EUSPC14JAN2021

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.

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
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).

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, 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 (≥ 65 years)
No dose adjustment is required (see section 5.2).

There is limited information in subjects aged ≥ 75 years.

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

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 prescribing information and the instructions for use.

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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

A total of 8,953 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, 6,343 patients were exposed to Taltz for at least one year, cumulatively representing 19,772.1 patient years of exposure.
In plaque psoriasis a total of 3,119 patients were evaluated in clinical trials (2,328 patients on ixekizumab).
In psoriatic arthritis a total of 678 patients were evaluated in clinical trials (454 patients on ixekizumab).
In axial spondyloarthritis (radiographic and non-radiographic axSpA) a total of 868 patients were evaluated in clinical trials (574 patients on ixekizumab).

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

System organ class	Frequency	Adverse reaction
Infections and infestations	Very common	Upper respiratory tract infection
	Common	Tinea infection, Herpes simplex (mucocutaneous)
	Uncommon	Influenza, Rhinitis, Oral candidiasis, Conjunctivitis, Cellulitis
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[a]

[a] *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 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.

Infections
In the placebo-controlled period of the phase III clinical studies in plaque psoriasis, 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 ≥1,000 cells/mm^3. Such levels of neutropenia may persist, fluctuate or be transient. 0.1% of patients receiving Taltz developed a neutrophil count <1,000 cells/mm^3. 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^3 to ≥75,000 cells/mm^3.
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 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 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.

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 to the Drug Office, Department of Health.

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

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)[a]	354 (81.8)[a]	73.1 (68.8, 77.5)	78.5 (74.5, 82.5)
sPGA of "0" (clear)	0	149 (34.5)[a]	160 (37.0)[a]	34.5 (30.0, 39.0)	37.0 (32.4, 41.5)
PASI 75	17 (3.9)	357 (82.6)[a]	386 (89.1)[a]	78.7 (74.7, 82.7)	85.2 (81.7, 88.7)
PASI 90	2 (0.5)	279 (64.6)[a]	307 (70.9)[a]	64.1 (59.6, 68.7)	70.4 (66.1, 74.8)
PASI 100	0	145 (33.6)[a]	153 (35.3)[a]	33.6 (29.1, 38.0)	35.3 (30.8, 39.8)
Itch NRS reduction ≥ 4[b]	58 (15.5)	305 (80.5)[a]	336 (85.9)[a]	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
[a] *$p < 0.001$ compared with placebo*
[b] *Patients with Itch NRS ≥ 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)[a,b]	292 (83.2)[a,b]	129 (36.0)[a]	70.5 (65.3, 75.7)	80.8 (76.3, 85.4)
sPGA of "0" (clear)	1 (0.6)	112 (32.3)[a,b]	147 (41.9)[a,b]	21 (5.9)[c]	31.7 (26.6, 36.7)	41.3 (36.0, 46.6)
PASI 75	4 (2.4)	269 (77.5)[a,b]	315 (89.7)[a,b]	149 (41.6)[a]	75.1 (70.2, 80.1)	87.4 (83.4, 91.3)
PASI 90	1 (0.6)	207 (59.7)[a,b]	248 (70.7)[a,b]	67 (18.7)[a]	59.1 (53.8, 64.4)	70.1 (65.2, 75.0)
PASI 100	1 (0.6)	107 (30.8)[a,b]	142 (40.5)[a,b]	19 (5.3)[c]	30.2 (25.2, 35.2)	39.9 (34.6, 45.1)
Itch NRS reduction ≥ 4[d]	19 (14.1)	225 (76.8)[a,b]	258 (85.1)[a,b]	177 (57.8)[a]	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.
[a] *$p < 0.001$ compared with placebo;* [b] *$p < 0.001$ compared with etanercept;*
[c] *$p < 0.01$ compared with placebo*
[d] *Patients with Itch NRS ≥ 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.

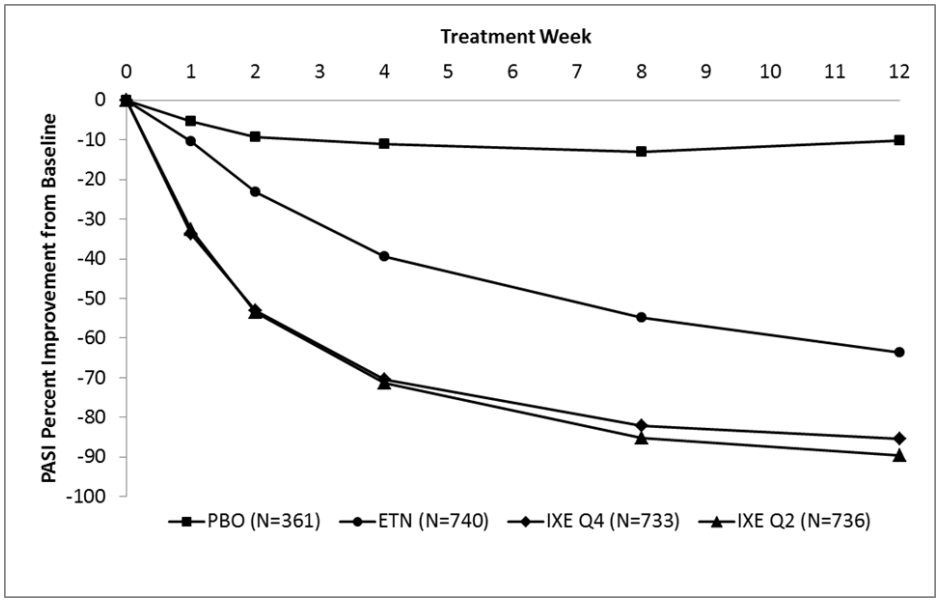
Table 4. Efficacy results at week 12 in UNCOVER-3

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)[a,b]	310 (80.5)[a,b]	159 (41.6)[a]	68.7 (63.1, 74.2)	73.8 (68.5, 79.1)
sPGA of "0" (clear)	0	139 (36.0)[a,b]	155 (40.3)[a,b]	33 (8.6)[a]	36.0 (31.2, 40.8)	40.3 (35.4, 45.2)
PASI 75	14 (7.3)	325 (84.2)[a,b]	336 (87.3)[a,b]	204 (53.4)[a]	76.9 (71.8, 82.1)	80.0 (75.1, 85.0)
PASI 90	6 (3.1)	252 (65.3)[a,b]	262 (68.1)[a,b]	98 (25.7)[a]	62.2 (56.8, 67.5)	64.9 (59.7, 70.2)
PASI 100	0	135 (35.0)[a,b]	145 (37.7)[a,b]	28 (7.3)[a]	35 (30.2, 39.7)	37.7 (32.8, 42.5)
Itch NRS reduction ≥ 4[c]	33 (20.9)	250 (79.9)[a,b]	264 (82.5)[a,b]	200 (64.1)[a]	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
[a] *$p < 0.001$ compared with placebo*
[b] *$p < 0.001$ compared with etanercept*
[c] *Patients with Itch NRS ≥ 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-naive, biologic-naive, 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 ≥ 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)[a]	173 (78.3)[a]	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)[a]	130 (58.8)[a]	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)[a]	184 (83.3)[a]	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)[a]	169 (76.5)[a]	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)[a]	127 (57.5)[a]	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
[a] $p < 0.001$ 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%)[§]	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)*
[§] $p < 0.001$ versus ustekinumab (p value only provided for primary endpoint)

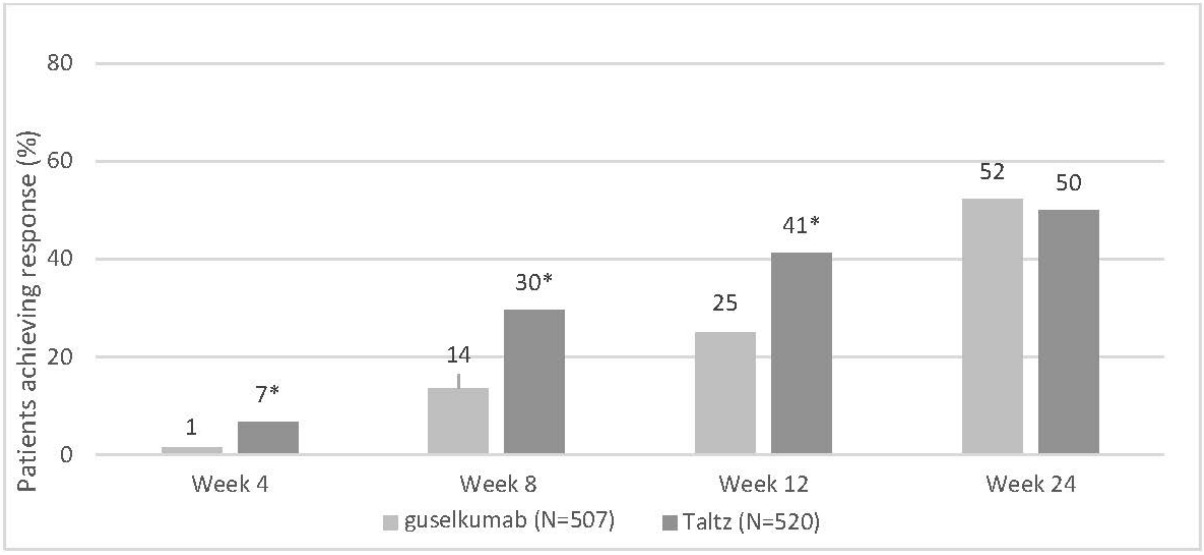
IXORA-R: Efficacy and safety of Taltz was also investigated in a 24-week randomized, double-blind, parallel-group study comparing Taltz to guselkumab, with Taltz being superior as early as Week 4 in achieving complete skin clearance and on the primary study objective (PASI 100 at week 12) and non-inferior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

Table 7. Efficacy Responses from comparative study ixekizumab versus guselkumab, Intent-to-Treat Population[a]

Endpoint	Time point	Guselkumab (N=507) response, n (%)	Ixekizumab (N=520) response, n (%)	Difference (IXE - GUS), % (CI)	p-value
Primary Objective					
PASI 100	Week 12	126 (24.9)	215 (41.3)	16.5 (10.8, 22.2)	<0.001
Major Secondary Objectives					
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.
[a] 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 ≥3), a minimum body surface area (BSA) involvement of 1% (60.4% had a BSA ≥ 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 ≥ 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. ≥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 [a]

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

[a] *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;* [b] *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

Psoriatic arthritis

Taltz was assessed in two randomised, double-blind, placebo-controlled phase III studies in 780 patients with active psoriatic arthritis (≥3 swollen and ≥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 ≥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 9).

Table 9. Efficacy results in SPIRIT-P1 and SPIRIT-P2 at week 24

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

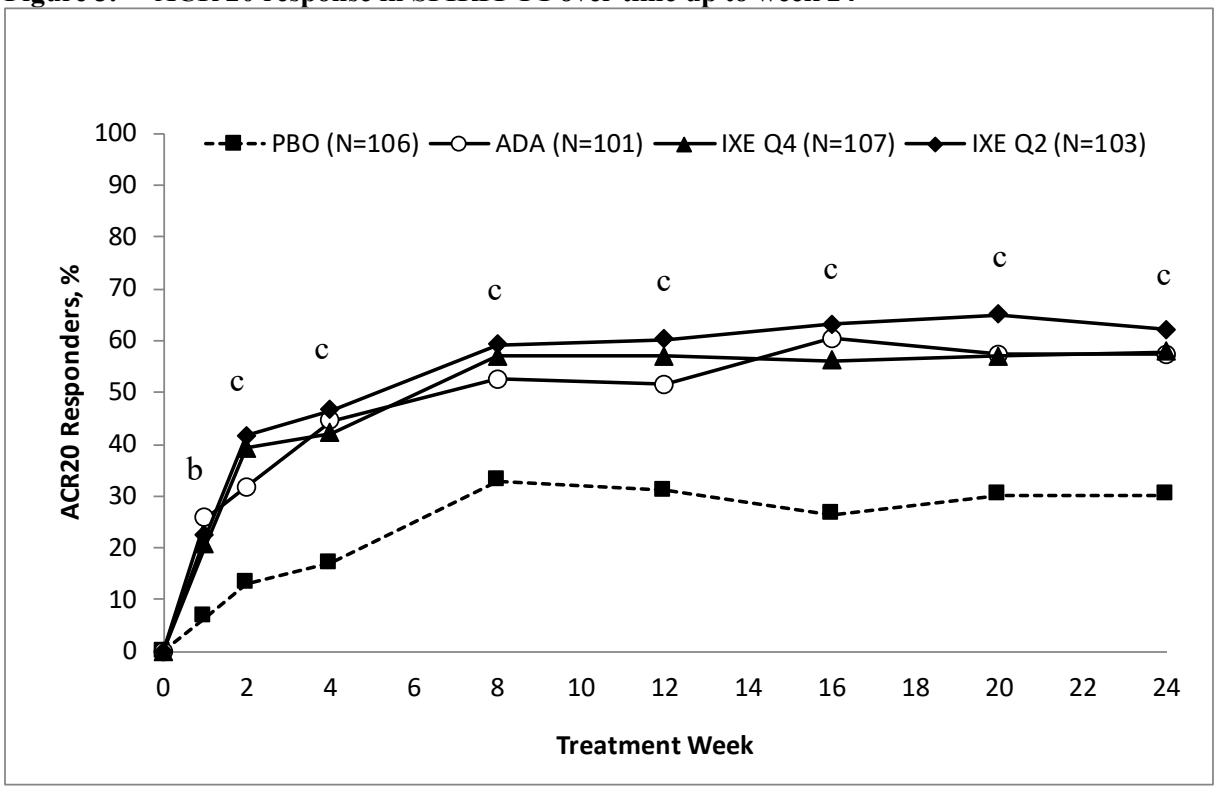
Abbreviations: ACR 20/50/70 = American College of Rheumatology 20%/50%/70% response rate; ADA = adalimumab; BSA = body surface area; CI = confidence interval; Q4W = Taltz 80 mg every 4 weeks; Q2W = Taltz 80 mg every 2 weeks; N = number of patients in the analysis population; n = number of patients in 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 ≥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 3. 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-P1and 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 10.

Table 10. 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)[b]	-0.42 (-0.66,-0.19)[c]

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.
[b] p<0.01; [c] p<0.001 compared with placebo.

Radiographic joint damage progression was inhibited by Taltz (Table 10) 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).

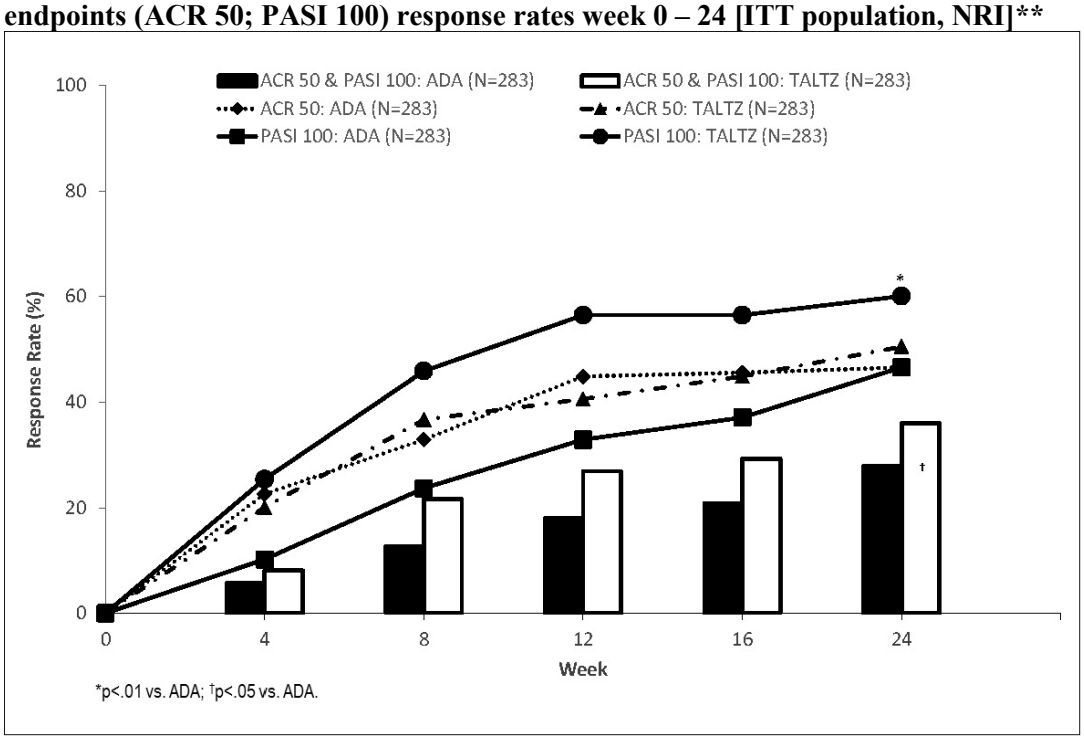
Physical function and health-related quality of life
In both SPIRIT-P1 and SPIRIT-P2, patients treated with Taltz Q2W (p<0.001) and Q4W (p<0.001) showed significant improvement in physical function compared to patients treated with placebo as assessed by Health Assessment Questionnaire-Disability Index (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 (PASI≥12, BSA≥10 and sPGA≥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 4. 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) ≥4 and total back pain ≥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 11). Responses were similar in patients regardless of concomitant therapies. In COAST-W, responses were seen regardless of the number of prior TNF inhibitors.

Table 11. Efficacy results in COAST-V and COAST-W at week 16

	COAST-V, biologic-naive				**COAST-W, TNF-inhibitor experienced**		
	Taltz 80 mg Q4W[a] (N=81)	**Placebo (N=87)**	**Difference from placebo [g]**	**Adalimumab 40 mg Q2W (N=90)**	**Taltz 80 mg Q4W[c] (N=114)**	**Placebo (N=104)**	**Difference from placebo [g]**
ASAS20 response[b], 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[b,c], 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 *Baseline*	-1.4 *3.7*	-0.5 *3.9*	-1.0 (-1.3, -0.7) ***	-1.3*** *3.7*	-1.2 *4.2*	-0.1 *4.1*	-1.1 (-1.3, -0.8) ***
BASDAI Score							
Change from baseline *Baseline*	-2.9 *6.8 [i]*	-1.4 *6.8 [i]*	-1.5 (-2.1, -0.9) ***	-2.5*** *6.7 [i]*	-2.2 *7.5*	-0.9 *7.3*	-1.2 (-1.8, -0.7) ***
MRI Spine SPARCC[d]							
Change from baseline *Baseline*	-11.0 *14.5*	*-1.5* *15.8*	-9.5 (-12.6, -6.4) ***	*-11.6**** *20.0*	-3.0 *8.3*	3.3 *6.4*	-6.3 (-10.0, -2.5) **
BASDAI50[e] n (%), NRI	34 (42.0%)	15 (17.2%)	24.7 (11.4, 38.1) ***	29 (32.2%)*	25 (21.9%)[i]	10 (9.6%)[i]	12.3 (2.8, 21.8)*
ASDAS <2.1, n (%) (low disease activity), NRI	35 (43.2%)[h]	11 (12.6%)[h]	30.6 (17.7,43.4) ***	34 (37.8%)*** [h]	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%)[i]	1 (1.0%)[i]	2.5 (-1.3, 6.4)
ASAS HI[f] Change from baseline *Baseline*	-2.4 *7.5*	-1.3 *8.1*	-1.1 (-2.0, -0.3) *	-2.3* *8.2*	-1.9 *10.0*	-0.9 *9.0*	-1.0 (-1.9, -0.1) *
SF-36 PCS Change from baseline *Baseline*	7.7 *34.0*	3.6 *32.0*	4.1 (1.9, 6.2) ***	6.9** *33.5*	6.6 *27.5*	*1.4* 30.6	5.2 (3.0, 7.4) ***

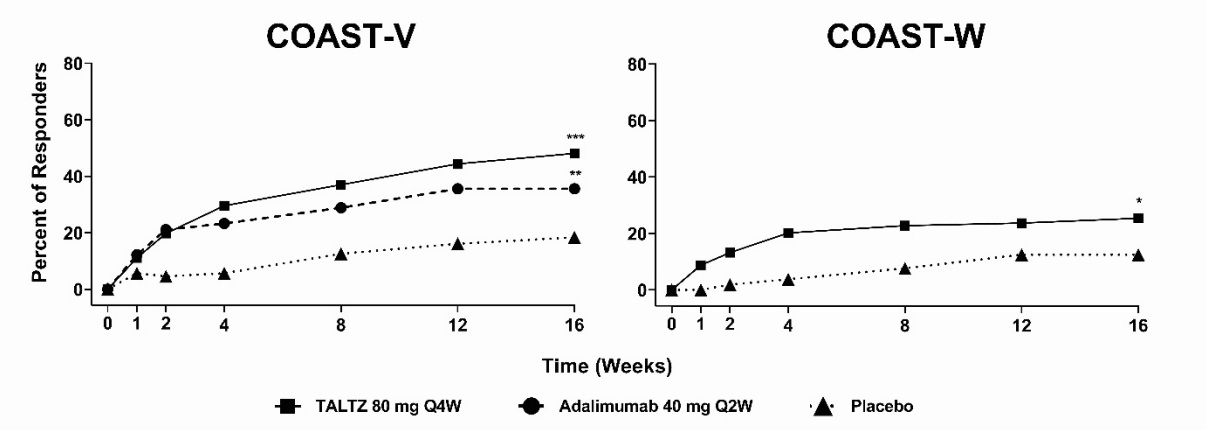
Abbreviations: N = number of patients in the intent-to-treat population; NRI = Non-responder Imputation; patients with missing data were counted as non-responders.
ASAS HI = Assessment of SpondyloArthritis International Society Health Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = 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)

[a] *At week 0, patients received 80 mg or 160 mg of Taltz.*
[b] *An ASAS20 response is defined as a ≥20% improvement and an absolute improvement from baseline of ≥1 unit (range 0 to 10) in ≥3 of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation), and no worsening of ≥20% and ≥1 unit (range 0 to 10) in the remaining domain. An ASAS40 response is defined as a ≥40% improvement and an absolute improvement from baseline of ≥2 units in ≥3 of 4 domains without any worsening in the remaining domain.*
[c] *Primary endpoint.*
[d] *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.*
[e] *BASDAI50 response defined as an improvement of ≥50% of the BASDAI score from baseline.*

[f] *ASAS HI: Assessment of SpondyloArthritis International Society Health Index (ASAS HI) across all domains.*
[g] *The reported values are difference in %(95% CI) for categorical variables, and difference in LSM (95% CI) for continuous variables.*
[h] *post hoc analysis, not multiplicity corrected.*
[i] *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 5. Percent of patients achieving ASAS40 responses in COAST-V and COAST-W through week 16, NRI[a]



[a] *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 11, 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) ≥4, and spinal pain ≥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 12). Responses were similar regardless of concomitant therapies.

Table 12. Efficacy results at week 16 in COAST-X, NRI [a,b]

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

[a] *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.*

[b] *Patients with missing data were counted as non-responders.*

[c] *At week 0, patients received 80 mg or 160 mg of Taltz.*

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

[e] *Primary endpoint at week 16.*

[f] *The numbers of ITT patients with MRI data at baseline and week 16 are as follows: Taltz, n = 85; PBO, n = 90.*

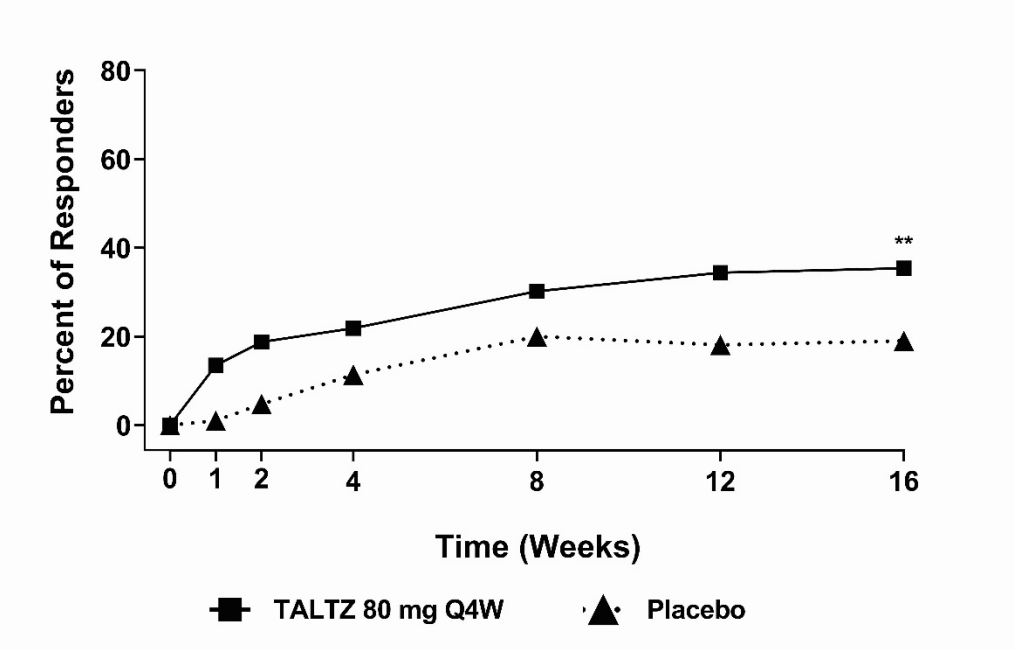
[g] *Patients with missing data were counted as non-responders. Percentages are based on the number of patients in the ITT population with baseline ASDAS ≥2.1.*

[h] *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 6. Percent of patients achieving ASAS40 response through week 16 in COAST-X, NRI[a]



[a] *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 12.

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 ≤5) at week 16 and week 52.

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.

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) µg/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) µg/ml, and 5.23 (3.19) µg/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) µg/ml, and 1.87 (1.30) µg/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 ≥ 65 years and n = 12 for age ≥ 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.

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

Sodium citrate
Citric acid, anhydrous
Sodium chloride
Polysorbate 80
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in a refrigerator (2 ºC to 8 ºC).
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 ºC.

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 prescribing information, 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.