SUPPLEMENTAL APPENDIX

Tezepelumab, an anti-TSLP monoclonal antibody, in the treatment of moderate to severe atopic dermatitis: A randomized phase 2a clinical trial

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Randomization

Once informed consent was obtained, a subject identification (SID) number was assigned by a central interactive voice/web response system. The SID number was used to identify the patient during the screening process and throughout study participation, if applicable.

A master log of all consented patients was maintained at the site and documented all screening failures, including the reasons for screening failure. Patients who failed to meet the inclusion/exclusion criteria were not randomized and did not receive study treatment.

Treatment Administration

This study used a single-dose regimen. Each patient received tezepelumab 280 mg or placebo as one 1 mL subcutaneous (SC) injection and two 1.5 mL SC injections every other week for 12 weeks (a total of six doses). The three required injections were administered using separate injection sites on the anterior thigh, abdomen, or upper arm. Injections administered in the same location were at least 1 inch apart. The upper arm was used only for the 1 mL injections.

Blinding

The patient or the patient's legal representative and the investigators or sponsor staff were blinded to the treatment received (International Conference on Harmonisation E9). Since tezepelumab and placebo are not identical, an unblinded investigational product manager prepared the study treatment in dosing syringes. The study treatment was then administered by a blinded-study team member. An unblinded investigational product monitor performed study treatment accountability. Each study site maintained a written plan detailing which staff members were blinded or unblinded, and the process of study treatment preparation used to maintain the blind.

Study Termination Guidelines

Reasons for temporary suspension or termination of the study included, but were not limited to, the following:

1. The incidence or severity of adverse events in this study or other studies where patients received tezepelumab indicated a potential health hazard
2. Patient enrollment was unsatisfactory
3. Non-compliance by patients that might have significantly jeopardized the validity or integrity of the study
4. Sponsor decision to terminate development

Full Inclusion Criteria

Patients must meet all of the following criteria:

1. Written informed consent and any locally required authorization obtained from the patient prior to performing any protocol-related procedures
2. Age 18–75 years at screening
3. Current disease state meeting the Hanifin and Rajka, 1980 criteria[1] for atopic dermatitis (AD)
4. AD that affects ≥10% body surface area at screening, as assessed by Eczema Area Severity Index (EASI)
5. An Investigator's Global Assessment (IGA) score of ≥3 at screening and baseline
6. An EASI score of ≥12 at screening and baseline
7. A Scoring of Atopic Dermatitis (SCORAD) of ≥20 at screening
8. No clinically significant abnormality on the basis of medical/medication history or physical examination
9. If receiving allergen-specific immunotherapy, patients must be treated with a maintenance dose and schedule for ≥1 month prior to screening. Allergen-specific immunotherapy refers

to subcutaneous immunotherapy to aeroallergens and/or venom (Hymenoptera) as well as sublingual immunotherapy to aeroallergens

10. Able and willing to comply with protocol requirements

11. Females of childbearing potential who are sexually active with a non-sterilized male partner must use highly effective contraception from enrollment and must agree to continue using such precautions through to study end. Females of childbearing potential are defined as those who are not surgically sterile or post-menopausal. A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly

Full Exclusion Criteria

Any of the following would exclude the patient from participation in the study:

1. Active dermatologic conditions, which may confound the AD diagnosis or treatment assessment

2. Known active allergic or irritant contact dermatitis

3. History of a clinically significant infection within 4 weeks prior to baseline which, in the opinion of the investigator, may compromise the safety of the patient, interfere with evaluation of the study treatment, or reduce the patient's ability to participate in the study. Clinically significant infections are defined as:

- A systemic infection
- A serious skin infection requiring parenteral antibiotics, antiviral, or antifungal medication

4. Diagnosis of a helminth parasitic infection within 6 months prior to screening that has not been treated with, or has failed to respond to standard of care therapy

5. History of cancer, except for basal cell carcinoma or *in situ* carcinoma of the cervix

treated with apparent success ≥12 months prior to screening or other malignancies treated with apparent success ≥5 years prior to screening

6. History of chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the investigator

7. Pregnant or breastfeeding women or pregnancy planned within the next 6 months from last dose

8. Use of tanning beds or phototherapy within 8 weeks of baseline

9. Receipt of any marketed or investigational biologic agent within 4 months or 5 half-lives prior to baseline, whichever is longer

10. Receipt of any investigational non-biologic agent within 3 months or 5 half-lives prior to baseline, whichever is longer

11. Treatment with the following medications within the last 4 weeks prior to baseline:

- Systemic immunosuppressive/immunomodulating drugs (eg, methotrexate, cyclosporine, azathioprine, mycophenolate mofetil, tacrolimus, interferon-γ)
- Immunoglobulin and/or blood products
- Systemic corticosteroids
- Topical calcineurin inhibitor use

12. Patients who have received a live or attenuated vaccine within 4 weeks prior to baseline. Receipt of inactive/killed vaccinations (eg, inactive influenza) is allowed provided they are not administered within 1 week before/after any study visit

13. Receipt of the Th2 cytokine inhibitor suplatast tosilate within 15 days prior to screening is allowed

14. Known history of allergy or reaction to any component of the study treatment formulation

15. History of anaphylaxis following any biologic therapy

16. Patients who are intolerant or contraindicated to use study-mandated topical corticosteroids for lesional skin

17. Any clinically relevant abnormal findings in physical electrocardiogram examination, vital signs, hematology, clinical chemistry, or urinalysis during screening, which in the opinion of the investigator may compromise the patient's safety, interfere with evaluation of the study treatment or reduce the patient's ability to participate in the study

18. Evidence of active liver disease, including jaundice or aspartate transaminase, alanine transaminase, or alkaline phosphatase greater than twice the upper limit of normal

19. Patients who, in the opinion of the investigator, have a positive QuantiFERON-tuberculosis Gold (QFT-G) test for tuberculosis (TB) during screening or have evidence of active treated or untreated TB. Patients with an indeterminate QFT-G result may be enrolled if they have all of the following:

- No symptoms of TB
- No known exposure to a case of active TB
- No evidence of active TB on chest radiograph within 3 months prior to baseline

Patients with an indeterminate QFT-G result will have repeat QFT-G testing at Week 12

20. Positive hepatitis B surface antigen or hepatitis C virus antibody serology. Patients with a history of hepatitis B vaccination without history of hepatitis B are allowed to enroll

21. A positive human immunodeficiency virus test at screening or patient taking antiretroviral medications

22. Concurrent enrollment in another clinical study where the patient is receiving study treatment

23. Employee of the clinical study site or any other individuals directly involved with the conduct of the study, or immediate family members of such individuals

24. Individuals who are legally institutionalized

25. Major surgery within 8 weeks prior to screening, or planned in-patient surgery or hospitalization during the study period

Secondary and Exploratory Clinical Endpoints

Secondary endpoints were measured at Week 12 and included the percentage of patients achieving a ≥75% reduction in EASI score (EASI75), change from baseline in EASI (total score), percentage of patients with an IGA response of 0 (clear) or 1 (almost clear) and a reduction of ≥two grades from baseline, change from baseline in SCORAD (total score), percentage of patients achieving a ≥50% or ≥75% reduction in SCORAD (SCORAD50 or SCORAD75), and patient-reported outcomes of change from baseline in pruritus numeric rating scale (NRS) (7-day mean), peak pruritus NRS (7-day mean), and 5-D itch scale[2] scores. Exploratory endpoints included the percentage of patients with a ≥90% reduction from baseline in EASI score (EASI90) at Week 12.

Clinical Assessments

EASI, IGA, and SCORAD assessments were performed at each treatment visit. A questionnaire to determine 5-D itch scale score was completed at randomization and Weeks 6, 12, and 22. During the run-in period, patients were trained to use an electronic diary, used to record pruritus severity each day according to the numeric rating scale (NRS). Serum samples were collected from all patients for the assessment of circulating biomarkers.

Serum Biomarker Concentration Determination

Serum periostin and DPP-4 concentrations were determined using proprietary immunoassays.[3,4] Serum CCL17/TARC concentrations were measured by an enzyme-linked immunosorbent assay (R&D Systems, MN, USA), and IgE concentrations by ImmunoCAP Total IgE immunoassay (Thermo Scientific, MI, USA). Selected endpoints were then measured in subgroups of patients defined by baseline biomarker concentration: periostin, DPP-4, and CCL17/TARC (< or ≥ the median baseline concentration), and IgE (<150 or ≥150 kU/L). Median serum baseline DPP-4, periostin, and CCL17/TARC concentrations were 257.4 ng/mL, 22.7 ng/mL, and 1313.6 pg/mL, respectively.

Table S1. Adjusted mean change (SE) in EASI and SCORAD lichenification scores at Week 12 and Week 16.

	EASI		SCORAD	
	Placebo plus TCS (N = 56)	**Tezepelumab 280 mg plus TCS (N = 55)**	**Placebo plus TCS (N = 56)**	**Tezepelumab 280 mg plus TCS (N = 55)**
n	47	48	50	49
Week 12	–3.26 (.40)	–3.23 (.40)	–.70 (.12)	–.82 (.12)
P-value	–	.956	–	.411
n	45	45	51	47
Week 16	–3.44 (.39)	–3.65 (.39)	–.71 (.12)	–.91 (.12)
P-value	–	.666	–	.155

EASI, Eczema Area Severity Index; SCORAD, Scoring of Atopic Dermatitis; SE, standard error; TCS, topical corticosteroid.

References

1. Hanifin JM , Rajka G. Diagnostic features of atopic eczema. Cambridge: Cambridge University Press; 1980.
2. Elman S, Hynan LS, Gabriel V et al. The 5-D itch scale: a new measure of pruritus. *Br J Dermatol*. 2010;162:587-593.
3. Jeanblanc NM, Hemken PM, Datwyler MJ et al. Development of a new ARCHITECT automated periostin immunoassay. *Clin Chim Acta*. 2017;464:228–235.
4. Hemken PM, Jeanblanc NM, Rae T et al. Development and analytical performance of a new ARCHITECT automated dipeptidyl peptidase-4 immunoassay. *Practical Laboratory Medicine*. 2017;9:58-68.