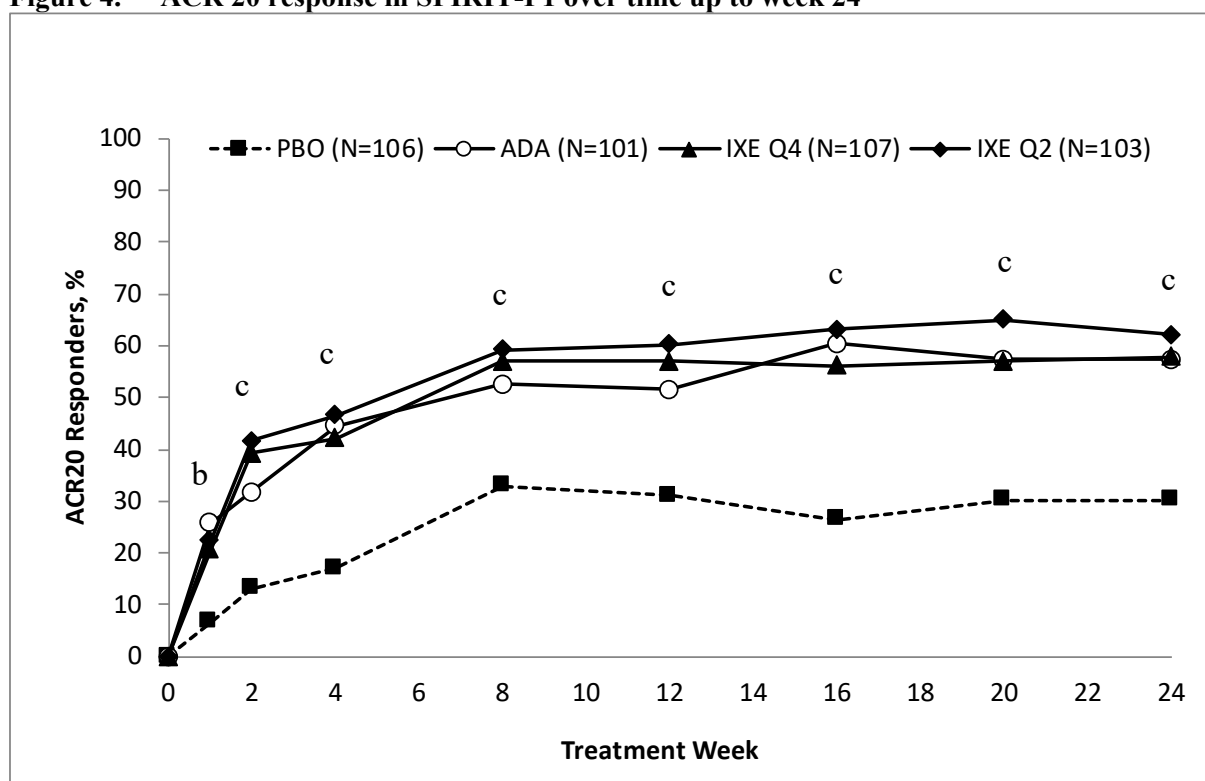
a  $p < 0.05$ ; b  $p < 0.01$ ; c  $p < 0.001$  compared with placebo.

In patients with pre-existing dactylitis or enthesitis, treatment with Taltz Q4W resulted in improvement in dactylitis and enthesitis at week 24 compared to placebo (resolution: 78% vs. 24%;  $p < 0.001$ , and 39% vs. 21%;  $p < 0.01$ , respectively).

In patients with  $\geq 3\%$  BSA, the improvement in skin clearance at week 12 as measured by 75% improvement in Psoriasis Area Severity Index (PASI 75), was 67% (94/141) for those treated with the Q4W dosing regimen, and 9% (12/134) for those treated with placebo ( $p < 0.001$ ). The proportion of patients achieving a PASI 75, PASI 90, and PASI 100 response at week 24 was greater with Taltz Q4W compared to placebo ( $p < 0.001$ ). In patients with concomitant moderate to severe psoriasis and psoriatic arthritis, Taltz Q2W dose regimen showed significantly higher response rate for PASI75, PASI 90 and PASI 100 compared to placebo ( $p < 0.001$ ) and demonstrated clinically meaningful benefit over the Q4W dose regimen.

Treatment responses on Taltz were significantly greater than those on placebo as early as week 1 for ACR 20, week 4 for ACR 50 and week 8 for ACR 70 and persisted through week 24; effects were maintained through 3 years for patients who remained in the study.

Figure 4. ACR 20 response in SPIRIT-P1 over time up to week 24



For both Taltz Q2W and Q4W: b  $p < 0.01$  and c  $p < 0.001$  compared with placebo.

In SPIRIT-P1 and SPIRIT-P2, similar responses for ACR 20/50/70 were seen in patients with psoriatic arthritis regardless of whether they were on concomitant cDMARDs, including MTX treatment, or not.

In SPIRIT-P1 and SPIRIT-P2, improvements were shown in all components of the ACR scores including patient assessment of pain. At week 24 the proportion of patients achieving a modified

Psoriatic Arthritis Response Criteria (PsARC) response was greater in the Taltz-treated patients compared to placebo.

In SPIRIT-P1, efficacy was maintained up to week 52 as assessed by ACR 20/50/70, MDA, enthesitis resolution, dactylitis resolution, and PASI 75/90/100 response rates.

The efficacy and safety of Taltz was demonstrated regardless of age, gender, race, disease duration, baseline body weight, baseline psoriasis involvement, baseline CRP, baseline DAS28-CRP, concomitant corticosteroid use, and previous treatment with a biologic. Taltz was efficacious in biologic-naive, biologic-exposed and biologic-failure patients.

In SPIRIT-P1, 63 patients completed 3 years of Q4W ixekizumab treatment. Among the 107 patients who were randomized to ixekizumab Q4W (NRI analysis in ITT population), 54 patients (50%), 41 patients (38%), 29 patients (27%), and 36 patients (34%) were observed to have ACR20, ACR50, ACR70, and MDA response, respectively, at week 156.

In SPIRIT-P2, 70 patients completed 3 years of Q4W ixekizumab treatment. Among the 122 patients who were randomized to ixekizumab Q4W (NRI analysis in ITT population), 56 patients (46%), 39 patients (32%), 24 patients (20%) and 33 (27%) were observed to have ACR20, ACR50, ACR70, and MDA response, respectively, at week 156.

#### Radiographic response

In SPIRIT-P1, inhibition of progression of structural damage was assessed radiographically and expressed as the change in modified total Sharp Score (mTSS) and its components, the Erosion Score (ES) and the Joint Space Narrowing score (JSN) at weeks 24 and 52, compared to baseline. week 24 data are presented in Table 11.

**Table 11. Change in modified Total Sharp Score in SPIRIT-P1**

					Difference from placebo (95% CI)	
	PBO (N = 106)	Taltz Q4W (N = 107)	Taltz Q2W (N = 103)	ADA (N = 101)	Taltz Q4W	Taltz Q2W
Baseline score, mean (SD)	17.6 (28.62)	19.2 (32.68)	15.2 (28.86)	15.9 (27.37)	NA	NA
Change from baseline at week 24, LSM (SE)	0.51 (0.092)	0.18 (0.090)	0.09 (0.091)	0.13 (0.093)	-0.33 (-0.57,-0.09) <sup>b</sup>	-0.42 (-0.66,-0.19) <sup>c</sup>

Abbreviations: ADA = adalimumab; CI = confidence interval; Q4W = Taltz 80 mg every 4 weeks; Q2W = Taltz 80 mg every 2 weeks; LSM = least squares mean; N = number of patients in the analysis population; PBO = placebo; SE = standard error; SD = standard deviation.

<sup>b</sup> p<0.01; <sup>c</sup> p<0.001 compared with placebo.

Radiographic joint damage progression was inhibited by Taltz (Table 11) at week 24, and the percentage of patients with no radiographic joint damage progression (defined as a change from baseline in mTSS of ≤0.5) from randomisation to week 24 was 94.8% for Taltz Q2W (p<0.001), 89.0% for Taltz Q4W (p=0.026), 95.8% for adalimumab (p<0.001), all compared to 77.4% for placebo. At week 52, the mean change from baseline in mTSS was 0.27 for placebo/Taltz Q4W, 0.54 for Taltz Q4W/Taltz Q4W, and 0.32 for adalimumab/Taltz Q4W. The percentage of patients with no radiographic joint damage progression from randomisation to week 52 was 90.9% for placebo/Taltz Q4W, 85.6% for Taltz Q4W/Taltz Q4W, and 89.4% for adalimumab/Taltz Q4W. Patients had no structural progression from baseline (defined as mTSS≤0.5) in the treatment arms as follows: Placebo/Taltz Q4W 81.5% (N=22/27), Taltz Q4W/Taltz Q4W 73.6% (N=53/72), and adalimumab/Taltz Q4W 88.2% (N=30/34).

#### Physical function and health-related quality of life

In both SPIRIT-P1 and SPIRIT-P2, patients treated with Taltz Q2W (p<0.001) and Q4W (p<0.001) showed significant improvement in physical function compared to patients treated with placebo as

assessed by Health Assessment Questionnaire-Disability Index (HAQ-DI) at week 24, and maintained at week 52 in SPIRIT-P1.

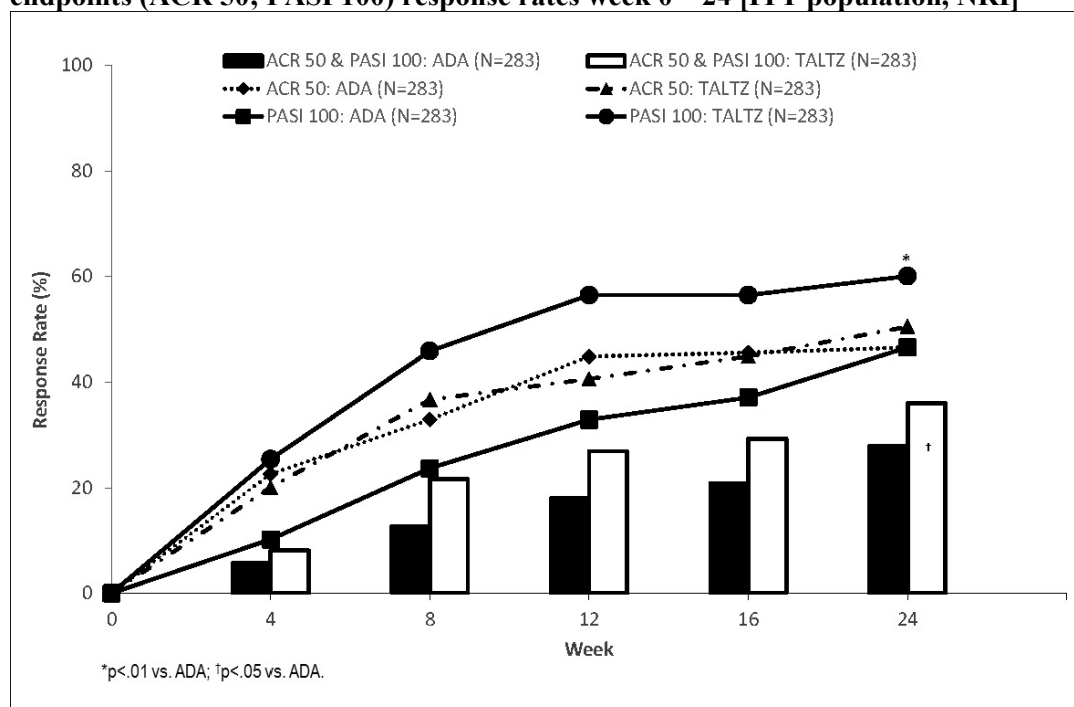
Taltz-treated patients reported improvements in health-related quality of life as measured by the Physical Component Summary of the Short Form-36 Health Survey (SF-36 PCS) score ( $p < 0.001$ ). There were also improvements demonstrated in fatigue as assessed by Fatigue severity NRS scores ( $p < 0.001$ ).

#### Postmarketing phase 4, direct comparative study

Efficacy and safety of Taltz was investigated in a multicenter, randomised, open-label, rater-blinded, parallel-group study (SPIRIT-H2H) compared to adalimumab (ADA) in 566 patients with PsA who were naïve to biologic disease-modifying anti-rheumatic drugs (bDMARD). Patients were stratified at baseline based on concomitant cDMARD use and presence of moderate-to-severe psoriasis ( $\text{PASI} \geq 12$ ,  $\text{BSA} \geq 10$  and  $\text{sPGA} \geq 3$ ).

Taltz was superior to ADA on the primary study objective: simultaneous achievement of ACR 50 and PASI 100 response at week 24 (Taltz 36.0% vs ADA 27.9%;  $p = 0.036$ ; 95% confidence interval [0.5%, 15.8%]). Taltz also showed non-inferiority (pre-specified margin of -12%) to ADA on ACR 50 (ITT analysis: Taltz 50.5% vs ADA 46.6%; 3.9% difference vs. ADA; 95% confidence interval [-4.3%; 12.1%]; PPS analysis Taltz: 52.3%, ADA: 53.1%, difference: -0.8% [CI: -10.3%; 8.7%]) and superiority on PASI 100 at week 24 (60.1% with Taltz vs 46.6% with ADA,  $p = 0.001$ ), which were the major secondary endpoints in the study. At week 52 a higher proportion of patients treated with Taltz versus ADA simultaneously achieved ACR50 and PASI 100 [39% (111/283) versus 26% (74/283)] and PASI 100 [64% (182/283) versus 41% (117/283)]. Taltz and ADA treatment resulted in similar responses for ACR50 [49.8% (141/283) versus 49.8% (141/283)]. Responses to Taltz were consistent when used as monotherapy or with concomitant use of methotrexate.

**Figure 5. Primary endpoint (simultaneous ACR 50 & PASI 100) and major secondary endpoints (ACR 50; PASI 100) response rates week 0 – 24 [ITT population, NRI]\*\***



\*\* Taltz 160 mg week 0, then 80 mg every 2 weeks to week 12 and every 4 weeks thereafter for patients with moderate to severe plaque psoriasis or 160 mg week 0, then 80 mg every 4 week for other patients, ADA 80 mg week 0, then 40 mg every 2 weeks from week 1 for patients with moderate to severe plaque psoriasis or 40 mg week 0, then 40 mg every 2 weeks for other patients. Significance level only provided for endpoint that was pre-defined and multiplicity tested.

### Axial spondyloarthritis

Taltz was assessed in a total of 960 adult patients with axial spondyloarthritis in three randomised placebo-controlled studies (two in radiographic and one in non-radiographic axial spondyloarthritis).

### Radiographic axial spondyloarthritis

Taltz was assessed in a total of 657 patients in two randomised, double-blind, placebo-controlled studies (COAST-V and COAST-W) in adult patients who had active disease as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)  $\geq 4$  and total back pain  $\geq 4$  on a numeric rating scale despite non-steroidal anti-inflammatory drug (NSAID) therapy. Across both studies at baseline, patients had symptoms for a mean of 17 years (median of 16 years). At baseline, approximately 32% of the patients were on a concomitant cDMARD.

COAST-V evaluated 341 biologic-naive patients treated with either Taltz 80 mg or 160 mg at week 0 followed by 80 mg every 2 weeks (Q2W) or 4 weeks (Q4W), adalimumab 40 mg every 2 weeks, or with placebo. Patients receiving placebo were re-randomised at week 16 to receive Taltz (160 mg starting dose, followed by 80 mg Q2W or Q4W). Patients receiving adalimumab were re-randomised at week 16 to receive Taltz (80 mg Q2W or Q4W).

COAST-W evaluated 316 patients who had prior experience with 1 or 2 TNF-inhibitors (90% were inadequate responders and 10% were intolerant to TNF inhibitors). All patients were treated with Taltz 80 or 160 mg at week 0 followed by 80 mg Q2W or Q4W, or with placebo. Patients receiving placebo were re-randomised at week 16 to receive Taltz (160 mg initial dose, followed by 80 mg Q2W or Q4W).

The primary endpoint in both studies was the percentage of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response at week 16.

### Clinical response

In both studies, patients treated with Taltz 80 mg Q2W or 80 mg Q4W demonstrated greater improvements in ASAS40 and ASAS20 responses compared to placebo at week 16 (Table 12). Responses were similar in patients regardless of concomitant therapies. In COAST-W, responses were seen regardless of the number of prior TNF inhibitors.

**Table 12. Efficacy results in COAST-V and COAST-W at week 16**

	COAST-V, biologic-naïve				COAST-W, TNF-inhibitor experienced		
	Taltz 80 mg Q4W <sup>a</sup> (N=81)	Placebo (N=87)	Difference from placebo <sup>g</sup>	Adalimumab 40 mg Q2W (N=90)	Taltz 80 mg Q4W <sup>c</sup> (N=114)	Placebo (N=104)	Difference from placebo <sup>g</sup>
ASAS20 response <sup>b</sup> , n (%), NRI	52 (64.2%)	35 (40.2%)	24.0 (9.3, 38.6)**	53 (58.9%)	55 (48.2%)	31 (29.8%)	18.4 (5.7, 31.1)**
ASAS40 response <sup>b,c</sup> , n (%), NRI	39 (48.1%)	16 (18.4%)	29.8 (16.2, 43.3)***	32 (35.6%)	29 (25.4%)	13 (12.5%)	12.9 (2.7, 23.2)*
ASDAS							
Change from baseline	-1.4	-0.5	-1.0 (-1.3, -0.7)	-1.3***	-1.2	-0.1	-1.1 (-1.3, -0.8)
Baseline	3.7	3.9	***	3.7	4.2	4.1	***
BASDAI Score							
Change from baseline	-2.9	-1.4	-1.5 (-2.1, -0.9)	-2.5***	-2.2	-0.9	-1.2 (-1.8, -0.7)
Baseline	6.8 <sup>i</sup>	6.8 <sup>i</sup>	***	6.7 <sup>i</sup>	7.5	7.3	***
MRI Spine SPARCC <sup>d</sup>							
Change from baseline	-11.0	-1.5	-9.5 (-12.6, -6.4)***	-11.6***	-3.0	3.3	-6.3 (-10.0, -2.5)**
Baseline	14.5	15.8	***	20.0	8.3	6.4	***
BASDAI50 <sup>e</sup> n (%), NRI	34 (42.0%)	15 (17.2%)	24.7 (11.4, 38.1)***	29 (32.2%)*	25 (21.9%) <sup>i</sup>	10 (9.6%) <sup>i</sup>	12.3 (2.8, 21.8)*
ASDAS <2.1, n (%) (low disease activity), NRI	35 (43.2%) <sup>h</sup>	11 (12.6%) <sup>h</sup>	30.6 (17.7, 43.4)***	34 (37.8%)*** <sup>h</sup>	20 (17.5%)	5 (4.8%)	12.7 (4.6, 20.8)**
ASDAS <1.3, n (%) (inactive disease), NRI	13 (16.0%)	2 (2.3%)	13.8 (5.2, 22.3)**	14 (15.6%)**	4 (3.5%) <sup>i</sup>	1 (1.0%) <sup>i</sup>	2.5 (-1.3, 6.4)
ASAS HI <sup>f</sup>							
Change from baseline	-2.4	-1.3	-1.1 (-2.0, -0.3)	-2.3*	-1.9	-0.9	-1.0 (-1.9, -0.1)
Baseline	7.5	8.1	*	8.2	10.0	9.0	*
SF-36 PCS							
Change from baseline	7.7	3.6	4.1 (1.9, 6.2)	6.9**	6.6	1.4	5.2 (3.0, 7.4)
Baseline	34.0	32.0	***	33.5	27.5	30.6	***

Abbreviations: N = number of patients in the intent-to-treat population; NRI = Non-responder Imputation; patients with missing data were counted as non-responders.

ASAS HI = Assessment of SpondyloArthritis International Society Health Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CFB = least square mean change from baseline at week 16; MRI Spine SPARCC = Spondyloarthritis Research Consortium of Canada Magnetic Resonance Imaging Scoring of the Spine (23 discovertebral unit scale)

<sup>a</sup> At week 0, patients received 80 mg or 160 mg of Taltz.

<sup>b</sup> An ASAS20 response is defined as a  $\geq 20\%$  improvement and an absolute improvement from baseline of  $\geq 1$  unit (range 0 to 10) in  $\geq 3$  of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation), and no worsening of  $\geq 20\%$  and  $\geq 1$  unit (range 0 to 10) in the remaining domain. An ASAS40 response is defined as a  $\geq 40\%$  improvement and an absolute improvement from baseline of  $\geq 2$  units in  $\geq 3$  of 4 domains without any worsening in the remaining domain.

<sup>c</sup> Primary endpoint.

<sup>d</sup> The numbers of ITT patients with MRI data at baseline are as follows: COAST-V: Taltz, n = 81; PBO, n = 82; ADA, n=85. COAST-W: Taltz, n = 58; PBO, n = 51.

<sup>e</sup> BASDAI50 response defined as an improvement of  $\geq 50\%$  of the BASDAI score from baseline.

<sup>f</sup> ASAS HI: Assessment of SpondyloArthritis International Society Health Index (ASAS HI) across all domains.

<sup>g</sup> The reported values are difference in % (95% CI) for categorical variables, and difference in LSM (95% CI) for continuous variables.

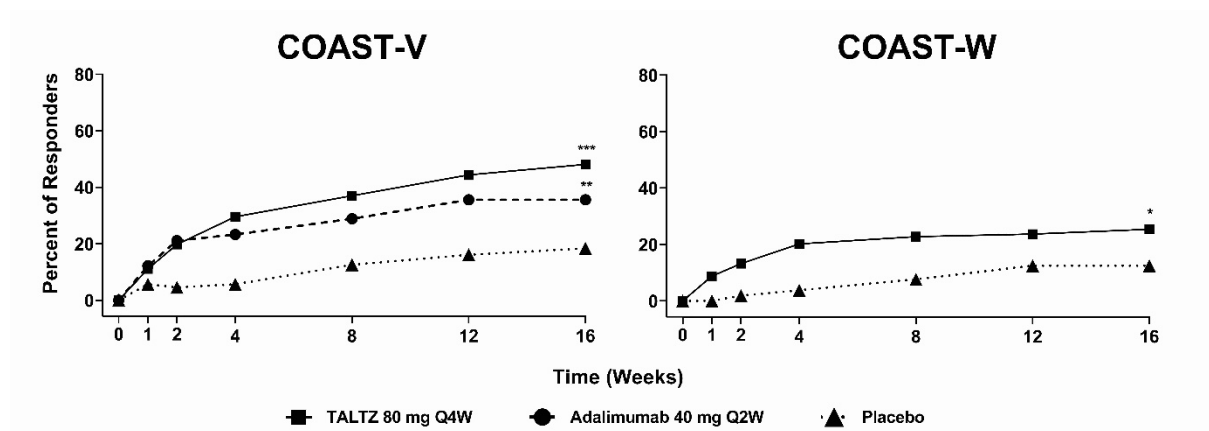
<sup>h</sup> post hoc analysis, not multiplicity corrected.

<sup>i</sup> prespecified, but not multiplicity gated.

\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$  compared with placebo.

There were improvements in the main components of the ASAS40 response criteria (spinal pain, BASFI, patient global assessment, stiffness) and other measures of disease activity, including CRP, at week 16.

**Figure 6. Percent of patients achieving ASAS40 responses in COAST-V and COAST-W through week 16, NRI<sup>a</sup>**



<sup>a</sup> Patients with missing data were counted as non-responders.

\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$  compared with placebo.

Similar response in ASAS40 was seen in patients regardless of baseline CRP levels, baseline ASDAS scores and MRI spine SPARCC scores. The ASAS40 response was demonstrated regardless of age, gender, race, disease duration, baseline body weight, baseline BASDAI score and prior biologic treatment.

In COAST-V and COAST-W efficacy was maintained up to week 52 as assessed by the endpoints presented in Table 12, including ASAS20, ASAS40, ASDAS, BASDAI, and ASAS HI response rates.

#### *Health-related outcomes*

Spinal pain showed improvements versus placebo as early as week 1, maintained through week 16 [Taltz vs placebo: COAST-V -3.2 vs -1.7; COAST-W -2.4 vs -1.0]; fatigue and spinal mobility showed improvements versus placebo at week 16. Improvements in spinal pain, fatigue and spinal mobility were maintained through week 52.

#### *Non-radiographic axial spondyloarthritis*

Taltz was assessed in a randomised, double-blind study with a 52-week placebo-controlled period (COAST-X) in 303 adult patients with active axial spondyloarthritis for at least 3 months. Patients must have had objective signs of inflammation indicated by elevated C-reactive protein (CRP) and/or sacroiliitis on magnetic resonance imaging (MRI), and no definitive radiographic evidence of structural damage on sacroiliac joints. Patients had active disease as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)  $\geq 4$ , and spinal pain  $\geq 4$  on a 0 to 10 Numerical Rating Scale (NRS), despite non-steroidal anti-inflammatory drug (NSAID) therapy. Patients were treated with either Taltz 80 mg or 160 mg at week 0, followed by 80 mg every 2 weeks (Q2W) or 80 mg every 4 weeks (Q4W) or with placebo. Dose adjustment and/or initiation of concomitant medications (NSAIDs, cDMARDs, corticosteroids, analgesics) were permitted starting at week 16.

At baseline, patients had symptoms of non-radiographic axSpA for an average of 11 years. Approximately 39% of the patients were on a concomitant cDMARD.

The primary endpoint was the percentage of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response at week 16.

#### *Clinical response*

Higher proportions of patients treated with Taltz 80 mg Q4W achieved ASAS40 response compared to placebo at week 16 (Table 13). Responses were similar regardless of concomitant therapies.

**Table 13. Efficacy results at week 16 in COAST-X, NRI <sup>a,b</sup>**

	<b>Taltz 80 mg Q4W<sup>c</sup> (N=96)</b>	<b>Placebo (N=105)</b>	<b>Difference from placebo <sup>h</sup></b>
ASAS20 response <sup>d</sup> , n (%), NRI	52 (54.2%)	41 (39.0%)	15.1 (1.5, 28.8)*
ASAS40 response <sup>d,e</sup> , n (%), NRI	34 (35.4%)	20 (19.0%)	16.4 (4.2, 28.5)**
<b>ASDAS</b>			
Change from baseline	-1.1	-0.6	-0.5 (-0.8, -0.3) ***
Baseline	3.8	3.8	
<b>BASDAI Score</b>			
Change from baseline	-2.2	-1.5	-0.7 (-1.3, -0.1) *
Baseline	7.0	7.2	
<b>MRI SIJ SPARCC<sup>f</sup></b>			
Change from baseline	-3.4	-0.3	-3.1 (-4.6, -1.6) ***
Baseline	5.1	6.3	
ASDAS <2.1, n (%) (low disease activity), NRI <sup>g</sup>	26 (27.7%)	13 (12.4%)	15.3 (4.3, 26.3) **
<b>SF-36 PCS</b>			
Change from baseline	8.1	5.2	2.9 (0.6, 5.1) *
Baseline	33.5	32.6	

<sup>a</sup> Abbreviations: N = number of patients in the intent-to-treat population; NRI = Non-responder Imputation. ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; Change from baseline = least square mean change from baseline at week 16; MRI SIJ SPARCC = Spondyloarthritis Research Consortium of Canada Magnetic Resonance Imaging Scoring of the sacroiliac joint.

<sup>b</sup> Patients with missing data were counted as non-responders.

<sup>c</sup> At week 0, patients received 80 mg or 160 mg of Taltz.

<sup>d</sup> An ASAS20 response is defined as a  $\geq 20\%$  improvement and an absolute improvement from baseline of  $\geq 1$  units (range 0 to 10) in  $\geq 3$  of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation), and no worsening of  $\geq 20\%$  and  $\geq 1$  unit (range 0 to 10) in the remaining domain. An ASAS40 response is defined as a  $\geq 40\%$  improvement and an absolute improvement from baseline of  $\geq 2$  units in  $\geq 3$  of 4 domains without any worsening in the remaining domain.

<sup>e</sup> Primary endpoint at week 16.

<sup>f</sup> The numbers of ITT patients with MRI data at baseline and week 16 are as follows: Taltz, n = 85; PBO, n = 90.

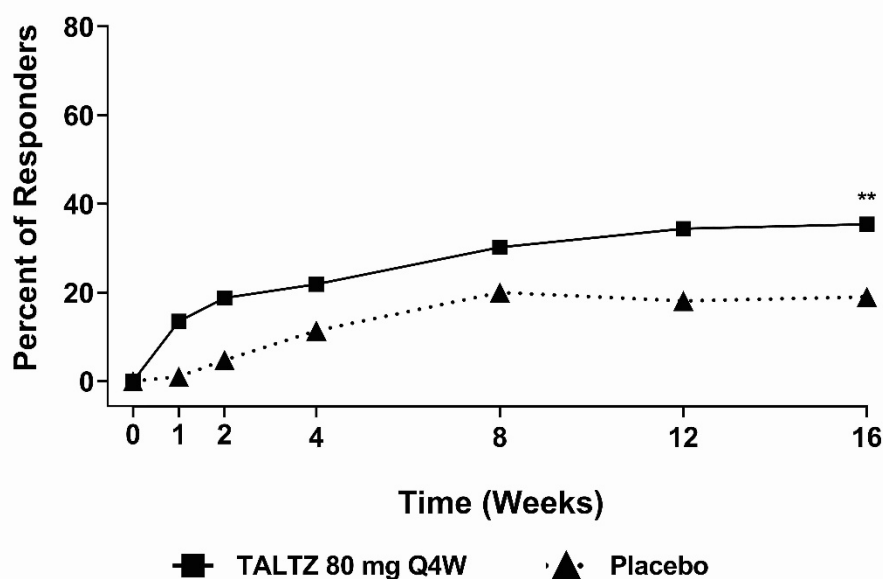
<sup>g</sup> Patients with missing data were counted as non-responders. Percentages are based on the number of patients in the ITT population with baseline ASDAS  $\geq 2.1$ .

<sup>h</sup> The reported values are difference in % (95% CI) for categorical variables, and difference in LSM (95% CI) for continuous variables.

\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$  compared with placebo.

The improvement in the main components of the ASAS40 response criteria (spinal pain, BASFI, patient global assessment, stiffness) and other measures of disease activity demonstrated significant clinical improvement at week 16.

Figure 7. Percent of patients achieving ASAS40 response through week 16 in COAST-X, NRI<sup>a</sup>



<sup>a</sup> Patients with missing data were counted as non-responders.

\*\*  $p < 0.01$  compared with placebo.

Efficacy was maintained up to week 52 as assessed by the endpoints presented in Table 13.

#### Health-related outcomes

Spinal pain showed improvements versus placebo as early as week 1 and was maintained through week 16 [Taltz vs placebo: COAST-X: -2.4 vs -1.5]. In addition, more patients on Taltz compared with placebo achieved good health status (ASAS HI  $\leq 5$ ) at week 16 and week 52.

#### Long-term outcomes Axial Spondyloarthritis

Patients who completed one of the three pivotal studies COAST-V/W/X (52 weeks) were offered participation in a long-term extension and randomised withdrawal study (COAST-Y, with 350 and 423 patients enrolled on Taltz Q4W and Q2W, respectively). Among those who achieved remission 157/773 (20.3%) (Ankylosing Spondylitis Disease Activity Score [ASDAS]  $< 1.3$  at least once, and no ASDAS score  $\geq 2.1$ , at weeks 16 and 20), 155 patients exposed to Taltz up to 76 weeks were randomised at week 24 of the COAST-Y study (Placebo, N=53; Taltz Q4W, N=48; and Taltz Q2W, N=54); of these, 148 (95.5%) completed the week 64 visit (Placebo, N=50; Taltz Q4W, N=47; Taltz Q2W, N=51). The primary endpoint was the proportion of patients in the randomised withdrawal population who did not experience a flare during weeks 24-64 (combined Taltz Q2W and Taltz Q4W groups versus placebo). A significantly larger proportion of patients (NRI) in the combined Taltz groups (83.3% (85/102),  $p < 0.001$ ) and Taltz Q4W (83.3% (40/48),  $p = 0.003$ ) had no flare during weeks 24-64 compared with those who withdrew from Taltz to placebo (54.7% (29/53)). Taltz (in both combined Taltz groups and Taltz Q4W group) significantly delayed the time to flare (Log-Rank Test  $p < 0.001$  and  $p < 0.01$ , respectively) compared to Placebo.

In patients who received Taltz Q4W continuously (N=157), the ASAS40, ASDAS  $< 2.1$  and BASDAI50 responses were maintained to week 116.

#### Immunisations

In a study in healthy subjects, no safety concerns were identified of two inactivated vaccines (tetanus and pneumococcal), received after two doses of ixekizumab (160 mg followed by a second dose of 80 mg two weeks later). However, the data concerning immunisation were insufficient to conclude on an adequate immune response to these vaccines following administration of Taltz.



## Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Taltz in one or more subsets of the paediatric population in the treatment of plaque psoriasis and psoriatic arthritis/axial spondyloarthritis (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

### Absorption

Following a single subcutaneous dose of ixekizumab in patients with psoriasis, mean peak concentrations were achieved within 4 to 7 days, across a dose range of 5 to 160 mg. The mean (SD) maximum plasma concentration ( $C_{max}$ ) of ixekizumab, after the 160 mg starting dose, was 19.9 (8.15)  $\mu\text{g/ml}$ .

After the 160 mg starting dose, steady state was achieved by week 8 with the 80 mg Q2W dosing regimen. Mean (SD)  $C_{max,ss}$ , and  $C_{trough,ss}$  estimates are 21.5 (9.16)  $\mu\text{g/ml}$ , and 5.23 (3.19)  $\mu\text{g/ml}$ .

After switching from the 80 mg Q2W dosing regimen to the 80 mg Q4W dosing regimen at week 12, steady state would be achieved after approximately 10 weeks. Mean (SD)  $C_{max,ss}$ , and  $C_{trough,ss}$  estimates are 14.6 (6.04)  $\mu\text{g/ml}$ , and 1.87 (1.30)  $\mu\text{g/ml}$ .

The average bioavailability of ixekizumab after subcutaneous administration was 54 % to 90 % across analyses.

### Distribution

From population pharmacokinetic analyses, the mean total volume of distribution at steady state was 7.11 L.

### Biotransformation

Ixekizumab is a monoclonal antibody and is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous immunoglobulins.

### Elimination

In the population PK analysis, mean serum clearance was 0.0161 L/hr. Clearance is independent of dose. The mean elimination half-life, as estimated from population pharmacokinetic analysis, is 13 days in patients with plaque psoriasis.

### Linearity/non-linearity

Exposure (AUC) increased proportionally over a dose range of 5 to 160 mg given as a subcutaneous injection.

### Pharmacokinetic properties across indications

The pharmacokinetic properties of Taltz were similar across the plaque psoriasis, psoriatic arthritis, radiographic axial spondyloarthritis and non-radiographic axial spondyloarthritis indications.

### Elderly

Of the 4,204 plaque psoriasis patients exposed to Taltz in clinical studies, a total of 301 were 65 years of age or older and 36 patients were 75 years of age or older. Of the 1,118 psoriatic arthritis patients

exposed to Taltz in clinical studies, a total of 122 patients were 65 years of age or older and 6 patients were 75 years of age or older.

Based on population pharmacokinetic analysis with a limited number of elderly patients (n = 94 for age  $\geq$  65 years and n = 12 for age  $\geq$  75 years), clearance in elderly patients and patients less than 65 years of age was similar.

### Renal or hepatic impairment

Specific clinical pharmacology studies to evaluate the effects of renal impairment and hepatic impairment on the PK of ixekizumab have not been conducted. Renal elimination of intact ixekizumab, an IgG MAb, is expected to be low and of minor importance; similarly, IgG MAbs are mainly eliminated via intracellular catabolism and hepatic impairment is not expected to influence clearance of ixekizumab.

### Paediatric population

Paediatric psoriasis patients (age 6 to less than 18 years) were administered ixekizumab at the recommended paediatric dosing regimen for 12 weeks. Patients weighing  $>50$  kg and 25 to 50 kg had a mean  $\pm$ SD steady-state trough concentration of  $3.8 \pm 2.2$   $\mu\text{g/ml}$  and  $3.9 \pm 2.4$   $\mu\text{g/ml}$ , respectively, at week 12.

## **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on repeat-dose toxicity studies, safety pharmacology evaluations, and reproductive and developmental toxicity studies.

Ixekizumab administration to cynomolgus monkeys for 39 weeks at subcutaneous doses up to 50 mg/kg weekly produced no organ toxicity or undesirable effects on immune function (e.g. T-cell dependent antibody response and NK cell activity). A weekly subcutaneous dose of 50 mg/kg to monkeys is approximately 19 times the 160 mg starting dose of Taltz and in monkeys results in exposure (AUC) that is at least 61-fold higher than the predicted mean steady-state exposure in humans administered the recommended dose regimen.

Non-clinical studies have not been conducted to evaluate the carcinogenic or mutagenic potential of ixekizumab.

No effects on reproductive organs, menstrual cycles or sperm were observed in sexually mature cynomolgus monkeys that received ixekizumab for 13 weeks at a weekly subcutaneous dose of 50 mg/kg.

In developmental toxicity studies, ixekizumab was shown to cross the placenta and was present in the blood of offspring for up to 6 months of age. A higher incidence of postnatal mortality occurred in the offspring of monkeys given ixekizumab compared to concurrent controls. This was related primarily to early delivery or maternal neglect of offspring, common findings in nonhuman primate studies, and considered clinically irrelevant.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sucrose

Polysorbate 80

Water for injections

Sodium hydroxide may be used to adjust pH

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

2 years.

## **6.4 Special precautions for storage**

Store in a refrigerator (2 °C to 8 °C).

Do not freeze.

Store in the original package in order to protect from light.

Taltz may be stored unrefrigerated for up to 5 days at a temperature not above 30 °C.

## **6.5 Nature and contents of container**

1 ml solution in a type I clear glass syringe.

The syringe is encased in a disposable, single-dose pen.

Packs of 1, 2, or 3 pre-filled pens.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal and other handling**

The instructions for using the pen, included with the package leaflet, must be followed carefully.

The pre-filled pen is for single use only.

Taltz should not be used if particles appear or if the solution is cloudy and/or distinctly brown.

Taltz that has been frozen must not be used.

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

## **7. MARKETING AUTHORISATION HOLDER**

Eli Lilly and Company (Ireland) Limited, Dunderrow, Kinsale, Co. Cork, Ireland.

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1085/001

EU/1/15/1085/002

EU/1/15/1085/003

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 25 April 2016

Date of latest renewal: 17 December 2020

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

### Name and address of the manufacturer of the biological active substance

Eli Lilly Kinsale Limited  
Dunderrow  
Kinsale  
Co. Cork  
Ireland

### Name and address of the manufacturer responsible for batch release

Eli Lilly Italia S.p.A.  
Via Gramsci 731/733  
50019 Sesto Fiorentino (FI)  
Italy.

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

### • **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

### • **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**



**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON – PRE-FILLED SYRINGE**

**1. NAME OF THE MEDICINAL PRODUCT**

Taltz 80 mg solution for injection in pre-filled syringe  
ixekizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pre-filled syringe contains 80 mg of ixekizumab in 1 ml solution.

**3. LIST OF EXCIPIENTS**

Excipients: sucrose; polysorbate 80; water for injections. In addition, sodium hydroxide may have been added for pH adjustment. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection.

1 pre-filled syringe of 1 ml solution  
2 pre-filled syringes of 1 ml solution  
3 pre-filled syringes of 1 ml solution

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For single use only.  
Read the package leaflet before use.  
Subcutaneous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

If seal is broken, do not use.  
Do not shake.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.  
Do not freeze.  
Store in the original package in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Eli Lilly and Company (Ireland) Limited  
Dunderrow,  
Kinsale,  
Co. Cork  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1085/004 1 pre-filled syringe  
EU/1/15/1085/005 2 pre-filled syringes  
EU/1/15/1085/006 3 pre-filled syringes

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Taltz

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS  
PRE-FILLED SYRINGE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Taltz 80 mg injection  
ixekizumab  
Subcutaneous use

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

1 ml

**6. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON - PRE-FILLED PEN**

**1. NAME OF THE MEDICINAL PRODUCT**

Taltz 80 mg solution for injection in pre-filled pen  
ixekizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pre-filled pen contains 80 mg of ixekizumab in 1 ml solution.

**3. LIST OF EXCIPIENTS**

Excipients: sucrose; polysorbate 80; water for injections. In addition, sodium hydroxide may have been added for pH adjustment. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection.

1 pre-filled pen of 1 ml solution  
2 pre-filled pens of 1 ml solution  
3 pre-filled pens of 1 ml solution

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For single use only.  
Read the package leaflet before use.  
Subcutaneous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

If seal is broken, do not use.  
Do not shake.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.  
Do not freeze.  
Store in the original package in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Eli Lilly and Company (Ireland) Limited  
Dunderrow,  
Kinsale,  
Co. Cork  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1085/001 1 pre-filled pen  
EU/1/15/1085/002 2 pre-filled pens  
EU/1/15/1085/003 3 pre-filled pens

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Taltz

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS  
PRE-FILLED PEN LABEL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Taltz 80 mg solution for injection  
ixekizumab  
Subcutaneous use

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

1 ml

**6. OTHER**

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the patient

### Taltz 80 mg solution for injection in pre-filled syringe ixekizumab

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### What is in this leaflet

1. What Taltz is and what it is used for
2. What you need to know before you use Taltz
3. How to use Taltz
4. Possible side effects
5. How to store Taltz
6. Contents of the pack and other information

#### 1. What Taltz is and what it is used for

Taltz contains the active substance ixekizumab.

Taltz is intended for the treatment of the inflammatory diseases described below:

- Plaque psoriasis in adults
- Plaque psoriasis in children from the age of 6 and with a body weight of at least 25 kg and in adolescents
- Psoriatic arthritis in adults
- Radiographic Axial Spondyloarthritis in adults
- Non-radiographic Axial Spondyloarthritis in adults

Ixekizumab belongs to a group of medicines called interleukin (IL) inhibitors. This medicine works by blocking the activity of a protein called IL-17A, which promotes psoriasis and inflammatory disease of the joints and the spine.

#### Plaque psoriasis

Taltz is used to treat a skin condition called “plaque psoriasis” in adults and in children from the age of 6 years and with a body weight of at least 25 kg and in adolescents with moderate to severe disease. Taltz reduces the signs and symptoms of the disease.

Using Taltz will benefit you by improvements of skin clearance and reducing your symptoms such as scaling, itching and pain.

#### Psoriatic arthritis

Taltz is used to treat a condition called “psoriatic arthritis” in adults, an inflammatory disease of the joints, often accompanied by psoriasis. If you have psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines or in case of intolerance, you will be given Taltz to reduce the signs and symptoms of the disease. Taltz can be used alone or with another medicine named methotrexate.

Using Taltz will benefit you by reducing the signs and symptoms of the disease, improving physical function (ability to do normal daily activities), and slowing down the damage to the joints.



### Axial spondyloarthritis

Taltz is used to treat adults with an inflammatory disease primarily affecting the spine which causes inflammation of the spinal joints, called axial spondyloarthritis. If the condition is visible using X-rays, it is referred to as “radiographic axial spondyloarthritis”; if it occurs in patients with no visible signs on X-rays, it is referred to as “non-radiographic axial spondyloarthritis”. If you have axial spondyloarthritis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Taltz to reduce the signs and symptoms of the disease, reduce inflammation and improve your physical function.

## **2. What you need to know before you use Taltz**

### **Do not use Taltz**

- if you are allergic to ixekizumab or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice before using Taltz.
- if you have an infection which your doctor thinks is important (for example, active tuberculosis).

### **Warnings and precautions**

Talk to your doctor before using Taltz:

- if you currently have an infection or if you have long-term or repeated infections.
- if you have an inflammatory disease affecting the gut named Crohn’s disease.
- if you have an inflammation of the large intestine named ulcerative colitis.
- if you are receiving any other treatment for psoriasis (such as immunosuppressant or phototherapy with ultraviolet light) or for psoriatic arthritis.

### Inflammatory bowel disease (Crohn's disease or ulcerative colitis)

Stop using Taltz and tell your doctor or seek medical help immediately if you notice abdominal cramps and pain, diarrhoea, weight loss or blood in the stool (any signs of bowel problems).

If you are not sure if any of the above applies to you, talk to your doctor or nurse before using Taltz.

### **Look out for infections and allergic reactions**

Taltz can potentially cause serious side effects, including infections and allergic reactions. You must look out for signs of these conditions while you are using Taltz.

Stop using Taltz and tell your doctor or seek medical help immediately if you notice any signs of a serious infection or an allergic reaction. Such signs are listed under “Serious side effects” in section 4.

### **Children and adolescents**

Do not use this medicine for the treatment of plaque psoriasis in children under 6 years of age because it has not been studied in this age group.

Do not use this medicine for the treatment of psoriatic arthritis in children and adolescents under 18 years of age because it has not been studied in this age group.

### **Other medicines and Taltz**

Tell your doctor, pharmacist or nurse

- if you are using, have recently used or might use any other medicines.
- if you have recently had or are due to have a vaccination. You should not be given certain types of vaccines while using Taltz.

### **Pregnancy and breast-feeding**

If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before using this medicine.

It is preferable to avoid the use of Taltz in pregnancy. The effects of this medicine in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Taltz and for at least 10 weeks after the last Taltz dose.

If you are breast-feeding or are planning to breast-feed, talk to your doctor before using this medicine. You and your doctor should decide if you can breast-feed or use Taltz. You should not do both.

### **Driving and using machines**

Taltz is unlikely to influence your ability to drive and use machines.

### **Taltz contains sodium**

This medicine contains less than 1 mmol sodium (23 mg) per 80 mg dose, that is to say essentially “sodium-free”.

## **3. How to use Taltz**

Always use this medicine exactly as your doctor or nurse has told you. Check with your doctor, nurse or pharmacist if you are not sure.

Taltz is given by injection under your skin (subcutaneous injection). You and your doctor or nurse should decide if you should inject Taltz yourself.

For use in children with a body weight of 25-50 kg ixekizumab doses of 40 mg must be prepared and administered by a qualified healthcare professional.

It is important not to try to inject yourself until you have been trained by your doctor or nurse. A caregiver may also give you your Taltz injection after proper training.

Use a reminder method such as notes in a calendar or diary to help you remember your next dose so that you avoid missing or repeating doses.

Taltz is for long-term treatment. Your doctor or nurse will regularly monitor your condition to check that the treatment is having the desired effect.

Each syringe contains one dose of Taltz (80 mg). Each syringe delivers only one dose. The syringe must not be shaken.

Read the “Instructions for use” for the syringe carefully before using Taltz.

### **How much Taltz is given and for how long**

Your doctor will explain to you how much Taltz you need and for how long.

#### Plaque psoriasis in adults

- The first dose is 160 mg (2 syringes with 80 mg each) by subcutaneous injection. This may be given by your doctor or nurse.
- After the first dose, you will use an 80 mg dose (1 syringe) at weeks 2, 4, 6, 8, 10, and 12. From week 12, you will use an 80 mg dose (1 syringe) every 4 weeks.

Plaque psoriasis in children (age 6 years and above and at least 25 kg body weight) and in adolescents. The recommended dose given by subcutaneous injection in children is based on the following weight categories:

<b>Children's body weight</b>	<b>Recommended starting dose (week 0)</b>	<b>Recommended dose every 4 weeks (Q4W) thereafter</b>
Greater than 50 kg	160 mg (2 syringes)	80 mg (1 syringe)
25 to 50 kg	80 mg (1 syringe)	40 mg (dose preparation required)

*40 mg preparation of ixekizumab in children*

Ixekizumab doses of 40 mg must be prepared and administered by a qualified healthcare professional. Taltz is not recommended for use in children with a body weight below 25 kg.

Psoriatic arthritis

For psoriatic arthritis patients who also have moderate to severe plaque psoriasis:

- The first dose is 160 mg (2 syringes with 80 mg each) by subcutaneous injection. This may be given by your doctor or nurse.
- After the first dose, you will use an 80 mg dose (1 syringe) at weeks 2, 4, 6, 8, 10, and 12. From week 12, you will use an 80 mg dose (1 syringe) every 4 weeks.

For other psoriatic arthritis patients

- The first dose is 160 mg (2 syringes with 80 mg each) by subcutaneous injection. This may be given by your doctor or nurse.
- After the first dose you will use an 80 mg dose (1 syringe) every 4 weeks.

Axial spondyloarthritis

The recommended dose is 160 mg (2 syringes with 80 mg each) by subcutaneous injection at week 0, followed by 80 mg (1 syringe) every 4 weeks.

**If you use more Taltz than you should**

If you have received more Taltz than you should or the dose has been given sooner than prescribed, inform your doctor.

**If you forget to use Taltz**

If you have forgotten to inject a dose of Taltz, talk to your doctor.

**If you stop using Taltz**

You should not stop using Taltz without speaking to your doctor first. If you stop treatment, symptoms of psoriasis or psoriatic arthritis may come back.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

**4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Serious side effects**

Stop using Taltz and tell your doctor or seek medical help immediately if you get any of the following side effects. Your doctor will decide if and when you may restart the treatment:

**Possible serious infection** (may affect up to 1 in 100 people) - the signs may include:

- fever, flu-like symptoms, night sweats
- feeling tired or short of breath, cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters

**Serious allergic reaction** (may affect up to 1 in 1,000 people) - the signs may include:

- difficulty breathing or swallowing
- low blood pressure, which can cause dizziness or light-headedness
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps

**Other side effects that have been reported:**

**Very common** (may affect more than 1 in 10 people)

- upper respiratory tract infections with symptoms such as sore throat and stuffy nose.
- injection site reactions (e.g. red skin, pain).

**Common** (may affect up to 1 in 10 people)

- nausea.
- fungal infections such as athlete's foot.
- pain in the back of the throat.
- cold sores of mouth, skin and mucous membranes (herpes simplex, mucocutaneous)

**Uncommon** (may affect up to 1 in 100 people)

- oral thrush (oral candidiasis).
- influenza.
- runny nose.
- bacterial skin infection.
- hives.
- discharge from the eye with itching, redness and swelling (conjunctivitis).
- signs of low levels of white blood cells, such as fever, sore throat or mouth ulcers due to infections (neutropenia).
- low blood platelet count (thrombocytopenia).
- eczema
- rash
- rapid swelling of the tissues of the neck, face, mouth or throat (angioedema)
- abdominal cramps and pain, diarrhoea, weight loss or blood in the stool (signs of bowel problems).

**Rare** (may affect up to 1 in 1 000 people)

- fungal infection of the oesophagus (oesophageal candidiasis)

### **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

## **5. How to store Taltz**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the syringe label and on the outer carton after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C to 8 °C). Do not freeze. Do not push to the back panel of the fridge.

Store in the original packaging in order to protect from light.

Taltz can be left out of the fridge for up to 5 days at a temperature not above 30 °C.

Do not use this medicine if you notice that the syringe is damaged, or the medicine is cloudy, distinctly brown, or has particles in it.

This medicine is for single use only.

Do not throw away any medicines via wastewater. Ask your doctor, nurse or pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Taltz contains

- The active substance is ixekizumab.  
Each pre-filled syringe contains 80 mg of ixekizumab in 1 ml solution.
- The other ingredients are sucrose; polysorbate 80; water for injections. In addition, sodium hydroxide may have been added for pH adjustment.

### What Taltz looks like and contents of the pack

Taltz is a solution in a clear glass syringe. Its colour may vary from colourless to slightly yellow.

Pack sizes of 1, 2, 3 pre-filled syringes. Not all pack sizes may be available in your country.

### Marketing Authorisation Holder

Eli Lilly and Company (Ireland) Limited, Dunderrow, Kinsale, Co. Cork, Ireland.

### Manufacturer

Eli Lilly Italia S.p.A., Via Gramsci 731/733, 50019, Sesto Fiorentino (FI), Italy.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

#### **Belgique/België/Belgien**

Eli Lilly Benelux S.A./N.V.  
Tél/Tel: + 32-(0)2 548 84 84

#### **Lietuva**

Eli Lilly Lietuva  
Tel. +370 (5) 2649600

#### **България**

ТП "Ели Лили Недерланд" Б.В. - България  
тел. + 359 2 491 41 40

#### **Luxembourg/Luxemburg**

Eli Lilly Benelux S.A./N.V.  
Tél/Tel: + 32-(0)2 548 84 84

#### **Česká republika**

ELI LILLY ČR, s.r.o.  
Tel: + 420 234 664 111

#### **Magyarország**

Lilly Hungária Kft.  
Tel: + 36 1 328 5100

#### **Danmark**

Eli Lilly Danmark A/S  
Tlf: +45 45 26 60 00

#### **Malta**

Charles de Giorgio Ltd.  
Tel: + 356 25600 500

#### **Deutschland**

Lilly Deutschland GmbH  
Tel. + 49-(0) 6172 273 2222

#### **Nederland**

Eli Lilly Nederland B.V.  
Tel: + 31-(0) 30 60 25 800

#### **Eesti**

Eli Lilly Nederland B.V.  
Tel: +372 6 817 280

#### **Norge**

Eli Lilly Norge A.S.  
Tlf: + 47 22 88 18 00

**Ελλάδα**

ΦΑΡΜΑΣΕΡΒ-ΛΙΛΛΥ Α.Ε.Β.Ε.

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Lilly France

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Eli Lilly Hrvatska d.o.o.

Tel: +385 1 2350 999

**Ireland**

Eli Lilly and Company (Ireland) Limited

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**Ísland**

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Phadisco Ltd

Τηλ: +357 22 715000

**Latvija**

Eli Lilly (Suisse) S.A Pārstāvniecība Latvijā

Tel: +371 67364000

**Österreich**

Eli Lilly Ges.m.b.H.

Tel: + 43-(0) 1 711 780

**Polska**

Eli Lilly Polska Sp. z o.o.

Tel: +48 22 440 33 00

**Portugal**

Lilly Portugal Produtos Farmacêuticos, Lda

Tel: + 351-21-4126600

**România**

Eli Lilly România S.R.L.

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**Slovenija**

Eli Lilly farmacevtska družba, d.o.o.

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**Slovenská republika**

Eli Lilly Slovakia s.r.o.

Tel: + 421 220 663 111

**Suomi/Finland**

Oy Eli Lilly Finland Ab

Puh/Tel: + 358-(0) 9 85 45 250

**Sverige**

Eli Lilly Sweden AB

Tel: + 46-(0) 8 7378800

**United Kingdom (Northern Ireland)**

Eli Lilly and Company (Ireland) Limited

Tel: + 353-(0) 1 661 4377

**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency website:

<http://www.ema.europa.eu>.

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**The following information is intended for medical or healthcare professionals only:**

**40 mg preparation of ixekizumab for children 25-50 kg body weight**

Ixekizumab doses of 40 mg must be prepared and administered by a qualified healthcare professional. Use only the Taltz 80 mg solution for injection in pre-filled syringe when preparing the prescribed 40 mg paediatric doses.

1. Expel the entire contents of the pre-filled syringe into a sterile, clear glass vial. DO NOT shake or swirl the vial.
2. Use a 0.5 ml or 1 ml disposable syringe and sterile needle to withdraw the prescribed dose (0.5 ml for 40 mg) from the vial.

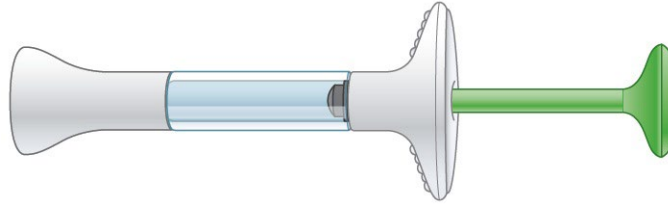
3. Change the needle and use a 27-gauge, sterile needle to inject the patient. Discard any unused ixekizumab in the vial.

The prepared ixekizumab must be administered within 4 hours of puncturing the sterile vial at room temperature.

## Instructions for use

### Taltz 80 mg solution for injection in pre-filled syringe

ixekizumab



Before using your pre-filled syringe:

#### Important points to know

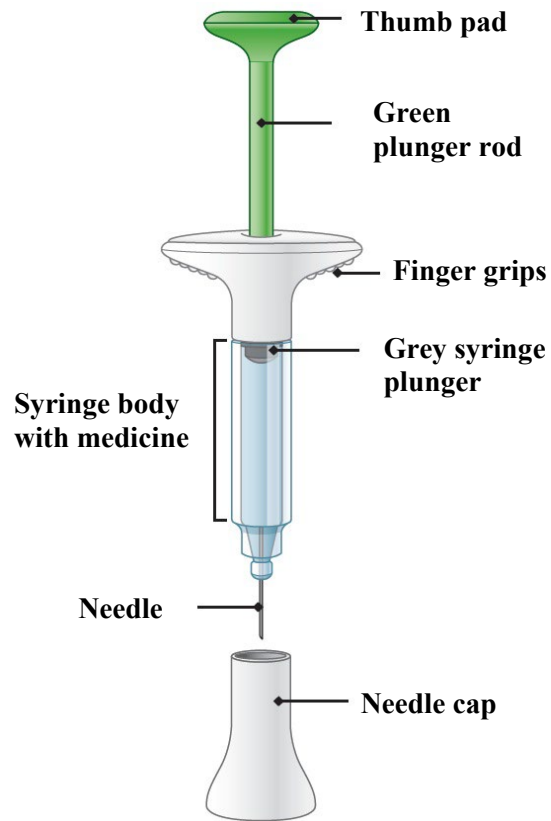
- Before you use the Taltz pre-filled syringe, read and carefully follow all the step-by-step instructions. Keep the Instructions for use and refer to them as needed.
- The pre-filled syringe contains 1 dose of Taltz. The syringe is for ONE-TIME USE ONLY.
- The syringe must not be shaken.
- Your doctor, pharmacist or nurse may help you decide where on your body to inject your dose.
- Read the Taltz Package Leaflet inside this box to learn more about your medicine.

#### INSTRUCTIONS FOR USE

**Before you use the Taltz pre-filled syringe, read and carefully follow all the step-by-step instructions.**



## Guide to the parts



### 1 GET READY

- 1a Take the syringe from the refrigerator.** Leave the needle cap on the syringe until you are ready to inject. **Wait 30 minutes** to let the syringe warm to room temperature before you use it.

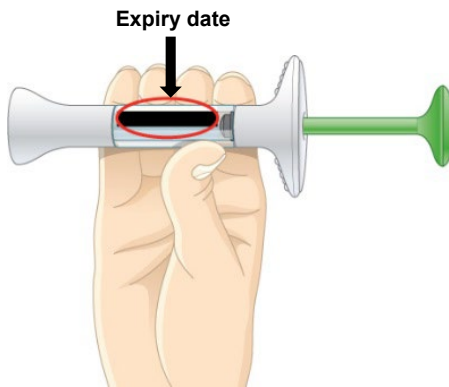


**DO NOT** use any heat sources to warm the medicine, for example: a microwave, hot water, or direct sunlight.

**1b Gather the supplies for your injection:**

- 1 alcohol wipe
- 1 cotton ball or piece of gauze
- 1 sharps container for disposal of syringes

1c



**Inspect the pre-filled syringe for damage to the outside.** Leave the needle cap on the syringe until you are ready to inject. Check the label. Make sure the name Taltz appears on the label.

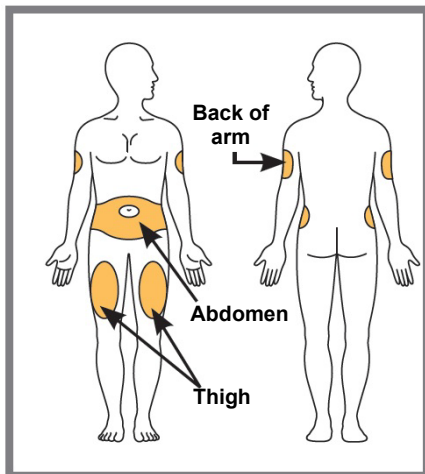
The medicine inside should be clear. Its colour may vary from colourless to slightly yellow.

If you see any of the following, **DO NOT USE** the syringe, and dispose of it as directed:

- It is past the expiry date.
- It looks damaged.
- The medicine is cloudy, is distinctly brown, or has small particles.

1d **Wash your hands before you inject your medicine.**

1e



**Choose your injection site.**

You may inject in your abdomen (stomach area), in your thigh, or in the back of your arm. To inject in your arm, you will need someone to help you.

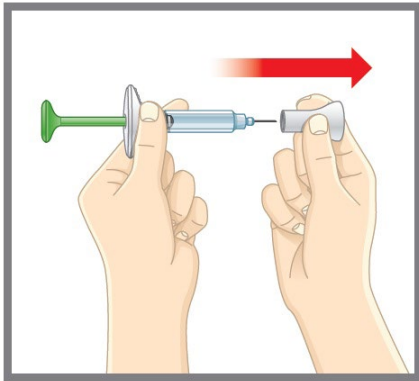
**DO NOT** inject into areas where the skin is tender, bruised, red, or hard or where you have scars or stretch marks. **DO NOT** inject within 2.5 centimetres of the navel (belly button).

**Alternate your injection sites. DO NOT** inject in the exact same spot every time. For example, if your last injection was in your left thigh, your next injection should be in your right thigh, your abdomen, or the back of either arm.

1f **Prepare your skin.** Clean your skin with an alcohol wipe. Let the injection site dry naturally before you inject your medicine.

## 2 INJECT

2a

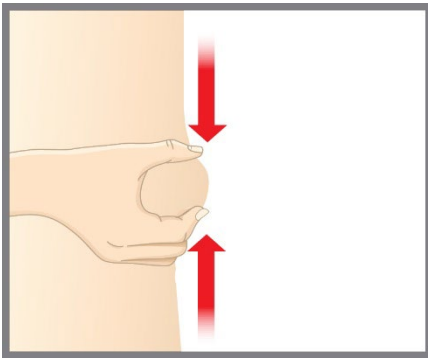


**Pull the needle cap off and throw it away.**

**DO NOT** put the needle cap back on—you could damage the needle or injure yourself by accident.

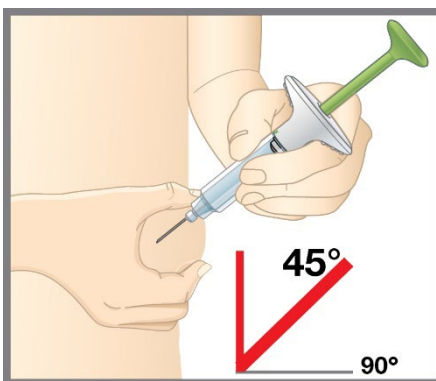
**DO NOT** touch the needle.

2b

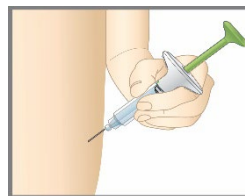


**Gently pinch and hold a fold of skin where you will inject.**

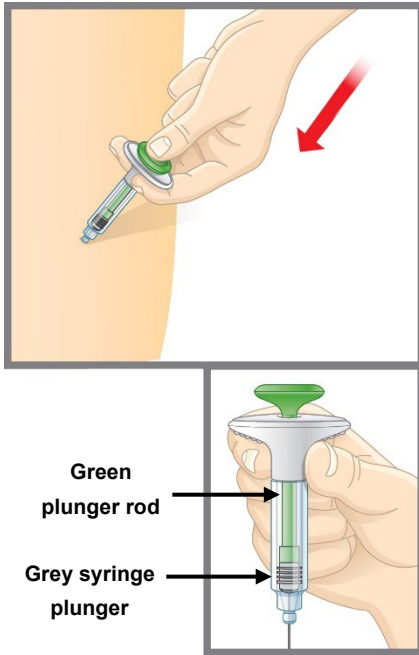
2c



**Insert the needle at a 45-degree angle.** Then gently let go of your skin. Make sure to keep the needle in place.



2d



### Push in the plunger.

Slowly push the plunger all the way in until all the medicine is injected. The grey syringe plunger should be pushed all the way to the end of the syringe. Gently remove the needle from your skin.

Press a cotton ball or gauze over the injection site. **DO NOT** rub the injection site, as this may cause bruising. You may have slight bleeding. This is normal.

**You should see the green plunger rod showing through the syringe body when the injection is complete.**

## 3 FINISH

3a



### Dispose of the pre-filled syringe.

**DO NOT** put the needle cap back on. Dispose of the syringe in a sharps container or as directed by your doctor, pharmacist or nurse.

### When you dispose of syringes and the sharps container:

- Dispose of the syringe in a sharps container or as directed by your doctor, pharmacist or nurse.
- Do not recycle the filled sharps container.
- Ask your doctor, pharmacist or nurse about how to dispose of medicines you no longer use.

## Safety tips

- If you have questions or need help with your pre-filled syringe, call your doctor, pharmacist or nurse.
- If you have vision problems, **DO NOT** use the pre-filled syringe without help from a person trained to use it.
- **DO NOT** share or reuse your Taltz pre-filled syringe. You may give or get an infection
- Keep the syringe out of the reach and sight of children.
- If you do not have a sharps container, ask your doctor, pharmacist or nurse about where you can get one.

## Commonly asked questions

### **Q. What if I see air bubbles in my syringe?**

- A.** It is normal to sometimes have air bubbles in the syringe. Taltz is injected under your skin (subcutaneous injection). Air bubbles are not a problem in this type of injection. They will not harm you or affect your dose.

### **Q. What if there is a drop of liquid on the tip of the needle when I remove the needle cap?**

- A.** It is okay to see a drop of liquid on the tip of the needle. This will not harm you or affect your dose.

### **Q. What if I cannot push in the plunger?**

**A. If the plunger is stuck or damaged:**

- **DO NOT** continue to use the syringe.
- Remove the needle from your skin.

### **Q. How can I tell if my injection is complete?**

**A. When your injection is complete:**

- The green plunger rod should show through the body of the syringe.
- The grey syringe plunger should be pushed all the way to the end of the syringe.

### **Q. What if the syringe is left at room temperature for longer than 30 minutes?**

- A.** If needed, the syringe may be left out of the fridge at temperature not above 30 °C for up to 5 days if protected from direct sunlight. Taltz should be discarded if not used within the 5 day period at room temperature.

**Read the full Instructions for use and the package leaflet inside this box to learn more about your medicine.**

## Package leaflet: Information for the patient

### Taltz 80 mg solution for injection in pre-filled pen ixekizumab

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### What is in this leaflet

1. What Taltz is and what it is used for
2. What you need to know before you use Taltz
3. How to use Taltz
4. Possible side effects
5. How to store Taltz
6. Contents of the pack and other information

#### 1. What Taltz is and what it is used for

Taltz contains the active substance ixekizumab.

Taltz is intended for the treatment of the inflammatory diseases described below:

- Plaque psoriasis in adults
- Plaque psoriasis in children from the age of 6 and with a body weight of at least 25 kg and in adolescents
- Psoriatic arthritis in adults
- Radiographic Axial Spondyloarthritis in adults
- Non-radiographic Axial Spondyloarthritis in adults

Ixekizumab belongs to a group of medicines called interleukin (IL) inhibitors. This medicine works by blocking the activity of a protein called IL-17A, which promotes psoriasis and inflammatory disease of the joints and the spine.

#### Plaque psoriasis

Taltz is used to treat a skin condition called “plaque psoriasis” in adults and in children from the age of 6 years and with a body weight of at least 25 kg and in adolescents with moderate to severe disease. Taltz reduces the signs and symptoms of the disease.

Using Taltz will benefit you by improvements of skin clearance and reducing your symptoms such as scaling, itching and pain.

#### Psoriatic arthritis

Taltz is used to treat a condition called “psoriatic arthritis” in adults, an inflammatory disease of the joints, often accompanied by psoriasis. If you have psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines or in case of intolerance, you will be given Taltz to reduce the signs and symptoms of the disease. Taltz can be used alone or with another medicine named methotrexate.

Using Taltz will benefit you by reducing the signs and symptoms of the disease, improving physical function (ability to do normal daily activities), and slowing down the damage to the joints.

### Axial spondyloarthritis

Taltz is used to treat adults with an inflammatory disease primarily affecting the spine which causes inflammation of the spinal joints, called axial spondyloarthritis. If the condition is visible using X-rays, it is referred to as “radiographic axial spondyloarthritis”; if it occurs in patients with no visible signs on X-rays, it is referred to as “non-radiographic axial spondyloarthritis”. If you have axial spondyloarthritis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Taltz to reduce the signs and symptoms of the disease, reduce inflammation and improve your physical function.

## **2. What you need to know before you use Taltz**

### **Do not use Taltz**

- if you are allergic to ixekizumab or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice before using Taltz.
- if you have an infection which your doctor thinks is important (for example, active tuberculosis).

### **Warnings and precautions**

Talk to your doctor before using Taltz:

- if you currently have an infection or if you have long-term or repeated infections.
- if you have an inflammatory disease affecting the gut named Crohn’s disease.
- if you have an inflammation of the large intestine named ulcerative colitis.
- if you are receiving any other treatment for psoriasis (such as immunosuppressant or phototherapy with ultraviolet light) or for psoriatic arthritis.

### Inflammatory bowel disease (Crohn's disease or ulcerative colitis)

Stop using Taltz and tell your doctor or seek medical help immediately if you notice abdominal cramps and pain, diarrhoea, weight loss or blood in the stool (any signs of bowel problems).

If you are not sure if any of the above applies to you, talk to your doctor or nurse before using Taltz.

### **Look out for infections and allergic reactions**

Taltz can potentially cause serious side effects, including infections and allergic reactions. You must look out for signs of these conditions while you are using Taltz.

Stop using Taltz and tell your doctor or seek medical help immediately if you notice any signs of a serious infection or an allergic reaction. Such signs are listed under “Serious side effects” in section 4.

### **Children and adolescents**

Do not use this medicine for the treatment of plaque psoriasis in children under 6 years of age because it has not been studied in this age group.

Do not use this medicine for the treatment of psoriatic arthritis in children and adolescents under 18 years of age because it has not been studied in this age group.

### **Other medicines and Taltz**

Tell your doctor, pharmacist or nurse

- if you are using, have recently used or might use any other medicines.
- if you have recently had or are due to have a vaccination. You should not be given certain types of vaccines while using Taltz.

### **Pregnancy and breast-feeding**

If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before using this medicine. It is preferable to avoid the use of Taltz in pregnancy. The effects

of this medicine in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Taltz and for at least 10 weeks after the last Taltz dose.

If you are breast-feeding or are planning to breast-feed, talk to your doctor before using this medicine. You and your doctor should decide if you can breast-feed or use Taltz. You should not do both.

### **Driving and using machines**

Taltz is unlikely to influence your ability to drive and use machines.

### **Taltz contains sodium**

This medicine contains less than 1 mmol sodium (23 mg) per 80 mg dose, that is to say essentially “sodium-free”.

## **3. How to use Taltz**

Always use this medicine exactly as your doctor or nurse has told you. Check with your doctor, nurse or pharmacist if you are not sure.

Taltz is given by injection under your skin (subcutaneous injection). You and your doctor or nurse should decide if you should inject Taltz yourself.

For use in children with a body weight of 25-50 kg ixekizumab doses of 40 mg must be prepared and administered by a qualified healthcare professional.

Use the Taltz 80 mg pre-filled pen only in those children that require a dose of 80 mg and do not require dose preparation.

It is important not to try to inject yourself until you have been trained by your doctor or nurse. A caregiver may also give you your Taltz injection after proper training.

Use a reminder method such as notes in a calendar or diary to help you remember your next dose so that you avoid missing or repeating doses.

Taltz is for long-term treatment. Your doctor or nurse will regularly monitor your condition to check that the treatment is having the desired effect.

Each pen contains one dose of Taltz (80 mg). Each pen delivers only one dose. The pen must not be shaken.

Read the “Instructions for use” for the pen carefully before using Taltz.

### **How much Taltz is given and for how long**

Your doctor will explain to you how much Taltz you need and for how long.

#### Plaque psoriasis in adults

- The first dose is 160 mg (2 pens with 80 mg each) by subcutaneous injection. This may be given by your doctor or nurse.
- After the first dose, you will use an 80 mg dose (1 pen) at weeks 2, 4, 6, 8, 10, and 12. From week 12, you will use an 80 mg dose (1 pen) every 4 weeks.



Plaque psoriasis in children (age 6 years and above and at least 25 kg body weight) and in adolescents. The recommended dose given by subcutaneous injection in children is based on the following weight categories:

<b>Children's body weight</b>	<b>Recommended starting dose (week 0)</b>	<b>Recommended dose every 4 weeks (Q4W) thereafter</b>
Greater than 50 kg	160 mg (2 pens)	80 mg (1 pen)
25 to 50 kg	80 mg (1 pen)	40 mg (dose preparation required)

Ixekizumab doses of 40 mg must be prepared and administered by a qualified healthcare professional using the commercial Taltz 80 mg/1 ml pre-filled syringe.

Use the Taltz 80 mg pre-filled pen only in those children that require a dose of 80 mg. Do not use the Taltz 80 mg pre-filled pen for the preparation of the 40 mg dose.

Taltz is not recommended for use in children with a body weight below 25 kg.

#### Psoriatic arthritis

For psoriatic arthritis patients who also have moderate to severe plaque psoriasis:

- The first dose is 160 mg (2 pens with 80 mg each) by subcutaneous injection. This may be given by your doctor or nurse.
- After the first dose, you will use an 80 mg dose (1 pen) at weeks 2, 4, 6, 8, 10, and 12. From week 12, you will use an 80 mg dose (1 pen) every 4 weeks.

#### For other psoriatic arthritis patients

- The first dose is 160 mg (2 pens with 80 mg each) by subcutaneous injection. This may be given by your doctor or nurse.
- After the first dose you will use an 80 mg dose (1 pen) every 4 weeks.

#### Axial spondyloarthritis

The recommended dose is 160 mg (2 pens with 80 mg each) by subcutaneous injection at week 0, followed by 80 mg (1 pen) every 4 weeks.

#### **If you use more Taltz than you should**

If you have received more Taltz than you should or the dose has been given sooner than prescribed, inform your doctor.

#### **If you forget to use Taltz**

If you have forgotten to inject a dose of Taltz, talk to your doctor.

#### **If you stop using Taltz**

You should not stop using Taltz without speaking to your doctor first. If you stop treatment, symptoms of psoriasis or psoriatic arthritis may come back.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

## **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

#### **Serious side effects**

Stop using Taltz and tell your doctor or seek medical help immediately if you get any of the following side effects. Your doctor will decide if and when you may restart the treatment:

**Possible serious infection** (may affect up to 1 in 100 people) - the signs may include:

- fever, flu-like symptoms, night sweats
- feeling tired or short of breath, cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters

**Serious allergic reaction** (may affect up to 1 in 1,000 people) - the signs may include:

- difficulty breathing or swallowing
- low blood pressure, which can cause dizziness or light-headedness
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps

**Other side effects that have been reported:**

**Very common** (may affect more than 1 in 10 people)

- upper respiratory tract infections with symptoms such as sore throat and stuffy nose.
- injection site reactions (e.g. red skin, pain).

**Common** (may affect up to 1 in 10 people)

- nausea.
- fungal infections such as athlete's foot.
- pain in the back of the throat.
- cold sores of mouth, skin and mucous membranes (herpes simplex, mucocutaneous)

**Uncommon** (may affect up to 1 in 100 people)

- oral thrush (oral candidiasis).
- influenza.
- runny nose.
- bacterial skin infection.
- hives.
- discharge from the eye with itching, redness and swelling (conjunctivitis).
- signs of low levels of white blood cells, such as fever, sore throat or mouth ulcers due to infections (neutropenia).
- low blood platelet count (thrombocytopenia).
- eczema
- rash
- rapid swelling of the tissues of the neck, face, mouth or throat (angioedema)
- abdominal cramps and pain, diarrhoea, weight loss or blood in the stool (signs of bowel problems).

**Rare** (may affect up to 1 in 1 000 people)

- fungal infection of the oesophagus (oesophageal candidiasis)

### **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

## **5. How to store Taltz**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pen label and on the outer carton after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C to 8 °C). Do not freeze. Do not push to the back panel of the fridge.

Store in the original packaging in order to protect from light.

Taltz can be left out of the fridge for up to 5 days at a temperature not above 30 °C.

Do not use this medicine if you notice that the pen is damaged, or the medicine is cloudy, distinctly brown, or has particles in it.

This medicine is for single use only.

Do not throw away any medicines via wastewater. Ask your doctor, nurse or pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Taltz contains

- The active substance is ixekizumab.  
Each pre-filled pen contains 80 mg of ixekizumab in 1 ml solution.
- The other ingredients are sucrose; polysorbate 80; water for injections. In addition, sodium hydroxide may have been added for pH adjustment.

### What Taltz looks like and contents of the pack

Taltz is a solution in a clear glass syringe. Its colour may vary from colourless to slightly yellow.

The syringe is encased in a disposable, single-dose pen.

Pack sizes of 1, 2, 3 pre-filled pens. Not all pack sizes may be available in your country.

### Marketing Authorisation Holder

Eli Lilly and Company (Ireland) Limited, Dunderrow, Kinsale, Co. Cork, Ireland.

### Manufacturer

Eli Lilly Italia S.p.A., Via Gramsci 731/733, 50019, Sesto Fiorentino (FI), Italy.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

#### **Belgique/België/Belgien**

Eli Lilly Benelux S.A./N.V.  
Tél/Tel: + 32-(0)2 548 84 84

#### **Lietuva**

Eli Lilly Lietuva  
Tel. +370 (5) 2649600

#### **България**

ТП "Ели Лили Недерланд" Б.В. - България  
тел. + 359 2 491 41 40

#### **Luxembourg/Luxemburg**

Eli Lilly Benelux S.A./N.V.  
Tél/Tel: + 32-(0)2 548 84 84

#### **Česká republika**

ELI LILLY ČR, s.r.o.  
Tel: + 420 234 664 111

#### **Magyarország**

Lilly Hungária Kft.  
Tel: + 36 1 328 5100

#### **Danmark**

Eli Lilly Danmark A/S  
Tlf: +45 45 26 60 00

#### **Malta**

Charles de Giorgio Ltd.  
Tel: + 356 25600 500

#### **Deutschland**

Lilly Deutschland GmbH  
Tel. + 49-(0) 6172 273 2222

#### **Nederland**

Eli Lilly Nederland B.V.  
Tel: + 31-(0) 30 60 25 800

**Eesti**

Eli Lilly Nederland B.V.  
Tel: +372 6 817 280

**Ελλάδα**

ΦΑΡΜΑΣΕΡΒ-ΛΙΛΛΥ Α.Ε.Β.Ε.  
Τηλ: +30 210 629 4600

**España**

Lilly S.A.  
Tel: + 34-91 663 50 00

**France**

Lilly France  
Tél: +33-(0) 1 55 49 34 34

**Hrvatska**

Eli Lilly Hrvatska d.o.o.  
Tel: +385 1 2350 999

**Ireland**

Eli Lilly and Company (Ireland) Limited  
Tel: + 353-(0) 1 661 4377

**Ísland**

Icepharma hf.  
Sími + 354 540 8000

**Italia**

Eli Lilly Italia S.p.A.  
Tel: + 39- 055 42571

**Κύπρος**

Phadisco Ltd  
Τηλ: +357 22 715000

**Latvija**

Eli Lilly (Suisse) S.A Pārstāvniecība Latvijā  
Tel: +371 67364000

**Norge**

Eli Lilly Norge A.S.  
Tlf: + 47 22 88 18 00

**Österreich**

Eli Lilly Ges.m.b.H.  
Tel: + 43-(0) 1 711 780

**Polska**

Eli Lilly Polska Sp. z o.o.  
Tel: +48 22 440 33 00

**Portugal**

Lilly Portugal Produtos Farmacêuticos, Lda  
Tel: + 351-21-4126600

**România**

Eli Lilly România S.R.L.  
Tel: + 40 21 4023000

**Slovenija**

Eli Lilly farmacevtska družba, d.o.o.  
Tel: +386 (0)1 580 00 10

**Slovenská republika**

Eli Lilly Slovakia s.r.o.  
Tel: + 421 220 663 111

**Suomi/Finland**

Oy Eli Lilly Finland Ab  
Puh/Tel: + 358-(0) 9 85 45 250

**Sverige**

Eli Lilly Sweden AB  
Tel: + 46-(0) 8 7378800

**United Kingdom (Northern Ireland)**

Eli Lilly and Company (Ireland) Limited  
Tel: + 353-(0) 1 661 4377

**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency website:  
<http://www.ema.europa.eu>.

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## Instructions for use

### Taltz 80 mg solution for injection in pre-filled pen

ixekizumab



Before using your pre-filled pen:

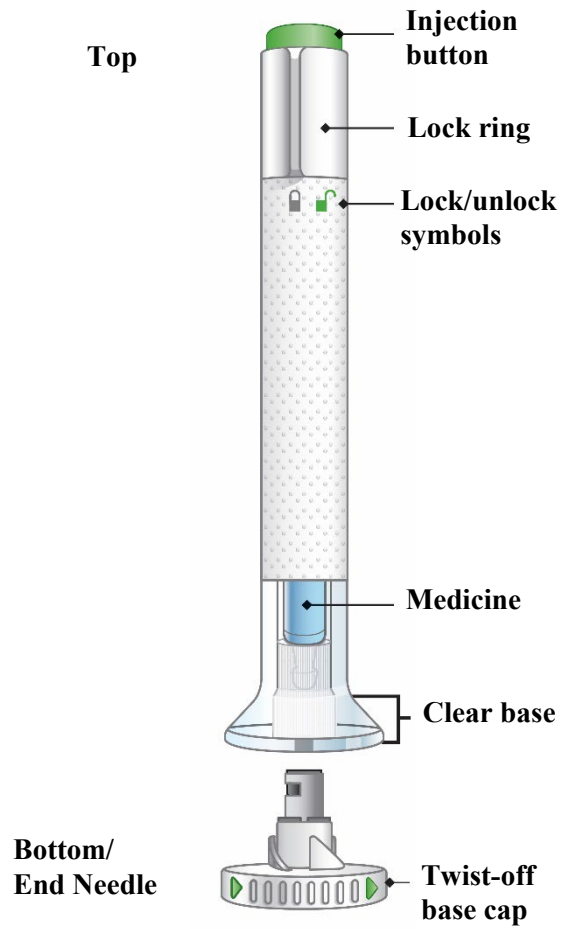
#### Important points to know

- Before you use the Taltz pre-filled pen, read and carefully follow all the step-by-step instructions. Keep the Instructions for use and refer to them as needed.
- The pre-filled pen contains 1 dose of Taltz. The pre-filled pen is for ONE-TIME USE ONLY.
- The pre-filled pen must not be shaken.
- The pre-filled pen contains glass parts. Handle it carefully. If you drop it on a hard surface, do not use it. Use a new pre-filled pen for your injection.
- Your doctor, pharmacist or nurse may help you decide where on your body to inject your dose.
- Read the Taltz Package Leaflet inside this box to learn more about your medicine.

#### INSTRUCTIONS FOR USE

**Before you use the Taltz pre-filled pen, read and carefully follow all the step-by-step instructions.**

## Guide to the parts



### 1 GET READY

- 1a** Take the pre-filled pen from the refrigerator. Leave the base cap on until you are ready to inject. **Wait 30 minutes** to let the pre-filled pen warm to room temperature before you use it.

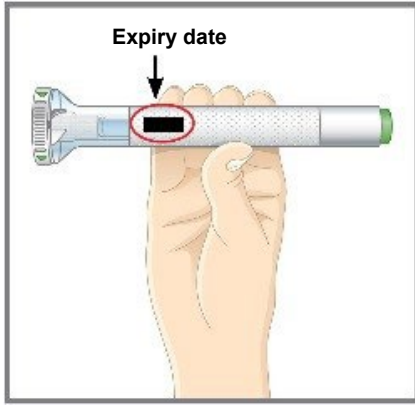


**DO NOT** use any heat sources to warm the medicine, for example: a microwave, hot water, or direct sunlight.

- 1b** Gather the supplies for your injection:

- 1 alcohol wipe
- 1 cotton ball or piece of gauze
- 1 sharps container for disposal of pre-filled pen

1c



**Inspect the pre-filled pen.** Check the label. Make sure the name Taltz appears on the label.

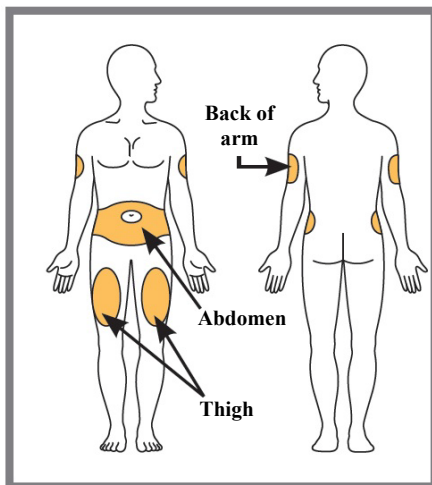
The medicine inside should be clear. Its colour may vary from colourless to slightly yellow.

If you see any of the following, **DO NOT USE** the pre-filled pen, and dispose of it as directed:

- It is past the expiry date.
- It looks damaged.
- The medicine is cloudy, is distinctly brown, or has small particles.

1d **Wash your hands before you inject your medicine.**

1e



**Choose your injection site.**

You may inject in your abdomen (stomach area), in your thigh, or in the back of your arm. To inject in your arm, you will need someone to help you.

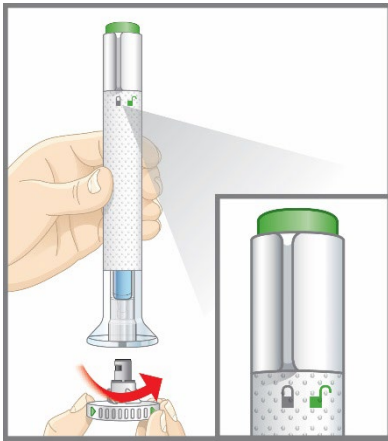
**DO NOT** inject into areas where the skin is tender, bruised, red, or hard or where you have scars or stretch marks. **DO NOT** inject within 2.5 centimetres of the navel (belly button).

**Alternate your injection sites. DO NOT** inject in the exact same spot every time. For example, if your last injection was in your left thigh, your next injection should be in your right thigh, your abdomen, or the back of either arm.

1f **Prepare your skin.** Clean your skin with an alcohol wipe. Let the injection site dry naturally before you inject your medicine.

## 2 INJECT

2a



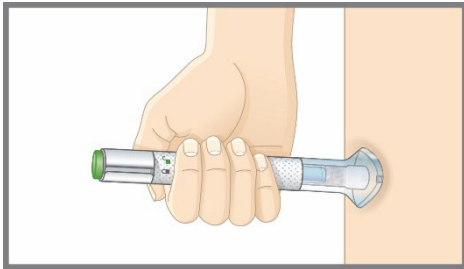
**Make sure the lock ring is in the lock position.**

Leave the base cap on until you are ready to inject. **DO NOT** touch the needle.

**Twist off the base cap.**

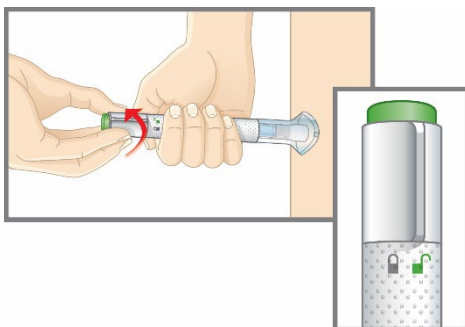
Throw the base cap in the bin. You will not need to put the base cap back on—doing so could damage the needle or cause you to injure yourself by accident.

2b



**Place the clear base flat and firmly against your skin.**

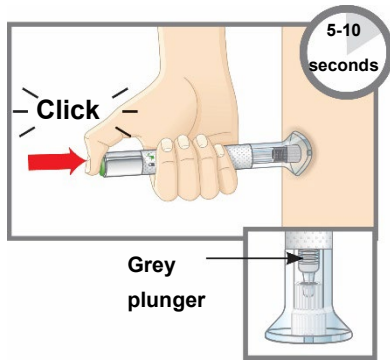
2c



**Keep the base on your skin, and then turn the lock ring to the unlock position.** You are now ready to inject.



2d



**Press the green injection button.** There will be a loud click.

**Keep holding the clear base firmly against your skin.** You will hear a second loud click in about 5 to 10 seconds after the first one. **The second loud click tells you that your injection is complete.**

You will also see the grey plunger at the top of the clear base.

Remove the pre-filled pen from your skin.

Press a cotton ball or gauze over the injection site. **DO NOT** rub the injection site, as this may cause bruising. You may have slight bleeding. This is normal.

### 3 FINISH

3a



**Dispose of the pre-filled pen.**

**DO NOT** put the base cap back on. Dispose of the pre-filled pen in a sharps container or as directed by your doctor, pharmacist or nurse.

#### **When you dispose of the pre-filled pen and the sharps container:**

- Dispose of the pen in a sharps container or as directed by your doctor, pharmacist or nurse.
- Do not recycle the filled sharps container.
- Ask your doctor, pharmacist or nurse about how to dispose of medicines you no longer use.

#### **Safety tips**

- If you have questions or need help with your pre-filled pen, call your doctor, pharmacist or nurse.
- If you have vision problems, **DO NOT** use the pre-filled pen without help from a person trained to use it.
- Keep the pre-filled pen out of the reach and sight of children.
- If you do not have a sharps container, ask your doctor, pharmacist or nurse where you can get one.

## Commonly asked questions

**Q. What if I see air bubbles in the pre-filled pen?**

- A. It is normal to have air bubbles in the pre-filled pen. Taltz is injected under the skin (subcutaneous injection). Air bubbles are not a problem in this type of injection. They will not harm you or affect your dose.

**Q. What if there is a drop of liquid on the tip of the needle when I remove the base cap?**

- A. It is okay to see a drop of liquid on the tip of the needle. This will not harm you or affect your dose.

**Q. What if I unlocked the pre-filled pen and pressed the green injection button before I twisted off the base cap?**

- A. Do not remove the base cap. Contact your doctor, pharmacist or nurse.

**Q. Do I need to hold the injection button down until the injection is complete?**

- A. This is not necessary, but it may help you keep the pre-filled pen steady and firm against your skin.

**Q. What if the needle did not retract after my injection?**

- A. Do not touch the needle or replace the base cap. Dispose of the pre-filled pen in a closable, puncture-resistant sharps container. Contact your doctor, pharmacist or nurse.

**Q. What if I heard more than 2 clicks during my injection—2 loud clicks and a soft one. Did I get my complete injection?**

- A. Some patients may hear a soft click right before the second loud click. That is normal. Do not remove the pre-filled pen from your skin until you hear the second loud click.

**Q. How can I tell if my injection is complete?**

- A. After you press the green injection button, you will hear 2 loud clicks. The second click tells you that your injection is complete. You will also see the grey plunger at the top of the clear base.

**Q. What if the pre-filled pen is left at room temperature for longer than 30 minutes?**

- A. If needed, the pre-filled pen may be left out of the fridge at temperature not above 30 °C for up to 5 days if protected from direct sunlight. Taltz should be discarded if not used within the 5 day period at room temperature.

**Read the full Instructions for use and the package leaflet inside this box to learn more about your medicine.**