▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

TALTZ (IXEKIZUMAB (RCH)) SOLUTION FOR INJECTION (CITRATE-FREE FORMULATION)

1. NAME OF THE MEDICINE

Ixekizumab (rch)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prefilled pen (autoinjector) or prefilled syringe contains ixekizumab 80 mg/mL.

TALTZ (ixekizumab (rch)) is a humanised immunoglobulin G subclass 4 (IgG4) monoclonal antibody (mAb) with neutralising activity against interleukin-17A (IL-17A). TALTZ is produced by recombinant DNA technology in a recombinant mammalian cell line and purified using standard technology for bioprocessing. Ixekizumab is comprised of two identical light chain polypeptides of 219 amino acids each and two identical heavy chain polypeptides of 445 amino acids each.

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

3. PHARMACEUTICAL FORM

TALTZ is supplied as a solution for injection.

The TALTZ solution is sterile, preservative free, clear and colourless to slightly yellow. The TALTZ solution has a pH of 5.2 to 6.2. TALTZ is administered as a subcutaneous (SC) injection. TALTZ is for single use, therefore contains no antimicrobial preservative.

TALTZ is available as a 1 mL single-dose prefilled pen (autoinjector) or a 1 mL single dose prefilled syringe. Each autoinjector or prefilled syringe is composed of ixekizumab (80 mg/mL).

The autoinjector and prefilled syringe each contain a 1 mL glass syringe with a fixed needle. The TALTZ autoinjector and prefilled syringe are manufactured to deliver 80 mg of ixekizumab. TALTZ is latex-free.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Plaque psoriasis

TALTZ is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Psoriatic arthritis

TALTZ is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately, or who are intolerant, to previous DMARD therapy.

TALTZ may be used as monotherapy or in combination with a conventional DMARD (e.g. methotrexate).

Axial spondyloarthritis

Ankylosing Spondylitis (Radiographic Axial Spondyloarthritis)

TALTZ is indicated for the treatment of active ankylosing spondylitis in adult patients.

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 MRI evidence, who have responded inadequately to, or are intolerant to, nonsteroidal anti-inflammatory drugs (NSAIDs).

4.2 DOSE AND ADMINISTRATION

Dosage

Plaque psoriasis

The recommended dose is 160 mg by SC injection (two 80 mg injections) at Week 0, followed by an 80 mg injection (one injection) every 2 weeks at Weeks 2, 4, 6, 8, 10 and 12, then 80 mg (one injection) every 4 weeks.

Psoriatic arthritis

The recommended dose is 160 mg by SC injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) every 4 weeks.

For psoriatic arthritis patients with coexistent moderate to severe plaque psoriasis, use the dosing regimen for plaque psoriasis.

Axial spondyloarthritis (radiographic and non-radiographic)

The recommended dose is 80 mg by subcutaneous injection every 4 weeks.

Conventional disease-modifying antirheumatic drugs (cDMARD) (e.g., sulfasalazine), corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and/or analgesics may be continued during treatment with ixekizumab.

Elderly patients (≥65 years)

No dose adjustment is required for elderly patients.

Renal impairment or hepatic impairment

TALTZ has not been studied in these patient populations. No dosage recommendations can be made.

Method of administration

TALTZ is for SC injection. After training in SC injection technique, a patient may self-inject with ixekizumab.

If possible, areas of the skin that show psoriasis should be avoided as injection sites.

TALTZ is for single-use in one patient only. Discard any residual product.

Special precautions for handling

The *Instructions for Use* included as a pack insert must be followed carefully.

Do not use TALTZ if it has been frozen.

4.3 CONTRAINDICATIONS

TALTZ is contraindicated in patients with known serious hypersensitivity to ixekizumab or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Infections

TALTZ may increase the risk of infections. In clinical trials, a higher rate of infection such as upper respiratory tract infection, oral candidiasis, conjunctivitis and tinea infections were observed in TALTZ treated patients compared to placebo **(see section 4.8 Adverse effects (Undesirable Effects)).**

TALTZ should be used with caution in patients with clinically important chronic or active infection. Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection or is not responding to standard therapy the patient should be closely monitored. TALTZ should be discontinued until the infection resolves.

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with TALTZ. Do not administer TALTZ to patients with active TB infection. Initiate treatment of latent TB prior to administering TALTZ. Consider anti-TB therapy prior to initiation of TALTZ in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving TALTZ should be monitored closely for signs and symptoms of active TB during and after treatment.

Hypersensitivity

Serious hypersensitivity reactions, including some cases of anaphylaxis, angioedema and urticaria, have been reported. If a serious hypersensitivity reaction occurs, administration of TALTZ should be discontinued immediately and appropriate therapy initiated.

Inflammatory bowel disease

Crohn's disease and ulcerative colitis, including exacerbations, occurred at a greater frequency in the TALTZ 80 mg Q2W group (Crohn's disease 0.1%, ulcerative colitis 0.2%)

than the placebo group (0%) during the 12-week, placebo-controlled period of the psoriasis clinical trials.

Crohn's disease and ulcerative colitis, including exacerbations, occurred in 2 patients (1.0%) and 1 patient (0.5%), respectively, in the TALTZ 80 mg Q4W group and 1 patient (0.5%) and 0%, respectively, in the placebo group during the 16-week, placebo-controlled period of the ankylosing spondylitis clinical trials.

Exercise caution when prescribing TALTZ to patients with inflammatory bowel disease, including Crohn's disease and ulcerative colitis, as new cases or exacerbations have been reported. Patients treated with TALTZ and who have inflammatory bowel disease should be monitored closely.

Immunisations

Consider completion of all age appropriate immunisations according to current immunisation guidelines **before commencing Taltz**.

TALTZ should not be used with live vaccines. No data are available on the response to live vaccines.

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

Use in the elderly

Of the 4204 psoriasis patients exposed to TALTZ in clinical trials, a total of 265 patients were aged ≥65 years and 34 patients were aged ≥75 years. Of the 1118 PsA patients exposed to TALTZ in clinical trials, a total of 122 patients were aged ≥65 years and 6 patients were aged ≥75 years. Although no differences in safety or efficacy were observed between older and younger patients, the number of patients aged ≥65 years is not sufficient to determine whether they respond differently from younger patients. **(See section 5.2 Pharmacokinetic properties, Special populations, Elderly Patients (≥65 years)).**

Paediatric use

Safety and effectiveness of TALTZ in paediatric patients (<18 years of age) have not been evaluated.

Effects on laboratory tests

No information on the effect of ixekizumab on laboratory tests is available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The safety of ixekizumab in combination with other immunomodulatory agents or phototherapy has not been evaluated.

Cytochrome P450 Substrates

Results from a drug-drug interaction study in patients with moderate-to-severe psoriasis determined that administration of ixekizumab with drugs 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 drugs.

No interaction was seen when TALTZ was administered concomitantly with methotrexate and/or corticosteroids in patients with psoriatic arthritis.

The clearance of ixekizumab was not affected by concomitant administration of oral corticosteroids, NSAIDs, or cDMARDs (i.e., sulfasalazine and methotrexate).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of ixekizumab on human fertility have not been evaluated. In animal studies, ixekizumab did not indicate harmful effects with respect to fertility as assessed by a lack of effects on reproductive organs, menstrual cycles or sperm in sexually mature cynomolgus monkeys that received ixekizumab for 13 weeks at a weekly SC dose of 50 mg/kg (at least 50 times the human exposure at 80 mg every 2 weeks based on AUC). The monkeys were not mated to evaluate fertility.

Use in pregnancy

Category C

There are no adequate and well controlled studies of TALTZ in pregnant women to establish the safety of TALTZ during pregnancy. The mechanism of action of ixekizumab suggests a theoretical risk that its use during pregnancy may affect neonatal immunity.

In developmental toxicity studies, SC administration of ixekizumab at doses up to 50 mg/kg once weekly to cynomolgus monkeys from the beginning of organogenesis through either near term pregnancy or until delivery of offspring, produced no embryotoxicity or teratogenicity, and no effects on offspring delivery, or on morphological, functional or immunological development of offspring from birth to 6 months of age. Ixekizumab was shown to cross the placenta and was present in the blood of offspring up to 6 months of age.

TALTZ should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in lactation

It is not known whether ixekizumab is excreted in human milk or absorbed systemically after ingestion. In a pre-/postnatal development study, ixekizumab was excreted at low levels in the milk of cynomolgus monkeys that had been dosed with ixekizumab during pregnancy until delivery of offspring. Ixekizumab was present in the blood of offspring, due primarily to placental transfer. 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no known effects on the ability to drive or use machines associated with the use of TALTZ.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials experience in plaque psoriasis

A total of 4204 plaque psoriasis patients were treated with TALTZ in clinical trials. Of these, 2190 patients were exposed to treatment with TALTZ for at least one year.

Three placebo-controlled phase III trials (UNCOVER-1, UNCOVER-2 and UNCOVER-3) in plaque psoriasis patients were integrated to evaluate the safety of TALTZ in comparison to placebo up to 12 weeks. In two of the clinical trials (UNCOVER-2 and UNCOVER-3), the safety of TALTZ included a comparison to an active comparator, etanercept, up to 12 weeks after treatment initiation **(see section 5.1 Pharmacodynamic properties, Mechanism of action, Clinical trials, Plaque Psoriasis)**. In total, 3858 patients were evaluated (1167 to TALTZ 80 mg every 2 weeks [Q2W], 1161 to TALTZ 80 mg every 4 weeks [Q4W], 739 to etanercept 50 mg twice weekly group and 791 to placebo group).

The most frequently reported adverse reactions were injection site reactions and upper respiratory tract infections (most frequently nasopharyngitis). Most of the reactions were mild or moderate in severity.

Adverse reactions that occurred at a rate of at least 1% and at a higher rate in the TALTZ groups compared to the placebo group during the placebo-controlled 12 week period of UNCOVER-1, UNCOVER-2 and UNCOVER-3 are summarised in Table 1.

Table 1. Adverse Drug Reactions Reported by ≥1% of Patients with Plaque Psoriasis through Week 12 in Phase III Clinical Trials

Adverse Reactions	TALTZ		Etanercept[b]	Placebo
	80 mg Q2W (N=1167) (n%)	80 mg Q4W (N=1161) (n%)	50 mg twice weekly (N=739) (n%)	(N=791) (n%)
Injection site reactions	196 (16.8%)	150 (12.9%)	121 (16.4%)	26 (3.3%)
Upper respiratory tract infection[a]	163 (14.0%)	155 (13.4%)	92 (12.4%)	101 (12.8%)
Nausea	23 (2.0%)	15 (1.3%)	3 (0.4%)	5 (0.6%)
Oropharyngeal pain	16 (1.4%)	20 (1.7%)	7 (0.9%)	4 (0.5%)
Tinea infections	17 (1.5%)	10 (0.9%)	1 (0.1%)	1 (0.1%)

N=number of patients in the integrated analysis population; n=number of patients.
[a] Upper respiratory tract infection includes: nasopharyngitis and upper respiratory tract infection
[b] Etanercept data from UNCOVER-2 and UNCOVER-3 only.

Adverse reactions that occurred at rates less than 1% in the placebo-controlled clinical trials UNCOVER-1, UNCOVER-2 and UNCOVER-3 through to week 12 included: influenza, rhinitis, conjunctivitis, urticaria, oral candidiasis and inflammatory bowel disease (including Crohn's disease and ulcerative colitis).

In the two clinical trials that included etanercept (UNCOVER-2 and UNCOVER-3), the rate of serious adverse events was 1.9% for both etanercept and 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 the majority of events being mild to moderate in severity. The rate of serious infections was 0.4% for etanercept and 0.5% for TALTZ.

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.

Infections

The majority of infections consisted of non-serious and mild to moderate adverse reactions such as nasopharyngitis and upper respiratory tract infection, which did not necessitate treatment discontinuation.

In the placebo-controlled period of the phase III clinical trials in plaque psoriasis, infections were reported in 27.2% of patients treated with TALTZ compared with 22.9% of patients treated with placebo.

Serious infections occurred in 13 (0.6%) patients treated with TALTZ and in 3 (0.4%) patients treated with placebo **(see section 4.4 Special warnings and precautions for use, Infections).** Infection-related serious adverse events (SAEs) reported by more than 1 patient in the TALTZ treated group were cellulitis (n=3), appendicitis (n=2) and erysipelas (n=2). The proportion of patients who discontinued due to an infection related adverse reaction was similar in the total TALTZ treated group (n=8 [0.3%]) and the placebo group (n=2 [0.3%]).

Consistent with the mechanism of action, there was an increase in oral candidiasis. All, except one case, were mild or moderate in severity. No SAEs or discontinuations from treatment due to candidiasis were reported.

Overall, infections were reported in 52.8% of patients treated with TALTZ (46.9 per 100 patient years) and serious infections were reported in 1.6% of patients treated with TALTZ (1.5 per 100 patient years).

Laboratory Assessment of Neutropenia

Neutropenia was observed in clinical trials. In general, neutropenia was transient and did not require discontinuation of TALTZ, and was not associated with an increased rate of infections. In the placebo-controlled period of clinical trials, neutropenia ≥ Grade 3 (<1,000 cells/mm^3) was observed infrequently (0.1%) in patients receiving TALTZ compared to etanercept (0.5%) and placebo (0.1%). The remaining cases of neutropenia were low grade, either Grade 2 (2.0% for TALTZ, 3.3% for etanercept and 0.3% for placebo; ≥1,000 to <1,500 cells/mm^3) or Grade 1 (5.7% for TALTZ, 9.0% for etanercept and 2.3% for placebo; ≥1,500 cells/mm^3 up to normal).

Immunogenicity

In the psoriasis clinical trials, approximately 9% to 17% of patients treated with ixekizumab at the recommended dosing regimen developed anti-drug antibodies, the majority of which were low titre 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.

Clinical trials experience in psoriatic arthritis

A total of 779 patients with active psoriatic arthritis were evaluated in two placebo-controlled phase III clinical trials SPIRIT-P1 and SPIRIT-P2 (229 patients on TALTZ 80 mg

every 4 weeks (Q4W), 225 patients on TALTZ 80 mg every 2 weeks (Q2W), 101 patients on adalimumab 40 mg every 2 weeks and 224 patients on placebo).

Table 2. Adverse Drug Reactions Reported by ≥1% of Patients with Active Psoriatic Arthritis through Week 24 in Phase III Clinical Trials

Adverse Reactions	TALTZ		Adalimumab[a]	Placebo
	80 mg Q4W (N=229) (n%)	80 mg Q2W (N=225) (n%)	40 mg Q2W (N=101) (n%)	(N=224) (n%)
Injection site reactions	40 (17.5%)	57 (25.3%)	6 (5.9%)	10 (4.5%)
Upper respiratory tract[b] infection	33 (14.4%)	23 (10.2%)	11 (10.9%)	25 (11.2%)
Nausea	1 (0.4%)	5 (2.2%)	4 (4.0%)	3 (1.3%)
Oropharyngeal pain	7 (3.1%)	2 (0.9%)	0	1 (0.4%)
Rhinitis	1 (0.4%)	4 (1.8%)	1 (1.0%)	0
Conjunctivitis	3 (1.3%)	3 (1.3%)	0	0
Influenza	3 (1.3%)	1 (0.4%)	2 (2.0%)	1 (0.4%)
Oral candidiasis	1 (0.4)	4 (1.8%)	0	0

N=number of patients in the integrated analysis population; n=number of patients.
[a] adalimumab data from SPIRIT-P1 only
[b] Upper respiratory tract infection includes: Upper respiratory tract infection, Nasopharyngitis and Viral upper respiratory tract

Adverse reactions that occurred in patients treated with ixekizumab at rates less than 1% in the placebo-controlled clinical trials SPIRIT-P1 and SPIRIT-P2 through to week 24 included tinea and urticaria.

During the 24-week placebo-controlled period of SPIRIT-P1 and SPIRIT-2, the proportion of patients with treatment-emergent adverse events was higher in the TALTZ 80 mg Q4W group compared to the placebo group (67% and 57%, respectively). The rate of SAEs was 3.9% (TALTZ 80mg Q4W), 4.9% (TALTZ 80mg Q2W), 2.7% (placebo), and the discontinuation due to adverse events were 3.1% (TALTZ 80mg Q4W), 5.3% (TALTZ 80mg Q2W), 3.6% (placebo).

Infections

In the double-blind treatment period of the phase III clinical studies in psoriatic arthritis, infections were reported in 32.8% of patients treated with TALTZ for up to 24 weeks compared with 27.7% 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 1.3% of patients treated with TALTZ and in 0% of patients treated with placebo. Over the entire ixekizumab exposure treatment period, infections were reported in 37.2% of patients treated with TALTZ (39.6 per 100 patient years). Serious infections were reported in 1.3% of patients treated with TALTZ (1.4 per 100 patient years).

Laboratory Assessment of Neutropenia

In psoriatic arthritis studies, 1.9% 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. 0.3% of patients receiving TALTZ developed a neutrophil count <1000 cells/mm^3. In general, neutropenia did not require discontinuation of TALTZ.

Immunogenicity

In psoriatic arthritis patients treated with ixekizumab at the recommended dosing regimen up to 52 weeks, approximately 11% (n = 12) developed anti-drug antibodies, the majority of which were low titre. Approximately 8% (n = 8) had confirmed neutralising antibodies, which were first detected at Week 24 (n=2), Week 32 (n=2), Week 36 (n=3) and Week 52 (n=1). No apparent association between the presence of neutralising antibodies and impact on drug concentration or efficacy was observed.

Clinical trials experience in axial spondyloarthritis (radiographic and non-radiographic)

TALTZ was studied in three placebo-controlled trials in patients with axial spondyloarthritis. A total of 868 patients were studied (574 patients on TALTZ (Q2W and Q4W) and 294 on placebo). A total of 291 patients in these trials received TALTZ 80 or 160 mg at Week 0, followed by 80 mg every 4 weeks (Q4W). Overall, the safety profile observed in patients with radiographic axial spondyloarthritis treated with TALTZ Q4W is consistent with the safety profile in patients with plaque psoriasis with the exception of rhinitis (1%).

Compared to all patients, adverse drug reactions in patients treated with ixekizumab (80 mg or 160 mg at week 0) by subcutaneous injection followed by 80 mg every 4 weeks in the axial spondyloarthritis clinical trials were similar, with the exception of:

- the frequency of inflammatory bowel disease (common) and rhinitis (common) in radiographic axial spondyloarthritis, and
- frequency of inflammatory bowel disease (common), influenza (common) and conjunctivitis (common) in non-radiographic axial spondyloarthritis.

Table 3. TEAEs occurring in ≥ 1% of patients with radiographic and non-radiographic axial spondyloarthritis weeks 0 to 16

Treatment Group	**PBO** **N = 294**	**IXE Q4W** **N = 291**
Category, n (%)	138 (46.9)	162 (55.7)
Injection site reaction	7 (2.4)	13 (4.5)
Nasopharyngitis	15 (5.1)	24 (8.2)
Upper respiratory tract infection	9 (3.1)	19 (6.5)
Headache	3 (1.0)	7 (2.4)
Injection site erythema	2 (0.7)	6 (2.1)
Diarrhoea	4 (1.4)	8 (2.7)
Arthralgia	4 (1.4)	10 (3.4)
Hypertension	8 (2.7)	6 (2.1)
Pharyngitis	4 (1.4)	6 (2.1)
Injection site pain	5 (1.7)	5 (1.7)
Back pain	5 (1.7)	3 (1.0)
Blood creatine phosphokinase increased	2 (0.7)	3 (1.0)
Pruritus	0	3 (1.0)
Iridocyclitis	2 (0.7)	4 (1.4)
Bronchitis	3 (1.0)	4 (1.4)

Oropharyngeal pain	0	5 (1.7)
Oral herpes	4 (1.4)	4 (1.4)
Musculoskeletal pain	2 (0.7)	4 (1.4)
Myalgia	4 (1.4)	2 (0.7)
Aspartate aminotransferase increased	3 (1.0)	3 (1.0)
Neck pain	2 (0.7)	3 (1.0)
Sinusitis	2 (0.7)	3 (1.0)
Fatigue	1 (0.3)	3 (1.0)
Gastroenteritis	0	3 (1.0)
Respiratory tract infection	0	3 (1.0)
Alanine aminotransferase increased	3 (1.0)	4 (1.4)
Rash	3 (1.0)	0
Abdominal pain	3 (1.0)	2 (0.7)
Pyrexia	3 (1.0)	2 (0.7)
Dizziness	3 (1.0)	3 (1.0)
Alopecia	1 (0.3)	3 (1.0)
Non-cardiac chest pain	1 (0.3)	3 (1.0)
Vulvovaginal candidiasis[a]	1 (1.1)	1 (1.2)
Bacterial vaginosis[a]	0	1 (1.2)
Bartholinitis[a]	0	1 (1.2)
Ovarian cyst[a]	0	1 (1.2)
Conjunctivitis	3 (1.0)	1 (0.3)
Fungal skin infection	0	3 (1.0)
Depression	5 (1.7)	0
Eye pain	3 (1.0)	0
Dysuria	4 (1.4)	0
Menstrual disorder[a]	1 (1.1)	0
Menstruation irregular[a]	1 (1.1)	0
Uterine dilation and curetage[a]	1 (1.1)	0
Anaemia	3 (1.0)	0

Abbreviations: ADR = adverse drug reaction; IXE = ixekizumab; IXE Q4W = ixekizumab 80 mg every 4 weeks; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; TEAE = treatment-emergent adverse event.

[a] Denominator adjusted because gender-specific event for females: N = 95 (Placebo), N = 82 (Ixekizumab 80 mg Q4W)

Injection site reactions

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 of TALTZ in the axial spondyloarthritis studies.

Infections

Infection rates observed in axial spondyloarthritis clinical studies were similar to those observed in psoriatic arthritis and 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

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

Immunogenicity

In radiographic axial spondyloarthritis patients treated with ixekizumab at the recommended dosing regimen up to 16 weeks, 10 patients (5.2%) developed anti-drug antibodies, the majority of which were low titre, and 3 patients (1.5%) had neutralising antibodies.

In non-radiographic axial spondyloarthritis patients treated with ixekizumab at the recommended dosing regimen for up to 52 weeks, 5 patients (8.9%) developed anti-drug antibodies, all of which were low titre; no patient had neutralising antibodies. 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.

Postmarketing data

The following undesirable effect (adverse drug reaction) is based on postmarketing spontaneous reports:

Immune system disorders:

Anaphylaxis: Rare (≥ 0.01%, <0.1%)

Infections and infestations:

Oesophageal candidiasis: Rare (≥ 0.01%, <0.1%)

Skin and subcutaneous tissue disorders:

Eczematous eruptions including:
- Dyshidrotic eczema: Uncommon (≥0.1% - <1%)
- Exfoliative dermatitis: Rare (≥0.01% - <0.1%)

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Doses up to 180 mg have been administered subcutaneously in clinical trials without dose-limiting toxicity. Overdoses up to 240 mg 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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Ixekizumab is an IgG4 monoclonal antibody that binds with high affinity (<3 pM) to IL-17A, a proinflammatory cytokine. Ixekizumab does not bind to ligands IL-17B, IL 17C, IL-17D, IL-17E or IL-17F. Elevated levels of IL-17A have been implicated in the pathogenesis of a variety of autoimmune diseases. In psoriasis, the IL-17A ligand plays a major role in driving excess keratinocyte proliferation and activation. Neutralisation of IL-17A by ixekizumab inhibits these actions.

In vitro binding assays showed that ixekizumab does not bind to human Fcγ receptors I, IIa and IIIa or to complement component C1q and is therefore not expected to elicit Fc-receptor mediated effects (e.g., antibody-dependent cell-mediated cytotoxicity, complement system activation).

Pharmacodynamics

Ixekizumab modulates biological responses that are induced or regulated by IL-17A.

Healthy individuals who received ixekizumab had similar antibody responses 1 month after vaccination with tetanus and pneumococcal vaccines compared to individuals who did not receive ixekizumab. The clinical effectiveness of vaccines has not been assessed in patients undergoing treatment with ixekizumab.

Clinical trials

Plaque Psoriasis

The efficacy and safety of TALTZ were assessed in three randomised, double-blind, placebo-controlled phase III clinical trials in adult patients with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy (UNCOVER-1 [RHAZ], UNCOVER-2 [RHBA] and UNCOVER-3 [RHBC]). Patients were ≥18 years of age with plaque psoriasis who had a minimum body surface area involvement of 10%, a static Physician Global Assessment (sPGA) score of ≥3 and Psoriasis Area and Severity Index (PASI) score ≥12. Patients with guttate, erythrodermic or pustular psoriasis were excluded from clinical trials.

The efficacy and safety of TALTZ were also evaluated compared to etanercept (UNCOVER-2 and UNCOVER-3). Patients randomised to TALTZ who were responders (sPGA 0 (clear) or 1 (minimal) at Week 12) were re-randomised to receive TALTZ or placebo for an additional 48 weeks (UNCOVER-1 and UNCOVER-2). Patients randomised to placebo, etanercept or TALTZ who were non-responders (sPGA ≥1 at Week 12) received TALTZ for up to 48 weeks.

Of the 3866 patients enrolled in the placebo-controlled trials, 64% had received prior systemic therapy (biologic, conventional systemic or PUVA), 43.5% had received prior phototherapy, 49.3% had received prior conventional systemic therapy and 26.4% had received prior biologic therapy for the treatment of psoriasis. Of all patients, 14.9% had received at least one anti-TNF alpha agent and 8.7% had received an anti-IL-12/IL-23. A total of 23.4% of patients had a history of psoriatic arthritis.

In all three clinical trials, the primary endpoints were the proportion of patients who achieved at least a 75% reduction in PASI score (PASI 75) from baseline to Week 12 and an sPGA (0,1) with at least a 2-point improvement from baseline. The sPGA is a 6 category scale ranging from 0 (clear) to 5 (very severe) that indicates the physician's overall assessment of psoriasis based on plaque thickness/induration, erythema and scaling.

Other evaluated outcomes included the proportion of patients with a sPGA 0, a reduction of at least 90% in PASI (PASI 90), a reduction of 100% in PASI (PASI 100) and an improvement of itch severity as measured by an Itch Numeric Rating Scale (Itch NRS).

Patients in all treatment groups had a median baseline PASI score ranging from approximately 17.4 to 18.3. Baseline sPGA score was severe or very severe in 51.2% of patients in UNCOVER-1, 49.7% in UNCOVER-2 and 48.3% in UNCOVER-3.

Clinical Response at Week 12

UNCOVER-1 enrolled 1296 patients, randomised to receive either TALTZ (80 mg every two or four weeks [Q2W or Q4W]) following a 160 mg starting dose (two injections) at Week 0, or placebo for 12 weeks (see Table 4).

Table 4. Efficacy Results at Week 12 in UNCOVER-1

	UNCOVER-1 – Number of Patients (%), NRI		
	TALTZ		**Placebo**
	80 mg Q2W (N=433)	**80 mg Q4W (N=432)**	**(N=431)**
sPGA of (0,1)	354 (81.8%)[a]	330 (76.4%)[a]	14 (3.2%)
PASI 75	386 (89.1%)[a]	357 (82.6%)[a]	17 (3.9%)
sPGA 0	160 (37.0%)[a]	149 (34.5%)[a]	0
PASI 90	307 (70.9%)[a]	279 (64.6%)[a]	2 (0.5%)
PASI 100	153 (35.3%)[a]	145 (33.6%)	0
Itch NRS Reduction ≥4[b]	336 (85.9%)[a]	305 (80.5 %)[a]	58 (15.5%)

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

[a] p<0.001 compared with placebo

[b] Patients with Itch NRS ≥4 at baseline: TALTZ 80 mg Q2W N=391, TALTZ 80 mg Q4W N=379, placebo N=374.

In the UNCOVER-2 and UNCOVER-3 trials, 1224 patients and 1346 patients were enrolled, respectively. Patients were randomised to receive either TALTZ (80 mg Q2W or Q4W) following a 160 mg starting dose at Week 0, placebo or etanercept 50 mg twice weekly for 12 weeks (see Table 5).

Table 5. Efficacy Results at Week 12 in UNCOVER-2 and UNCOVER-3

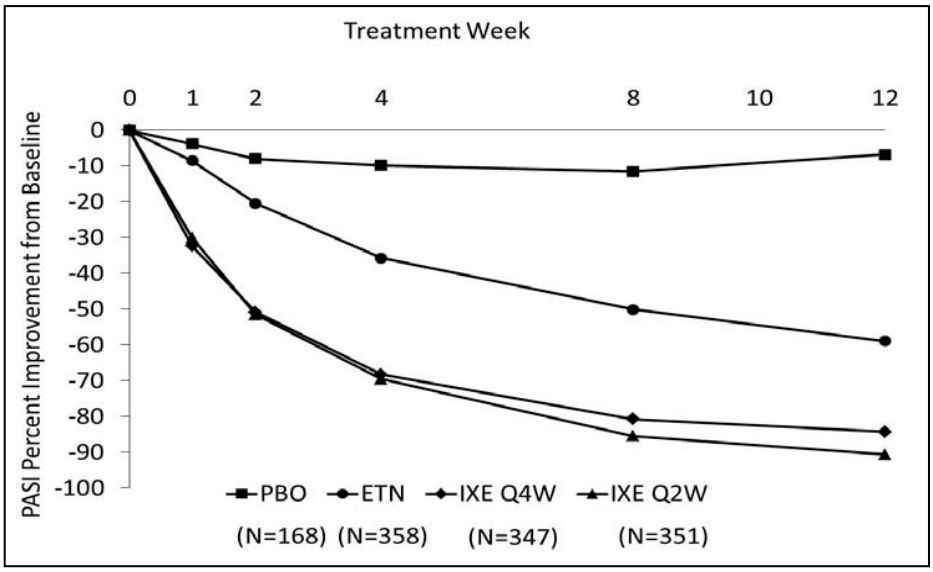
	UNCOVER-2 Number of Patients (%), NRI				UNCOVER-3 Number of Patients (%), NRI			
	TALTZ		Etanercept	Placebo	TALTZ		Etanercept	Placebo
	80 mg Q2W (N=351)	80 mg Q4W (N=347)	50 mg twice/week (N=358)	(N=168)	80 mg Q2W (N=385)	80 mg Q4W (N=386)	50 mg twice/week (N=382)	(N=193)
sPGA (0,1)	292 (83.2%)[a,b]	253 (72.9%)[a,b]	129 (36.0%)	4 (2.4%)	310 (80.5%)[a,b]	291 (75.4%)[a,b]	159 (41.6%)[a]	13 (6.7%)
PASI 75	315 (89.7%)[a,b]	269 (77.5%)[a,b]	149 (41.6%)[a]	4 (2.4%)	336 (87.3%)[a,b]	325 (84.2%)[a,b]	204 (53.4%)[a]	14 (7.3%)
sPGA 0	147 (41.9%)[a,c]	112 (32.3%)[a,c]	21 (5.9%)[d]	1 (0.6%)	155 (40.3%)[a,c]	139 (36.0%)[a,c]	33 (8.6%)[a]	0
PASI 90	248 (70.7%)[a,c]	207 (59.7%)[a,c]	67 (18.7%)[a]	1 (0.6%)	262 (68.1%)[a,c]	252 (65.3%)[a,c]	98 (25.7%)[a]	6 (3.1%)
PASI 100	142 (40.5%)[a,c]	107 (30.8%)[a,c]	19 (5.3%)[d]	1 (0.6%)	145 (37.7%)[a,c]	135 (35.0%)[a,c]	28 (7.3%)[a]	0
Itch NRS Reduction ≥4[e]	258 (85.1%)[f,c]	225 (76.8%)[f,c]	177 (57.8%)[f]	19 (14.1%)	264 (82.5%)[a,c]	250 (79.9%)[a,c]	200 (64.1%)[a]	33 (20.9%)

Abbreviations: N=number of patients in the intent-to-treat population; NRI=Non-Responder Imputation.
[a] p<0.001 compared with placebo, adjusted for multiplicity.
[b] Superior to etanercept using retention rate approach.
[c] p<0.001 compared with etanercept.
[d] p<0.01 compared with placebo.
[e] Patients with Itch NRS ≥ 4 at baseline: TALTZ 80 mg Q2W N=303, TALTZ 80 mg Q4W N=293, etanercept N=306, placebo N=135.
[f] p<0.001 compared with placebo.

The TALTZ 80 mg Q2W dose regimen provided superior efficacy (p<0.001) at Week 12 across all endpoints for all three clinical trials. Further, all TALTZ treatment groups consistently demonstrated superiority to placebo and to etanercept in achieving high rates of response (PASI 90) and complete resolution of psoriatic plaque (PASI 100). Further, TALTZ treatment groups had significantly greater improvements in itch severity, as early as Week 1 compared to placebo and to etanercept (p<0.001). The percentage of patients achieving a sPGA 0 (clear) or 1 (minimal) was statistically significant compared to placebo as early as Week 1 in all three clinical trials.

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).

Figure 1. PASI Score (Mean), Percent Improvement at Each Post Baseline Visit (LOCF) in the Intent-to-Treat Population During the Induction Dosing Period – UNCOVER-2



Note: Comparisons between each group were statistically significant ($p<0.001$) at each visit.

The efficacy and safety of TALTZ was demonstrated regardless of age, gender, race, body weight, PASI baseline severity and previous treatment with a biologic. Responses to TALTZ were consistent among patients who had nail psoriasis, facial psoriasis or scalp psoriasis at baseline.

TALTZ was efficacious in systemic treatment-naïve, biologic-naïve, biologic/anti-TNF-exposed and biologic/anti-TNF-failure patients. Improvements in sPGA and PASI endpoints in patients with concurrent psoriatic arthritis at baseline were similar to those in the overall moderate to severe plaque psoriasis population. Approximately 45% of patients had baseline facial psoriasis. Of these patients, 80.4% of patients treated with TALTZ had complete resolution of their facial psoriasis at Week 12.

Maintenance of Response

To evaluate the maintenance of response, patients originally randomised to TALTZ and who were responders at Week 12 (sPGA 0,1) in UNCOVER-1 and UNCOVER-2 trials, were re-randomised to an additional 48 weeks of one of the following treatment regimens: TALTZ 80 mg Q4W, TALTZ 80 mg Q12W or placebo. Patients who were non-responders (sPGA >1) at Week 12 and who relapsed (sPGA ≥3) during the maintenance period were placed on TALTZ 80 mg Q4W.

For responders at Week 12, the percentage of patients who maintained this response at Week 60 was higher for patients treated with TALTZ 80 mg Q4W (71%) compared to those treated with TALTZ 80 mg Q12W (35.5%) or placebo (7%). Further, of the responders at Week 12 who were treated with maintenance Q4W dosing, the proportion who maintained or achieved complete resolution of psoriatic plaques at Week 60 as measured by a sPGA (0) or PASI 100 was 52.0% and 51.4%, respectively. Additionally, 76.4% of patients achieved or maintained a PASI <5 at Week 60.

The response rates for those patients re-randomised to the recommended maintenance dose of TALTZ 80 mg Q4W based on induction dose are provided in Table 6.

Table 6. Maintenance of Response and Efficacy at Week 60 (Studies UNCOVER-1 and UNCOVER-2) for Patients Treated with 80 mg Q4W Maintenance Dosing Regimen Based on Induction Dosing Regimen; NRI

Endpoints at Week 60	80 mg Q4W (induction) / Placebo (maintenance) (N=181)	80 mg Q2W (induction) / Placebo (maintenance) (N=203)	80 mg Q4W (induction) / 80 mg Q4W (maintenance) (N=167)	80 mg Q2W (induction) / 80 mg Q4W (maintenance) (N=181)
Maintained sPGA (0,1)	6.1%	7.4%	67.1%	74.6%
Maintained or Achieved sPGA 0	1.1%	3.0%	48.5%	55.2%
Maintained or Achieved PASI 75	6.6%	7.9%	73.1%	80.1%
Maintained or Achieved PASI 90	3.3%	4.4%	65.9%	72.9%
Maintained or Achieved PASI 100	1.1%	3.0%	49.1%	53.6%

Abbreviations: N=number of patients in the integrated analysis population; NRI=Non-Responder Imputation

The improvements in itch severity were sustained up to Week 60 in patients treated with TALTZ who were responders at Week 12. TALTZ was efficacious in the maintenance of response in systemic treatment-naïve, biologic-naïve, biologic/anti-TNF-exposed and biologic/anti-TNF-failure patients.

For responders at Week 12 re-randomised to treatment withdrawal (i.e. placebo), the median time to relapse (sPGA ≥3) was 148 days in integrated UNCOVER-1 and UNCOVER-2 trials. Among these patients, 69.6% regained at least a sPGA (0,1) response within 12 weeks of restarting treatment with TALTZ 80 mg Q4W.

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]), in facial psoriasis (as measured by proportion who had complete resolution) and in palmoplantar psoriasis (as measured by Psoriasis Palmoplantar Severity Index [PPASI]). These improvements in nail, scalp and palmoplantar psoriasis were maintained at Week 60 in patients treated with TALTZ who were responders at Week 12.

Efficacy in Non-Responders to Etanercept

In the UNCOVER-2 clinical trial, patients identified as non-responder to etanercept (sPGA >1 at Week 12) were switched to TALTZ 80 mg Q4W after a 4-week washout period (N=200). Of these, 73% and 83.5% of patients were able to achieve sPGA (0,1) and PASI 75, respectively, after 12 weeks treatment with TALTZ. In the subset of etanercept non-responders who were biologic-naïve at baseline (N=154), the sPGA (0,1) and PASI 75 after 12 weeks of treatment with TALTZ were consistent (72.7% and 83.8%, respectively) with the overall etanercept non-responder population.

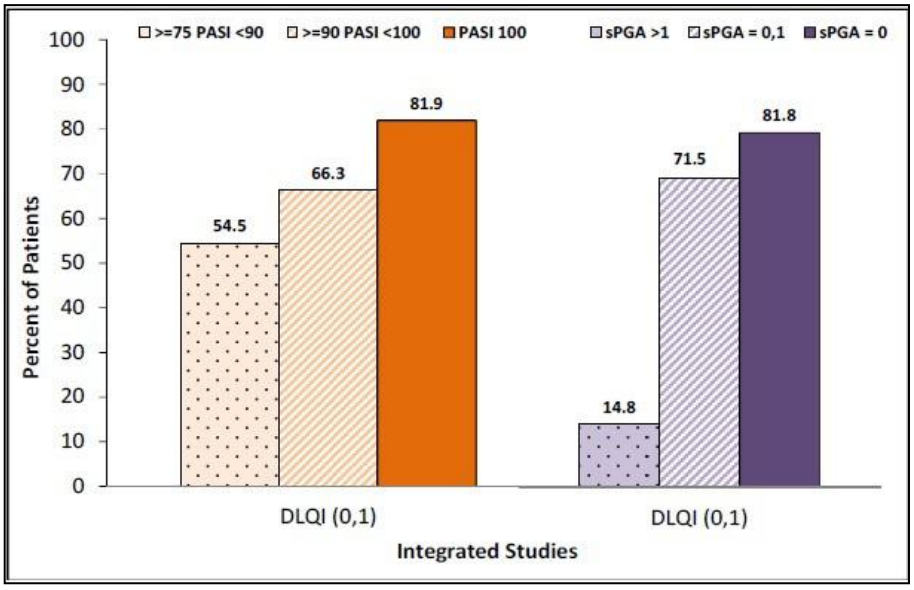
Quality of Life

Across all clinical trials at Week 12, TALTZ was associated with statistically significant improvement in Health-Related Quality of Life (HRQoL) as measured by the Dermatology Life Quality Index (DLQI). A DLQI (0,1) indicates no impact of psoriasis on quality of life. A significantly greater proportion of patients treated with TALTZ achieved a DLQI (0,1) compared with patients treated with placebo or etanercept, with higher response rates for the TALTZ Q2W group than for the Q4W group.

Across all treatments, patients who achieved sPGA (0) at Week 12 reported higher rates of DLQI (0,1) than patients who achieved sPGA (0,1), who likewise had higher DLQI (0,1) response rates than patients who achieved sPGA (>1). Similarly, each incremental increase in

PASI was associated with greater responses of DLQI (0,1). For patients who achieved complete resolution of their psoriasis at 12 weeks, 82% reported that their psoriasis no longer had impact on their HRQoL (see Figure 2).

Figure 2. DLQI (0,1) Status at Week 12 by Level of Clinical Response (PASI or sPGA) at Week 12 (NRI), Intent-to-Treat Population, Integrated Analysis (UNCOVER-1, UNCOVER-2 and UNCOVER-3)



Abbreviations: NRI=Non-Responder Imputation
Note: For PASI and sPGA categories, comparisons between each group were statistically significant (p<0.001).

The statistically significant superior benefit of TALTZ over placebo and etanercept was seen as early as Week 2, increased over time to Week 12 and was sustained up to Week 60 in patients treated with TALTZ who were responders (sPGA 0,1) at Week 12. At Week 12 and in comparison with etanercept and placebo, TALTZ was associated with a significantly greater decrease in skin pain (measured by the Skin Pain Visual Analogue Scale), greater improvements in the physical and mental component summary scores of the SF-36; patients treated with TALTZ also reported feeling significantly less bothered by redness/discolouration, thickness and scaling/flaking of skin as measured by the PSAB (Psoriasis Skin Appearance and Bothersomeness).

In patients treated with TALTZ who were responders at Week 12, these additional benefits were maintained up to Week 60. At Week 12 and in comparison with etanercept and placebo, TALTZ was associated with statistically significant improvement in depression as measured by the QIDS-SR16 and productivity as measured by the Work Productivity and Activity Impairment (WPAI).

Some patients who did not respond to the initial 12 weeks of treatment with TALTZ showed improvement in psoriasis with continued treatment up to 20 weeks. Patients not responding to TALTZ within 20 weeks of initial treatment are unlikely to respond to continued treatment.

Postmarketing Phase 3b, direct comparative study

Efficacy and safety of ixekizumab was also investigated in a double-blind study compared to ustekinumab with ixekizumab being superior on the primary study objective (PASI 90 response at week 12, Table 7). 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 ixekizumab versus ustekinumab was also demonstrated in the subgroups stratified by weight.

Table 7. PASI Response Rates from comparative study ixekizumab versus ustekinumab

	Week 12		Week 24		Week 52	
	Ixekizumab*	**Ustekinumab****	**Ixekizumab***	**Ustekinumab****	**Ixekizumab***	**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 was 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)

Genital Psoriasis

A randomized, 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 randomized 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 a Dermatology Quality of Life Index (DLQI).

Table 8. Efficacy Results at Week 12 in Adults with Genital Psoriasis in Trial IXORA-Q; NRIa

Endpoints	TALTZ	Placebo	Difference from placebo (95% CI)
Number of patients (N) randomized	**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 0,1b	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

The efficacy and safety of TALTZ were 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 in these studies had a diagnosis of psoriatic arthritis (Classification Criteria for Psoriatic Arthritis [CASPAR] criteria) for a median of 5.33 years. Randomised patients also 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. 58.9% and 22.3% of patients had dactylitis at baseline. For both studies, the primary endpoint was American College of Rheumatology (ACR) 20 response at Week 24.

In Psoriatic Arthritis Study 1 (SPIRIT-P1), patients naïve to biologic therapy with active psoriatic arthritis were randomised to subcutaneous injections of placebo, adalimumab 40 mg once every 2 weeks (active control reference arm), TALTZ 80 mg once every 4 weeks (Q4W), or TALTZ 80 mg once every 2 weeks (Q2W). Both TALTZ regimens included a 160 mg starting dose. In this study, 53% of patients had concomitant use of MTX at a mean weekly dose of 15.8 mg, with 67% of these patients receiving an MTX dose of 15 mg or greater. Most patients (85.3%) in this study had received prior treatment with ≥ 1 conventional disease-modifying anti-rheumatic drug (cDMARD). Patients in all treatment groups with an inadequate response at week 16 received rescue therapy (modification to background therapy). Patients on TALTZ Q4W or Q2W remained on their originally assigned dose of TALTZ. Patients receiving adalimumab or placebo were re-randomised 1:1 to TALTZ Q4W or Q2W at week 16 or 24 based on responder status.

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): 56% and 35% of patients were inadequate responders to 1 TNF or 2 TNFs, respectively. SPIRIT-P2 evaluated 363 patients, of whom 41% had concomitant use of MTX at a mean weekly dose of 16.1 mg. Of the patients with concomitant MTX, 73.2% had a dose of 15 mg or greater. Patients in all treatment groups with an inadequate response at week 16 received rescue therapy (modification to background therapy). Patients in TALTZ Q4W or Q2W remained on their originally assigned dose of TALTZ. Patients receiving placebo were re-randomised 1:1 to TALTZ Q4W or Q2W at week 16 or 24 based on responder status.

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

Endpoints	SPIRIT-P1 Anti-TNFα naive						SPIRIT-P2 Anti-TNFα - experienced				
					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
ACR20 response, n (%)[d]											
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]
ACR50 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]
ACR70 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, n (%)[e]											
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]
PASI 75 response, n (%) of patients with ≥3% BSA psoriasis skin involvement at baseline[f]											
Week 24	7 (10.4)	52 (71.2)	47 (79.7)	37 (54.4)	60.8 (48.1, 73.5)[c]	69.2 (56.6, 81.8)[c]	10 (14.9)	38 (55.9)	41 (60.3)	41.0 (26.4, 55.5)[c]	45.4 (30.9, 59.8)[c]
PASI 90 response, n (%) of patients with ≥3% BSA psoriasis skin involvement at baseline[f]											
Week 24	4 (6.0)	41 (56.2)	40 (67.8)	25 (36.8)	50.2 (37.5, 62.9)[c]	61.8 (48.6, 75.0)[c]	8 (11.9)	30 (44.1)	34 (50.0)	32.2 (18.1, 46.3)[c]	38.1 (23.9, 52.3)[c]
ACR50 and PASI 100, n (%) in patients with ≥3% BSA psoriasis skin involvement at baseline											
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	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 75/90/100 = psoriasis area and severity index 75%/90%/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
[d] Primary endpoint for both SPIRIT-P1 and SPIRIT-P2
[e] Multiplicity-controlled secondary endpoint for SPIRIT-P2
[f] In patients with psoriasis ≥3% BSA at baseline (SPIRIT-P1; n=67, 73, 59, 68, respectively; SPIRIT-P2; n=67, 68, 68, respectively)

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).

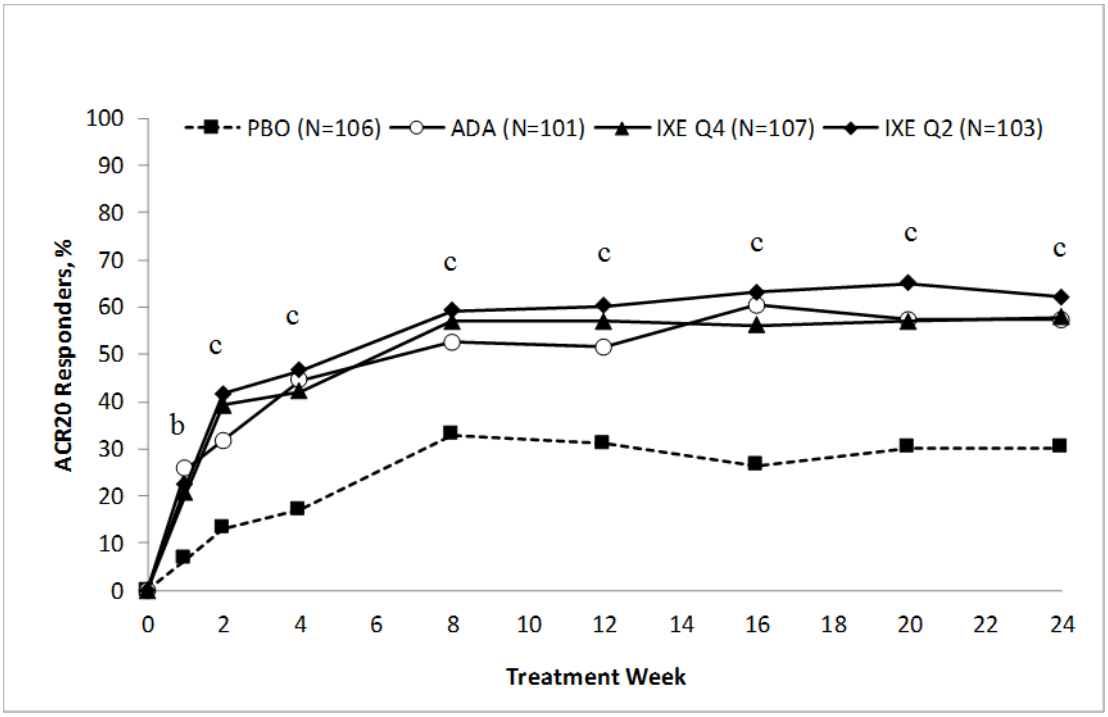
In patients with ≥3% BSA, the improvement in skin clearance at Week 12 as measured by 75% improvement in Psoriasis Area Severity Index (PASI 75), was 67% (94/141) for those

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 PASI 90 and PASI 100 compared to placebo ($p < 0.001$) and demonstrated clinical meaningful benefit over the Q4W dose regimen.

The onset of action of TALTZ occurred as early as Week 1, with significantly higher responses ($p \leq 0.01$) in ACR 20 (20.6% and 22.3% for Q4W and Q2W, respectively) compared to placebo (6.6%). The differences were maintained throughout the 24-week period ($p \leq 0.01$). The treatment responses on TALTZ were significantly greater than those on placebo as early as week 4 for ACR 50 and week 8 for ACR 70 and persisted through week 24 ($p < 0.05$).

Figure 3. ACR20 response in SPIRIT-P1 over time up to Week 24



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

In SPIRIT-P1 and SPIRIT-P2, similar responses were seen in patients with psoriatic arthritis regardless of whether they were on concomitant MTX treatment or not. At Week 24, TALTZ-treated patients with concomitant MTX use had a higher ACR 20 response (52.4% for Q4W and 56.1% for Q2W), compared to placebo (25.3%) and ACR 50 response (33.3% for Q4W and 39.5% for Q2W), compared to placebo (14.1%). TALTZ-treated patients without concomitant MTX use had a higher ACR 20 response (58.1% for Q4W and 51.8% for Q2W), compared to placebo (24.0%) and ACR 50 response (41.1% for Q4W and 39.3% for Q2W), compared to placebo (6.4%).

In SPIRIT-P1and SPIRIT-P2, improvements were shown in all components of the ACR scores, including patient assessment of pain. The proportion of patients achieving a modified Psoriatic Arthritis Response Criteria (PsARC) response was greater in the TALTZ-treated patients (55.9% for Q4W and 54.9% for Q2W) compared to placebo (25.9%) at Week 24.

In SPIRIT-P1, efficacy was maintained up to Week 52. Among patients who had achieved an ACR 20, 50 or 70 response at Week 24, 80.6%, 81.4% and 80.0% respectively of responders on Q4W and 81.5%, 77.1% and 80.0% respectively of responders on Q2W maintained their ACR response at Week 52.

Among patients with baseline psoriatic lesions involving ≥ 3% who achieved a PASI 75, 90 or 100 response at Week 24, 90.4%, 87.8% and 80.6% respectively of responders on Q4W and 91.5%, 92.5% and 90.3% respectively of responders on Q2W maintained their PASI response at Week 52.

The majority of patients achieving HAQ-DI ≥ 0.35, MDA response, resolution of dactylitis or of enthesitis at Week 24 maintained that response at Week 52.

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-naïve and biologic-exposed patients.

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

Inhibition of structural damage was maintained with TALTZ treatment up to Week 52. 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 89.0% for TALTZ Q4W, 94.8% for TALTZ Q2W, 95.8% for adalimumab, and 77.4% for placebo. The percentage of

patients with no disease progression from Week 24 to Week 52 for TALTZ Q4W and TALTZ Q2W was 85.6% and 89.6% respectively; and it was 90.9% and 73.3% respectively for placebo patients who switched to TALTZ Q4W or TALTZ Q2W at Week 16 or Week 24.

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 in the TALTZ Q2W and TALTZ Q4W groups (SPIRIT-P1 and SPIRIT-P2 combined) reported significant improvements from baseline in health-related quality of life at Weeks 12 and 24 as measured by the Short Form-36 Health Survey Physical

Component Summary (SF-36 PCS) score (p<0.001). There were also statistically significant improvements demonstrated in fatigue from baseline at Weeks 12 and 24 in TALTZ-treated patients in the TALTZ Q2W and TALTZ Q4W groups (SPIRIT-P1 and SPIRIT-P2 combined), as measured by the Fatigue Numeric Rating Scale Worst Level (p<0.001).

Ankylosing Spondylitis

The safety and efficacy of TALTZ were assessed in 567 patients, in 2 randomised, double-blind, placebo-controlled studies (COAST-V and COAST-W) in adult patients, age 18 years and older with active ankylosing spondylitis. Patients had active disease as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid, or disease modifying anti-rheumatic drug (DMARD) therapy. At baseline, patients had symptoms of ankylosing spondylitis for an average of 17 years across both studies. At baseline, approximately 32% of the patients were on a concomitant cDMARD. In COAST-W, all patients discontinued previous treatment with 1 or 2 TNF inhibitors due to either inadequate response or intolerance.

COAST-V evaluated 341 biologic-naive patients, who were 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 TNF-inhibitor experienced patients (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 and 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.

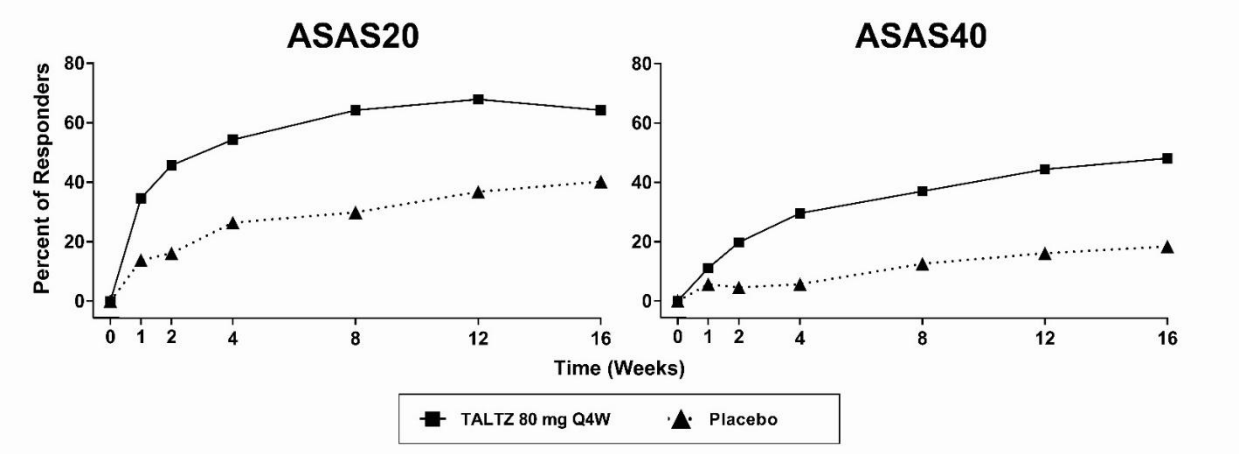
Table 11. ASAS20 and ASAS40 Responses at Week 16, NRI[a,b]

	COAST-V – biologic-naive			COAST-W – TNF-inhibitor experienced		
	TALTZ 80 mg Q4W[c] (N=81)	Placebo (N=87)	Difference from placebo (95% CI)	TALTZ 80 mg Q4W[c] (N=114)	Placebo (N=104)	Difference from placebo (95% CI)
ASAS20 response[d], %	64	40	24 (9, 39)	48	30	18 (6, 31)
ASAS40 response[d,e], %	48	18	30 (16, 43)	25	13	13 (3, 23)

[a] Abbreviations: N = number of patients in the intent-to-treat population; NRI = Non-responder Imputation.
[b] Patients with missing data were counted as non-responders.
[c] At Week 0, patients received 80 mg or 160 mg of TALTZ. For COAST-V 80 mg N=42, 160 mg N=39. For COAST-W 80 mg N=60, 160 mg N= 54. The ixekizumab starting dose (160 mg vs. 80 mg at Week 0) did not appear to have an impact on treatment effect at Week 16, as assessed by ASAS20/40 response rates, the percentage of patients achieving ASDAS clinically important improvement, major improvement, or inactive disease, change from baseline in CRP, and change from baseline in BASFI.
[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.

The percent of patients achieving ASAS20 and ASAS40 responses by visit in COAST-V is shown in Figure 4.

Figure 4. ASAS20 and ASAS40 Responses through Week 16, NRI[a]



[a] Patients with missing data were counted as non-responders.
N = 81 (80 mg Q4W) and N = 87 (Placebo)

The improvement in the main components of the ASAS40 response criteria and other measures of disease activity are shown in Table 12.

Table 12. ASAS Components and Other Measures of Disease Activity at Week 16a

	COAST-V – biologic-naive		COAST-W – TNF-inhibitor experienced	
	TALTZ 80 mg Q4W[b] (N=81)	Placebo (N=87)	TALTZ 80 mg Q4W[b] (N=114)	Placebo (N=104)
ASAS Components				
Patient Global Assessment (0-10)				
Baseline	6.9	7.1	8.0	7.8
Mean Change from Baseline	-2.5	-1.4	-2.4	-0.7
Total Spinal Pain (0-10)				
Baseline	7.2	7.4	7.9	7.8
Mean Change from Baseline	-3.2	-1.7	-2.4	-1.0
BASFI (0-10)				
Baseline	6.06	6.35	7.35	7.01
Mean Change from Baseline	-2.39	-1.16	-1.69	-0.64
Inflammation (0-10)[c]				
Baseline	6.51	6.76	7.21	7.20
Mean Change from Baseline	-3.18	-1.27	-2.42	-0.70
ASDAS				
Baseline	3.71	3.89	4.15	4.05
Mean Change from Baseline	-1.43	-0.46	-1.16	-0.11
BASDAI Score				
Baseline	6.75	6.81	7.54	7.32
Mean Change from Baseline	-2.92	-1.39	-2.17	-0.92
BASMI				
Baseline	3.87	4.51	4.68	4.88
Mean Change from Baseline	-0.50	-0.08	-0.35	-0.05
hsCRP (mg/L)				
Baseline	12.19	15.97	20.16	16.02
Mean Change from Baseline	-5.21	1.43	-11.10	9.72
MRI Spine SPARCC[d]				
Baseline	14.53	15.80	8.30	6.37
Mean Change from Baseline	-11.02	-1.51	-2.99	3.29
BASDAI50[e] (%), NRI[f]	42	17	22	10
ASDAS <2.1 (%) (Low Disease Activity), NRI[f]	43	13	18	5

[a] Abbreviations: ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; hsCRP = High sensitivity C-reactive protein; MRI Spine SPARCC = Spondyloarthritis Research Consortium of Canada Magnetic Resonance Imaging Scoring of the Spine (23 discovertebral unit scale); NRI = Non-responder Imputation.
[b] At Week 0, patients received 80 or 160 mg of TALTZ.
[c] Inflammation is the mean of patient-reported stiffness self-assessments (questions 5 and 6) in BASDAI.
[d] The numbers of ITT patients with MRI data at baseline are as follows: COAST-V: TALTZ, n = 81; PBO, n = 82. COAST-W: TALTZ, n = 58; PBO, n = 51.
[e] BASDAI50 response defined as an improvement of ≥50% of the BASDAI score from baseline.
[f] Patients with missing data were counted as non-responders.

Health-Related Outcomes

General health status and quality of life was assessed by the Short Form health survey (SF-36). At Week 16, in COAST-V and COAST-W, compared to placebo, patients treated with

TALTZ showed greater improvement from baseline in the SF-36 physical component summary (PCS) score and the physical functioning, role physical, bodily pain, vitality, and general health domains, with no consistent improvements in the mental component summary (MCS), social functioning, role emotional, and mental health domains. At Week 16, patients treated with TALTZ showed improvement in overall functioning, and quality of life as assessed by the Assessment of SpondyloArthritis International Society Health Index (ASAS HI) compared to patients treated with placebo.

Data on withdrawal or rebound effects in the AS population has not been evaluated.

Non-radiographic axial spondyloarthritis

The efficacy and safety of TALTZ were assessed in a randomised, double-blind, study with a 52 week placebo-controlled period (COAST-X) in 303 patients ≥18 years of age 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 13). Responses were similar regardless of concomitant therapies.

Table 13. Efficacy results at Week 16 in COAST-X, NRI a,b

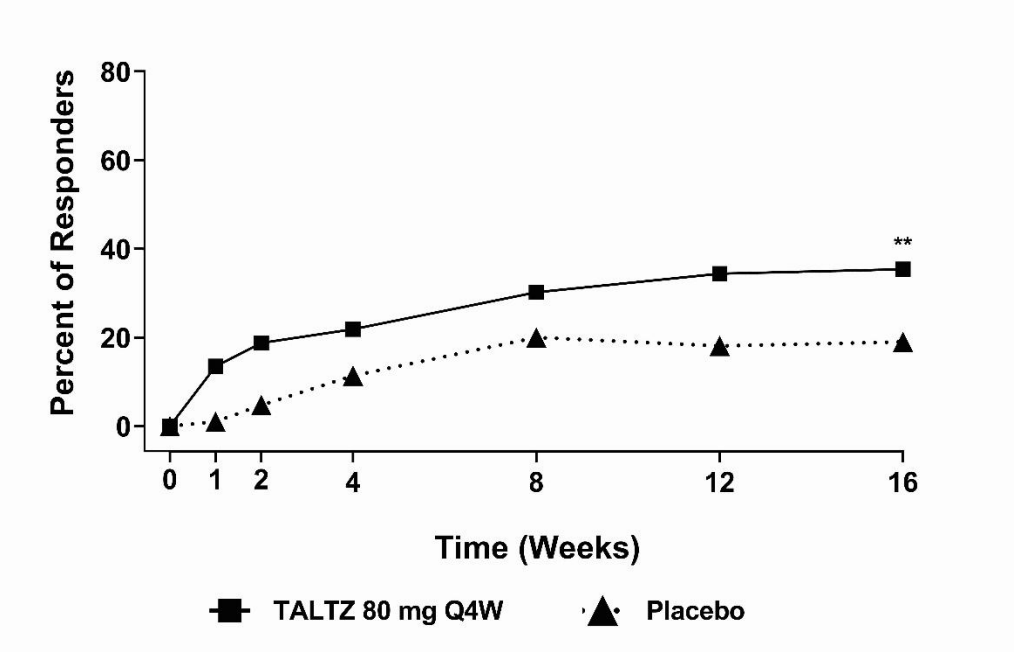
	TALTZ 80 mg Q4W[c] (N=96)	**Placebo (N=105)**	**Difference from placebo [h]**
ASAS20 response[d], n (%), NRI	52 (54.2%)	41 (39.0%)	15.1 (1.5, 28.8)*
ASAS40 response[d,e], n (%), NRI	34 (35.4%)	20 (19.0%)	16.4 (4.2, 28.5)*
ASDAS			
Change from Baseline *Baseline*	-1.1 *3.8*	-0.6 *3.8*	-0.5 (-0.8, -0.3) *
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 compared with placebo (multiplicity-adjusted p-value, except for ASAS20).

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.

The percent of patients achieving ASAS40 response by visit is shown in Figure 5.

Figure 5. 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.*

In COAST-X 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 ≤5) at Week 16 and Week 52.

Long-term outcomes Axial Spondyloarthritis (Ankylosing spondylitis and Non-radiographic 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 the 157 (20.3%) patients who achieved remission (defined as Ankylosing Spondylitis Disease Activity Score [ASDAS] <1.3 at least once, and no ASDAS score ≥2.1, at weeks 16 and 20), 155 patients 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 (placebo, N=50; Taltz Q4W, N=47; TALTZ Q2W, N=51) completed the week 64 visit (representing 116 weeks TALTZ treatment). 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.

A total of 683 participants who completed 64 weeks of the COAST-Y study, were entered into the long-term extension period for a further 40 weeks (representing 156 weeks TALTZ treatment). A total of 531 participants completed the long-term extension period (week 64 to week 104).

In the randomised withdrawal intent-to-treat population, patients who continued TALTZ therapy (combined Q4W and Q2W) through to week 104 were less likely to experience a flare than participants who withdrew to placebo (75.5% (77/102) versus 35.8% (19/53) of participants, respectively, remained flare free).

The safety profile was consistent with the known safety profile of TALTZ.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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

After the 160 mg starting dose, steady state was achieved by Week 8 with the ixekizumab 80 mg every 2 weeks (Q2W) dosing regimen. Mean (SD) $C_{max,ss}$ and $C_{trough,ss}$ estimates are 21.5 (9.16) microgram/mL and 5.23 (3.19) microgram/mL, respectively. After switching from the ixekizumab 80 mg Q2W dosing regimen to the ixekizumab 80 mg every 4 weeks (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) microgram/mL and 1.87 (1.30) microgram/mL, respectively.

The average SC bioavailability of ixekizumab was estimated in the range of 54% to 90% across analyses.

Distribution

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

Metabolism

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 IgGs.

Excretion

In the population pharmacokinetic analysis, mean serum clearance was 0.0161 L/hour. Clearance is independent of dose. The mean elimination half-life is 13 days in plaque psoriasis patients. Ixekizumab clearance increases as body weight increases.

Dose proportionality

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

Special populations

Elderly Patients (≥65 years)

Based on population pharmacokinetic analysis with limited number of elderly patients (N=82 for ≥65 years and N=7 for ≥75 years), clearance of ixekizumab in elderly patients was similar to patients aged less than 65 years.

Renal Impairment or Hepatic Impairment

Specific clinical pharmacology studies to evaluate the effects of renal impairment and hepatic impairment on the pharmacokinetics of ixekizumab have not been conducted.

The pharmacokinetic properties of ixekizumab were similar in the plaque psoriasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis indications.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The genotoxic potential of ixekizumab has not been studied.

Carcinogenicity

Nonclinical studies have not been conducted to evaluate the carcinogenic potential of ixekizumab.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each autoinjector or prefilled syringe is composed of ixekizumab (80 mg/mL) and the inactive ingredients:

sucrose 80 mg/mL

polysorbate 80 0.30 mg/mL

water for injections q.s. to 1 mL

Sodium hydroxide may be added to adjust pH.

TALTZ contains less than 1 mmoL sodium (23 mg) per 80 mg dose.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF-LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

TALTZ single use autoinjector and prefilled syringe are to be stored at 2°C to 8°C. Refrigerate. Do not freeze. Protect from light. Do not shake.

If needed, for example while travelling or transporting the pens/syringes from the pharmacy, TALTZ may be exposed to temperatures not exceeding 30°C for up to 5 days in total. After 5 days at temperatures not exceeding 30°C the product must be used within these 5 days or discarded.

6.5 NATURE AND CONTENTS OF CONTAINER

TALTZ is available as a 1 mL single-dose prefilled pen (autoinjector) or prefilled syringe containing 80 mg ixekizumab. The solution is contained in a clear glass syringe barrel with bromobutyl plunger.

TALTZ is available in pack sizes of 1, 2 or 3 single-dose autoinjector or prefilled syringe*. *Not all pack sizes or presentations may be marketed.

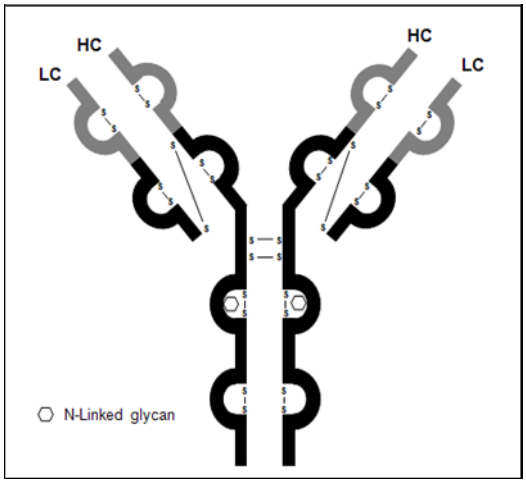
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

TALTZ contains no antimicrobial preservative therefore discard any unused portion in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Ixekizumab has a molecular weight of 146,158 Daltons for the protein backbone of the molecule.



CAS number

CAS registry number 1143503-69-8.

7. MEDICINE SCHEDULE

Prescription Medicine – Schedule 4

8. SPONSOR

Eli Lilly Australia Pty Ltd
Level 9, 60 Margaret Street, Sydney, NSW 2000
AUSTRALIA

1800 454 559
www.lilly.com.au

9. DATE OF FIRST APPROVAL

15 August 2024

10. DATE OF REVISION

10 January 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Addition of eczematous eruptions in post marketing data.

TALTZ® is a registered trademark of Eli Lilly and Company