SILUMYA®

Solution for Injection, Prefilled Syringe 100mg/mL

Formulation:
Each mL in a single-dose prefilled syringe contains:
Tildrakizumab……100mg

Excipients:
L-histidine (0.495 mg), L-Histidine hydrochloride monohydrate (1.42 mg), Polysorbate 80 (0.5 mg), sucrose (70.0 mg) and Water for Injection. No preservative.

CLINICAL PHARMACOLOGY

Mechanism of Action
Tildrakizumab is a humanized IgG1/k monoclonal antibody that selectively binds to the p19 subunit of IL-23 and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses. Tildrakizumab inhibits the release of pro inflammatory cytokines and chemokines.

Pharmacodynamics
No formal pharmacodynamics studies have been conducted with tildrakizumab.

Pharmacokinetics
Tildrakizumab pharmacokinetics increases proportionally over a dose range from 50 mg to 200 mg (0.5 to 2 times the approved recommended dosage) following subcutaneous administration in subjects with plaque psoriasis. Steady-state concentrations were achieved by Week 16 following subcutaneous administration of tildrakizumab at Weeks 0, 4, and every 12 weeks thereafter. At the 100 mg dose at Week 16, the mean (± SD) steady-state trough concentrations ranged from 1.22 ± 0.94 mcg/mL to 1.47 ± 1.12 mcg/mL. The geometric mean (CV%) steady-state C_{max} was 8.1 mcg/mL (34%).

Absorption
The absolute bioavailability of tildrakizumab was estimated to be 73-80% following subcutaneous injection. The peak concentration (C_{max}) was reached by approximately 6 days.

Distribution
The geometric mean (CV%) volume of distribution is 10.8 L (24%).

Elimination
The geometric mean (CV%) systemic clearance was 0.32 L/day (38%) and the half-life was approximately 23 days (23%).

Metabolism

The metabolic pathway of tildrakizumab has not been characterized. As a humanized IgG1/k monoclonal antibody, tildrakizumab is expected to be degraded into small peptides and amino acids via catabolic pathways in a manner similar to endogenous IgG.

Specific Populations
No clinically significant differences in the pharmacokinetics of tildrakizumab were observed based on age (≥18 years). No specific studies have been conducted to determine the effect of renal or hepatic impairment on the pharmacokinetics of tildrakizumab. Tildrakizumab concentrations were lower in subjects with higher body weight.

DESCRIPTION
Tildrakizumab is a humanized IgG1/k antibody that specifically binds to the p19 subunit of interleukin-23 (IL-23).

Tildrakizumab is produced in a recombinant Chinese hamster ovary (CHO) cell line and has an approximate molecular mass of 147 kilodaltons.

Tildrakizumab injection, for subcutaneous use, is a sterile, clear to slightly opalescent, colorless to slightly yellow solution. Tildrakizumab is supplied in a single-dose prefilled syringe with a glass barrel and 29-gauge fixed, 1/2-inch needle.

The syringe is fitted with a passive needle guard and a needle cover.

INDICATION
Tildrakizumab is an interleukin-23 antagonist indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

DOSAGE AND ADMINISTRATION
Tildrakizumab is administered by subcutaneous injection. The recommended dose is 100 mg at Weeks 0, 4, and every twelve weeks thereafter.

In the Phase III clinical studies, the results showed that patients had a PASI 75 response of 61% – 64% and PASI 90 response of 35% – 39% after 12 weeks of treatment with tildrakizumab 100 mg [see Clinical Studies]. It is recommended that patients should be monitored for the clinical response to treatment. Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.

Tuberculosis Assessment Prior to Initiation of Tildrakizumab

Evaluate patients for Tuberculosis (TB) infection prior to initiating treatment with tildrakizumab [*see Warnings and Precautions]*.

Method of Administration:
Tildrakizumab is administered by subcutaneous injection. Injection sites should be alternated. Tildrakizumab should not be injected into areas where the skin is affected by plaque psoriasis or is tender, bruised, red, hard, thick, or scaly. The pre-filled syringe must not be shaken. Each pre-filled syringe is for single use only.

Inject the full amount of tildrakizumab according to the instructions for use provided in the Section of Preparation and Administration.

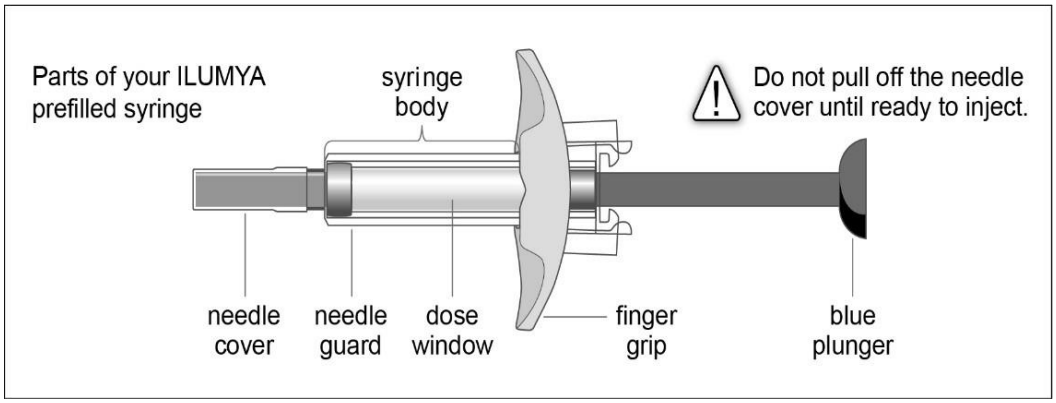
After proper training in subcutaneous injection technique, patients may self-inject tildrakizumab if a physician determines that it is appropriate. However, the physician should ensure appropriate follow-up of patients. Patients should be instructed to inject the full amount of tildrakizumab.

Preparation and Administration:
Before injection, remove tildrakizumab carton from the refrigerator, and let the prefilled syringe (in the carton with the lid closed) sit at room temperature for 30 minutes.

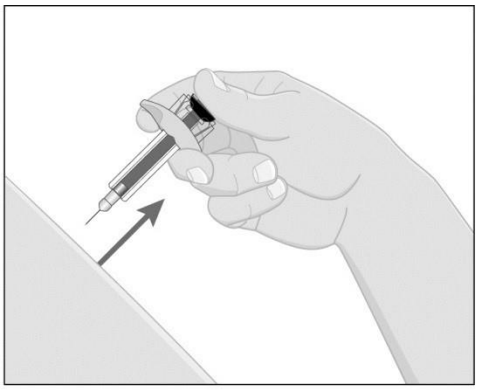
Follow the instructions on the tildrakizumab carton to remove the prefilled syringe correctly, and remove only when ready to inject. Do not pull off the needle cover until you are ready to inject.

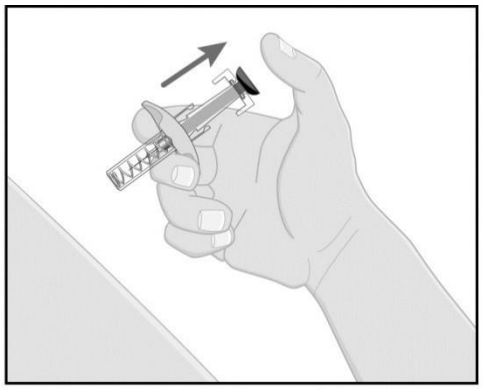
Inspect tildrakizumab visually for particulate matter and discoloration prior to administration. tildrakizumab is a clear to slightly opalescent, colorless to slightly yellow solution. Do not use if the liquid contains visible particles or the syringe is damaged. Air bubbles may be present; there is no need to remove them.

Choose an injection site with clear skin and easy access (such as abdomen, thighs, or upper arm). Do not administer 2 inches around the navel or where the skin is tender, bruised, erythematous, indurated, or affected by psoriasis. Also, do not inject into scars, stretch marks, or blood vessels.



- While holding the body of the syringe, pull the needle cover straight off (do not twist) and discard.
- Inject tildrakizumab subcutaneously as recommended [*see Dosage and Administration*].
- Press down the blue plunger until it can go no further. This activates the safety mechanism that will ensure full retraction of the needle after the injection is given.
- Remove the needle from the skin entirely before letting go of the blue plunger. After the blue plunger is released, the safety lock will draw the needle inside the needle guard.





- Discard any unused portion. Dispose of used syringe.

CONTRADICTIONS

Tildrakizumab is contraindicated in patients with a previous serious hypersensitivity reaction to tildrakizumab or to any of the excipients [*see Warnings and Precautions*].

WARNINGS AND PRECAUTIONS

Hypersensitivity

Cases of angioedema and urticaria occurred in tildrakizumab treated subjects in clinical trials. If a serious hypersensitivity reaction occurs, discontinue tildrakizumab immediately and initiate appropriate therapy [*see Adverse Reactions*].

Infections

Tildrakizumab may increase the risk of infection. Although infections were more common in the tildrakizumab group (23%), the difference in frequency of infections between the tildrakizumab group and the placebo group (22%) was less than 1% during the placebo-controlled period. However, subjects with active infections or a history of recurrent infections were not included in clinical trials. Upper respiratory infections occurred more frequently in the tildrakizumab group than in the placebo group [*see Adverse Reactions*].

The rates of serious infections for the tildrakizumab group and the placebo group were ≤0.3%. Treatment with tildrakizumab should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing tildrakizumab. Instruct patients to seek medical help if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a clinically important or serious infection or is not responding to standard therapy, monitor the patient closely and consider discontinuation of tildrakizumab until the infection resolves [*see Adverse Reactions*].

Pre-treatment Evaluation for Tuberculosis

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with tildrakizumab. Initiate treatment of latent TB prior to administering tildrakizumab. In clinical trials, of 55 subjects with latent TB who were concurrently treated with tildrakizumab and appropriate TB prophylaxis, no subjects developed active TB (during the mean follow-up of 56.5 weeks). One other subject developed TB while receiving tildrakizumab. Monitor patients for signs and symptoms of active TB during and after tildrakizumab treatment. Consider anti-TB therapy prior to initiation of tildrakizumab in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Do not administer tildrakizumab to patients with active TB infection.

Immunizations

Prior to initiating therapy with tildrakizumab, consider completion of all age appropriate immunizations according to current immunization guidelines. Avoid the use of live vaccines in patients treated with tildrakizumab. No data are available on the response to live or inactive vaccines.

If a patient has received live viral or bacterial vaccination it is recommended to wait at least 4 weeks prior to starting treatment with tildrakizumab. Patients treated with tildrakizumab should not receive live vaccines during treatment and for at least 17 weeks after treatment.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Limited available data with tildrakizumab, use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. Human IgG is known to cross the placental barrier; therefore, tildrakizumab may be transferred from the mother to the fetus. An embryo fetal developmental study conducted with tildrakizumab in pregnant monkeys revealed no treatment-related effects to the developing fetus when tildrakizumab was administered subcutaneously during organogenesis to near parturition at doses up to 159 times the maximum recommended human dose (MRHD). When dosing was continued until parturition, a small increase in neonatal death was observed at 59 times the MRHD [*see Data*]. The clinical significance of this nonclinical finding is unknown.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Women of Childbearing potential

Women of childbearing potential should use an effective method of contraception during treatment and for at least 17 weeks after treatment.

Data

Animal Data

In an embryo fetal developmental study, subcutaneous doses up to 300 mg/kg tildrakizumab were administered to pregnant cynomolgus monkeys once every two weeks during organogenesis to gestation day 118 (22 days from parturition). No maternal or embryo fetal toxicities were observed at doses up to 300 mg/kg (159 times the MRHD of 100 mg, based on AUC comparison). Tildrakizumab crossed the placenta in monkeys.

In a pre- and postnatal developmental study, subcutaneous doses up to 100 mg/kg tildrakizumab were administered to pregnant cynomolgus monkeys once every two weeks from gestation day 50 to parturition. Neonatal deaths occurred in the offspring of one control monkey, two monkeys at 10 mg/kg dose (6 times the MRHD based on AUC comparison), and four monkeys at 100 mg/kg dose (59 times the MRHD based on AUC comparison). The clinical significance of these nonclinical findings is unknown. No tildrakizumab related adverse effects were noted in the remaining infants from birth through 6 months of age.

Lactation

Risk Summary

There are no data on the presence of tildrakizumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is known to be present in human milk. Tildrakizumab was detected in the milk of monkeys [*see Data*].

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for tildrakizumab and any potential adverse effects on the breastfed child from tildrakizumab or from the underlying maternal condition.

Data

Animal Data

Very low levels of tildrakizumab were detected in breast milk of monkeys in the pre- and postnatal developmental study described [*See Use in Special Populations*]. The mean tildrakizumab concentrations in milk were approximately 0.09 – 0.2% of that in serum on postpartum days 28 and 91.

Pediatric Use
Safety and effectiveness of tildrakizumab in pediatric patients (<18 years of age) have not been established.

Geriatric Use
A total of 1083 subjects were exposed to tildrakizumab 100 mg during Phase 2 and 3 trials. A total of 92 subjects were 65 years or older, and 17 subjects were 75 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects [*see Clinical Pharmacology*].

Drug Interaction Studies
Cytochrome P450 Substrates

The AUC_{inf} of dextromethorphan (CYP2D6 substrate) increased by 20% when used concomitantly with tildrakizumab200 mg (two times the approved recommended dose) administered subcutaneously at Weeks 0 and 4 in subjects with plaque psoriasis. No clinically significant changes in AUC_{inf} of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), and midazolam (CYP3A4 substrate) were observed.

NON-CLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility
Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of tildrakizumab.

No effects on fertility parameters were observed in male or female cynomolgus monkeys that were administered tildrakizumab at subcutaneous or intravenous doses up to 140 mg/kg once every two weeks for 3 months (133 or 155 times the MRHD, respectively, based on AUC comparison). The monkeys were not mated to evaluate fertility.

CLINICAL STUDIES

Plaque Psoriasis
In two multicentre, randomized, double-blind, placebo-controlled trials (Trial 2 [NCT01722331] and Trial 3 [NCT01729754]), 926 subjects were treated with tildrakizumab 100 mg (N=616) or placebo (N=310). Subjects had a Physician Global Assessment (PGA) score of ≥3 (moderate) on a 5-point scale of overall disease severity, Psoriasis Area and Severity Index (PASI) score ≥12, and a minimum body surface area (BSA) involvement of 10%. Subjects with guttate, erythrodermic, or pustular psoriasis were excluded.

In both trials, subjects were randomized to either placebo or tildrakizumab (100 mg at Week 0, Week 4, and every twelve weeks thereafter [Q12W]) up to 64 weeks.

Trials 2 and 3 assessed the changes from baseline to Week 12 in the two co-primary endpoints:

- PASI 75, the proportion of subjects who achieved at least a 75% reduction in the PASI composite score.
- PGA of 0 ("cleared") or 1 ("minimal"), the proportion of subjects with a PGA of 0 or 1 and at least a 2-point improvement.

Other evaluated outcomes in Trials 2 and 3 included the proportion of subjects who achieved a reduction from baseline in PASI score of at least 90% (PASI 90) and a reduction of 100% in PASI score (PASI 100) at Week 12 and maintenance of efficacy up to Week 64.

In both trials, subjects in the tildrakizumab 100 mg and placebo treatment groups were predominantly men (69%) and White (80%), with a mean age of 46 years. At baseline, these subjects had a median affected BSA of 27%, a median PASI score of 17.8, and approximately 33% had a PGA score of 4 ("marked") or 5 ("severe"). Approximately 34% had received prior phototherapy, 39% had received prior conventional systemic therapy, and 18% had received prior biologic therapy for the treatment of psoriasis. Approximately 16% of subjects had a history of psoriatic arthritis.

Clinical Response at Week 12
The results of Trials 2 and 3 are presented in Table 1.

Table 1: Efficacy Results at Week 12 in Adults with Plaque Psoriasis in Trials 2 and 3 (NRI*)

	Trial 2 (NCT01722331)		**Trial 3 (NCT01729754)**	
	Tildrakizumab 100 mg (N=309) n (%)	**Placebo (N=154) n (%)**	**Tildrakizumab 100 mg (N=307) n (%)**	**Placebo (N=156) n (%)**
PGA of 0 or 1[†,‡]	179 (58)	11 (7)	168 (55)	7 (4)
PASI 75[†]	197 (64)	9 (6)	188 (61)	9 (6)
PASI 90	107 (35)	4 (3)	119 (39)	2 (1)
PASI 100	43 (14)	2 (1)	38 (12)	0 (0)

* NRI = Non-Responder Imputation
[†] Co-Primary Endpoints
[‡] PGA score of 0 ("cleared") or 1 ("minimal")

Examination of age, gender, race, and previous treatment with a biologic did not identify differences in response to tildrakizumab among these subgroups at Week 12.

Results obtained at Weeks 12, 28 and beyond (up to Week 64 in reSURFACE 1 (Trial 2) and up to Week 52 in reSURFACE 2 (Trial 3)) are presented in Table 2.

Table 2: Summary of Response Rates in Studies reSURFACE 1 and reSURFACE 2

reSURFACE 1	**Primary Analysis Week 12 (2 doses)***				**Week 28 (3 doses)***			**Long term response**[a]	
	Tildrakizumab		**Placebo**	**Etanercept**	**Tildrakizumab**		**Etanercept**	**Tildrakizumab**	
	100 mg	**200 mg**			**100 mg**	**200 mg**		**100 mg**	**200 mg**
Number of patients	309	308	154	–	299	298	–	112	114
PASI 75[b], n (%)	197 (63.8)[†c]	192 (62.3)[†c]	9 (5.8)[c]	–	229 (80.4)[d]	236 (81.9)[d]	–	98 (87.5)[d]	107 (93.9)[d]

PGA of "clear" or "minimal" with ≥ 2 grade improvement from Baseline [b], n (%)	179 (57.9) †c	182 (59.1) †c	11 (7.1) c	–	188 (66.0) d	199 (69.1) d	–	69 (61.6) d	87 (76.3) d
PASI 90, n (%)	107 (34.6) †c	109 (35.4) †c	4 (2.6) c	–	147 (51.6) d	170 (59.0) d	–	65 (58.0) d	85 (74.6) d
PASI 100, n (%)	43 (13.9) †c	43 (14.0) †c	2 (1.3) c	–	67 (23.5) d	91 (31.5) d	–	36 (32.1) d	46 (40.4) d
DLQI Score 0 or 1, n (%)	126 (41.5) †	132 (44.2) †	8 (5.3)	–	152 (52.4) d	164 (56.7) d	–	59 (52.2) d	78 (68.4) d
reSURFACE 2									
Number of patients	307	314	156	313	294	299	289	204	105
PASI 75 [b], n (%)	188 (61.2) †‡c	206 (65.6) †‡c	9 (5.8) c	151 (48.2) c	216 (73.5) ‡c	217 (72.6) ‡c	155 (53.6) c	191 (93.6) d	102 (97.1) d
PGA of "clear" or "minimal" with ≥ 2 grade improvement from Baseline [b], n (%)	168 (54.7) †c	186 (59.2) †¥c	7 (4.5) c	149 (47.6) c	190 (64.6) ‡c	207 (69.2) ‡c	131 (45.3) c	162 (79.4) d	89 (84.8) d
PASI 90, n (%)	119 (38.8) †‡c	115 (36.6) †‡c	2 (1.3) c	67 (21.4) c	161 (55.5) ‡d	169 (57.7) ‡d	85 (29.4) d	160 (78.4) d	86 (81.9) d
PASI 100, n (%)	38 (12.4) †‡c	37 (11.8) †‡c	0	15 (4.8) c	66 (22.8) ‡d	79 (27.0) ‡d	31 (10.7) d	72 (35.3) d	49 (46.7) d
DLQI Score 0 or 1, n (%)	119 (40.2) †	145 (47.4) †¥	12 (8.0)	108 (35.5)	157 (54.1) ‡d	193 (65.0) ‡d	111 (39.4) d	141 (68.8) d	76 (72.4) d

[a] Long-term response in patients who were responders (had achieved at least PASI 75) to tildrakizumab at Week 28. (64 weeks in reSURFACE 1 and 52 weeks in reSURFACE 2)

[b] Co-primary efficacy endpoint at week 12

[c] Non-responder imputation for missing data

[d] No imputation for missing data

n = number of patients in the full analysis set for which data was available, after imputation when applicable

p-values calculated using the Cochran-Mantel-Haenszel (CMH) test stratified by body weight (≤90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no)

† p≤0.001 versus placebo; ‡ p≤0.001 versus etanercept; ¥ p≤0.05 versus etanercept.

*The number of doses administered refers only to tildrakizumab groups.

Maintenance of Response and Durability of Response

In Trial 2, subjects originally randomized to tildrakizumab and who were responders at Week 28 (i.e., PASI 75) were re-randomized to an additional 36 weeks of either maintaining the same dose of tildrakizumab Q12W (every twelve weeks) or placebo.

At Week 28, 229 (74%) subjects treated with tildrakizumab 100 mg were PASI 75 responders. At Week 64, 84% of subjects who continued on tildrakizumab 100 mg Q12W maintained PASI 75 compared to 22% of subjects who were re-randomized to placebo. In addition, for subjects who were re-randomized and also had a PGA score of 0 or 1 at Week 28, 69% of subjects who continued on tildrakizumab 100 mg Q12W maintained this response (PGA 0 or 1) at Week 64 compared to 14% of subjects who were re-randomized to placebo.

For PASI 75 responders at Week 28 who were re-randomized to treatment withdrawal (i.e., placebo), the median time to loss of PASI 75 was approximately 20 weeks.

In addition, for subjects who were re-randomized to placebo and also had a PGA score of 0 or 1 at Week 28, the median time to loss of PGA score of 0 or 1 was approximately 16 weeks.

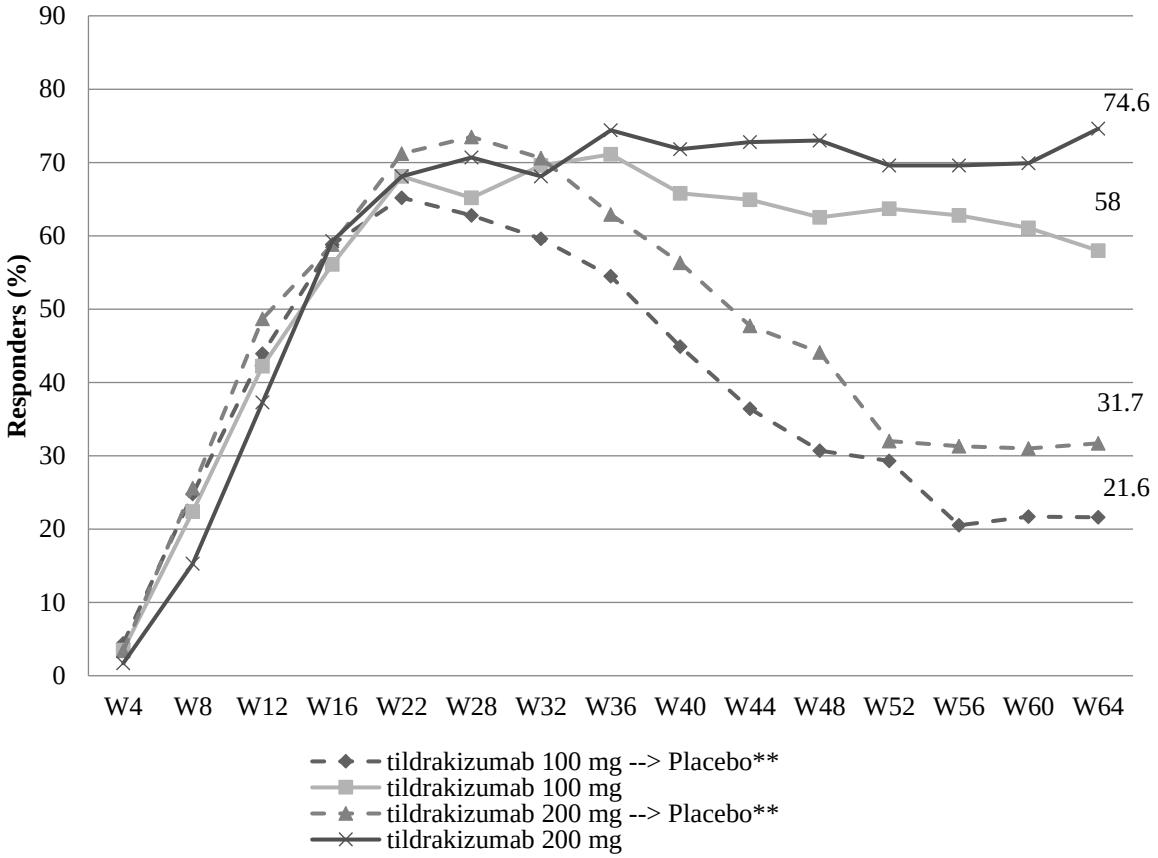
The maintenance of response in studies reSURFACE 1 and reSURFACE 2 are presented in Table 3. Maintenance and durability of PASI 90 response over time is presented in Figure 1

Table 3: Maintenance of response in studies reSURFACE 1 and reSURFACE 2

	Long term response[a,b]			
	200 mg		**100 mg**	
reSURFACE 1	**Week 28**	**Week 64**	**Week 28**	**Week 64**
Number of patients	116	114	115	112
PGA of "clear" or "minimal" with ≥2 grade improvement from Baseline (%)	80.2	76.3	80.9	61.6
PASI 90 (%)	70.7	74.6	65.2	58.0
PASI 100 (%)	38.8	40.4	25.2	32.1
reSURFACE 2	**Week 28**	**Week 52**	**Week 28**	**Week 52**
Number of patients	108	105	213	204
PGA of "clear" or "minimal" with ≥2 grade improvement from Baseline (%)	88.0	84.8	84.0	79.4
PASI 90 (%)	75.0	81.9	74.2	78.4
PASI 100 (%)	34.3	46.7	30.2	35.3

[a] Long-term response in patients who were responders (had achieved at least PASI 75) tildrakizumab at week 28.
[b] No imputation for missing data.

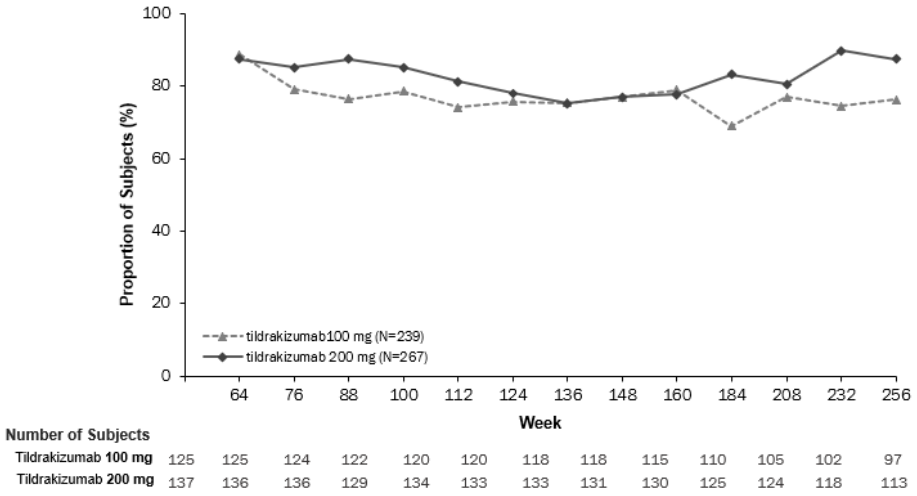
Figure 1: Maintenance and Durability of PASI 90 Response. Proportion of Patients with PASI 90 Response Over Time up to Week 64



Patients randomised to tildrakizumab 100 mg or tildrakizumab 200 mg in Part 1 who were PASI 75 responders at week 28 (reSURFACE1).
**These patients were switched to placebo at week 28

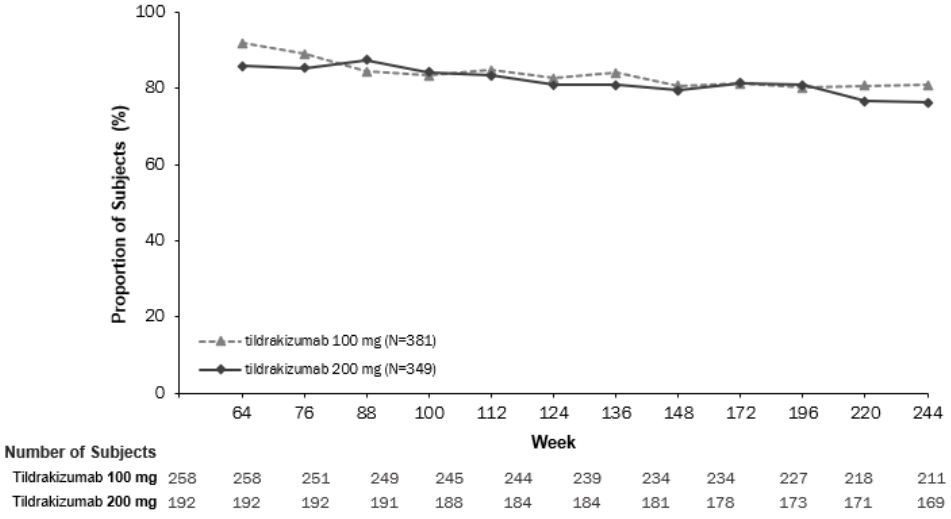
Of the patients who completed the double-blind period, 506 (79%) in reSURFACE 1 and 730 (97%) in reSURFACE 2 entered the extension period. Across studies, at least 76% of patients who had a PASI 90 response at the end of the double-blind period, maintained a PASI 90 response at the end of the double-blind period, maintained a PASI 90 response during the extension period, when tildrakizumab 100 mg or 200 mg treatment was continued during a period of 192 weeks (Figures 2 and 3).

Figure 2. Percentage of patients who maintained a PASI 90 response by visit in the open-label extension of reSURFACE 1 (Full Analysis Set, Extension Period*)



*Among PASI 90 responders at the end of the double-blind study period. No imputation of missing data.
Note: Visit week is nominal, as study participants had a window of up to approximately 12 weeks from week 64 to begin the extension.

Figure 3. Percentage of patients who maintained a PASI 90 response by visit in the open-label extension of reSURFACE 2 (Full Analysis Set, Extension Period*)



*Among PASI 90 responders at the end of the double-blind study period. No imputation of missing data.

ADVERSE EVENTS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hypersensitivity Reactions [*see Warnings and Precautions*]
- Infections [*see Warnings and Precautions*]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

<u>Plaque Psoriasis</u>

In clinical trials, a total of 1994 subjects with plaque psoriasis were treated with tildrakizumab, of which 1083 subjects were treated with tildrakizumab 100 mg. Of these, 672 subjects were exposed for at least 12 months, 587 for 18 months, and 469 for 24 months.

Data from three placebo-controlled trials (Trials 1, 2, and 3) in 705 subjects (mean age 46 years, 71% males, 81% white) were pooled to evaluate the safety of tildrakizumab (100 mg administered subcutaneously at Weeks 0 and 4, followed by every 12 weeks [Q12W]) [*see Clinical Studies*].

Placebo-Controlled Period (Weeks 0-16 of Trial 1 and Weeks 0-12 of Trials 2 and 3)
In the placebo-controlled period of Trials 1, 2, and 3 in the 100 mg group, adverse events occurred in 48.2% of subjects in the tildrakizumab group compared to 53.8% of subjects in the placebo group. The rates of serious adverse events were 1.4% in the tildrakizumab group and 1.7% in the placebo group.

Table 4 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the tildrakizumab group than in the placebo group.

Table 4: Adverse Reactions Occurring in ≥1% of Subjects in the tildrakizumab group and More Frequently than in the Placebo Group in the Plaque Psoriasis Trials 1, 2, and 3

Adverse Reaction	TILDRAKIZUMAB 100 mg (N=705) N (%)	Placebo (N=355) N (%)
Upper respiratory infections*	98 (14)	41 (12)
Injection Site Reactions†	24 (3)	7 (2)
Diarrhea	13 (2)	5 (1)

* Upper respiratory infections include nasopharyngitis, upper respiratory tract infection, viral upper respiratory tract infection, and pharyngitis.
† Injection site reactions include injection site urticaria, pruritus, pain, reaction, erythema, inflammation, edema, swelling, bruising, hematoma, and hemorrhage.

During the placebo-controlled period of Trials 1, 2, and 3, adverse reactions that occurred at rates less than 1% but greater than 0.1% in the tildrakizumab group and at a higher rate than in the placebo group included dizziness and pain in extremity.

Cases of angioedema and urticaria were reported in tildrakizumab-treated subjects in clinical trials.

Infections
Infections were slightly more common. The difference in frequency of infections between the tildrakizumab group (23%) and the placebo group was less than 1% during the placebo-controlled period. The most common (≥1%) infections were upper respiratory infections. The rates of severe infections for the tildrakizumab group and the placebo group were ≤0.3%.

Other commonly seen adverse events include: gastroenteritis, headache, back pain and nausea.

Safety through Week 52/64

Through Week 52 (Trials 1 and 3) and Week 64 (Trial 2), no new adverse reactions were identified with tildrakizumab use and the frequency of the adverse reactions was similar to that observed during the placebo-controlled period.

Adverse Reactions Open-Label Extension Portions of reSURFACE 1 and reSURFACE 2 Studies
In the extension period of reSURFACE 1 the incidence rates of drug-related adverse events showed no notable difference between the two treatment groups (18.4% and 18.7% in the tildrakizumab 100 mg and 200 mg groups, respectively).

In the extension period of reSURFACE 2 no meaningful differences were observed in the overall frequencies of drug-related AEs between the two treatment groups (23.9% and 28.4% in the tildrakizumab 100 mg and 200 mg groups, respectively).

Long-term Safety
The safety profile of tildrakizumab observed during the long-term extensions period of reSURFACE1 and reSURFACE2 was consistent with that of the double-blind periods.

Immunogenicity
As with all therapeutic proteins there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to tildrakizumab in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

Up to Week 64, approximately 6.5% of subjects treated with tildrakizumab 100 mg developed antibodies to tildrakizumab. Of the subjects who developed antibodies to tildrakizumab, approximately 40% (2.5% of all subjects receiving tildrakizumab) had antibodies that were classified as neutralizing.

The development of neutralizing antibodies to tildrakizumab was associated with lower serum tildrakizumab concentrations.

Driving and using machines
Tildrakizumab has no or little effect on the ability to drive and use machines.

DRUG INTERACTIONS
Live Vaccinations
Avoid use of live vaccines in patients treated with tildrakizumab [*see Warnings and Precautions*].

OVERDOSAGE
In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment immediately.

Storage Condition
Store refrigerated at temperatures between 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until the time of use.

Tildrakizumab can be kept at 25°C (77°F) for up to 30 days or at 30°C (86°F) for up to 3 days in the original carton to protect from light. Once stored at 25°C or 30°C, do not place back in the refrigerator. If not used within 30 days at 25°C or within 3 days at 30°C, discard tildrakizumab.
Do not freeze. Do not shake.

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Tildrakizumab Injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution. Tildrakizumab is supplied as a single-dose prefilled syringe per carton which contains 1mL of a 100mg/mL solution.
Each prefilled syringe is equipped with a passive needle guard and a needle cover.

Manufactured By:
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