AUSTRALIAN PRODUCT INFORMATION – OTEZLA® (APREMILAST)

1. NAME OF THE MEDICINE

Apremilast

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Refer to Section 6.1 – List of excipients.

Excipients with known effect

Sugars (as lactose).

3. PHARMACEUTICAL FORM

Otezla 10 mg Tablets: Pink, diamond shaped 10 mg film-coated tablet with “APR” engraved on one side and “10” on the opposite side.

Otezla 20 mg Tablets: Brown, diamond shaped 20 mg film-coated tablet with “APR” engraved on one side and “20” on the opposite side.

Otezla 30 mg Tablets: Beige, diamond shaped 30 mg film-coated tablet with “APR” engraved on one side and “30” on the opposite side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Otezla is indicated for:

- The treatment of signs and symptoms of active psoriatic arthritis in adult patients.
- The treatment of adult patients with plaque psoriasis who are candidates for phototherapy or systemic therapy.
- The treatment of adult patients with oral ulcers associated with Behçet’s Disease who are candidates for systemic therapy.

4.2 Dose and method of administration

Dosage (dose and interval)

For psoriasis, psoriatic arthritis and Behçet’s Disease, treatment with Otezla should be initiated by physicians experienced in the diagnosis and treatment of these diseases.

The recommended dose of Otezla is 30 mg twice daily taken orally approximately 12 hours apart. An initial titration schedule is required as shown below in Table 1. No re-titration is required after initial titration.

Table 1. Dose Titration Schedule

Day 1	Day2		Day 3		Day 4		Day 5		Day 6 & thereafter	
AM	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

Method of administration

Otezla tablets should be swallowed whole, either with or without food. The tablets should not be crushed, split or chewed.

If patients miss a dose, the next dose should be taken as soon as possible. If it is close to the time for their next dose, the missed dose should not be taken and the next dose should be taken at the regular time.

Dosage adjustment

No dosage adjustment is necessary for elderly patients.

Renal impairment

No dose adjustment is needed in patients with mild renal impairment. There are limited data on moderate renal impairment. Otezla should be dose reduced to 30 mg once daily in patients with severe renal impairment (creatinine clearance of less than 30 mL per minute estimated by the Cockroft-Gault equation). For initial dosage titration in this group, it is recommended that Otezla be titrated using only the AM schedule listed in Table 1 and the PM doses be skipped.

Hepatic impairment

Dose adjustment is not required in patients with hepatic impairment. The safety of Otezla was not evaluated in psoriatic arthritis (PsA), psoriasis (PSOR) or Behçet's Disease patients with hepatic impairment.

Monitoring advice

In the event of intolerable adverse events, interruption or discontinuation of Otezla should be considered.

4.3 Contraindications

Otezla is contraindicated:

- In patients with known hypersensitivity to the active substance or to any of the excipients.
- During pregnancy and in nursing women.

4.4 Special warnings and precautions for use

Weight decrease

In some patients treatment with Otezla has been associated with weight decrease. Patients treated with Otezla should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of Otezla should be considered (see section 4.8 Adverse effects (Undesirable effects)).

Depression

Treatment with Otezla is associated with an increase in occurrences of depression (see section 4.8 Adverse effects (Undesirable effects)). Before using Otezla in patients with a history of depression and/or suicidal thoughts or behaviour, prescribers should carefully weigh the risks and benefits of treatment with Otezla in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with Otezla if such events occur.

Diarrhoea, Nausea and Vomiting

There have been post-marketing reports of severe diarrhoea, nausea, and vomiting associated with the use of Otezla. Most events occurred within the first few weeks of treatment. In some cases, patients were hospitalised. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications. Patients who reduced dosage or discontinued Otezla generally improved quickly. Consider Otezla dose reduction or suspension if patients develop severe diarrhoea, nausea or vomiting.

Use in patients with lactose intolerance

Otezla tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Use in renal impairment

Assessment of renal function is recommended prior to initiation of Otezla.

Use in the elderly

Otezla was studied in young and elderly healthy subjects. The exposure in elderly subjects (65 to 85 years of age) is about 13% higher in AUC and about 6% higher in C_{max} for Otezla than that in young subjects (18 to 55 years of age).

No overall differences were observed in the safety or efficacy profile of elderly patients ≥ 65 years of age and younger adult patients < 65 years of age in the clinical studies.

No dosage adjustment is necessary for elderly patients.

Paediatric use

The safety and effectiveness of Otezla has not been established in patients under the age of 18 years.

Effects on laboratory tests

No data available.

4.5 Interaction with other medicines and other forms of interaction

Otezla has not been studied in combination with cyclosporin or biologic therapies.

Effect of Otezla on other medicinal products

There was no pharmacokinetic drug-drug interaction between Otezla and methotrexate. Otezla can be co-administered with methotrexate.

There was no pharmacokinetic drug-drug interaction between Otezla and oral contraceptives containing ethinyl oestradiol and norgestimate. Otezla can be taken with oral contraceptives without clinically relevant drug-drug interaction.

In vitro, apremilast is not an inhibitor or inducer of cytochrome P450 enzymes. Hence, apremilast co-administered with substrates of CYP enzymes is unlikely to affect the clearance and exposure of drugs that are metabolised by CYP enzymes.

In vitro, apremilast is a substrate, and a weak inhibitor of P-glycoprotein (IC > 50 µM).

In vitro, apremilast has little to no inhibitory effect (IC_{50} > 10μM) on Organic Anion Transporter (OAT)1 and OAT3, Organic Cation Transporter (OCT)2, Organic Anion Transporting Polypeptide (OATP)1B1 and OATP1B3, or breast cancer resistance protein (BCRP) and is not a substrate for these transporters. Hence, clinically relevant drug-drug interactions are unlikely when apremilast is co-administered with drugs that are substrates or inhibitors of these transporters.

Effect of other medicinal products on Otezla

Co-administration of Otezla with multiple doses of rifampicin resulted in a decrease in apremilast area-under-the concentration time curve (AUC) and maximum serum concentration (C_{max}) by approximately 72% and 43%, respectively. Apremilast exposure is decreased when administered concomitantly with strong inducers of CYP3A4 (e.g. rifampicin, phenobarbitone, carbamazepine, phenytoin and St. John's Wort) and may result in reduced clinical response.

Ketoconazole co-administration increased mean apremilast $AUC_{0-\infty}$ and C_{max} by approximately 36% and by 5%, respectively, which is not clinically meaningful. Otezla can be co-administered with a potent CYP3A4 inhibitor like ketoconazole.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No fertility data is available in humans.

In a male mouse fertility study, apremilast at oral dosages of 1, 10, 25, and 50 mg/kg/day produced no effects on male fertility; the no observed adverse effect level (NOAEL) for male fertility was greater than 50 mg/kg/day (3-fold clinical exposure).

In a combined female mouse fertility and embryo-fetal developmental toxicity study with oral dosages of 10, 20, 40, and 80 mg/kg/day, a prolongation of oestrous cycles and increased time to mating were observed at 20 mg/kg/day and above; despite this, all mice mated and pregnancy rates were unaffected. The no observed effect level (NOEL) for female fertility was 10 mg/kg/day (1.0-fold clinical exposure).

Use in pregnancy (Pregnancy Category B3)

Otezla is contraindicated in pregnant women and should not be used in women attempting to become pregnant.

There are no adequate and well-controlled studies of Otezla in pregnant women, and other available data in pregnant women are limited. A pregnancy registry conducted by

the Organization of Teratology Information Specialists (OTIS) in the United States and Canada assessed the risk of major birth defects in liveborn infants of women with psoriatic arthritis, psoriasis, or Behçet's Disease exposed to apremilast in the first trimester. The study compared pregnant women treated with apremilast (n = 15) with disease-matched pregnant women who were not exposed to apremilast (n = 106). No liveborn infants had a major birth defect in the apremilast-exposed cohort, and 3 liveborn infants had a major birth defect in the diseased unexposed cohort. There were no spontaneous abortions reported in the apremilast-exposed cohort and 3 spontaneous abortions in the diseased unexposed cohort. One stillbirth was reported in the apremilast-exposed cohort, and no stillbirths were reported in the diseased unexposed cohort. These data are limited by the small sample size of apremilast-exposed pregnancies.

Fetal loss has also been reported in pregnant women exposed to apremilast through post-marketing surveillance. Overall, while no clear patterns of fetal or maternal risk have been observed, the available data are insufficient to exclude an increased risk of fetal loss with apremilast use.

Apremilast was not teratogenic in mice or monkeys. Other effects of apremilast on pregnancy included embryofetal loss in mice and monkeys, reduced fetal weights and delayed ossification in mice at doses higher than the currently recommended highest human dose. No such effects were observed when exposure in animals was at 1.3-fold the clinical exposure.

In a combined female mouse fertility and embryofetal developmental toxicity study, the maternal and developmental NOEL observed was 10 mg/kg/day (1.3-fold clinical exposure). No treatment-related developmental malformations were observed up to the highest dosage of 80 mg/kg/day (4.0-fold clinical exposure).

In a monkey embryofetal developmental toxicity study, oral dosages of 20, 50, 200, and 1,000 mg/kg/day resulted in a dose-related increase in prenatal loss (abortions) at dosages of 50 mg/kg/day and above; no test article-related effect in prenatal loss was observed at 20 mg/kg/day (1.4-fold clinical exposure). No treatment-related fetal developmental effects or malformations were observed in the monkey up to the highest dosage of 1,000 mg/kg/day in the study (3.5-fold clinical exposure).

In a pre- and postnatal study, in which apremilast was administered orally to pregnant female mice, clinical signs of maternal toxicity associated with delivering pups were observed in one mouse at each of 80 and 300 mg/kg/day. Increased pre- and postnatal

pup mortality and reduced pup body weights during the first week of lactation were observed at ≥ 80 mg/kg/day (≥ 4.0-fold clinical exposure). The NOEL in the mouse for maternal toxicity and F1 generation was 10 mg/kg/day (1.3-fold clinical AUC).

Use in lactation

Apremilast was detected in milk of lactating mice.

It is not known whether apremilast or its metabolites are excreted in human milk. Therefore, the use of Otezla is contraindicated in mothers who are breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use of machines have been performed.

4.8 Adverse effects (Undesirable effects)

Psoriatic Arthritis and Plaque Psoriasis

Otezla was evaluated in 4 multi-centre, randomised, double-blind, placebo-controlled trials (Studies PALACE 1, PALACE 2, PALACE 3 and PALACE 4) of similar design in adult patients with active psoriatic arthritis. Across the 4 studies, there were 1,945 patients who received at least one dose of Otezla 20 mg twice daily or Otezla 30 mg twice daily.

Otezla was evaluated in 2 multi-centre, randomised, double-blind, placebo-controlled trials (Studies ESTEEM 1 and ESTEEM 2) of similar design in adult patients with moderate to severe plaque psoriasis. Across the two studies, 1,184 psoriasis patients were exposed to Otezla 30 mg twice daily.

Otezla was evaluated in a Phase 3, placebo-controlled study (ADVANCE) in adult patients with mild to moderate plaque psoriasis. A total of 544 patients received Otezla 30 mg twice daily.

Hypersensitivity reactions were observed infrequently in clinical studies with Otezla.

Tabulated list of adverse events

The observed Treatment Emergent Adverse Events (TEAEs) with patient incidence of at least 2% in any treatment group during ESTEEM and PALACE clinical studies is presented in Table 2. The frequencies of TEAEs are based on those reported in the Otezla 30 mg twice daily arm in either psoriatic arthritis or moderate to severe plaque psoriasis Phase 3 studies during weeks 0-16 of therapy. The highest incidence from either indication is shown below. The most frequently reported TEAEs were

gastrointestinal related. The overall incidence of serious adverse events was low and similar to placebo.

Table 2. Otezla Data Pool: TEAEs with Patient Incidence of at Least 2% in Psoriatic Arthritis (PALACE) or Psoriasis (ESTEEM) Phase 3 studies in any Treatment Group (highest incidence from either indication) During Weeks 0-16

Preferred Term[a]	Placebo n (%)	Otezla 30 mg twice daily n (%)
Diarrhoea	28 (6.7)	186 (15.7)
Nausea	28 (6.7)	164 (13.9)
Upper respiratory tract infection	27 (6.5)	100 (8.4)
Headache	24 (3.6)	77 (7.9)
Nasopharyngitis	29 (6.9)	89 (7.5)
Tension headache	14 (3.3)	85 (7.2)
Vomiting	7 (1.7)	39 (3.3)
Fatigue	6 (1.4)	32 (2.7)
Dyspepsia	4 (1.0)	31 (2.6)
Hypertension	15 (2.2)	25 (2.6)
Decreased appetite	4 (1.0)	28 (2.4)
Arthralgia	7 (1.7)	25 (2.1)
Back pain	4 (1.0)	25 (2.1)
Migraine	4 (1.0)	25 (2.1)
Sinusitis	6 (1.4)	25 (2.1)
Abdominal discomfort	6 (1.4)	24 (2.0)
Frequent bowel movements	1 (0.2)	24 (2.0)
Gastroenteritis	9 (2.2)	20 (1.7)
Urinary tract infection	9 (2.2)	17 (1.4)
Psoriasis	13 (3.1)	10 (0.8)

[a] Preferred Terms are coded using the MedDRA (Version 14.0)

In the Phase 3 study in adults with mild to moderate plaque psoriasis, the safety profile observed in the Otezla group during the placebo controlled phase was overall consistent with the safety profile previously established in adult patients with moderate to severe plaque psoriasis. This safety profile remained similar throughout the study.

In STYLE the most commonly reported TEAEs that occurred at a higher rate in the Otezla group than in the placebo group were: diarrhoea (31% vs. 11%), nausea (22% vs. 6%), headache (12% vs. 5%), and vomiting (6% vs. 2%), which are considered to be

adverse reactions for apremilast. The proportion of subjects who discontinued treatment because of any TEAE during the 16 week placebo controlled period of the trial was 6% for subjects who received Otezla 30 mg twice daily and 3% for subjects who received placebo. In the Otezla group compared to the placebo group, gastrointestinal adverse reactions that led to discontinuation of treatment were diarrhoea (3% vs. 0%), nausea (1.5% vs. 1%), and vomiting (1.5% vs. 0%).

Behçet's Disease

Otezla was evaluated in a Phase 3, placebo-controlled trial (RELIEF) in adult patients with Behçet's Disease (BD) with active oral ulcers. A total of 207 patients were randomised to receive Otezla 30 mg twice daily (104 patients) or placebo twice daily (103 patients) during the placebo-controlled phase of the study. The study also included an open-label extension phase during which all patients received Otezla 30 mg twice daily. During the placebo-controlled period, very common adverse reactions in the Otezla group included diarrhoea (41.3%), nausea (19.2%), headache (14.4%) and upper respiratory tract infection (11.5%). Most of these were mild to moderate in severity. The incidence of serious adverse reactions in the Otezla group was low (2.9%) and did not indicate any specific system organ involvement.

Adverse reactions

Tabulated list of adverse reactions

The adverse reactions observed in patients treated with Otezla are listed below by system organ class (SOC) and frequency for all adverse reactions. Within each SOC and frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The adverse drug reactions were determined based on data from the Otezla Phase 3 clinical development program. The frequencies of adverse drug reactions are those reported in the Otezla arms of the four Phase 3 studies in psoriatic arthritis (n = 1,945) or the two Phase 3 studies in moderate to severe plaque psoriasis (n = 1,184) (highest frequency from either data pool is represented in Table 3).

Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10); and uncommon (≥ 1/1,000 to < 1/100) or rare (≥ 1/10,000 to < 1/1,000).

Table 3. Summary of Adverse Reactions in Phase 3 Psoriatic Arthritis and Psoriasis Clinical Studies

System Organ Class	Frequency	Preferred Term [a]
Gastrointestinal disorders	Very common	Diarrhoea
		Nausea
	Common	Vomiting
		Frequent bowel movements
		Abdominal pain upper
		Gastroesophageal reflux disease
		Dyspepsia
General disorders and administrative site conditions	Common	Fatigue
Immune system disorders	Uncommon	Hypersensitivity
Infections and infestations	Common	Bronchitis
		Upper respiratory tract infection
		Nasopharyngitis
Investigations	Uncommon	Weight decrease
Metabolism and nutrition disorders	Common	Decreased appetite
Musculoskeletal and connective tissue	Common	Back pain
Nervous system disorders	Common	Migraine
		Tension headache
		Headache
Psychiatric disorders	Common	Insomnia
Respiratory, thoracic, and mediastinal disorders	Common	Cough
Skin and subcutaneous tissue disorders	Uncommon	Rash

[a] Preferred Terms are coded using the MedDRA (Version 14.0)

The most commonly reported adverse reactions in Phase 3 (Studies PALACE 1, PALACE 2, PALACE 3, PALACE 4 and ESTEEM 1 and ESTEEM 2) clinical studies have been gastrointestinal (GI) disorders including diarrhoea (15.7%) and nausea (13.9%). These GI adverse reactions were mostly mild to moderate in severity, with 0.3% of patients reporting severe diarrhoea and 0.3% of patients reporting severe nausea. These adverse reactions generally occurred within the first 2 weeks of treatment and

usually resolved within 4 weeks. The other most commonly reported adverse reactions included upper respiratory tract infections (8.4%), headache (7.9%), and tension headache (7.2%).

Overall, most adverse reactions were considered to be mild or moderate in severity. The most common adverse reactions leading to discontinuation during the first 16 weeks of treatment were diarrhoea (1.7%) and nausea (1.5%).

Description of selected adverse reactions:

Weight decrease

Patient weight was measured routinely in clinical studies.

In Studies ESTEEM 1 and ESTEEM 2, the mean observed weight loss in patients treated for up to 52 weeks with Otezla was 1.99 kg. A total of 14.3% of patients receiving Otezla had observed weight loss between 5-10% while 5.7% of the patients receiving Otezla had observed weight loss greater than 10%. None of these patients had overt clinical consequences resulting from weight loss. A total of 0.2% of patients treated with Otezla discontinued due to adverse reaction of weight decreased. Weight decreases of greater than 5% of baseline body weight were observed more frequently in women than in men.

Depression

Psoriatic Arthritis:

During the 0 to 16-week placebo-controlled period of the phase 3 controlled clinical trials (PALACE 1, PALACE 2, PALACE 3, and PALACE 4), 0.9% (18/1,945) of subjects treated with Otezla reported depression or depressed mood compared to 0.7% (5/671) treated with placebo. During the clinical trials, 0.2 % (4/1,945) of subjects treated with Otezla discontinued treatment due to depression or depressed mood compared with none in placebo treated subjects (0/671). Depression was reported as serious in 0.2% (3/1,945) of subjects exposed to Otezla, compared to none in placebo-treated subjects (0/671). Instances of suicidal ideation and behaviour have been observed in 0.2% (3/1,945) of subjects while receiving Otezla, compared to none in placebo treated subjects (0/671). In the clinical trials, 2 subjects who received placebo committed suicide compared to none in Otezla treated subjects.

Psoriasis:

During the 0 to 16-week placebo-controlled period of the 2 controlled clinical trials (ESTEEM 1 and ESTEEM 2), 1.2% (14/1,184) of subjects treated with Otezla reported depression compared to 0.5% (2/418) treated with placebo. During the clinical trials, 0.1% (1/1,184) of subjects treated with Otezla discontinued treatment due to depression compared with none in placebo-treated subjects (0/418). Depression was reported as serious in 0.1% (1/1,184) of subjects exposed to Otezla, compared to none in placebo-treated subjects (0/418). Instances of suicidal behaviour have been observed in 0.1% (1/1,184) of subjects while receiving Otezla, compared to 0.2% (1/418) in placebo-treated subjects. In the clinical trials, one subject treated with Otezla attempted suicide while one who received placebo committed suicide.

Safety in elderly patients

No overall differences were observed in the safety profile of elderly patients ≥ 65 years of age and younger adult patients < 65 years of age in the clinical studies.

Long-term experience

The long-term safety of Otezla 30 mg twice daily in patients with psoriatic arthritis and plaque psoriasis was assessed for a total duration of treatment up to 5 years (see 5.1 Pharmacodynamic properties, Clinical trials). Overall, the long-term safety profile of Otezla was consistent with the safety profile previously established in patients with psoriatic arthritis and plaque psoriasis.

Reporting of suspected adverse effects

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 https://www.tga.gov.au/reporting-problems.

4.9 Overdose

Otezla was studied in healthy subjects at a maximum total daily dose of 100 mg (given as 50 mg twice daily) for 4.5 days without evidence of dose limiting toxicities. Patients should be managed by symptomatic and supportive care should there be an overdose.

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

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Selective immunosuppressants.

5.1 Pharmacodynamic properties

Mechanism of action

Apremilast, an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4), works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. PDE4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of TNF-α, IL-23, IL-17 and other inflammatory cytokines. Cyclic AMP also modulates levels of anti-inflammatory cytokines such as IL-10. These pro- and anti-inflammatory mediators have been implicated in PsA and PSOR.

Clinical pharmacodynamics

In clinical studies in patients with psoriatic arthritis, apremilast significantly modulated, but did not fully inhibit, plasma protein levels of IL-1α, IL-6, IL-8, MCP-1, MIP-1β, MMP-3, and TNF-α. After 40 weeks of treatment with apremilast, there was a decrease in plasma protein levels of IL-17 and IL-23, and an increase in IL-10. In clinical trials in patients with psoriasis, apremilast decreased lesional skin epidermal thickness, inflammatory cell infiltration, and expression of pro-inflammatory genes, including inducible nitric oxide synthase (iNOS), IL-12/IL-23p40, IL-17A, IL-22 and IL-8.

Cardiac electrophysiology

Apremilast administered at doses of up to 50 mg twice daily did not prolong the QT interval in healthy subjects.

Clinical trials

Clinical trial experience in Psoriatic Arthritis patients previously treated with DMARDs.

The safety and efficacy of Otezla were evaluated in 3 multi-centre, randomised, double-blind, placebo-controlled studies (Studies PALACE 1, PALACE 2, and PALACE 3) of similar design in 1,493 adult patients with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite prior DMARD treatment, including biologic DMARD treatment (e.g. TNF-blockers), or current treatment with oral DMARD therapy.

Patients in these studies had a diagnosis of PsA for at least 6 months. One qualifying psoriatic skin lesion (at least 2 cm in diameter) was also required in PALACE 3. The

patients who were therapeutic failures of > 3 agents for PsA (small molecules or biologics), or > 1 biologic TNF blocker, were excluded. Patients with each subtype of PsA were enrolled across the 3 studies, including symmetric polyarthritis (62.0%), asymmetric oligoarthritis (26.9%), distal interphalangeal (DIP) joint arthritis (6.2%), arthritis mutilans (2.7%), and predominant spondylitis (2.1%). Patients with pre-existing enthesitis (63%) and pre-existing dactylitis (42%) were enrolled. Patients were allowed to receive stable doses of concomitant methotrexate (MTX) (≤ 25 mg/week), sulfasalazine (SSZ) (≤ 2 g/day), leflunomide (LEF) (≤ 20 mg/day), low dose oral corticosteroids (equivalent to ≤ 10 mg of prednisone a day), and/or nonsteroidal anti-inflammatory drugs (NSAIDs) during the trial; the combination of apremilast with biologic DMARDs was not studied.

Across the 3 studies, patients were randomly assigned to placebo (n = 496), Otezla 20 mg (n = 500), or Otezla 30 mg (n = 497) given orally twice daily. Treatment assignments were stratified based on small-molecule DMARD use at baseline in Studies PALACE 1, PALACE 2 and PALACE 3. There was an additional stratification of body surface area (BSA ≥ 3% with psoriasis in PALACE 3).

Patients received concomitant therapy with at least one DMARD (total 65.2%), MTX (54.5%), SSZ (9.0%), LEF (7.4%), low dose oral corticosteroids (13.9%), and NSAIDs (70.7%). Prior treatment with only small-molecule DMARDs was reported in 76.4% of patients and prior treatment with biologic DMARDs was reported in 22.4% of patients, which includes 7.8% who had a therapeutic failure with a prior biologic DMARD. The median duration of PsA disease was 5 years.

The primary endpoint was the percentage of patients achieving American College of Rheumatology (ACR) 20 response at Week 16. Patients whose tender and swollen joint counts had not improved by at least 20% were considered non-responders at Week 16. Placebo non-responders were re-randomised 1:1 in a blinded fashion to either Otezla 20 mg twice daily or 30 mg twice daily. Otezla patients remained on their initial treatment. At Week 24, all remaining placebo patients were re-randomised to either Otezla 20 mg twice daily or Otezla 30 mg twice daily. At the end of 52 weeks, patients could enter a long-term open-label extension of the PALACE 1, PALACE 2, and PALACE 3 studies for a total duration of treatment up to 5 years (260 weeks). These studies did not investigate the effects of Otezla on structural progression.

Clinical responses

Treatment with Otezla resulted in significant improvements in the signs and symptoms of PsA, as assessed by the ACR 20 response criteria, compared to placebo at Week 16. The proportion of patients with ACR 20/50/70 responses in Studies PALACE 1, PALACE 2 and PALACE 3, for Otezla 30 mg twice daily at Week 16, are shown in Table 4. ACR 20/50/70 responses were maintained at Week 24.

Table 4. Proportion of Patients with ACR Responses in Studies PALACE 1, PALACE 2 and PALACE 3 at Week 16

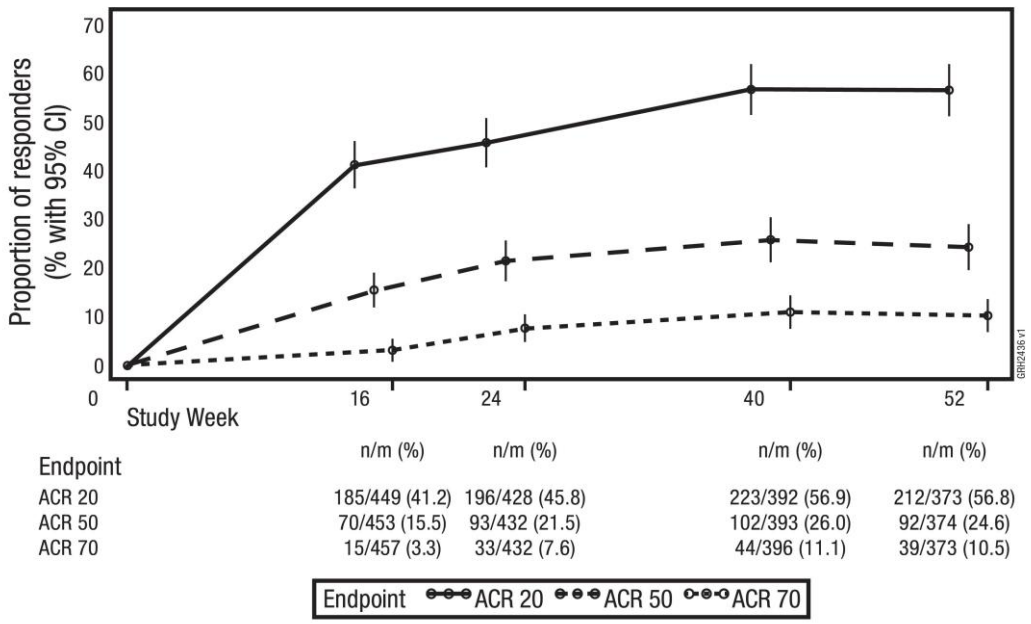
	PALACE 1		PALACE 2		PALACE 3	
	Placebo +/- DMARDs	**Otezla 30 mg BID +/- DMARDs**	**Placebo +/- DMARDs**	**Otezla 30 mg BID +/- DMARDs**	**Placebo +/- DMARDs**	**Otezla 30 mg BID +/- DMARDs**
N[a]	**N = 168**	**N = 168**	**N = 159**	**N = 162**	**N = 169**	**N = 167**
ACR 20						
Week 16	19.0%	38.1%**	18.9%	32.1%*	18.3%	40.7%**
ACR 50						
Week 16	6.0%	16.1%*	5.0%	10.5%	8.3%	15.0%
ACR 70						
Week 16	1.2%	4.2%	0.6%	1.2%	2.4%	3.6%

*p ≤ 0.01 for Otezla vs. placebo.
**p ≤ 0.001 for Otezla vs. placebo.
[a] N is the number of randomised and treated patients at Week 16.

ACR 20/50/70 response through Week 52

Among 497 patients initially randomised to Otezla 30 mg twice daily, 373 (75%) patients were still on this treatment at Week 52. In these patients, ACR 20/50/70 responses at week 52 were 57%, 25%, and 11% respectively (see Figure 1).

Figure 1. Proportion of ACR 20/50/70 Responders Through Week 52 in the Pooled Studies PALACE 1 PALACE 2 and PALACE 3



Note: n/m is the number of responders/number of patients with sufficient data for definitive determination of response status at each time point, which includes patients who discontinued early between the preceding time point and the time point in question.

ACR 20 responses were higher in patients treated with Otezla than in patients treated with placebo when used alone or in combination with DMARDs. In Study PALACE 1, the proportion of patients with an ACR 20 response at Week 16 with concomitant DMARD use was 33.0% for Otezla 30 mg twice daily and 23.6% for placebo. The proportion of patients with an ACR 20 response at Week 16 without concomitant DMARD use was 46.8% for Otezla 30 mg twice daily and 10.3% for placebo. Similar results were observed in Studies PALACE 2 and PALACE 3.

A greater proportion of patients achieved an ACR 20 response with the use of Otezla 30 mg twice daily, irrespective of prior small molecule or prior biologic DMARD use. In Study PALACE 1, the proportion of patients with prior treatment of only small-molecule DMARDs (biologic-naïve) with an ACR 20 response at Week 16 were 41.1% for Otezla 30 mg twice daily and 23.3% for placebo and the proportion of patients with prior biologic use with an ACR 20 response at Week 16 were 26.8% for Otezla 30 mg twice daily and 4.9% for placebo. Similar results were observed in Studies PALACE 2 and PALACE 3.

Similar ACR 20 responses were observed in patients with different PsA subtypes including distal interphalangeal (DIP); however, the number of patients with arthritis mutilans and predominant spondylitis subtypes was too small to allow for a meaningful assessment.

Otezla 30 mg twice daily resulted in greater improvement for each ACR component [number of swollen and tender joints, physician and patient assessment of disease activity and patient assessment of pain, Health Assessment Questionnaire-Disability Index (HAQ-DI) scores and CRP values], compared to placebo at Weeks 16 and 24 in Study PALACE 1. Among patients who were continuously treated with Otezla, sustained improvements in individual ACR components were observed at Week 52. Similar results were observed in Studies PALACE 2 and PALACE 3 at Weeks 16, 24 and 52.

The proportion of patients achieving modified PsA response criteria (PsARC) was significantly greater in the Otezla 30 mg twice daily group compared to placebo at Week 16 (46.4% and 29.8% respectively; $p < 0.01$) in Study PALACE 1. The response was maintained at Week 24. Among patients who were continuously treated with Otezla, a PsARC response of 73.6% was observed at Week 52. Similar results were observed in Studies PALACE 2 and PALACE 3 at Weeks 16, 24 and 52.

A greater proportion of patients treated with Otezla 30 mg twice daily achieved remission, as measured by a DAS28 (CRP) less than 2.6, compared to placebo at Weeks 16 (13.1% and 3.6% respectively; $p < 0.01$) in Study PALACE 1. The response was maintained at Week 24. Among patients who were continuously treated with Otezla, a DAS28 (CRP) response of 23.3% was observed at Week 52. Similar results were observed in Studies PALACE 2 and PALACE 3 at Weeks 16, 24 and 52.

In patients with pre-existing enthesitis or dactylitis, treatment with Otezla 30 mg twice daily resulted in improvement in enthesitis and dactylitis. Among patients who were continuously treated with Otezla, improvement in enthesitis and dactylitis continued through Week 52.

Physical function responses and health-related quality of life

Patients treated with Otezla 30 mg twice daily demonstrated a significantly greater improvement in physical function compared to placebo treated patients, as shown in the mean change from baseline in HAQ-DI score at Week 16 (-0.244 and -0.086 respectively; $p < 0.01$) and Week 24 (-0.258 vs, -0.076, respectively; $p < 0.001$) in Study PALACE 1. Among patients who were continuously treated with Otezla, a mean change from baseline in HAQ-DI score of -0.318 was observed at Week 52. In addition, there was a greater proportion of HAQ-DI responders who showed improvement (≥ 0.3 improvement from baseline) at Week 16 for the Otezla 30 mg twice daily group compared to the placebo group (38.1% vs 26.8% respectively, $p < 0.05$). The response was maintained at Week 24. Among patients who were continuously treated with Otezla,

the proportion of HAQ-DI responders was 44.7% at Week 52. Similar results in the mean change from baseline in HAQ-DI and in the proportion of HAQ-DI responders were observed in Studies PALACE 2 and PALACE 3 at Weeks 16, 24 and 52.

Patients treated with Otezla 30 mg twice daily demonstrated a significantly greater improvement compared to placebo treated patients in the mean change from baseline in the SF-36v2 Physical Functioning (PF) Domain Score at Week 16 (4.23 and 1.81 respectively; $p < 0.01$) in Study PALACE 1. A greater improvement, compared to placebo, in the mean change from baseline was also observed in the Physical Component Summary (PCS) Score at Week 16 (4.59 and 2.39 respectively; $p < 0.01$). The responses were maintained at Week 24. Among patients who were continuously treated with Otezla, mean changes from baseline in SF-36v2 PF and PCS scores of 5.69 and 6.45, respectively, were observed at Week 52. Similar results were observed in Studies PALACE 2 and PALACE 3 at Weeks 16, 24 and 52.

There was no worsening observed in the mean change from baseline in the Mental Component Summary score (MCS) in patients treated with Otezla 30 mg twice daily in comparison to placebo patients at Week 16 (0.69 and 0.07 respectively) and Week 24 in Study PALACE 1. Among patients who were continuously treated with Otezla, a mean change from baseline in the MCS score of 0.34 was observed at Week 52. Similar results were observed in Studies PALACE 2 and PALACE 3 at Weeks 16, 24 and 52.

A greater improvement was observed in Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-fatigue) scores in the patients treated with Otezla 30 mg twice daily when compared with the placebo group at Weeks 16 (3.88 and 1.55 respectively; $p < 0.05$) in Study PALACE 1. The response was maintained at Week 24. Among patients who were continuously treated with Otezla, a mean change from baseline in the FACIT-fatigue score of 3.67 was observed at Week 52. Similar results were observed in Studies PALACE 2 and PALACE 3 at Weeks 16, 24 and 52.

PASI-75 response

Treatment with Otezla 30 mg twice daily resulted in improvement in the skin manifestations of psoriasis. Patients with psoriasis involvement of at least 3% BSA were evaluated using the PASI-75 responses. In Study PALACE 3, a significantly greater proportion of patients achieved a PASI-75 in the Otezla group compared to the placebo group (22.2% and 7.9%, respectively; $p < 0.01$) at Week 16. The response was maintained at Week 24. There were more patients with PASI-75 responses in the Otezla group than in patients treated with placebo, with or without concomitant DMARD

treatment. Among patients who were continuously treated with Otezla, a PASI-75 response of 39.1% was observed at Week 52. Similar responses were observed in Studies PALACE 1 and PALACE 2 at Weeks 16, 24 and 52.

Long-term experience

Among 497 patients initially randomised to Otezla 30 mg twice daily, 351 (71%) patients entered the long term extension studies, and of these 351 patients, 221 patients (63%) were still on this treatment at week 260 (5 years).

Clinical trial experience in DMARD naive Psoriatic Arthritis patients

The safety and efficacy of Otezla were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (Study PALACE 4) in 527 adult patients with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) who were DMARD-naive. Patients enrolled in this study had a diagnosis of PsA for at least 3 months. Previous treatment with DMARDs or biologics was not allowed.

Patients were randomly assigned to placebo (n = 176), Otezla 20 mg (n = 175), or Otezla 30 mg (n = 176) given orally twice daily. Patients were allowed to receive stable doses of prednisone (equivalent to ≤ 10 mg/day) and/or nonsteroidal anti-inflammatory drugs (NSAIDs). The use of other DMARDs including methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), or biologics was prohibited. Patients with each subtype of PsA were enrolled, including symmetric polyarthritis (61.3%), asymmetric oligoarthritis (30%), distal interphalangeal (DIP) joint arthritis (6.6%), arthritis mutilans (0.8%), and predominant spondylitis (1.3%). Patients with pre-existing enthesitis (65%) and pre-existing dactylitis (50%) were enrolled. The median duration of PsA disease was 1.1 years.

Patients received concomitant therapy including low dose oral corticosteroids (7.2%) and NSAIDs (73.1%); the combination of Otezla with small molecule or biologic DMARDs was not studied.

The primary endpoint was the percentage of patients achieving American College of Rheumatology (ACR) 20 response at Week 16. Patients whose tender and swollen joint counts had not improved by at least 20% were considered non-responders at Week 16. Placebo non-responders were re-randomised 1:1 in a blinded fashion to either Otezla 20 mg twice daily or 30 mg twice daily. Otezla patients remained on their initial treatment. At Week 24, all remaining placebo patients were re-randomised to either Otezla 20 mg twice daily or Otezla 30 mg twice daily. At the end of 52 weeks, patients

could enter a long-term open-label extension study for a total duration of up to 5 years. This study did not investigate the effects of Otezla on structural progression.

Clinical responses

The percent of patients achieving ACR 20/50/70 responses at Week 16 in Study PALACE 4 is presented below in Table 5. Otezla, compared with placebo, resulted in significantly greater improvement in signs and symptoms of psoriatic arthritis, as demonstrated by the proportion of patients with ACR 20 response at Week 16. Improvement in ACR 50/70 responses were also demonstrated at Week 16. ACR 20/50/70 responses were maintained at Week 24.

Table 5. Proportion of Patients with ACR Responses at Week16 in Study PALACE 4

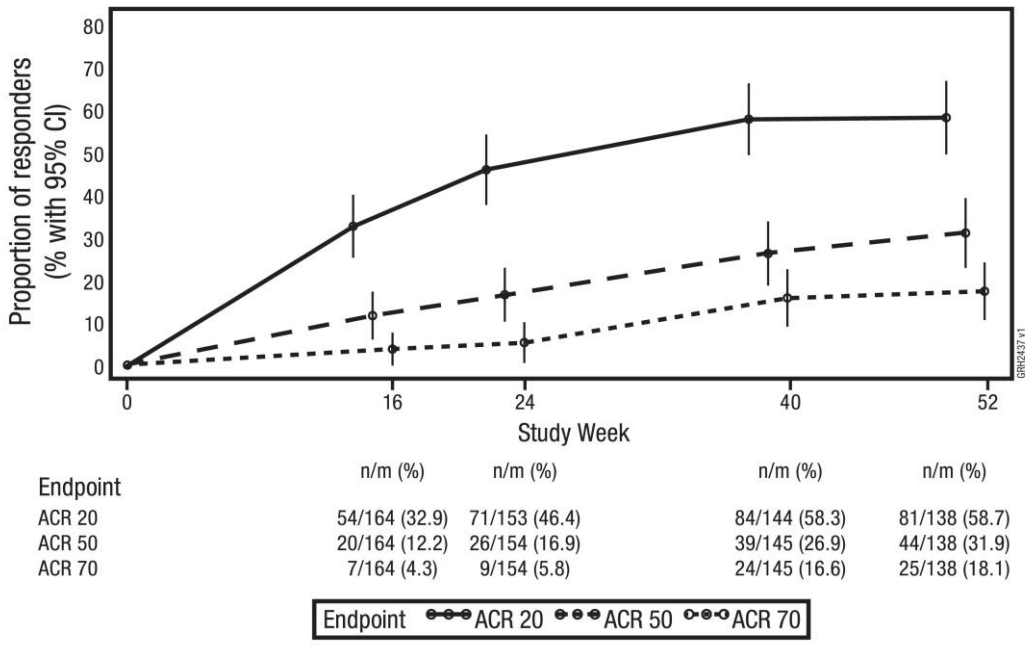
PALACE 4		
	Placebo	**Otezla 30 mg twice daily**
N[a]	176	176
ACR 20		
Week 16	16%	31%**
ACR 50		
Week 16	5%	11%*
ACR 70		
Week 16	1%	4%

[a] N is number of randomised and treated patients
*p ≤ 0.05 for Otezla vs. placebo.
**p ≤ 0.001 for Otezla vs. placebo.

ACR 20/50/70 response through Week 52

Among 176 patients initially randomised to Otezla 30 mg twice daily, 138 (78%) patients were still on this treatment at Week 52. In these patients, ACR 20/50/70 responses at week 52 were 59%, 32% and 18% respectively (see Figure 2).

Figure 2. Proportion of ACR 20/50/70 Responders Through Week 52 in Study PALACE 4 (Data as Observed)



Endpoint	n/m (%)	n/m (%)	n/m (%)	n/m (%)
ACR 20	54/164 (32.9)	71/153 (46.4)	84/144 (58.3)	81/138 (58.7)
ACR 50	20/164 (12.2)	26/154 (16.9)	39/145 (26.9)	44/138 (31.9)
ACR 70	7/164 (4.3)	9/154 (5.8)	24/145 (16.6)	25/138 (18.1)

Endpoint ACR 20 ACR 50 ACR 70

Note: n/m is the number of responders/number of patients with sufficient data for definitive determination of response status at each time point, which includes patients who discontinued early between the preceding time point and the time point in question.

Treatment with Otezla 30 mg twice daily resulted in greater improvement for each ACR component [number of swollen and tender joints, physician and patient assessment of disease activity and patient assessment of pain, HAQ-DI score and CRP value], compared to placebo at Weeks 16 and 24 in Study PALACE 4. Among patients who were continuously treated with Otezla, sustained improvements in individual ACR components were observed at Week 52.

The proportion of patients achieving a modified PsARC was significantly greater in the Otezla 30 mg twice daily group compared with placebo at Week 16 (45.5% and 24.4% respectively; $p < 0.001$) in Study PALACE 4. The response was maintained at Week 24. Among patients who were continuously treated with Otezla, the modified PsARC response was 75.9% at Week 52.

In patients with pre-existing enthesitis or dactylitis, treatment with Otezla 30 mg twice daily resulted in improvement in enthesitis and dactylitis, compared to placebo at Week 16. The responses were maintained at Week 24. Among patients who were continuously treated with Otezla, sustained improvement in enthesitis and dactylitis was observed through Week 52.

Physical function response and health-related quality of life

Patients treated with Otezla 30 mg twice daily demonstrated a significantly greater improvement in physical function compared to placebo treated patients, as shown in the mean change from baseline in HAQ-DI score at Week 16 (-0.205 and -0.012, respectively; $p < 0.001$) and Week 24 (-0.207 vs. -0.012, respectively; $p < 0.001$) in Study PALACE 4. Among patients who were continuously treated with Otezla, the mean change from baseline in HAQ-DI score was -0.392 at Week 52. In addition, there was a greater proportion of HAQ-DI responders who showed improvement (≥ 0.3 improvement from baseline) at Week 16 for the Otezla 30 mg twice daily group compared to the placebo group (34.7% and 19.3%, respectively). The response was maintained at Week 24. Among patients who were continuously treated with Otezla, the proportion of HAQ-DI responders was 48.9% at Week 52.

Treatment with Otezla 30 mg twice daily demonstrated a significantly greater improvement, compared to placebo, in the mean change from baseline in the SF-36v2 PF at Week 16 (3.19 and 0.01 respectively; $p < 0.001$) in Study PALACE 4. In addition, treatment with Otezla 30 mg twice daily demonstrated a greater improvement, compared to placebo in the mean change from baseline in the PCS at Week 16 (4.20 and 0.93 respectively; $p < 0.001$). The responses were maintained at Week 24. Among patients who were continuously treated with Otezla, the mean change from baseline in SF-36v2 PF and PCS scores of 6.41 and 6.67, respectively, were observed at Week 52.

There was no worsening observed in the mean change from baseline in the SF-36v2 MCS at Week 16 and Week 24 in Study PALACE 4. Among patients who were continuously treated with Otezla 30 mg twice daily, the mean change from baseline in the SF-36v2 MCS score was 2.19 at Week 52.

There was greater improvement in Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-fatigue) scores in the Otezla group when compared with placebo at Week 16 (2.62 and 0.07 respectively; $p < 0.01$) in Study PALACE 4. The response was maintained at Week 24. Among patients who were continuously treated with Otezla, the mean change from baseline in the FACIT-fatigue score was 5.89 at Week 52.

PASI-75 response

Treatment with Otezla 30 mg twice daily resulted in improvement in the skin manifestations of psoriasis. Patients with psoriasis involvement of at least 3% BSA were

evaluated using the PASI-75 response. At Week 16, there was a greater proportion of patients achieving a PASI-75 in the Otezla 30 mg twice daily group compared to the placebo group (26.6% and 10.8% respectively; $p < 0.01$) in Study PALACE 4. The response was maintained at Week 24. Among patients who were continuously treated with Otezla, the PASI-75 response was 31.9% at Week 52.

Clinical trial experience in Moderate to Severe Plaque Psoriasis patients

The safety and efficacy of Otezla were evaluated in two multi-centre, randomised, double-blind, placebo-controlled studies (Studies ESTEEM 1 and ESTEEM 2) which enrolled a total of 1,257 patients 18 years of age and older with moderate to severe plaque psoriasis who had a BSA involvement of ≥ 10%, Psoriasis Area and Severity Index (PASI) score ≥ 12, static Physician Global Assessment (sPGA) of ≥ 3 (moderate or severe), and who were candidates for phototherapy or systemic therapy. The studies did not include an active comparator arm.

These studies had a similar design through Week 32. In both studies, patients were randomised 2:1 to Otezla 30 mg twice daily or placebo for 16 weeks (placebo-controlled phase) and from Weeks 16-32, all patients received Otezla 30 mg twice daily (maintenance phase). During the Randomised Treatment Withdrawal Phase (Weeks 32-52), patients originally randomised to Otezla who achieved at least a 75% reduction in their PASI score (PASI-75) (ESTEEM 1) or a 50% reduction in their PASI score (PASI-50) (ESTEEM 2) were re-randomised at week 32 to either placebo or Otezla 30 mg twice daily. Patients who were re-randomised to placebo and who lost PASI-75 response (ESTEEM 1) or lost 50% of the PASI improvement at Week 32 compared to baseline (ESTEEM 2) were retreated with Otezla 30 mg twice daily. Patients who did not achieve the designated PASI response by Week 32, or who were initially randomised to placebo, remained on Otezla until Week 52. The use of low potency topical corticosteroids on the face, axillae, and groin, coal tar shampoo and/or salicylic acid scalp preparations was permitted throughout the studies. In addition, at Week 32, subjects who did not achieve a PASI-75 response in ESTEEM 1, or a PASI-50 response in ESTEEM 2, were permitted to use topical psoriasis therapies and/or phototherapy in addition to Otezla 30 mg twice daily treatment.

Following 52 weeks of treatment, patients could continue within the long-term extension of the ESTEEM 1 and ESTEEM 2 studies for a total duration of treatment up to 5 years (260 weeks).

In both studies, the primary endpoint was the proportion of patients who achieved PASI-75 at Week 16. The major secondary endpoint was the proportion of patients who achieved a sPGA score of clear (0) or almost clear (1) at Week 16. Other endpoints included BSA, Pruritus VAS, nail disease (NAPSI), scalp involvement (ScPGA), and quality of life measures (DLQI and SF-36 MCS).

Across both studies, patients ranged in age from 18 to 83 years, with an overall median age of 45.8 years. The mean baseline BSA involvement was 25.19% (median 21.0%), the mean baseline PASI score was 19.07 (median 16.80), and the proportion of patients with sPGA score of 3 (moderate) and 4 (severe) at baseline were 70.0% and 29.8%, respectively. Approximately 30% of all patients had received prior phototherapy and 54% had received prior conventional systemic and/or biologic therapy for the treatment of psoriasis (including treatment failures), with 37% receiving prior conventional systemic therapy and 30% receiving prior biologic therapy. Approximately one-third of patients had not received prior phototherapy, conventional systemic or biologic therapy. A total of 18% of patients had a history of psoriatic arthritis.

Clinical response

The proportion of patients achieving PASI-50, -75 and -90 responses, and sPGA score of clear or almost clear, are presented in Table 6 below. Otezla resulted in significant improvements in moderate to severe plaque psoriasis as demonstrated by the proportion of patients with PASI-75 response at Week 16 compared with placebo. Clinical improvement measured by sPGA, PASI-50 and PASI-90 responses were also demonstrated at Week 16. In addition, Otezla demonstrated a treatment benefit across multiple manifestations of psoriasis including pruritus, nail disease, scalp involvement and quality of life measures.

Table 6. Clinical Response at Week 16 in Studies ESTEEM 1 and ESTEEM 2[a]

	ESTEEM 1		ESTEEM 2	
	Placebo	**30 mg twice daily Otezla**	**Placebo**	**30 mg twice daily Otezla**
N	282	562	137	274
PASI 75[b], n (%)	15 (5.3)	186 (33.1)	8 (5.8)	79 (28.8)
sPGA[c] of clear or Almost clear, n (%)	11 (3.9)	122 (21.7)	6 (4.4)	56 (20.4)
PASI 50, n (%)	48 (17.0)	330 (58.7)	27 (19.7)	152 (55.5)
PASI 90, n (%)	1 (0.4)	55 (9.8)	2 (1.5)	24 (8.8)
Percent change BSA[d,h] (%)	- 6.9 ± 38.95	- 47.8 ± 38.48	- 6.1 ± 47.57	- 48.4 ± 40.78
Change in Pruritus VAS[e,h] (mm)	- 7.3 ± 27.08	- 31.5 ± 32.43	- 12.2 ± 30.94	- 33.5 ± 35.46
Change in DLQI[f,h]	- 2.1 ± 5.69	- 6.6 ± 6.66	- 2.8 ± 7.22	- 6.7 ± 6.95
Change in SF-36 MCS[g,h]	- 1.02 ± 9.161	2.39 ± 9.504	0 ± 10.498	2.58 ± 10.129

[#] $p < 0.0001$ for all comparisons vs. placebo, except for ESTEEM 2 PASI 90 and change in SF-36 MCS where $p = 0.0042$ and $p = 0.0078$, respectively.
[a] Full Analysis Set, Last Observation Carried Forward
[b] PASI = Psoriasis Area and Severity Index
[c] sPGA = Static Physician Global Assessment
[d] BSA = Body Surface Area
[e] VAS = Visual Analog Scale; 0 = best, 100 = worst
[f] DLQI = Dermatology Life Quality Index; 0 = best, 30 = worst
[g] SF-36 MCS = Medical Outcome Study Short Form 36-Item Health Survey, Mental Component Summary
[h] mean +/- standard deviation

The clinical benefit of Otezla was demonstrated across multiple subgroups defined by baseline demographics, baseline clinical disease characteristics (including psoriasis disease duration and patients with a history of psoriatic arthritis), prior psoriasis medication usage and response to prior psoriasis treatments. Similar response rates were observed across all weight ranges.

Significantly greater improvements compared to placebo in mean % change in PASI from baseline, skin discomfort/pain and pruritus were observed at Week 2. In general, PASI responses were achieved by Week 16 and were sustained through Week 32.

During the Randomised Treatment Withdrawal Phase (Weeks 32 – 52) in Study ESTEEM 1, the mean percent improvement in PASI from baseline remained stable

(81-88%) for patients re-randomised to Otezla at Week 32. Approximately 61% of these patients had a PASI-75 response at Week 52. Of the patients re-randomised to placebo at Week 32, 11.7% achieved PASI-75 response at Week 52. Patients who were re-randomised to placebo lost PASI-75 response faster than patients re-randomised to Otezla. The median time to first loss of PASI-75 response for patients re-randomised to placebo and Otezla at Week 32 was 5.1 and 17.7 weeks, respectively.

In Study ESTEEM 2, 80.3% of patients re-randomised to Otezla at Week 32 had a PASI-50 response at Week 52. Of the patients with at least a PASI-50 response who were re-randomised to placebo at Week 32, 24.2% were PASI-50 responders at Week 52. Patients who were re-randomised to placebo lost 50% of their Week 32 PASI response significantly faster than patients re-randomised to Otezla. The median time to first loss of PASI-50 response for patients re-randomised to placebo and Otezla at Week 32 was 12.4 and 21.9 weeks, respectively.

After randomised withdrawal from therapy at Week 32, approximately 70% of patients in Study ESTEEM 1, and 65.6% of patients in Study ESTEEM 2, regained PASI-75 (Study ESTEEM 1) or PASI-50 (Study ESTEEM 2) responses after re-initiation of Otezla treatment. The duration of re-treatment was variable, and ranged from 3.4 to 22.1 weeks in Study ESTEEM 1 and from 2.6 to 18.3 weeks in Study ESTEEM 2.

Among 832 patients initially randomised to Otezla 30 mg twice daily, 443 patients (53%) entered the open-label extension studies of ESTEEM 1 and ESTEEM 2 studies, and of these 115 patients (26%) were still on treatment at week 260.

Nail Psoriasis

In Study ESTEEM 1, significant improvements (reductions) in nail psoriasis, as measured by the mean percent change in Nail Psoriasis Severity Index (NAPSI) from baseline, were detected in patients receiving Otezla compared with placebo-treated patients at Week 16 (Otezla 30 mg twice daily: -22.5%; placebo: +6.5%; $p < 0.0001$). Similar improvements were observed in Study ESTEEM 2 (Otezla 30 mg twice daily: -29.0%; placebo: -7.1%, $p = 0.0052$). Further improvements in nail psoriasis were observed in patients continuously treated with Otezla, with mean percent changes from baseline in NAPSI at Week 32 of -43.6% in Study ESTEEM 1 and -60.0% in Study ESTEEM 2.

Scalp Psoriasis

In Study ESTEEM 1, significant improvements in scalp psoriasis of at least moderate severity (≥ 3), measured by the proportion of patients achieving Scalp Psoriasis Physician's Global Assessment (ScPGA) of clear (0) or minimal (1) at Week 16, were detected in patients receiving Otezla compared with placebo-treated patients (46.5% and 17.5%, respectively, $p < 0.0001$). Similar results were observed in Study ESTEEM 2 (APR 30 twice daily 40.9%; placebo 17.2%, $p < 0.0001$).

Quality of life

In Studies ESTEEM 1 and 2, significant improvements in quality of life as measured by the Dermatology Life Quality Index (DLQI) and the SF-36v2 MCS were demonstrated in patients receiving Otezla compared with placebo-treated patients. In addition, in Study ESTEEM 1, significant improvement in the Work Limitations Questionnaire (WLQ-25) index was achieved in patients receiving Otezla compared with placebo.

Clinical trial experience in Mild to Moderate Plaque Psoriasis

A Phase 3, randomised, double-blind, placebo-controlled study (ADVANCE) was conducted in 595 adult patients with mild to moderate plaque psoriasis (sPGA score of 2 (mild) or 3 (moderate), BSA involvement of 2-15%, PASI score of 2-15). Enrolled patients had an inadequate response or intolerance to at least one topical therapy and were biologic naïve to plaque psoriasis. Patients were allowed to use unmedicated emollients for lesions on non-scalp areas of the body and nonmedicated shampoos for lesions on the scalp.

Patients were randomised 1:1 to receive either Otezla 30 mg twice daily (n = 297) or placebo (n = 298) for 16 weeks (Placebo-controlled Phase). At Week 16, the placebo group was switched to Otezla and patients in the Otezla group continued taking the drug through Week 32. The primary endpoint was the proportion of patients with sPGA response (defined as a score of clear [0] or almost clear [1] and with at least a 2-point reduction from baseline) at Week 16. Other evaluated endpoints include the proportion of patients with a Whole Body Itch numeric rating scale (NRS) response (defined as a ≥ 4-point reduction from baseline) at Week 16 among patients with a baseline Whole Body Itch NRS ≥ 4 and the proportion of patients with an ScPGA response (defined as an ScPGA score of clear [0] or almost clear [1] with at least a 2-point reduction from baseline) at Week 16 among patients with a baseline ScPGA score ≥ 2.

Patients ranged in age from 18 to 85, with a median age of 50 years at baseline. The mean baseline BSA involvement was 6.4%, the mean baseline PASI score was 6.5, and the proportions of patients with a sPGA score of 2 (mild) to 3 (moderate) at baseline were 30.6% and 69.4%, respectively.

Clinical Response

Otezla 30 mg twice daily resulted in significant improvement in mild to moderate psoriasis as demonstrated by the proportion of patients with sPGA response, Whole Body Itch NRS response, and an ScPGA at Week 16 (Table 7).

Table 7. Efficacy Results at Week 16 in Adults with Mild to Moderate Plaque Psoriasis

	ADVANCE		
Endpoint	**Placebo**	**Otezla 30 mg BID**	**Treatment Difference[a,b] (95% CI[c])**
Number of patients randomised	**N = 298**	**N = 297**	
sPGA response[d]	4.1%	21.6%	17.5% (12.2%, 22.8%)
Number of Subjects with Baseline Whole Body Itch NRS Score ≥ 4	**N = 249**	**N = 253**	
Whole body itch NRS response[e]	18.6%	43.2%	24.7% (16.5%, 32.8%)
Number of patients with baseline ScPGA ≥ 2	**N = 199**	**N = 212**	
ScPGA response[f]	16.6%	44.0%	27.4% (18.6%, 36.3%)

[a] Otezla – Placebo
[b] Adjusted difference in proportions is the weighted average of the treatment differences across baseline sPGA scores with the Cochran-Mantel-Haenszel weights.
[c] CI = confidence interval.
[d] sPGA score of clear [0] or almost clear [1] with at least a 2-point reduction from baseline.
[e] Whole Body Itch NRS score reduction of ≥ 4points from baseline.
[f] ScPGA score of clear [0] or almost clear [1] with at least a 2-point reduction from baseline.

Among patients originally randomised to Otezla, the sPGA, ScPGA, and Whole Body Itch responses were maintained through Week 32.

Quality of Life

At Week 16, a statistically significantly greater improvement in quality of life as measured by change from baseline in the DLQI total score (Otezla twice daily, compared with placebo-treated patients).

Psoriasis Involving the Scalp Area

A randomized, double-blind, placebo-controlled trial (STYLE) was conducted in 303 adult subjects with moderate to severe plaque psoriasis of the scalp. Enrolled subjects had a Scalp Physician Global Assessment (ScPGA) score of ≥ 3, Scalp Surface Area (SSA) involvement of ≥ 20%, an inadequate response or intolerance to at least one topical therapy for plaque psoriasis of the scalp and moderate to severe plaque psoriasis (BSA involvement of ≥ 10%, sPGA of ≥3 [moderate or severe disease], and PASI score ≥ 12).

Subjects were randomized 2:1 to receive either Otezla 30 mg twice daily (n = 201) or placebo twice daily (n = 102) for 16 weeks. The primary endpoint was the proportion of subjects who achieved ScPGA response at Week 16 (defined as ScPGA score of clear [0] or almost clear [1] with at least a 2-point reduction from baseline at Week 16). Secondary endpoints included the proportion of subjects with Whole Body Itch Numerical Rating Scale (NRS) response (defined as ≥ 4 point reduction from baseline) at Week 16 and the proportion of subjects with a Scalp Itch NRS response (defined as ≥ 4 point reduction from baseline) at Week 16. The secondary endpoints also included assessment of Whole Body Itch NRS response and Scalp Itch NRS response at each of the other post-baseline visits during the placebo-controlled phase (Weeks 2, 4, 8, 12, and 16).

Subjects had a mean age of 46.9 years, 61.7% were men and 75.6 % were white. At baseline, 76.9% of subjects had moderate scalp psoriasis (ScPGA of 3), 23.1% having severe scalp psoriasis (ScPGA of 4), 71.6% of subjects were biologic naïve, and 58.8% had failed 1 or 2 topicals. At baseline, the mean Whole Body Itch NRS score was 7.2 (median [min, max]: 8.0 [0, 10]) and the mean Scalp Itch NRS score was 6.7 (median [min,max]: 7.0 [0,10]) with the scales ranging from 0 to 10. The mean baseline SSA involvement was 60.6% (median [min, max]: 60.0% [20%, 100%]) and the mean baseline BSA involvement was 19.8% (median [min, max]: 15.5% [10.0%, 91.0%]).

Otezla 30 mg twice daily resulted in significant improvement in scalp psoriasis as demonstrated by the proportion of subjects with a ScPGA response, Whole Body Itch

NRS response, and Scalp Itch NRS response at Week 16 ($p < 0.0001$), compared with placebo (Table 7).

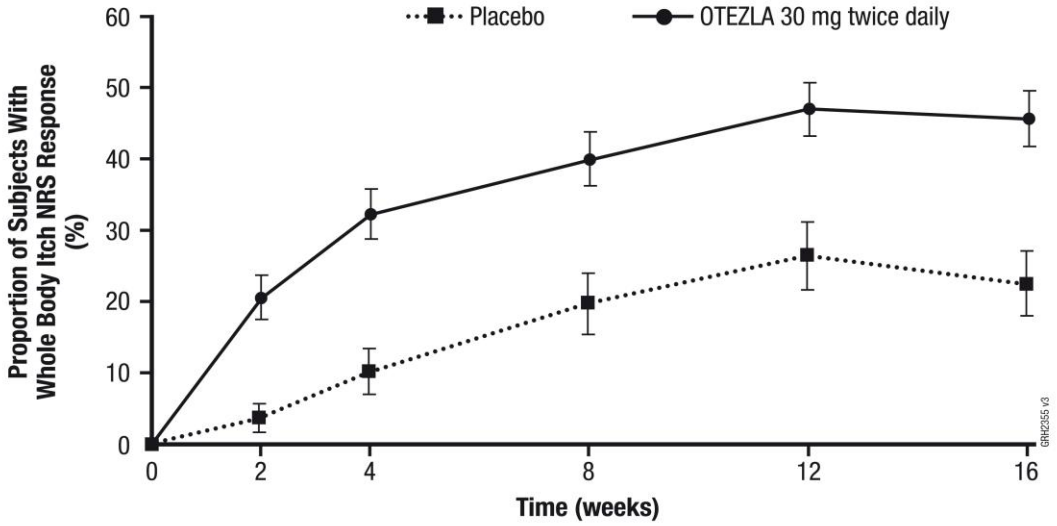
Table 7: Efficacy Results at Week 16 in Adults with Scalp Psoriasis

	STYLE		
	Placebo	**OTEZLA 30 mg twice daily**	**Treatment Difference[a,b] (95% CI[c])**
Number of subjects randomized	**N=102**	**N=201**	
ScPGA response[d, e]	13.7%	43.3%	29.6% (19.5%, 39.7%)
Number of subjects with baseline Whole Body Itch NRS Score ≥4	**N=94**	**N=185**	
Whole Body Itch NRS response[e]	22.5%	45.5%	23.0% (11.5%, 34.6%)
Number of subjects with baseline Scalp Itch NRS Score ≥4	**N=90**	**N=175**	
Scalp Itch NRS response[e]	21.1%	47.1%	26.2% (13.9%, 38.5%)

[a] OTEZLA – Placebo.
[b] Adjusted difference in proportions is the weighted average of the treatment differences across baseline ScPGA scores with the Cochran-Mantel-Haenszel weights.
[c] CI = confidence interval.
[d] ScPGA score of clear [0] or almost clear [1] with at least a 2-point reduction from baseline.
[e] $p < 0.0001$ for OTEZLA 30 mg twice daily vs. placebo at Week 16

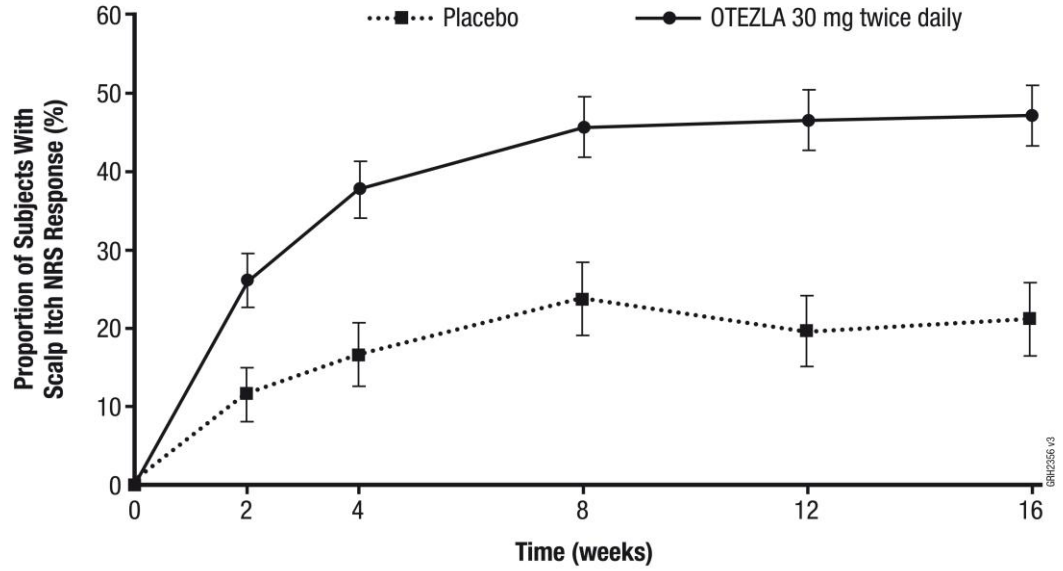
Otezla 30 mg twice daily resulted in significant improvements in Whole Body Itch as demonstrated by the proportion of subjects with Whole Body Itch NRS response as early as Week 2 and at every visit through Week 16, compared with placebo (Figure 3). Otezla 30 mg twice daily achieved similar improvement in Scalp Itch as demonstrated in Figure 4.

Figure 3: Proportion (± SE) of Subjects Achieving Whole Body Itch NRS Response through Week 16



NRS = Numeric Rating Scale; SE = standard error.

Figure 4: Proportion (± SE) of Subjects Achieving Scalp Itch NRS Response through Week 16



NRS = Numeric Rating Scale; SE = standard error.

Behçet's Disease

The safety and efficacy of Otezla were evaluated in a Phase 3, randomised, placebo--controlled study (RELIEF) in adult patients with active Behçet's Disease (BD) with oral ulcers. Patients were previously treated with at least one non-biologic BD medication for oral ulcers and were candidates for systemic therapy. Concomitant

treatment for BD was not allowed. The population studies met the International Study Group (ISG) criteria for BD. Patients had at least 2 oral ulcers at screening and at least 2 oral ulcers at randomization without currently active major organ involvement. Patients with severe BD, defined as those with active major organ involvement (for ex. meningoencephalitis or pulmonary artery aneurysm) were excluded.

A total of 207 BD patients were randomised 1:1 to receive either Otezla 30 mg twice daily (n = 104) or placebo (n = 103) for 12-weeks (Placebo--controlled Phase) and from weeks 12 to 64, all patients received Otezla 30 mg twice daily (Active Treatment Phase).

The primary endpoint was the area under the curve (AUC) for the number of oral ulcers from baseline through Week 12. Secondary endpoints included other measures of oral ulcers (oral ulcer pain Visual Analog Scale (VAS)), proportion of patients who are oral ulcer-free (complete response), time to onset of oral ulcer resolution, and proportion of patients achieving resolution of oral ulcers by Week 6, and who remain oral ulcer free at every visit for at least 6 additional weeks during the 12-week Placebo--controlled Treatment Phase). Other endpoints included Behçet's Syndrome Activity Score (BSAS), BD current activity form (BDCAF), including the BD current activity index (BDCAI) score, the Patient's Perception of Disease Activity, the Clinician's Overall Perception of Disease Activity and the BD Quality of Life Questionnaire (BD QoL).

Patients ranged in age from 19 to 72, with a mean age of 40 years. The mean duration of BD was 6.84 years. All patients had a history of recurrent oral ulcers that were currently active. Patients had a history of skin lesions (98.6%), genital ulcers (90.3%), musculoskeletal manifestations (72.5%), ocular manifestations (17.4%), central nervous system (9.7%), GI manifestations (9.2%) and vascular involvement (1.4%). The mean baseline oral ulcer counts were 4.2 and 3.9 in the Otezla and placebo groups, respectively.

Measure of Oral Ulcers

Otezla 30 mg twice daily resulted in significant improvement in oral ulcers as demonstrated by the AUC for the number of oral ulcers from baseline through Week 12 ($p < 0.0001$), compared with placebo. Significant improvements in other measures of oral ulcers were demonstrated at Week 12, see Table 8.

Table 8. Clinical Response of Oral Ulcers at Week 12 in RELIEF[a]

Endpoint	Placebo N = 103	Otezla 30 mg BID N = 104	Absolute Adjusted Treatment Difference[d] or HR
AUC[b] for the number of oral ulcers from baseline through Week 12 (ITT, MI)	LS Mean 222.14	LS Mean 129.54	92.60[e]
Change from baseline in the pain of oral ulcers as measured by VAS[c] at Week 12 (ITT, MMRM)	LS Mean -18.7	LS Mean -42.7	24.1[e]
Proportion of patients achieving resolution of oral ulcers (oral ulcer-free) by Week 6, and who remain oral ulcer free at every visit for at least 6 additional weeks during the 12-week Placebo-controlled Treatment Phase (ITT)	4.9%	29.8%	25.1%[e]
Median time (weeks) to oral ulcer resolution during the Placebo-controlled Treatment Phase (ITT)	8.1 weeks	2.1 weeks	HR = 2.40[e]
Proportion of patients with complete oral ulcer response at Week 12 (ITT, NRI)	22.3%	52.9%	30.6%[e]

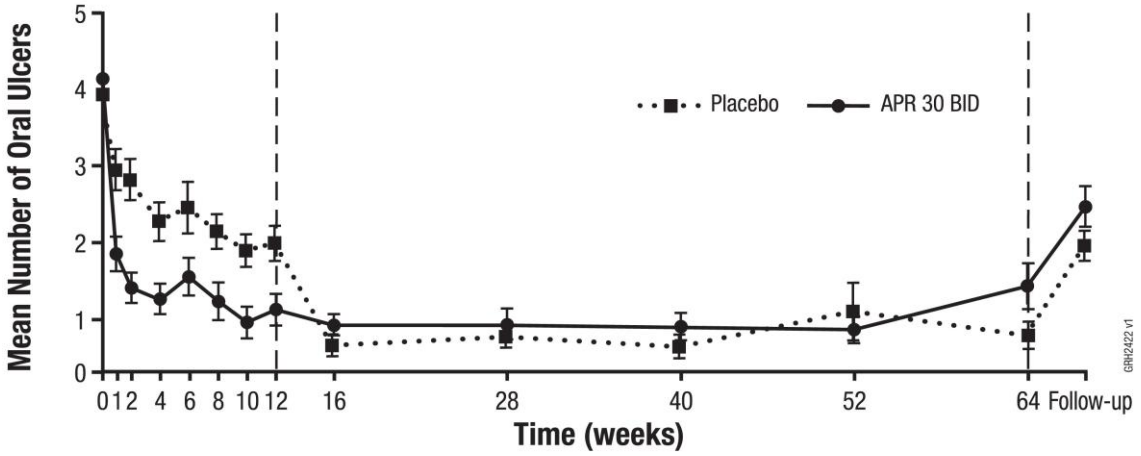
[a] HR = hazard ratio; ITT = intent to treat; LS = least squares; MI = multiple imputation; MMRM = mixed-effects model for repeated measures; NRI = non-responder imputation.
[b] AUC = area under the curve.
[c] VAS = visual analog scale; 0 = no pain, 100 = worst possible pain.
[d] Adjusted difference in proportions is the weighted average of the treatment differences across the 4 strata of combined sex and region factors with the Cochran-Mantel-Haenszel weights.
[e] p-value < 0.0001 for apremilast vs. placebo.

Among 104 patients originally randomised to Otezla 30 mg twice daily, 75 patients (approximately 72%) remained on this treatment at Week 64. Among patients who were continuously treated with Otezla and remained in the study, improvements in oral ulcers and reduction of oral ulcer pain were maintained through Week 64 (

Figure 1 and Figure).

Among patients originally randomised to Otezla 30 mg twice daily who remained in the study, the proportion of patients with a complete response of oral ulcers was maintained through Week 64.

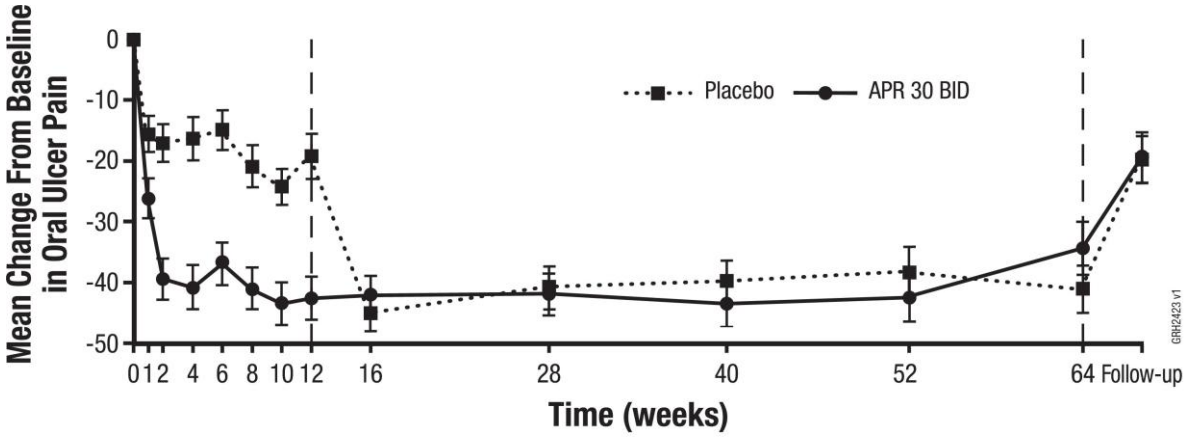
Figure 1. Mean Number of Oral Ulcers by Time Point through Week 64 (ITT Population; DAO)



Weeks:	0	1	2	4	6	8	10	12	16	28	40	52	64	Follow-up
Placebo, n (Mean)	103/3.9	98/2.9	97/2.8	93/2.3	91/2.5	86/2.2	83/1.9	82/2.0	83/0.7	78/0.8	73/0.7	70/1.1	67/0.8	82/2.0
APR 30 BID, n (Mean)	104/4.2	101/1.9	101/1.4	101/1.3	98/1.6	94/1.2	94/1.0	97/1.1	95/0.9	92/0.9	85/0.9	79/0.9	75/1.4	85/2.5

PBO = placebo; APR 30 mg BID = Otezla twice daily; ITT = intent-to-treat; DAO = data as observed
Note: Placebo or APR 30 mg BID indicates the treatment group in which patients were randomized. Placebo treatment group patients switched to Otezla 30 mg BID at Week 12. The follow-up time point was 4 weeks after patients completed Week 64 or 4 weeks after patients discontinued treatment before Week 64.

Figure 6. Mean Change from Baseline in Oral Ulcer Pain on a Visual Analog Scale by Time Point through Week 64 (ITT Population; DAO)



Weeks:	1	2	4	6	8	10	12	16	28	40	52	64	Follow-up
Placebo, n (Mean)	95/-15.5	96/-17.0	91/-16.3	90/-14.9	85/-20.9	82/-24.3	81/-19.1	82/-44.8	77/-40.6	73/-39.8	70/-38.3	68/-41.0	81/-19.7
APR 30 BID, n (Mean)	95/-26.1	97/-39.4	99/-40.7	97/-36.8	92/-41.0	93/-43.4	95/-42.5	94/-42.1	91/-41.9	84/-43.5	78/-42.4	75/-34.3	84/-19.3

PBO = placebo; APR 30 BID = Otezla twice daily; ITT = intent-to-treat; DAO = data as observed
Note: Placebo or APR 30 mg BID indicates the treatment group in which patients were randomized. Placebo treatment group patients switched to Otezla 30 mg BID at Week 12. The follow-up time point was 4 weeks after patients completed Week 64 or 4 weeks after patients discontinued treatment before Week 64.

Quality of Life

Otezla 30 mg twice daily, compared with placebo, resulted in significantly greater improvement in quality of life (QoL) at Week 12, as demonstrated by the BD QoL Questionnaire (p = 0.0003).

5.2 Pharmacokinetic properties

Absorption

Apremilast is well absorbed with an absolute oral bioavailability of approximately 73%, with peak plasma concentrations (C_{max}) occurring at a median time (t_{max}) of approximately 2.5 hours. Apremilast pharmacokinetics is linear, with a dose-proportional increase in systemic exposure in the dose range of 10 to 100 mg daily. Accumulation is minimal when apremilast is administered once daily and approximately 53% in healthy subjects and 68% in patients with psoriasis when administered twice daily.
Co-administration with food does not alter the bioavailability; therefore, apremilast can be administered with or without food.

Distribution

Human plasma protein binding of apremilast is approximately 68%. Mean apparent volume of distribution (Vd) is 87 L indicative of extra vascular distribution.

Metabolism

Apremilast is extensively metabolised by both CYP and non-CYP mediated pathways including oxidation, hydrolysis, and conjugation, suggesting inhibition of a single clearance pathway is not likely to cause a marked drug-drug interaction. Oxidative metabolism of apremilast is primarily mediated by CYP3A4, with minor contributions from CYP1A2 and CYP2A6. Apremilast is the major circulating component following oral administration. Apremilast undergoes extensive metabolism with only 3% and 7% of the administered drug recovered in urine and faeces, respectively. The major circulating metabolite, M12, is the glucuronide conjugate of *O*-demethylated apremilast which is inactive.

Excretion

The plasma clearance of apremilast is on average about 10 L/hr in healthy subjects, with a terminal elimination half-life of approximately 9 hours. There is approximately 30% reduction in apremilast clearance observed in female subjects compared to male subjects. No dose adjustment is necessary for female patients. Following oral

administration of radiolabelled apremilast, about 58% and 39% of the radioactivity is recovered in urine and faeces, respectively, with about 3% and 7% of the radioactive dose recovered as apremilast in urine and faeces, respectively.

Renal impairment

No formal studies have been conducted in subjects with mild to moderately impaired renal function. In 8 subjects with severe renal impairment administered a single dose of 30 mg apremilast, the AUC and C_{max} of apremilast increased by approximately 89% and 42%, respectively. See section 4.2 Dose and method of administration for dose adjustments for patients with severe renal impairment.

Hepatic impairment

The pharmacokinetics of apremilast and its major metabolite M12 is not affected by moderate or severe hepatic impairment. No dosage adjustment is necessary for patients with hepatic impairment.

5.3 Preclinical safety data

Genotoxicity

Apremilast is not genotoxic. Apremilast did not induce mutations in an Ames assay or chromosome aberrations in cultured human peripheral blood lymphocytes in the presence or absence of metabolic activation. Apremilast was not clastogenic in an *in vivo* mouse micronucleus assay at doses up to 2,000 mg/kg/day.

Carcinogenicity

Carcinogenicity studies showed no evidence of treatment-related tumours following oral treatment with apremilast at plasma exposure levels (AUC) that were 7 to 10-fold (mice) and 0.1 to 1-fold (rats) than anticipated clinically.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each Otezla tablet contains either 10 mg, 20 mg or 30 mg of apremilast with the following excipients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol, talc, iron oxide red, iron oxide yellow (20 mg and 30 mg only) and iron oxide black (30 mg only).

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

Store below 30°C.

6.5 Nature and contents of container

Presentation#

A two-week titration pack (4 × 10 mg, 4 × 20 mg and 5 × 30 mg for the first week for dose titration and 14 × 30 mg tablets for the second week).

A two-week titration starter pack (4 × 10 mg, 4 × 20 mg and 5 × 30 mg for the first week for dose titration and 14 × 30 mg tablets for the second week).

A four-week pack (56 × 30 mg tablets).

A 12-week pack (168 × 30 mg tablets).

Not all pack sizes are marketed in Australia

Container type

The tablets are provided in polyvinylchloride (PVC) blisters with push through aluminium foil.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

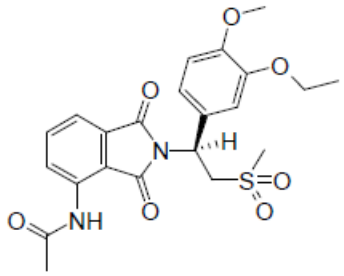
Apremilast is a white to pale yellow non-hygroscopic powder with a melting point of approximately 156.1°C.

It is practically insoluble in water, slightly soluble in ethanol, and soluble in acetone. Apremilast is the S-enantiomer with a specific rotation of +28.1° in acetonitrile at a concentration of 20 mg/mL.

Molecular formula:	$C_{22}H_{24}N_2O_7S$
Molecular weight:	460.5
ATC code:	L04AA32

Chemical name: N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl] acetamide

Chemical structure



CAS number

608141-41-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8. SPONSOR

Amgen Australia Pty Ltd

Level 11, 10 Carrington St

Sydney, NSW 2000

Ph: 1800 803 638

www.amgenmedinfo.com.au

9. DATE OF FIRST APPROVAL

Date of first inclusion in the Australian Register of Therapeutic Goods: 19 March 2015

10. DATE OF REVISION

19 June 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.6 Fertility, pregnancy and lactation	Additional information from observational studies added to 'Use in pregnancy'.